112TH CONGRESS
2d Session

COMMITTEE PRINT

S. PRT.
112–38

STAFF REPORT ON MEDTRONIC'S INFLUENCE ON INFUSE CLINICAL STUDIES

PREPARED BY THE STAFF OF THE

COMMITTEE ON FINANCE
UNITED STATES SENATE

OCTOBER 2012

Printed for the use of the Committee on Finance

U.S. GOVERNMENT PRINTING OFFICE
76–091 WASHINGTON : 2006

For sale by the Superintendent of Documents, U.S. Government Printing Office
Internet: bookstore.gpo.gov Phone: toll free (866) 512–1800; DC area (202) 512–1800
Fax: (202) 512–2104 Mail: Stop IDCC, Washington, DC 20402–0001

COMMITTEE ON FINANCE

MAX BAUCUS, Montana, *Chairman*

JOHN D. ROCKEFELLER IV, West Virginia
KENT CONRAD, North Dakota
JEFF BINGAMAN, New Mexico
JOHN F. KERRY, Massachusetts
RON WYDEN, Oregon
CHARLES E. SCHUMER, New York
DEBBIE STABENOW, Michigan
MARIA CANTWELL, Washington
BILL NELSON, Florida
ROBERT MENENDEZ, New Jersey
THOMAS R. CARPER, Delaware
BENJAMIN L. CARDIN, Maryland

ORRIN G. HATCH, Utah
CHUCK GRASSLEY, Iowa
OLYMPIA J. SNOWE, Maine
JON KYL, Arizona
MIKE CRAPO, Idaho
PAT ROBERTS, Kansas
MICHAEL B. ENZI, Wyoming
JOHN CORNYN, Texas
TOM COBURN, Oklahoma
JOHN THUNE, South Dakota
RICHARD BURR, North Carolina

RUSSELL SULLIVAN, *Staff Director*
CHRIS CAMPBELL, *Republican Staff Director*

CONTENTS

	Page
Introduction	1
Findings	2
Background on InFuse	2
Medtronic's Financial Relationships to Physician Authors of rhBMP–2 Studies	4
Medtronic Employees Were Substantively Involved in Producing Journal Articles Authored by the Company's Physician Consultants	6
Medtronic Recommended Omitting Discussion of Adverse Events Possibly Associated With the Product in a 2005 Publication	8
Medtronic Sought to Emphasize Pain in Alternative Treatments	11
Medtronic Attempted to Downplay Cervical Spine Side Effects in a 2006 Publication	13
Omission of Retrograde Ejaculation Rates in Investigative Patient Groups	14
Medtronic Wrote Author Responses to Peer-Review	15
PEEK Spacer Cervical Spine Study	17
Expert Testimony to the FDA Written By Medtronic	18
Conclusion	18
Appendix—Exhibits	21

Introduction

The United States Senate Committee on Finance (Committee) has jurisdiction over the Medicare and Medicaid programs. As the Chairman and a senior member and former Chairman of the Committee, we have a responsibility to the more than 100 million Americans who receive health care coverage under these programs to oversee their proper administration and ensure the taxpayer dollars are appropriately spent on safe and effective medical treatments. On June 21, 2011, the Committee staff initiated an inquiry into whether Medtronic, Inc. (Medtronic or the Company) improperly influenced peer-reviewed studies of Medtronic's bone-growth product InFuse, also known as bone morphogenetic protein 2 (BMP–2).

The Committee staff's inquiry was prompted by reports alleging that physician authors who had financial ties to Medtronic failed to report dangerous side effects associated with InFuse. These dangerous side effects were subsequently reported by medical researchers that did not have financial relationships with the company.[1]

A week later, on June 28, 2011, *The Spine Journal* devoted an entire publication to exposing a pattern of academic surgeons with financial ties to Medtronic omitting mention of serious side effects associated with InFuse.[2] The analysis, led by Dr. Eugene Carragee at Stanford University, identified 13 studies sponsored by Medtronic where there was absolutely no reporting of adverse events associated with InFuse.[3] However, *The Spine Journal* found the rate of adverse events related to the use of InFuse ranged from 10%–50%.[4]

In response to the June 21, 2011 request by Chairman Baucus and Senator Grassley, Medtronic produced more than 5,000 documents pertaining to the 13 rhBMP–2 studies analyzed in *The Spine Journal*. The documents included the amount of money Medtronic paid to physician authors, e-mail communication between Medtronic employees, and e-mails between Medtronic employees and physician authors pertaining to drafts of peer-reviewed articles reporting the results of the Medtronic-sponsored clinical trials. After thorough review of the documents submitted by Medtronic and other materials, the Committee staff makes the following findings:

---

[1] "New Study Links Spine Product From Medtronic to Risk of Sterility in Men," *New York Times*, May 25, 2011; "Researchers get royalties, papers omit sterility link," *Milwaukee Journal Sentinel,* May 25, 2011.

[2] "Spine Experts Repudiate Medtronic Studies," *New York Times*, June 28, 2011.

[3] "A critical review of recombinant human bone morphogenetic protein–2 trials in spinal surgery: emerging safety concerns and lessons learned," *The Spine Journal* 11 (2011) 471–491 at *http://www.spine.org/Documents/TSJJune2011__Carragee__etal__CriticalRev.pdf.*

[4] *Id.*

Findings

- Medtronic was heavily involved in drafting, editing, and shaping the content of medical journal articles authored by its physician consultants who received significant amounts of money through royalties and consulting fees from Medtronic. The company's significant role in authoring or substantively editing these articles was not disclosed in the published articles. Medical journals should ensure industry role contributions be fully disclosed.
- Medtronic paid a total of approximately $210 million to physician authors of Medtronic-sponsored studies from November 1996 through December 2010 for consulting, royalty, and other miscellaneous arrangements.
- An e-mail exchange shows that a Medtronic employee recommended against publishing a complete list of adverse events possibly associated with InFuse in a 2005 *Journal of Bone and Joint Surgery* article.
- Medtronic officials inserted language into studies that promoted InFuse as a better technique than taking a bone graft from the pelvic bone (autograft technique) by emphasizing the pain of the autograft technique.
- Documents indicate that Medtronic prepared Dr. Hal Mathew's remarks to the U.S. Food and Drug Administration (FDA) advisory panel meeting prior to InFuse being approved. At the time, Dr. Mathews was a private physician but was hired as a vice president at Medtronic in 2007.
- Medtronic documents show the company unsuccessfully attempted to adopt weaker safety rules for a clinical trial studying InFuse in the cervical spine that would have allowed the company to continue the trial in the event that patients experienced severe swelling in the neck.

Background on InFuse

In 2002, the FDA approved InFuse (also known as rh–BMP–2 or bone morphogenetic protein 2), a genetically engineered protein that stimulates bone growth for use in spinal fusion surgery in conjunction with the LT-Cage Lumbar Tapered Fusion Device to treat degenerative disc disease in the lower spine.[5]

Degenerative disc disease is a condition where the discs between spinal vertebrae deteriorate with age and can be a source of back pain. In some cases, degenerative disc disease is treated with spinal fusion surgery where the degenerated disc is removed and the adjacent vertebrae are joined together with a bone graft material to eliminate pain.[6] Medtronic promotes the use of InFuse for spinal surgery as a way to eliminate surgery and pain associated with the

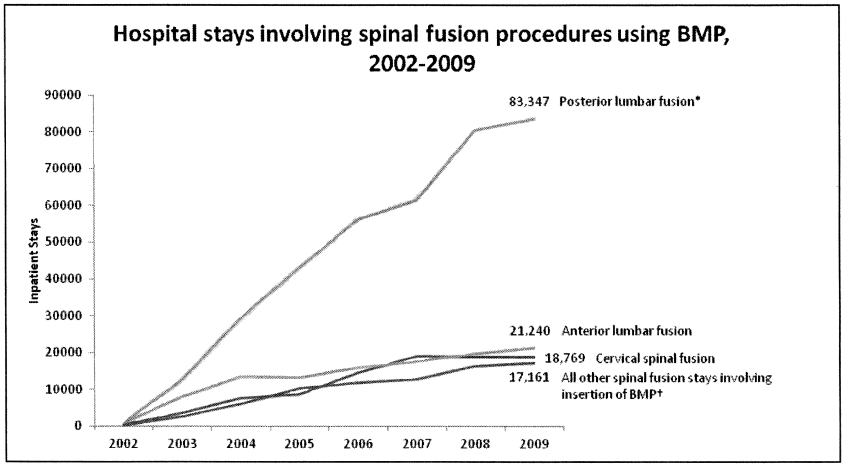
[5] See FDA's brief overview of the InFUSE™ Bone Graft/LT–CAGE™ Lumbar Tapered Fusion Device at *http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm083423.htm.*

[6] Handout on Health: Back Pain, April 2012, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH at *http://www.niams.nih.gov/health_info/back_pain/default.asp.*

autograft procedure, where bone is harvested from the patient's hip for use in the spine.[7]

The FDA's 2002 approval of InFuse was limited to spinal surgeries using the anterior lumbar interbody fusion (ALIF) technique. The ALIF approach allows surgeons to access the spine through the abdomen but does not involve "retraction of the spinal nerves and neurologic structures" which decreases the "risk of neurologic injury."[8] During the FDA advisory committee hearing prior to the approval of InFuse, concerns were expressed about the high potential for off-label use.[9] The Agency for Healthcare Research and Quality (AHRQ) estimates that, in 2009, only 21,240 of 140,467 spinal fusion surgeries with InFuse were performed using the anterior lumbar technique. The remaining 119,227 hospital stays were associated with off-label spinal fusion techniques such as posterior lumbar fusion and cervical spinal fusion.[10] This AHRQ estimate is consistent with a widely cited figure that "at least 85% of InFuse use is now off-label."[11]

Figure 1.



*Includes posterior lumbar interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF), and extreme lateral interbody fusion (XLIF).
†Includes anterior dorsal fusion, posterior dorsal fusion, lateral transverse lumbar fusion, and posterolateral lumbar fusion.
Source: Agency for Healthcare Reserach and Quality, Center for Delivery, Organization, and Markets, Healthcare Cost and Utilization Project, Nationwide Inpatient Sample, 2002–2009.

[7] "Questions and Answers—Infuse Bone Graft and LT Cage Device," available on Medtronic website.
[8] "Anterior Lumbar Interbody Fusion (ALIF)—Overview and Indications," USC Center for Spinal Surgery, University of Southern California at *http://www.uscspine.com/treatment/anterior-lumbar-fusion.cfm.*
[9] FDA Advisory Panel Meeting, January 10, 2002, FDA at *http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3828t1.htm.*
[10] "Trends in Hospital Stays For Spinal Fusion Using Recombinant Human Bone Morphogenetic Protein," Healthcare Cost and Utilization Project, AHRQ.
[11] "Medtronic Surgeons Held Back, Study Says," *Wall Street Journal*, June 29, 2011.

Table 1.

Hospital stays involving spinal fusion procedures using BMP, 2002–2009

	2002	2003	2004	2005	2006	2007	2008	2009
Cervical spinal fusion	377	3,656	7,590	8,805	14,548	18,955	18,887	18,769
Anterior lumbar fusion	920	8,166	13,511	13,239	15,870	17,774	19,820	21,240
Posterior lumbar fusion *	978	12,667	29,460	42,997	56,185	61,382	80,367	83,347
All other spinal fusion stays involving insertion of BMP †	174	2,783	6,126	10,351	11,828	12,862	16,329	17,161

* Includes posterior lumbar interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF), and extreme lateral interbody fusion (XLIF).

† Includes anterior dorsal fusion, posterior dorsal fusion, lateral transverse lumbar fusion, and posterolateral lumbar fusion.

Source: Agency for Healthcare Reserach and Quality, Center for Delivery, Organization, and Markets, Healthcare Cost and Utilization Project, Nationwide Inpatient Sample, 2002–2009.

In 2008, the FDA published a public health notification linking the off-label use of InFuse in the cervical spine with life-threatening swelling in patient's throats and necks.[12] The *Wall Street Journal* reported at the time that "the agency . . . received 38 reports over four years of side effects, mainly swelling of neck and throat tissue, which resulted in compression of the airway and other structures in the neck."[13] In addition, the *Wall Street Journal* reported that "[a]t least three-quarters of the roughly 200 'adverse events' reported to the FDA involve off-label uses of InFuse."[14]

In March 2011, the FDA declined to approve a higher-strength version of InFuse called Amplify due to concerns that the product may cause cancer.[15] Later that year, Dr. Eugene Carragee of Stanford University presented data at a spinal surgeon conference that he believes demonstrates that the patient group that received Amplify experienced a "significantly higher number of cancers . . . compared to a control group that received a bone graft" but was not reported in a 2009 industry-sponsored publication on Amplify.[16] Dr. Carragee told the *New York Times* that "doctors often administered InFuse off-label at levels significantly above the recommended dosages, ones that approach or exceed the amount of rhBMP–2 found in a dose of Amplify."[17]

Medtronic's Financial Relationships to Physician Authors of rhBMP–2 Studies

Medtronic produced a list of payments to physician authors of the 13 industry studies that were the subject of *The Spine Journal* article published in June 2011. The physicians who received pay-

[12] "Medtronic Product Linked to Surgery Problems," *Wall Street Journal*, September 4, 2008.
[13] *Id.*
[14] *Id.*
[15] "FDA sets back Medtronic spine product," *Star Tribune,* March 10, 2011.
[16] "Data Links High Doses of Bone Drug to Cancer," November 3, 2011, *New York Times* at *http://www.nytimes.com/2011/11/04/health/research/amplify-by-medtronic-may-raise-chance-of-cancer-data-shows.html.*
[17] *Id.*

ments of over $1 million from Medtronic from 1996 through 2010 are listed below along with the amount of money received.

Year	Scott D. Boden	Charles L. Branch	J. Kenneth Burkus	Concept Properties, LLC [18]	Curtis A. Dickman
1996	$18,750.00	—	—	—	—
1997	$75,000.00	—	—	—	$5,003.70
1998	$75,000.00	$140,703.15	$18,700.00	—	$73,239.25
1999	$86,957.00	$49,238.87	$34,712.12	—	$130,352.64
2000	$75,000.00	$104,495.00	$29,285.75	—	$41,419.50
2001	$73,750.00	$150,000.00	$149,920.00	$636,182.00	$56,960.00
2002	$80,000.00	$201,997.75	$220,539.50	$1,028,882.00	$72,881.00
2003	$82,500.00	$180,219.99	$268,742.50	$1,226,179.00	$316,215.00
2004	$138,500.00	$175,473.78	$360,447.78	$4,992,137.00	$320,045.99
2005	$1,364,100.00	$127,087.44	$331,070.44	$13,141,165.00	$339,338.00
2006	$1,782,550.00	$136,390.58	$613,849.71	$8,842,157.00	$401,138.77
2007	$3,400,875.00	$114,159.39	$719,281.84	$9,683,098.00	$383,192.00
2008	$21,543,052.00	$487,688.50	$1,928,503.35	$9,159,891.00	$388,248.00
2009	—	$460,319.35	$732,563.85	$7,117,112.00	$355,809.00
2010	—	$827,851.81	$972,719.99	$9,004,465.00	$389,099.00
Total	$28,796,034.00	$3,155,625.61	$6,380,336.83	$64,831,268.00	$3,272,941.85

Year	John R. Dimar, III	Steven D. Glassman	Matthew F. Gornet	Regis W. Haid, Jr.	John G. Heller
1996	$6,250.00	$6,250.00	—	—	—
1997	$27,000.00	$25,000.00	$1,880.00	$27,500.00	—
1998	$50,000.00	$50,000.00	—	$216,842.44	$10,892.00
1999	$52,022.65	$52,216.41	$29,900.00	$1,019,832.54	$70,817.57
2000	$50,000.00	$50,976.43	$16,369.97	$1,507,242.15	$30,000.00
2001	$188,428.00	$194,528.00	$15,128.00	$1,394,390.61	$37,975.10
2002	$100,100.00	$71,750.00	$4,762.00	$1,669,745.11	$1,161.73
2003	$116,283.65	$138,941.44	$10,194.00	$1,957,742.86	$49,191.50
2004	$104,043.67	$146,137.07	$17,924.00	$2,484,450.94	$42,957.44
2005	$147,207.99	$248,019.59	$67,763.93	$2,473,518.00	$154,835.70
2006	$236,306.95	$155,753.16	$238,787.49	$2,454,569.00	$149,215.39
2007	$130,767.60	$257,926.16	$649,542.33	$2,626,576.07	$330,792.15
2008	$234,094.50	$187,605.50	$1,181,039.87	$2,467,911.23	$288,957.11
2009	$160,551.00	$88,139.80	$892,500.87	$2,525,743.88	$255,236.24
2010	$163,310.20	$75,019.80	$859,983.76	$2,723,749.13	$352,404.36
Total	$1,766,366.21	$1,748,263.36	$3,985,776.22	$25,549,813.96	$1,774,436.29

Year	Inspire, LLC [19]	Gerald E. Rodts, Jr.	Volker Sonntag	Ensor E. Transfeldt	Thomas A. Zdeblick
1996	—	—	—	$12,500.00	$95,185.34
1997	—	—	$34,745.92	$50,000.00	$422,668.65
1998	—	$25,065.54	$207,622.16	$56,196.00	$838,794.89
1999	—	$44,748.08	$795,053.91	$61,219.28	$1,131,463.17
2000	—	$ 152,496.47	$1,756,041.55	$56,170.90	$1,037,381.49
2001	—	$140,343.39	$1,036,993.00	$71,117.56	$1,984,356.45
2002	—	$172,278.04	$1,646,050.49	$115,315.16	$3,471,930.41
2003	—	$142,025.68	$1,904,689.00	$258,912.62	$4,580,361.62
2004	—	$161,149.02	$2,728,639.00	$299,477.72	$4,447,269.00
2005	—	$303,877.98	$2,202,595.00	$30,474.70	$3,950,516.08
2006	—	$396,139.57	$2,090,998.00	$206,388.76	$3,469,863.71
2007	$247,365.00	$629,451.53	$2,163,661.90	$722,779.00	$2,961,272.00
2008	$329,998.00	$581,984.26	$2,271,477.00	$548,584.74	$2,521,170.00
2009	$698,829.00	$432,403.00	$1,772,361.00	$483,254.00	$1,582,156.00
2010	$1,632,813.00	—	$2,241,156.00	$589,930.00	$1,674,351.00
Total	$2,909,005.00	$3,181,962.56	$22,852,083.93	$3,562,320.44	$34,168,739.81

More detailed information concerning Medtronic's physician payments is available in the appendix to this report.[20]

[18] According to filings with the Office of the Secretary of State of Kentucky, John R. Dimar, III and Steven D. Glassman are listed as current officers of Concept Properties, LLC as of June 18th, 2012.

[19] According to an attachment to Medtronic's June 21, 2011 letter to the Committee, the Company "believes that Inspire, LLC is owned by physicians including Dr. Transfeldt."

[20] See page 22.

Medtronic Employees Were Substantively Involved in Producing Journal Articles Authored by the Company's Physician Consultants

A review of the documents Medtronic provided to the Committee demonstrates that Medtronic employees, including employees working for its marketing department, collaborated with physician authors, many of whom had significant financial relationships with Medtronic, to draft the following studies:

- Burkus JK, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP–2 with tapered interbody cages. *J. Spinal Disord. Tech.* 2002; 15:337–49.[21]
- Burkus JK, Transfeldt EE, Kitchel SH, et al. Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein–2. *Spine* 2002.[22]
- Burkus JK, Heim SE, Gornet MF, Zdeblick TA. Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT–CAGE lumbar tapered fusion device. *J. Spinal Disord. Tech.* 2003.[23]
- Baskin DS, Ryan P, Sonntag V, et al. A prospective, randomized, controlled cervical fusion study using recombinant human bone morphogenetic protein–2 with the CORNERSTONE–SR allograft ring and the ATLANTIS anterior cervical plate. *Spine* 2003.[24]
- Burkus JK, Dorchak JD, Sanders DL. Radiographic assessment of interbody fusion using recombinant human bone morphogenetic protein type 2. *Spine* 2003.[25]
- Haid RW, Branch CL, Alexander JT, Burkus JK. Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages. *Spine J.* 2004.[26]
- Burkus JK, Sandhu HS, Gornet MF, Longley MC. Use of rhBMP–2 in combination with structural cortical allografts

---

[21] See correspondence and draft articles MSD–R062111–033531—MSD–R062111–033562; MSD–R062111–033566—MSD–R062111–033568—MSD–R062111–033612; MSD–R062111–033616; MSD–R062111–040460—MSD–R062111–040463; MSD–R062111–077880—MSD–R062111–077920; MSD–R062111–033822—MSD–R062111–033862; MSD–R062111–080852—MSD–R062111–080894.

[22] See correspondence and draft articles MSD–R062111–033047—MSD–R062111–033079; MSD–R062111–033225—MSD–R062111–033256; MSD–R062111–033631—MSD–R062111–033668; MSD–R062111–033748—MSD–R062111–033784; MSD–R062111–055062—MSD–R062111–055067; MSD–R062111–033972—034006.

[23] See correspondence and draft articles MSD–R062111–064299—MSD–R062111–064284; MSD–R062111–064346—MSD–R062111–064373; MSD–R062111–067943—MSD–R062111–067971; MSD–R062111–080895—MSD–R062111–080899; MSD–R062111–080956—MSD–R062111–080983.

[24] See correspondence and draft articles MSD–R062111–034007—MSD–R062111–034039; MSD–R062111–034087—MSD–R062111–034189.

[25] See correspondence and draft articles MSD–R062111–033112—MSD–R062111–033126; MSD–R062111–064232—MSD–R062111—064245; MSD–R062111–033434—MSD–R062111–033450; MSD–R062111–033669—MSD–R062111–033688.

[26] See correspondence and draft articles MSD–R062111–040537—MSD–R062111–040561; MSD–R062111–069990—MSD–R062111–069997; MSD–R062111–078885—MSD–R062111–078895; MSD–R062111–034221—MSD–R062111–034224; MSD–R062111–068009—MSD–R062111–068070; MSD–062111–040735—MSD–062111–040773; MSD–R062111–040848—R062111–040887; MSD–R062111–068275—MSD–R062111–068309; MSD–R062111–040912—MSD–R062111–041018; MSD–R062111–068487—MSD–R062111–068541; MSD–R062111–079038—MSD–R062111–079039.

surgery: clinical and radiographic outcomes in anterior lumbar spinal fusion. *J. Bone Joint Surg. Am.* 2005; 87:1205–12.[27]

- Glassman SD, Dimar JR, Burkus K, et al. The efficacy of rhBMP–2 for posterolateral lumbar fusion in smokers. *Spine* 2007.[28]
- Dimar JR, Glassman SD, Burkus JK, et al. Clinical and radiographic analysis of an optimized rhBMP–2 formulation as an autograft replacement in posterolateral lumbar spine arthrodesis. *J. Bone Joint Surg. Am.* 2009. [29]
- Burkus JK, Gornet MF. Six-Year Outcomes of Anterior Lumbar Interbody Arthrodesis with Use of Interbody Fusion Cages and Recombinant Human Bone Morphogenetic Protein–2. *JBJS* 2009.[30]
- Dawson E, Bae HW, Burkus JK, et al. Recombinant human bone morphogenetic protein–2 on an absorbable collagen sponge with an osteoconductive bulking agent in posterolateral arthrodesis with instrumentation. A prospective randomized trial. *J. Bone Joint Surg. Am.* 2009.[31]

Medtronic told the Committee that it instituted policies, beginning in the mid-2000s, to ensure that interactions between the company and physician authors regarding peer-reviewed publications are "appropriate."[32] These policies include:

- Prohibiting the compensation of "a researcher to speak about or broadly disseminate research findings prior to FDA approval of the unapproved uses, other than providing a report of publishable quality to Medtronic and/or a peer reviewed journal for publication."—implemented in April 2006.
- Requiring "that clinical trial outcomes be presented without bias and with full disclosure."—implemented on January 8, 2008.
- Requiring "that a Medtronic employee's contribution to any publication must be appropriately disclosed, according to the standards of the International Committee of Medical Journal Editors ("ICMJE")."—implemented in 2009.
- Barring "Sales and Marketing personnel from participating in a publication project as an author or contributor. Only employees in the Clinical, Medical Affairs, or Research and Development Departments were permitted to serve as authors or contributors (as defined by ICMJE Guidelines), and only with disclosure."—implemented on August 8, 2010.

---

[27] See correspondence and draft articles MSD–R062111–034854—MSD–R062111–034894; MSD–R062111–034957—MSD062111–034994; MSD–R062111–061701—MSD–R062111–061708; MSD–R062111–064785—MSD–R062111–064787.

[28] See correspondence and draft articles MSD–R062111–065102—MSD–R062111–065120; R062111–065287—R062111–065317; MSD–R062111–043742—MSD–R062111–043775.

[29] See correspondence and draft articles MSD–062111–R065138—MSD–R062111–065155; MSD–R062111–043226—MSD–R062111–043246; MSD–R062111–056122—MSD–R062111–056142; MSD–R062111–037519—MSD–R062111–037546; MSD–R062111–046108—MSD–R062111–046160; MSD–R062111–067520—MSD–R062111–067566.

[30] See correspondence and draft articles MSD–R062111–058250—MSD–R062111–058285; MSD–R062111–045886—MSD–R062111–045954; MSD–R062111–046823—MSD–R062111–046900; MSD–R062111–037797—MSD–R062111–037821; MSD–R062111–047304—MSD–R062111–047332; MSD–R062111–060896—060898; MSD–R062111–049092—MSD–R02111–049100.

[31] See correspondence and draft articles MSD–R062111–059388—MSD–R062111–059410; MSD–R062111–060390—MSD–R062111–060421.

[32] Letter from Medtronic to the Senate Finance Committee, May 1, 2012; Medtronic policies, MSD–R021612–000187—MSD–R021612–000435.

- Prohibiting "Marketing personnel from making any contributions to the Discussion section of a publication, whether or not their contribution rises to the level of contributorship under ICMJE Guidelines" and prohibiting "any employees not identified as authors or contributors from contributing to the Discussion section."—implemented on October 11, 2011.
- Requiring that "all authors sign a standardized authorship agreement clarifying (1) the authors' responsibility to fully disclose relationships with Medtronic in any related publication, (2) the authors' responsibility to ensure appropriate attribution of authorship and contributorship, and (3) the authors' acknowledgement that Medtronic will not compensate physicians for writing or editing activities."—implemented on December 6, 2011.

The company defends collaboration between company employers and physician authors as "a well-established and widely-accepted part of the peer review process used to subject articles to critical scrutiny, as a medical device company like Medtronic typically maintains the most complete set of data relating to the use, as well as properties of its devices and thus is uniquely positioned to make valuable contributions to potential articles."[33] Further, Medtronic maintains that "the content of these articles is ultimately controlled by the authors."[34] The company wrote:

> Some of the employees who reviewed these articles resided nominally in the "Marketing" Department, but these employees generally are technically and scientifically trained who have earned doctoral or other advanced degrees in relevant disciplines and draw on deep expertise in the science of bone morphogenetic proteins, in the design and implementation of clinical studies, in technical expression of clinical practice, and in statistical analysis. Importantly, at [Medtronic Spinal Biologics] the Marketing Department is distinct from the Sales Department. Marketing personnel are tasked with, among other things, anticipating the needs of Medtronic's physician customers, following the latest scientific and clinical developments in the field, and using evidence to obtain wider approvals, use, and acceptance of products. Sales personnel, on the other hand, are designated to interact directly with customers for the purpose of effecting sales. In every case, however, physicians—not Medtronic personnel—prepare draft manuscripts, select content, approve suggested modifications, and are responsible for the final article content that they submit for publication and review by the scientific community.[35]

Medtronic Recommended Omitting Discussion of Adverse Events Possibly Associated With the Product in a 2005 Publication

According to the FDA's Summary of Safety and Effectiveness Data of the 2002 IDE InFuse product, "the incidence of adverse

[33] *Id.*
[34] *Id.*
[35] *Id.*

events that were considered device related, including implant displacement/loosening, implant malposition and subsidence were all greater in the investigational groups [that received InFuse] compared to the control group."[36] However, documents indicate that a Medtronic employee involved in editing a draft of the 2005 *Journal of Bone and Joint Surgery (JBJS)* article by Burkus, et al. about a similar InFuse procedure involving allograft bone (a cage made from donated bone rather than the FDA-approved titanium), recommended that "significant detail" concerning adverse event data should not be published.[37]

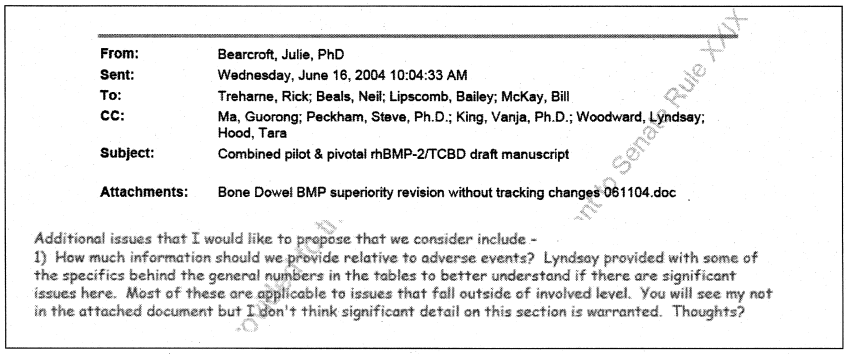
On June 16, 2004, Dr. Julie Bearcroft, Director of Technology Management in Medtronic's Biologics Marketing Department, wrote an e-mail to other Medtronic employees, commenting on a draft of the study, "I have made some significant changes to this document (some at the request of Dr. Burkus) both in format and content."[38] In this e-mail, she asked: "How much information should we provide relative to adverse events? . . . You will see my [note] in the attached document but I don't think significant detail on this section is warranted."[39] The referenced note in the draft article stated: "I don't believe we want to report in the same manner as we do in IDE studies. I personally think it is appropriate to simply report the adverse events were equivalent in the two groups without the detail."[40] According to an internal e-mail, the adverse events were observed in the trial and formatted in a detailed table.[41] But following the advice of Bearcroft, this table of adverse events was not included in the published paper.[42]

On July 3, 2004, after Medtronic edited the paper, Dr. Burkus sent a draft to his co-authors writing that "this manuscript documents the superiority in clinical and radiographic outcomes with the use of rhBMP2 in a study population of only 133 patients."[43]

According to the Carragee et al. *Spine Journal* article published in 2011, the 2005 *JBJS* article "reported no complications, such as end-plate fracture, collapse, and implant migration associated with rhBMP–2 despite the clear radiographic findings in at least the one presented case."[44] The e-mail exchange indicates that, in addition to Medtronic editing the manuscript without attribution, the company was recommending that the article omit a complete accounting of adverse event data, including serious adverse event data that were already considered a documented concern by FDA in similar application.

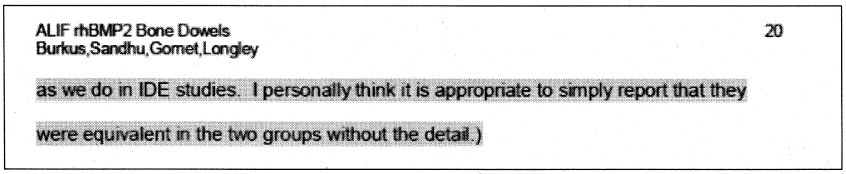
---

[36] FDA Summary of Safety and Effectiveness for InFuse Bone Graft/LT–Cage Lumbar Tapered Fusion Device, available at *http://www.accessdata.fda.gov/cdrh_docs/pdf/P000058b.pdf.*
[37] E-mail from Julie Bearcroft, June 16, 2004, MSD–R062111–034854.
[38] *Id.*
[39] E-mail from Dr. Burkus, July 3, 2004, MSD–R062111–034957.
[40] *Id.*
[41] E-mail between Medtronic Employees on June 7, 2004, MSD–R062111–064785.
[42] E-mail between Medtronic Employees on June 7, 2004, MSD–R062111–064785.
[43] E-mail from Dr. Burkus, July 3, 2004, MSD–R062111–034957.
[44] *The Spine Journal* 11 (2011) 471–491.



From: Bearcroft, Julie, PhD
Sent: Wednesday, June 16, 2004 10:04:33 AM
To: Treharne, Rick; Beals, Neil; Lipscomb, Bailey; McKay, Bill
CC: Ma, Guorong; Peckham, Steve, Ph.D.; King, Vanja, Ph.D.; Woodward, Lyndsay; Hood, Tara
Subject: Combined pilot & pivotal rhBMP-2/TCBD draft manuscript
Attachments: Bone Dowel BMP superiority revision without tracking changes 061104.doc

Additional issues that I would like to propose that we consider include -
1) How much information should we provide relative to adverse events? Lyndsay provided with some of the specifics behind the general numbers in the tables to better understand if there are significant issues here. Most of these are applicable to issues that fall outside of involved level. You will see my not in the attached document but I don't think significant detail on this section is warranted. Thoughts?



ALIF rhBMP2 Bone Dowels 20
Burkus,Sandhu,Gornet,Langley

as we do in IDE studies. I personally think it is appropriate to simply report that they were equivalent in the two groups without the detail.)

These types of adverse events were disclosed in Table V of a 2009 follow-up article concerning the original IDE study.[45] Studies published in 2007 revealed that InFuse is associated with "a clinically important early inflammatory and osteoclastic effect of the rhBMP–2 in soft tissue and bone, respectively."[46] In other words, Medtronic recommended against including information in the study that was ultimately revealed to have an association between InFuse and weakening that could lead to collapse of the bone and implant and required that patients undergo additional surgery.

The CONSORT (Consolidated Standards of Reporting Trials) Group, an organization that develops guidelines for reporting randomized controlled trials endorsed by medical journals such as the *New England Journal of Medicine* and the *Journal of the American Medical Association,* recommended in its guidelines in 2001 that "[a]ll important adverse events or side effects in each intervention group" should be reported in the "Results" section of a publication of a randomized trial.[47] Although not in effect at the time Bearcroft made the recommendation, in 2004, the CONSORT group identified the practice of "providing summed numbers for all adverse events for each study arm, without separate data for each type of adverse event" as a "poor reporting practice."[48] The adverse events observed in the allograft trial were observed and formatted in a table, but following the advice of Bearcroft, the table was not included in the published paper.[49]

[45] Burkus, et al., "Six-Year Outcomes of Anterior Lumbar Interbody Arthrodesis with Use of Interbody Fusion Cages and Recombinant Human Bone Morphogenetic Protein–2," *JBJS* 2009.
[46] *The Spine Journal* 11 (2011) 471–491.
[47] Moher, et al., "The CONSORT Statement: Revised Recommendations for Improving the Quality of Reports of Parallel-Group Randomized Trials," *JAMA,* April 18, 2001.
[48] "Better Reporting of Harms in Randomized Trials: An Extension of the CONSORT Statement," *Ann. Intern. Med.,* 2004; 141:781–788 at *http://www.annals.org/content/141/10/781.full.pdf+html.*
[49] E-mail between Medtronic Employees on June 7, 2004, MSD–R062111–064785.

Medtronic Sought to Emphasize Pain in Alternative Treatments

Documents show that Medtronic edited draft publications to stress the pain patients experienced from undergoing a bone graft procedure instead of receiving InFuse. Medtronic markets InFuse as a less painful alternative to bone graft procedures for patients undergoing spinal fusion surgery. Medtronic's website states: "According to numerous studies, the harvesting procedure is actually more painful than the fusion itself, and nearly a third of patients experience hip pain two years following surgery. When compared to traditional spinal fusion procedures, INFUSE® Bone Graft, when used with the LT–CAGE® Device, eliminates the pain and blood loss, and reduces the amount of time spent in the hospital to treat complications resulting from the second site of surgery." [50]

However, spinal surgeons are beginning to question whether "the oft-cited 'painful iliac crest donor site' is less serious and frequent than BMP enthusiasts would have us believe" after a recent study showed that "[t]he incidence of pain over the iliac crest was similar in patients in which iliac crest was harvested and those in which no graft was harvested." [51]

After receiving a draft of an early InFuse study [52] to review in October 2001, Medtronic's Neil Beals, whose "primary job responsibility was to manage Biologics marketing programs and initiatives," [53] recommended that the physician authors of the study emphasize pain experienced by patients who received the bone graft. The patients were divided into an investigative group that received InFuse and a control group that received a bone graft obtained from the iliac crest of their pelvis.[54] An October 31, 2001 e-mail shows that Beals suggested to Dr. Burkus that "a bigger deal should be made of elimination of donor site pain with INFUSE . . . so that 'equivalent' results aren't received as a let down." [55] Again, after reviewing a later draft of the study, Beals asked Dr. Burkus on March 8, 2002, "would it be appropriate to make a bigger deal out of donor site pain and include more discussion and references?" [56] Subsequently, a sentence was inserted at the end of a later draft, and included in the published version of the article, that read, "The use of rhBMP–2 is associated with high fusion

---

[50] Medtronic INFUSE® Bone Graft + LT–CAGE® Lumbar Tapered Fusion Device Fact Sheet, *http://wwwp.medtronic.com/Newsroom/LinkedItemDetails.do?itemId=1101769224707&itemType=fact_sheet&lang=en_US.*

[51] Hu, Serena S., "Commentary: Illiac crest bone graft: are the complications overrated?" *The Spine Journal*, June 2011, *http://www.spine.org/Documents/TSJJune2011_Hu_Commentary.pdf;* Howard et. al., "Posterior iliac crest pain after posterolateral fusion with or without iliac crest graft harvest," *The Spine Journal*, June 2011, *http://www.spine.org/Documents/TSJJune2011_Howard_etal_PosteriorIliacCre.pdf.*

[52] "Anterior lumbar interbody fusion using rhBMP–2 with tapered interbody cages," *J. Spinal Disord. Tech.* 2002 Oct; 15(5):337–49, *http://www.ncbi.nlm.nih.gov/pubmed/12394656.*

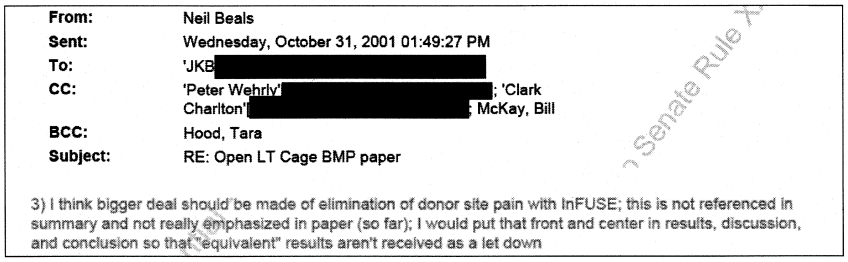
[53] Medtronic provided the Committee with this summary of Neil Beals's job titles and corporate responsibilities in a correspondence on May 5, 2012: "Neal Beals, M.S., M.B.A. is the former Vice President of Biologics Marketing, a position he held from February 2003 to August 2011. Mr. Beals joined Sofamor Danek in 1998 as Group Director, Tissue/Biologics within the Interbody Division. He held this position until October 2000 when he became Group Director, Biologics. He became Vice President of Biologics Marketing in 2003 and a Corporate Vice President in 2007. In these positions, his primary job responsibility was to manage Biologics marketing programs and initiatives."

[54] "Anterior lumbar interbody fusion using rhBMP–2 with tapered interbody cages," *supra* at 32.

[55] E-mail from Neil Beals to Dr. Burkus, October 31, 2001, MSD–R062111–033566.

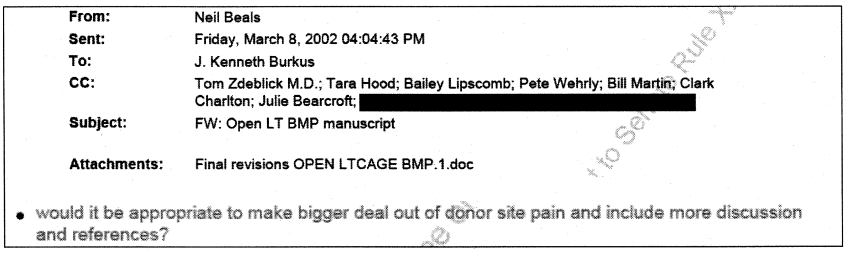
[56] E-mail from Neil Beals to Dr. Burkus, March 8, 2002, MSD–R062111–077880.

rates without the need for harvesting bone graft from the iliac crest and exposing the patient to the adverse effects associated with that procedure." [57]



From: Neil Beals
Sent: Wednesday, October 31, 2001 01:49:27 PM
To: 'JKB[redacted]
CC: 'Peter Wehrly'[redacted]; 'Clark Charlton'[redacted]; McKay, Bill
BCC: Hood, Tara
Subject: RE: Open LT Cage BMP paper

3) I think bigger deal should be made of elimination of donor site pain with InFUSE; this is not referenced in summary and not really emphasized in paper (so far); I would put that front and center in results, discussion, and conclusion so that "equivalent" results aren't received as a let down



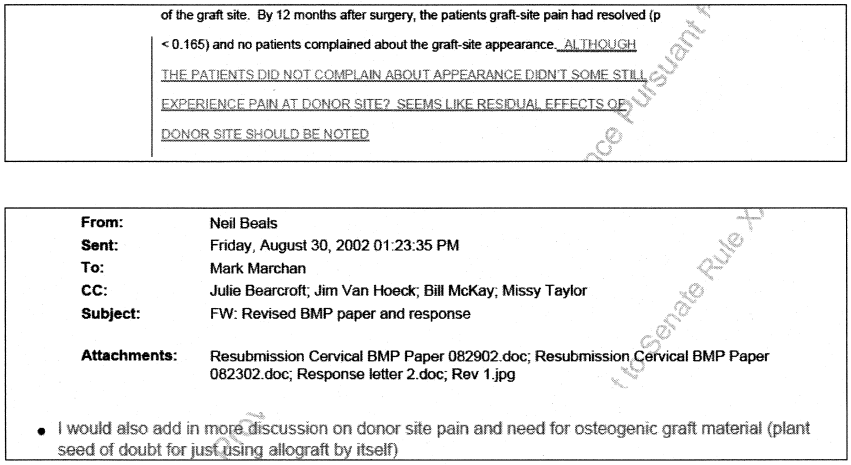
From: Neil Beals
Sent: Friday, March 8, 2002 04:04:43 PM
To: J. Kenneth Burkus
CC: Tom Zdeblick M.D.; Tara Hood; Bailey Lipscomb; Pete Wehrly; Bill Martin; Clark Charlton; Julie Bearcroft; [redacted]
Subject: FW: Open LT BMP manuscript

Attachments: Final revisions OPEN LTCAGE BMP.1.doc

- would it be appropriate to make bigger deal out of donor site pain and include more discussion and references?

Medtronic also sought to include discussion of long-term pain in the Baskin, et. al. 2003 paper on InFuse in the cervical spine. In a draft of the publication that was being circulated on August 30, 2002, the authors wrote, "[b]y 12 months after surgery, the patients [sic] graft-site pain had resolved . . . and no patients complained about the graft-site appearance." Beals inserted comments after this sentence stating, "ALTHOUGH THE PATIENTS DID NOT COMPLAIN ABOUT APPEARANCE DIDN'T SOME STILL EXPERIENCE PAIN AT THE DONOR SITE? SEEMS LIKE RESIDUAL EFFECTS OF DONOR SITE SHOULD BE NOTED." [58] [sic] [emphasis in original]. In an e-mail to his colleague, Beals wrote, "I would also add in more discussion on donor site pain and need for osteogenetic graft material (plant seed of doubt for just using allograft by itself)." [59] A review of the final published article reveals that, after Beals made the suggestion to emphasize pain at the bone graft site, a sentence was added in the final version of the article that read, ". . . even at the 24-month follow-up assessment, some patients continued to experience residual pain at the donor site, and rated the appearance of the site as only fair."

[57] Compare drafts attached to e-mails from Dr. Burkus to Neil Beils on March 8, 2002, MSD–R062111–078880, MSD–R062111–077882 and April 4, 2002, MSD–R062111–033863, MSD–R062111–033825.
[58] Draft copy of Baskin et. al. study e-mailed on August 30, 2002, MSD–R062111–034124.
[59] *Id.*



of the graft site. By 12 months after surgery, the patients graft-site pain had resolved (p < 0.165) and no patients complained about the graft-site appearance. ALTHOUGH THE PATIENTS DID NOT COMPLAIN ABOUT APPEARANCE DIDN'T SOME STILL EXPERIENCE PAIN AT DONOR SITE? SEEMS LIKE RESIDUAL EFFECTS OF DONOR SITE SHOULD BE NOTED

From: Neil Beals
Sent: Friday, August 30, 2002 01:23:35 PM
To: Mark Marchan
CC: Julie Bearcroft; Jim Van Hoeck; Bill McKay; Missy Taylor
Subject: FW: Revised BMP paper and response

Attachments: Resubmission Cervical BMP Paper 082902.doc; Resubmission Cervical BMP Paper 082302.doc; Response letter 2.doc; Rev 1.jpg

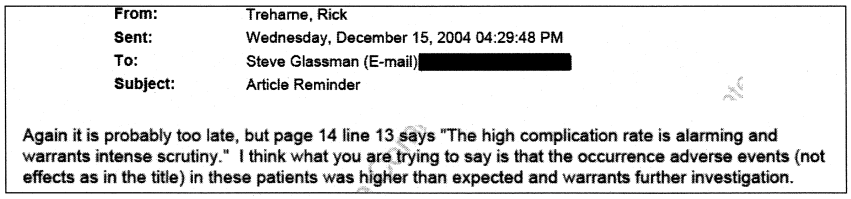
- I would also add in more discussion on donor site pain and need for osteogenic graft material (plant seed of doubt for just using allograft by itself)

Medtronic Attempted to Downplay Cervical Spine Side Effects in a 2006 Publication

In 2008, "the FDA issued an alert after receiving reports of life-threatening complication following cervical fusion procedures involving [bioengineered proteins such as InFuse], including breathing difficulty and swelling of the neck."[60] Additionally, a study published in the *Journal of the American Medical Association* found that "[p]atients who received a bioengineered protein during spinal fusion procedures to correct neck pain had far more complications than patients who did not get it."[61]

E-mails show that Rick Treharne, Senior Vice President of Clinical and Regulatory Affairs at Medtronic, unsuccessfully attempted to tone down a study SPINE published in 2006 that found a "significant rate of complications . . . after the use of a high dose of [rhBMP–2] in anterior cervical fusions." In December 2004, Rick Treharne e-mailed a co-author of this study, Dr. Glassman, in an unsuccessful attempt to have some of the critical language in the study modified. Treharne wrote, "Again it is probably too late, but page 14 line 13 says 'The high complication rate is alarming and warrants intense scrutiny.' I think what you are trying to say is that the occurrence [sic] adverse events (not effects as in the title) in these patients was higher than expected and warrants further investigation."[62] The e-mail from Treharne was sent after the paper was submitted to SPINE.

[60] "Bone-Growth Problems Show Risk in New Study," *New York Times,* June 30, 2009.
[61] *Id.*
[62] E-mail from Rick Treharn to Steve Glassman, December 15, 2004, MSD–R062111–035348.



From: Treharne, Rick
Sent: Wednesday, December 15, 2004 04:29:48 PM
To: Steve Glassman (E-mail)[redacted]
Subject: Article Reminder

Again it is probably too late, but page 14 line 13 says "The high complication rate is alarming and warrants intense scrutiny." I think what you are trying to say is that the occurrence adverse events (not effects as in the title) in these patients was higher than expected and warrants further investigation.

Additionally, even after Medtronic attempted to include a warning about cervical swelling on the FDA label, one Medtronic physician consultant recommended against raising alarms with the physician community. On April 8, 2004, Rick Treharne e-mailed Medtronic physician consultant Scott Boden, informing him that the company received complaints related to off-label use of InFuse in the cervical spine.[63] Dr. Boden responded that he was aware of a case of swelling where there was a "golf ball size mass in the neck clearly visible through the skin."[64] Boden recommended that surgeons needed to be continually warned about off-label use of BMP in the cervical spine.[65] Medtronic told the Committee that during this time, it voluntarily sought changes to the InFuse product label in June 17th, 2004 to notify the public of a risk of swelling when used in the cervical spine, but the effort was opposed by the FDA due to the agency's concern that adding a warning to the label about an off-label use was a form of off-label promotion. In June 2004, Rick Treharne wrote to Dr. Burkus that, based on his statistical analysis of new cases versus what was observed in the clinical trials, he did not, "at this time, see anything to worry about."[66] In August 2004, despite Dr. Boden's recommendation to Rick Treharne earlier that year that physicians should be "continually warned" about off-label use, Dr. Boden told Dr. Charles Mick of the North American Spine Society that because there wasn't enough information to identify the cause of the swellings, "it may be premature for any 'official' warning."[67] Medtronic paid Dr. Boden $705,457 through 2004 and $28,796,034 by the end of 2008. FDA granted Medtronic permission to send a "Dear Doctor" letter to physicians conveying concerns about InFuse on September 14, 2004 and placed a warning on the product label on December 7, 2004.

Omission of Retrograde Ejaculation Rates in Investigative Patient Groups

In his 2011 *Spine Journal* article, Dr. Carragee reported that "multiple independent studies have found that the rate of [retrograde ejaculation (a condition that causes sterility)] in ALIF with rhBMP–2 is approximately 5% to 7% and possibly two to four times higher than the rate observed without rhBMP–2."[68] However, the physician authors who reported the clinical results of a major Medtronic-sponsored study in the *Journal of Spinal Disorders and*

[63] E-mail from Rick Treharne to Scott Boden, April 8, 2004, MSD–R062111–068997.
[64] E-mail from Scott Boden to Rick Treharne, April 10, 2004, MSD–R062111–068997.
[65] *Id.*
[66] E-mail from Rick Treharne to Dr. Burkus, June 14, 2004, MSD–R062111–069316.
[67] E-mail from Scott Boden to NASS President Charles Mick, August 16, 2004, MSD–R062111–069477.
[68] *http://www.spine.org/Documents/TSJJune2011__Carragee__etal__CriticalRev.pdf*, page 479.

Techniques attributed the adverse event to the surgical technique used without comparing the investigational study group receiving InFuse to the control group.[69] Dr. Carragee told the *New York Times* that the omission is significant because "[i]t is important that men who are considering having children have the opportunity to weigh the risks of the various available procedures." [70]

A February 2001 PowerPoint presentation indicates that Dr. Zdeblick was aware that retrograde ejaculation rates were higher in both investigational groups than the control group. In a PowerPoint presentation to study investigators in February 2001, Dr. Zdeblick reported a 10.3% rate of retrograde ejaculation using the laparoscopic technique, a 6.3% for patients who underwent an "open" technique, and a 1.5% rate for the control group. The 10.3% rate was noted in the presentation to be "[s]tatiscally different from [the] control [group]." [71]

Medtronic Wrote Author Responses to Peer-Review

E-mail exchanges between Dr. Burkus and Medtronic employees regarding a study of InFuse utilizing the posterior lumbar interbody fusion (PLIF) technique and published in *The Spine Journal* in 2004 demonstrates that Medtronic employees not only edited the draft manuscript to include comments supportive of InFuse, they also covertly participated in the peer-review process by drafting responses to peer-reviewers on behalf of the physician authors named on the paper.

On December 21, 2002, Dr. Burkus sent a draft manuscript of the study to Medtronic officials asking for assistance with "further data analysis." [72] Bill Martin, Vice President for Spinal Marketing, Global Communications, and Medical Education at Medtronic, made it clear to other Medtronic employees that Medtronic would be in a "supporting cast" in assisting Dr. Burkus with this study rather than reworking the paper.[73]

According to a January 1, 2003, e-mail written by Bill Martin, "Dr. Burkus wanted his name last (and all the neuro's first) so that it would be well accepted by the Neurosurgical community." In addition, Martin wrote that, "I'm sure none of us believe the PLIF *technique* is going to have a resurgence from this, but we may want to steer clear of calling it a flawed technique. There are still quite a few surgeons utilizing this technique and we probably don't want to put them in that position" [74] (emphasis in original).

In a January 10, 2003, e-mail to Dr. Burkus, Rick Treharne wrote, "In looking over the data, I was impressed with how well the BMP patients actually did. So much so that I added a few paragraphs at the end that you may not agree with." In the draft article, Treharne wrote:

---

[69] *Id.*

[70] "New Study Links Spine Product From Medtronic to Risk of Sterility in Men," *New York Times*, May 25, 2011.

[71] PowerPoint presentation attached to a February 2, 2001 e-mail between Medtronic employees, MSD–R062111–032878; MSD–R062111–032916.

[72] E-mail from Dr. Burkus to Medtronic officials, December 21, 2002, MSD–R062111–040537.

[73] E-mail from Bill Martin to Neil Beals and Peter Wehrly, January 1, 2003, MSD–R062111–078885.

[74] *Id.*

> In conclusion, this detailed, independent review of the results, which represent the first use of osteoinductive proteins in a PLIF procedure, are encouraging. These findings along with other studies for other indications imply that future larger PLIF studies with BMP–2 are needed. In future studies using modified surgical techniques, such as using more recessed cages to allow for extra posterior bone formation, adding steps to minimize bleeding, and/or adding secondary instrumentation may be beneficial. Further, possibly modifying patient selection, such as entering patients with less vertebral slip, may also help minimize confounding variables. All of these changes may produce even better, more convincing evidence that INFUSE Bone Graft can also be used as substitute for autograft in PLIF procedures.[75]

On February 1, 2003, Dr. Burkus e-mailed another draft of the BMP manuscript to Medtronic officials asking for "final comments."[76] On March 7, 2003, Julie Bearcroft e-mailed Dr. Burkus an updated version of this manuscript with her proposed changes to the draft.[77]

After submission of the initial draft of this study to *The Spine Journal*, physicians who peer-reviewed the article were critical of its presentation of the study results. One reviewer wrote: "Unless the authors can discuss the results of this study in an unbiased manner, which they have been unable to do in its present form, this data should not be published." Another reviewer wrote: "The manuscript is full of biased statements that are a reflection of the data evaluators—the company that markets the product." That reviewer recommended a discussion of potential bias in the text of the paper writing, "As it stands it is an advertisement for a specific product without significant scientific merit."[78]

Reviewer A

The manuscript is full of biased statements that are a reflection of the data evaluators - the company that markets the product. No mention is made in the

have benefit to the readership. As it stands it is an advertisement for a specific product without significant scientific merit.

E-mail correspondence on May 28, 2003, indicates that Medtronic's Rick Treharne wrote and sent Dr. Burkus a draft letter to Dr. Tom Mayer, Editor-in-Chief of *The Spine Journal*, to address concerns raised by orthopedic surgeons tasked with peer-reviewing the submitted PLIF paper.[79] A subsequent e-mail by Julie Bearcroft notes that she and Dr. Burkus collaborated further on the re-

[75] E-mail from Rick Treharne to Dr. Burkus, January 10, 2003, MSD–R062111–068009.
[76] E-mail from Dr. Burkus to Medtronic officials, February 1, 2003, MSD–R062111–040735.
[77] E-mail from Julie Bearcroft to Dr. Burkus, March 7, 2003, MSD–R062111–040848.
[78] E-mail from Rick Treharne to Dr. Burkus, May 28, 2003, MSD–R062111–040930.
[79] *Id.*

sponse to the peer-reviewers of this study during a Lumbar Spine Study Group event.[80]

In response to the peer-reviewers' concerns about bias in the manuscript, the response letter seemingly misled *The Spine Journal* by stating that "To help eliminate any potential bias, only one of the co-authors was a clinical investigator—the other three were independent reviewers of all the data. Since these data are taken from a clinical IDE study sponsored by a company, only the company would have all the data in its database—data that is reviewed by FDA auditors. We don't believe any discussion of bias is needed for the text."[81] By the end of 2003, "independent reviewers" Dr. Haid and Dr. Burkus would have received $7,793,000 and $722,000 from Medtronic, respectively. This draft letter, written at least in part by Medtronic on behalf of Dr. Burkus, did not disclose the company's role in directly editing the paper nor did it disclose the magnitude of financial payments made to the supposed "independent reviewers."

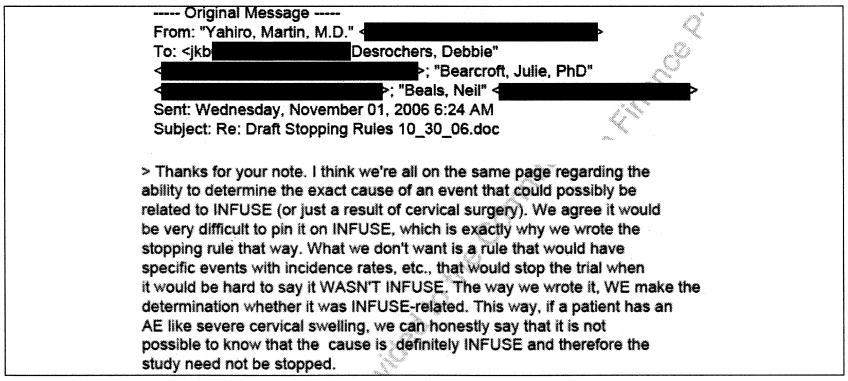
Upon hearing the news that there would be an editorial by Dr. Neal Kahanovitz criticizing the PLIF study along with the paper, Medtronic Senior Vice President and President for Europe, Canada, Latin America, and Emerging Markets, Michael Demane wrote in an e-mail to Bill Martin, "this is going to hurt more than help because of the reviewers [sic] comments. Too late to turn back tho."[82] [sic]

PEEK Spacer Cervical Spine Study

Documents show that Medtronic unsuccessfully proposed that the FDA approve a less restrictive rule for when the company must suspend patient enrollment in a clinical study of InFuse used in the cervical spine for safety reasons.[83] According to a November 1, 2006, e-mail written by Medtronic's Senior Director of Medical and Regulatory Affairs Dr. Martin Yahiro, the company proposed a weaker rule because "it would be very difficult to pin [an adverse event] on INFUSE."[84] Yahiro explained that a rule required by the FDA based on "specific events with incidence rates . . . would stop the trial when it would be hard to say it WASN'T INFUSE" (emphasis in original.)[85] Medtronic's proposed rule, according to Yahiro, was written to allow the company to continue the trial even "if a patient has an [adverse event] like severe cervical swelling" because Medtronic "can honestly say that it is not possible to know that the cause is definitely INFUSE."[86] However, the FDA rejected Medtronic's proposal and required that the company adopt stricter rules based on specific adverse event rates in its final protocol.[87]

---

[80] E-mail from Julie Bearcroft to Dr. Burkus, June 3, 2003, MSD–R062111–068487.
[81] E-mail from Rick Treharne to Dr. Burkus, May 28, 2003, MSD–R062111–040930 at 041013.
[82] E-mail from Michael DeMane to Bill Martin, March 9, 2004, MSD–R062111–079038.
[83] See documents relating to Medtronic's Investigational Device Exemptions application for a clinical trial of the Infuse Bone Graft/PEEK Interbody Spacer/Anterior Cervical Plate, MSD–R021612–000767—MSD–R021612–000790.
[84] E-mail from Dr. Martin Yahiro, November 1, 2006, MSD–R062111–073578.
[85] *Id.*
[86] *Id.*
[87] Section 6.24 of the InFuse Bone Graft/PEEK Interbody Spacer/Anterior Cervical Plate Investigational Plan Protocal, MSD–R021612–000791.



----- Original Message -----
From: "Yahiro, Martin, M.D." <[redacted]>
To: <jkb[redacted]Desrochers, Debbie"
<[redacted]>; "Bearcroft, Julie, PhD"
<[redacted]>; "Beals, Neil" <[redacted]>
Sent: Wednesday, November 01, 2006 6:24 AM
Subject: Re: Draft Stopping Rules 10_30_06.doc

> Thanks for your note. I think we're all on the same page regarding the ability to determine the exact cause of an event that could possibly be related to INFUSE (or just a result of cervical surgery). We agree it would be very difficult to pin it on INFUSE, which is exactly why we wrote the stopping rule that way. What we don't want is a rule that would have specific events with incidence rates, etc., that would stop the trial when it would be hard to say it WASN'T INFUSE. The way we wrote it, WE make the determination whether it was INFUSE-related. This way, if a patient has an AE like severe cervical swelling, we can honestly say that it is not possible to know that the cause is definitely INFUSE and therefore the study need not be stopped.

Expert Testimony to the FDA Written By Medtronic

E-mails indicate that Medtronic drafted Dr. Hallet Mathew's presentation to the FDA Advisory Panel in January 2002. Dr. Mathews told the FDA Advisory Panel during his presentation, "I have no direct financial interest in the product under review here today and am not being paid for my participation in this meeting."[88] The implication of that narrowly crafted disclaimer is that Dr. Mathew's testimony was independent. However, an e-mail from December 2001 shows that Medtronic worked with the public relations firm Ketchum on preparing Mathew's speech.[89] Medtronic told the Committee that Mathews was not compensated for any activity undertaken in January 2002.[90] But Medtronic did pay Dr. Hal Mathews under consulting arrangements with the company in 2001[91] and was hired by the company as the vice president of medical and clinical affairs in 2007.[92]

Conclusion

The Committee's investigation discovered troubling evidence that Medtronic officials influenced the content of articles in peer-reviewed scientific publications to present InFuse in the best possible light. As physicians depend on peer-reviewed literature when making clinical decisions, biased articles in professional publications that downplay potential risks and exaggerate the benefits of a product have the potential to put patients' lives at risk. The Medicare and Medicaid programs also rely on peer-reviewed medical literature when determining covered benefits and services. While collaboration between study authors and industry is necessary to publish the results of clinical trials, as the data being presented is often controlled by the company that sponsored the research, the resulting articles must be untainted by industry bias.

---

[88] Transcript, FDA Advisory Panel, January 10, 2002, *http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3828t1.htm.*

[89] E-mail from Ketchum to Barry Lipscomb, December 11, 2001, MSD–R062111–077826.

[90] Correspondence between the Committee and Medtronic on June 22, 2012.

[91] *Id.*

[92] "Report: Medtronic lawyer filed whistleblower suit," Minneapolis Star Tribune, September 25, 2008.

In order to address the problem of biased research in medical literature, drug and device manufacturers and journal editors need to implement stringent disclosure policies that detail industry funding to physician authors. In addition, medical journals should follow the example of *The Spine Journal* and critically examine past studies that may exhibit industry bias that harms patients and misleads physicians. Further, in the event that company employees are involved in the drafting of a scientific article, the employee should be listed as an author. Medtronic's revised policies governing proper interactions with physician authors are a step in the right direction. However, it is unlikely that this problem is limited to one company and a handful of medical journals and doctors. Medical device manufacturers, pharmaceutical companies, and other health care stakeholders should ensure that they have transparency along with strict rules preventing improper interactions between their employees and study authors. Medical journals, if they are to remain credible, must aggressively require contributors to disclose all ties to industry and any assistance they received in preparing the manuscript.

APPENDIX

EXHIBITS

Medtronic Spinal & Biologics
Payments to Physicians

Note: Footnotes following each physician's name correspond to article titles listed at the bottom of the chart to denote the article(s) with respect to which the physician is a listed author.

Author Name	Payments																		
	Type	1996 [1]	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006 [2]	2007	2008	2009	2010
Joseph T. Alexander[9]	Consulting	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ -	$ -	$ -	$ -	$ 89.27	$ -	$ 2,319.39	$ -	$ 1,091.20	$ 1,177.85	$ -	$ 4,427.29	$ -	$ -	$ -
	Total	$ -	$ -	$ -	$ -	$ 89.27	$ -	$ 2,319.39	$ -	$ 1,091.20	$ 1,177.85	$ -	$ 4,427.29	$ -	$ -	$ -
Hyun W. Bae[15]	Consulting	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 6,500.00	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ -	$ -	$ -	$ -	$ 1,632.20	$ -	$ 3,456.56	$ 4,800.00	$ 695.00	$ 325.80	$ 683.20	$ 7,000.00	$ 5,255.00	$ 6,470.00	$ 7,450.00
	Total	$ -	$ -	$ -	$ -	$ 1,632.20	$ -	$ 3,456.56	$ 4,800.00	$ 695.00	$ 325.80	$ 7,183.20	$ 7,000.00	$ 5,255.00	$ 6,470.00	$ 7,450.00
Richard A. Balderston[4]	Consulting	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ -	$ -	$ -	$ 2,780.00	$ 520.00	$ 20.00	$ -	$ 340.00	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Total	$ -	$ -	$ -	$ 2,780.00	$ 520.00	$ 20.00	$ -	$ 340.00	$ -	$ -	$ -	$ -	$ -	$ -	$ -
David S. Baskin[7]	Consulting	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ -	$ 1,082.00	$ 1,404.00	$ 120.00	$ 3,200.64	$ 1,070.00	$ 4,110.83	$ -	$ -	$ -	$ -	$ 1,000.00	$ -	$ -	$ -
	Total	$ -	$ 1,082.00	$ 1,404.00	$ 120.00	$ 3,200.64	$ 1,070.00	$ 4,110.83	$ -	$ -	$ -	$ -	$ 1,000.00	$ -	$ -	$ -
Maxwell Boakye[11]	Consulting	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Total	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
Scott D. Boden[3,5,13]	Consulting	$ 18,750.00	$ 75,000.00	$ 75,000.00	$ 75,000.00	$ 75,000.00	$ 73,750.00	$ 80,000.00	$ 82,500.00	$ 132,500.00	$ 165,900.00	$ 182,550.00	$ 100,875.00	$ 100,875.00	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 1,198,200.00	$ 1,600,000.00	$ 3,300,000.00	$ 21,442,177.00	$ -	$ -
	Other	$ -	$ -	$ -	$ 11,957.00	$ -	$ -	$ -	$ -	$ 6,000.00	$ -	$ -	$ -	$ -	$ -	$ -
	Total	$ 18,750.00	$ 75,000.00	$ 75,000.00	$ 86,957.00	$ 75,000.00	$ 73,750.00	$ 80,000.00	$ 82,500.00	$ 138,500.00	$ 1,364,100.00	$ 1,782,550.00	$ 3,400,875.00	$ 21,543,052.00	$ -	$ -
Charles L. Branch[9]	Consulting	$ -	$ -	$ -	$ -	$ 99,000.00	$ 150,000.00	$ 201,000.00	$ 180,000.00	$ 174,437.50	$ 126,968.75	$ 134,937.50	$ 112,082.75	$ 81,812.50	$ 32,937.50	$ 51,420.21
	Royalties	$ -	$ -	$ 140,000.00	$ 40,000.00	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 403,800.00	$ 426,126.00	$ 772,384.00
	Other	$ -	$ -	$ 703.15	$ 9,238.87	$ 5,498.00	$ -	$ 997.75	$ 219.99	$ 1,036.28	$ 118.69	$ 1,453.08	$ 2,076.64	$ 2,076.00	$ 1,255.85	$ 4,047.60
	Total	$ -	$ -	$ 140,703.15	$ 49,238.87	$ 104,498.00	$ 150,000.00	$ 201,997.75	$ 180,219.99	$ 175,473.78	$ 127,087.44	$ 136,390.58	$ 114,159.39	$ 487,688.50	$ 460,319.35	$ 827,851.81
J. Kenneth Burkus[1,6,8,9,10,12, 13,14,15]	Consulting	$ -	$ -	$ -	$ -	$ -	$ 120,000.00	$ 217,500.00	$ 225,000.00	$ 271,368.75	$ 285,000.00	$ 423,975.00	$ 574,900.00	$ 218,662.50	$ 149,050.00	$ 133,218.75
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 1,631,084.00	$ 512,981.00	$ 781,715.00
	Other	$ -	$ -	$ 18,700.00	$ 34,712.12	$ 29,285.75	$ 29,920.00	$ 3,039.50	$ 43,742.50	$ 89,079.03	$ 46,070.44	$ 189,874.71	$ 144,381.84	$ 78,756.85	$ 70,532.85	$ 57,786.24
	Total	$ -	$ -	$ 18,700.00	$ 34,712.12	$ 29,285.75	$ 149,920.00	$ 220,539.50	$ 268,742.50	$ 360,447.78	$ 331,070.44	$ 613,849.71	$ 719,281.84	$ 1,928,503.35	$ 732,563.85	$ 972,719.99
Leah Y. Carreon[12,13,14]	Consulting	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 100.00	$ 200.00	$ -	$ -	$ 325.46	$ 2,500.00	
	Total	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 100.00	$ 200.00	$ -	$ -	$ -	$ 325.46	$ 2,500.00
Concept Properties, LLC[16]	Consulting	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ 636,182.00	$ 1,028,882.00	$ 1,226,179.00	$ 4,992,137.00	$ 13,141,165.00	$ 8,842,157.00	$ 9,683,098.00	$ 9,159,891.00	$ 7,117,112.00	$ 9,004,465.00
	Other	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Total	$ -	$ -	$ -	$ -	$ -	$ -	$ 636,182.00	$ 1,028,882.00	$ 1,226,179.00	$ 4,992,137.00	$ 13,141,165.00	$ 8,842,157.00	$ 9,683,098.00	$ 9,159,891.00	$ 7,117,112.00	$ 9,004,465.00
Edgar G. Dawson[15]	Consulting	$ -	$ 25,217.30	$ 25,000.00	$ 25,000.00	$ 18,750.00	$ 23,125.00	$ 22,500.00	$ 25,000.00	$ 31,250.00	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ 2,709.00	$ 16,256.62	$ 11,445.49	$ 10,441.95	$ 5,541.40	$ 4,335.42	$ 7,165.80	$ 933.00	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Total	$ 2,709.00	$ 41,473.92	$ 36,445.49	$ 35,441.95	$ 24,291.40	$ 27,460.42	$ 29,665.80	$ 25,933.00	$ 31,250.00	$ -	$ -	$ -	$ -	$ -	$ -	$ -

Author Name	Type	Payments																
		1996 [1]	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006 [2]	2007	2008	2009	2010
Curtis A. Dickman[4]	Consulting	$ -	$ -	$ 65,000.00	$ 65,000.00	$ -	$ -	$ -	$ 117,926.00	$ 26,300.00	$ -	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ 3,050.25	$ 8,239.25	$ 62,352.64	$ 39,419.50	$ 56,960.00	$ 72,881.00	$ 198,289.00	$ 293,270.00	$ 331,338.00	$ 400,343.00	$ 383,192.00	$ 388,248.00	$ 355,809.00	$ 389,099.00
	Other	$ -	$ 1,953.45	$ -	$ 3,000.00	$ 2,000.00	$ -	$ -	$ -	$ 475.99	$ 8,000.00	$ 795.77	$ -	$ -	$ -	$ -
	Total	$ -	$ 5,003.70	$ 73,239.25	$ 130,352.64	$ 41,419.50	$ 56,960.00	$ 72,881.00	$ 316,215.00	$ 320,045.99	$ 339,338.00	$ 401,138.77	$ 383,192.00	$ 388,248.00	$ 355,809.00	$ 389,099.00
John R. Dimar, III[12,13,14]	Consulting	$ 6,250.00	$ 25,000.00	$ 50,000.00	$ 50,000.00	$ 50,000.00	$ 115,400.00	$ 100,000.00	$ 114,500.00	$ 89,375.00	$ 144,000.00	$ 232,700.00	$ 126,900.00	$ 232,450.00	$ 159,150.00	$ 153,525.00
	Royalties	$ -	$ -	$ -	$ -	$ -	$ 73,028.00	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ -	$ 2,000.00	$ -	$ 2,022.65	$ -	$ -	$ 100.00	$ 1,783.65	$ 14,668.67	$ 3,207.99	$ 3,606.95	$ 3,867.60	$ 1,694.50	$ 1,401.00	$ 9,785.20
	Total	$ 6,250.00	$ 27,000.00	$ 50,000.00	$ 52,022.65	$ 50,000.00	$ 188,428.00	$ 100,100.00	$ 116,283.65	$ 104,043.67	$ 147,207.99	$ 236,306.95	$ 130,767.60	$ 234,094.50	$ 160,551.00	$ 163,310.20
Mark Garrett[11]	Consulting	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 75.00	$ 331.10
	Total	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 75.00	$ 331.10
Steven D. Glassman[12,13,14,15]	Consulting	$ 6,250.00	$ 25,000.00	$ 50,000.00	$ 50,000.00	$ 50,000.00	$ 121,500.00	$ 71,750.00	$ 135,750.00	$ 144,500.00	$ 246,000.00	$ 133,350.00	$ 102,150.00	$ 185,900.00	$ 85,700.00	$ 73,925.00
	Royalties	$ -	$ -	$ -	$ -	$ -	$ 73,028.00	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ -	$ -	$ -	$ 2,216.41	$ 976.43	$ -	$ -	$ 3,191.44	$ 1,637.07	$ 2,409.59	$ 2,403.16	$ 155,776.16	$ 1,705.50	$ 2,439.80	$ 1,094.80
	Total	$ 6,250.00	$ 25,000.00	$ 50,000.00	$ 52,216.41	$ 50,976.43	$ 194,528.00	$ 71,750.00	$ 138,941.44	$ 146,137.07	$ 248,409.59	$ 155,753.16	$ 257,926.16	$ 187,605.50	$ 88,139.80	$ 75,019.80
Matthew F. Gornet[5,8,10]	Consulting	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 315,339.00	$ 939,400.00	$ 205,526.00	$ -
	Other	$ -	$ 1,880.00	$ -	$ 29,900.00	$ 16,369.97	$ 15,128.00	$ 4,762.00	$ 10,194.00	$ 17,924.00	$ 67,763.93	$ 238,787.49	$ 334,203.33	$ 241,639.87	$ 686,974.87	$ 859,983.76
	Total	$ -	$ 1,880.00	$ -	$ 29,900.00	$ 16,369.97	$ 15,128.00	$ 4,762.00	$ 10,194.00	$ 17,924.00	$ 67,763.93	$ 238,787.49	$ 649,542.33	$ 1,181,039.87	$ 892,500.87	$ 859,983.76
Regis W. Haid, Jr.[9,11]	Consulting	$ -	$ 27,500.00	$ 27,500.00	$ 38,750.00	$ 75,000.00	$ 75,000.00	$ -	$ -	$ -	$ -	$ -	$ -	$ 150,046.87	$ 67,921.88	$ 32,203.13
	Royalties	$ -	$ -	$ 177,460.33	$ 826,753.05	$ 1,403,001.26	$ 1,308,834.00	$ 1,660,060.00	$ 1,948,427.00	$ 2,472,452.00	$ 2,473,518.00	$ 2,453,855.00	$ 2,621,031.00	$ 2,314,423.00	$ 2,184,822.00	$ 2,691,546.00
	Other	$ -	$ -	$ 11,882.11	$ 154,329.49	$ 29,240.89	$ 10,556.61	$ 9,685.11	$ 13,245.86	$ 11,998.94	$ -	$ 714.00	$ 5,545.07	$ 3,441.36	$ -	$ -
	Total	$ -	$ 27,500.00	$ 216,842.44	$ 1,019,832.54	$ 1,507,242.15	$ 1,394,390.61	$ 1,669,745.11	$ 1,957,742.86	$ 2,484,450.94	$ 2,473,518.00	$ 2,454,569.00	$ 2,626,576.07	$ 2,467,911.23	$ 2,252,743.88	$ 2,723,749.13
James W. Hardacker[12,14]	Consulting	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 4,687.50	$ 6,607.00	$ 7,070.00	$ -	$ 67,320.00
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Total	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 4,687.50	$ 6,607.00	$ 7,070.00	$ -	$ 67,320.00
Stephen E. Heim[5,8]	Consulting	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ 80,750.00	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ 1,133.00	$ 5,000.00	$ 8,500.00	$ 9,000.00	$ 4,340.00	$ 1,260.00	$ 2,000.00	$ -	$ 750.00	$ 534.90	$ -	$ -	$ -	$ -	$ -
	Total	$ 1,133.00	$ 5,000.00	$ 8,500.00	$ 89,750.00	$ 4,340.00	$ 1,260.00	$ 2,000.00	$ -	$ 750.00	$ 534.90	$ -	$ -	$ -	$ -	$ -
John G. Heller[5]	Consulting	$ -	$ -	$ -	$ -	$ 15,000.00	$ 15,000.00	$ -	$ 15,000.00	$ 20,000.00	$ 135,375.00	$ 109,500.00	$ 138,475.00	$ 52,250.00	$ 71,650.00	$ 91,050.00
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 21,273.00	$ -	$ -	$ 38,140.00	$ 190,968.00	$ 228,667.00	$ 182,918.00	$ 258,775.00
	Other	$ -	$ -	$ 10,892.00	$ 20,817.57	$ 15,000.00	$ 22,975.10	$ 1,161.73	$ 12,918.50	$ 22,957.44	$ 19,460.70	$ 1,575.39	$ 1,349.15	$ 8,040.11	$ 668.24	$ 2,579.36
	Total	$ -	$ -	$ 10,892.00	$ 20,817.57	$ 30,000.00	$ 37,975.10	$ 1,161.73	$ 49,191.50	$ 42,957.44	$ 154,835.70	$ 149,215.39	$ 330,792.15	$ 288,957.11	$ 255,236.24	$ 352,404.36
James Kang[5]	Consulting	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ -	$ -	$ -	$ 2,680.00	$ 2,460.00	$ 4,534.31	$ 394.00	$ 20.00	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Total	$ -	$ -	$ -	$ 2,680.00	$ 2,460.00	$ 4,534.31	$ 394.00	$ 20.00	$ -	$ -	$ -	$ -	$ -	$ -	$ -
Scott H. Kitchel[4]	Consulting	$ -	$ -	$ -	$ -	$ -	$ 37,500.00	$ 50,000.00	$ 50,000.00	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ -	$ 14,790.65	$ 11,092.00	$ 25,617.87	$ 13,102.43	$ 14,600.42	$ 710.00	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Total	$ -	$ 14,790.65	$ 11,092.00	$ 25,617.87	$ 50,602.43	$ 64,600.42	$ 50,710.00	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
Michael C. Longley[10]	Consulting	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ -	$ -	$ -	$ -	$ 1,000.00	$ 3,268.00	$ 1,760.00	$ 242.38	$ -	$ 1,000.00	$ -	$ -	$ -	$ -	$ -
	Total	$ -	$ -	$ -	$ -	$ 1,000.00	$ 3,268.00	$ 1,760.00	$ 242.38	$ -	$ 1,000.00	$ -	$ -	$ -	$ -	$ -

Author Name		Payments															
	Type	1996 [1]	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006 [2]	2007	2008	2009	2010
Praveen V. Mummaneni[11]	Consulting	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 17,500.00	$ 17,500.00	$ -	$ -	$ 26,562.50	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ -	$ -	$ -	$ -	$ -	$ 72.00	$ -	$ 1,725.82	$ 3,235.79	$ 6,839.31	$ 1,760.97	$ 2,002.00	$ 918.29	$ -	$ 6,250.00
	Total	$ -	$ -	$ -	$ -	$ -	$ 72.00	$ -	$ 19,225.82	$ 20,735.79	$ 6,839.31	$ 1,760.97	$ 28,564.50	$ 918.29	$ -	$ 6,250.00
Philip M. Pryor[13,14]	Consulting	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 6,637.50	$ 3,232.00	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ -	$ -	$ -	$ -	$ -	$ -	$ 1,536.25	$ 21,880.00	$ 18,420.00	$ 10,980.00	$ 15,720.00	$ 8,115.00	$ 13,195.00	$ 5,410.00	$ 200.00
	Total	$ -	$ -	$ -	$ -	$ -	$ -	$ 1,536.25	$ 21,880.00	$ 18,420.00	$ 10,980.00	$ 22,357.50	$ 11,347.00	$ 18,547.50	$ 5,410.00	$ 200.00
Gerald E. Rodts, Jr.[11]	Consulting	$ -	$ -	$ 25,000.00	$ 31,250.00	$ 18,750.00	$ 60,000.00	$ 80,000.00	$ 60,000.00	$ 40,000.00	$ 16,593.75	$ 30,937.50	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ 6,010.00	$ 97,109.49	$ 73,101.45	$ 83,013.24	$ 76,390.32	$ 119,009.45	$ 287,284.23	$ 362,936.00	$ 238,711.00	$ 580,622.00	$ 432,390.00	$ -
	Other	$ -	$ -	$ 65.54	$ 7,488.08	$ 36,636.98	$ 7,241.94	$ 9,264.80	$ 5,635.36	$ 2,139.57	$ -	$ 2,266.00	740.53	$ 1,362.26	$ 13.00	$ -
	Total	$ -	$ -	$ 25,065.54	$ 44,748.08	$ 152,496.47	$ 140,343.39	$ 172,278.04	$ 142,025.68	$ 161,149.02	$ 303,877.98	$ 396,139.50	$ 629,451.53	$ 581,984.26	$ 432,403.00	$ -
Patrick Ryan[7]	Consulting	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 6,500.00	$ -	$ -	$ -
	Total	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 6,500.00	$ -	$ -	$ -
Harvinder S. Sandhu[3,5,10]	Consulting	$ -	$ -	$ 2,500.00	$ -	$ -	$ 72,000.00	$ 42,000.00	$ 163,500.00	$ 75,000.00	$ 75,000.00	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ 56,226.00	$ 147,722.00	$ 256,018.46	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ -	$ -	$ 235.04	$ 246.47	$ -	$ -	$ 188.20	$ 2,577.75	$ 1,106.40	$ -	$ 1,483.85	$ 125.36	$ -	$ -	$ -
	Total	$ -	$ -	$ 58,961.04	$ 147,968.47	$ 256,018.46	$ 72,000.00	$ 42,188.20	$ 166,077.75	$ 76,106.40	$ 75,000.00	$ 1,483.85	$ 125.36	$ -	$ -	$ -
Jeffrey L. Stambough[15]	Consulting	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 1,000.00	$ 100.00	$ -	$ -	$ -	$ -	$ -	$ 1,670.00
	Total	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 1,000.00	$ 100.00	$ -	$ -	$ -	$ -	$ -	$ 1,670.00
Volker Sonntag[7]	Consulting	$ -	$ 27,500.00	$ 27,500.00	$ 13,750.00	$ -	$ 5,000.00	$ 15,000.00	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ 7,245.92	$ 179,266.16	$ 780,303.91	$ 1,751,448.26	$ 1,031,993.00	$ 1,629,860.00	$ 1,904,689.00	$ 2,728,639.00	$ 2,202,595.00	$ 2,090,998.00	$ 2,146,712.00	$ 2,271,477.00	$ 1,772,361.00	$ 2,239,156.00
	Other	$ -	$ -	$ 856.00	$ 1,000.00	$ 4,593.29	$ -	$ 2,420.49	$ -	$ -	$ -	$ -	$ 16,949.90	$ -	$ -	$ 2,000.00
	Total	$ -	$ 34,745.92	$ 207,622.16	$ 795,053.91	$ 1,756,041.55	$ 1,036,993.00	$ 1,646,050.49	$ 1,904,689.00	$ 2,728,639.00	$ 2,202,595.00	$ 2,090,998.00	$ 2,163,661.90	$ 2,271,477.00	$ 1,772,361.00	$ 2,241,156.00
Ensor E. Transfeldt[6]	Consulting	$ 12,500.00	$ 50,000.00	$ 50,000.00	$ 50,000.00	$ 50,000.00	$ 47,875.00	$ 107,225.00	$ 240,550.00	$ 275,125.00	$ 11,500.00	$ 148,250.00	$ 378,250.00	$ 124,250.00	$ 153,000.00	$ 103,625.00
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 53,551.00	$ 334,045.00	$ 410,737.00	$ 328,825.00	$ 485,630.00
	Other	$ -	$ -	$ 6,196.00	$ 11,219.28	$ 6,170.90	$ 17,742.56	$ 8,090.16	$ 18,362.62	$ 24,352.72	$ 18,974.70	$ 4,587.76	$ 10,484.00	$ 13,597.74	$ 1,429.00	$ 675.00
	Total	$ 12,500.00	$ 50,000.00	$ 56,196.00	$ 61,219.28	$ 56,170.90	$ 71,117.56	$ 115,315.16	$ 258,912.62	$ 299,477.72	$ 30,474.70	$ 206,388.76	$ 722,779.00	$ 548,584.74	$ 483,254.00	$ 589,930.00
Inspire, LLC[17]	Consulting	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 247,365.00	$ 329,998.00	$ 698,829.00	$ 1,632,813.00
	Other	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Total	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 247,365.00	$ 329,998.00	$ 698,829.00	$ 1,632,813.00
Robert G. Watkins[8]	Consulting	$ 18,750.00	$ 37,500.00	$ -	$ 37,500.00	$ 15,000.00	$ 37,500.00	$ 15,000.00	$ -	$ -	$ -	$ -	$ -	$ 3,426.25	$ 31,002.50	$ 80,237.50
	Royalties	$ -	$ 125,000.00	$ 125,000.00	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 36,804.00	$ 49,300.00	$ 50,593.00	$ 37,929.00	$ 46,559.00
	Other	$ 8,250.00	$ 1,848.02	$ 9,353.18	$ 8,016.46	$ 8,634.88	$ 6,216.49	$ -	$ 403.95	$ -	$ -	$ 238.60	$ -	$ -	$ -	$ -
	Total	$ 27,000.00	$ 164,348.02	$ 134,353.18	$ 45,516.46	$ 23,634.88	$ 43,716.49	$ 15,000.00	$ 403.95	$ -	$ -	$ 37,042.60	$ 49,300.00	$ 54,019.25	$ 68,931.50	$ 126,796.50
Richard M. Westmark[7]	Consulting	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ -	$ -	$ -	$ 2,500.00	$ 250.00	$ 9,900.00	$ 1,100.00	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Total	$ -	$ -	$ -	$ 2,500.00	$ 250.00	$ 9,900.00	$ 1,100.00	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
Marsha A. Widmayer[7]	Consulting	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Royalties	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Other	$ -	$ -	$ -	$ -	$ 550.00	$ -	$ 55.00	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
	Total	$ -	$ -	$ -	$ -	$ 550.00	$ -	$ 55.00	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -

Author Name	Payments																
	Type	1996 [1]	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006 [2]	2007	2008	2009	2010
Thomas A. Zdeblick[3,4,5]	Consulting	$ 25,000.00	$ 75,000.00	$ 425,000.00	$ 400,000.00	$ 400,000.00	$ 300,000.00	$ 500,000.00	$ 300,000.00	$ 173,500.00	$ 33,750.00	$ 13,500.00	$ 23,350.00	$ -	$ -	$ -
	Royalties	$ 68,365.34	$ 346,875.55	$ 406,680.11	$ 730,913.28	$ 636,840.26	$ 1,682,248.00	$ 2,970,296.00	$ 4,279,879.00	$ 4,273,769.00	$ 3,911,291.00	$ 3,455,161.00	$ 2,936,864.00	$ 2,521,170.00	$ 1,579,856.00	$ 1,669,046.00
	Other	$ 1,820.00	$ 793.10	$ 7,114.78	$ 549.89	$ 541.23	$ 2,108.45	$ 1,634.41	$ 482.62	$ -	$ 5,475.08	$ 1,202.71	$ 1,058.00	$ -	$ 2,100.00	$ 5,305.00
	Total	$ 95,185.34	$ 422,668.65	$ 838,794.89	$ 1,131,463.17	$ 1,037,381.49	$ 1,984,356.45	$ 3,471,930.41	$ 4,580,361.62	$ 4,447,269.00	$ 3,950,516.08	$ 3,469,863.71	$ 2,961,272.00	$ 2,521,170.00	$ 1,582,156.00	$ 1,674,351.00

[1]Payment data for 1996 reflects the partial-year period from November 20, 1996 to December 31, 1996.

[2]Payment data for the period from October 31, 2006 to December 31, 2010 also includes payments made by Medtronic, Inc., the corporate parent of Medtronic Sofamor Danek.

[3]Boden, *et. al.*, The Use of rhBMP-2 in Interbody Fusion Cages. Definitive Evidence of OsteoInduction in Humans: A Preliminary Report. Spine 2000; 25:376-81.

[4]Burkus, *et. al.*, Anterior Lumbar Interbody Fusion Using rhBMP-2 with Tapered Interbody Cages. J. Spinal Disord. Tech. 2002; 15:357-49.

[5]Boden, *et. al.*, Use of Recombinant Bone Morphogenetic Protein-2 to Achieve Posterolateral Lumbar Spine Fusion in Humans: A Prospective, Randomized Clinical Pilot Trial. Spine 2002; 27:2662-73.

[6]Burkus, *et. al.*, Clinical and Radiographic Outcomes of Anterior Lumbar Interbody Fusion Using Recombinant Human Bone Morphogenetic Protein-2. Spine 2002; 27:2396-408.

[7]Baskin, *et. al.*, A Prospective, Randomized, Controlled Cervical Fusion Study Using Recombinant Bone Morphogenetic Protein-2 with the CORNERSTONE-SR Allograft Ring and the ATLANTIS Anterior Cervical Plate. Spine 2003; 28:1219-24.

[8]Burkus, *et. al.*, Is INFUSE Bone Graft Superior to Autograft Bone? An Integrated Analysis of Clinical Trials Using the LT-CAGE Lumbar Tapered Fusion Device. J. Spinal Disord. Tech. 2003; 16:113-22.

[9]Haid, *et. al.*, Posterior Lumbar Interbody Fusion Using Recombinant Human Bone Morphogenetic Protein Type 2 with Cylindrical Interbody Cages. Spine J. 2004; 4:527-38.

[10]Burkus, *et. al.*, Use of rhBMP-2 in Combination with Structural Cortical Allografts Surgery: Clinical and Radiographic Outcomes in Anterior Lumbar Spinal Fusion. J. Bone Joint Surg. Am. 2005; 87:1205-12.

[11]Boakye, *et. al.*, Anterior Cervical Discectomy and Fusion Involving a Polyetheretherketone Spacer and Bone Morphogenetic Protein. J. Neurosurg. Spine 2005; 2:521-5.

[12]Dimar, *et. al.*, Clinical Outcomes and Fusion Success at 2 Years of Single-Level Instrumented Posterolateral Fusions with Recombinant Human Bone Morphogenetic Protein-2/Compression Resistant Matrix Verus Iliac Crest Bone Graft. Spine 2006; 31:2534-9.

[13]Glassman, *et. al.*, The Efficacy of rhBMP-2 for Posterolateral Lumbar Fusion in Smokers. Spine 2007; 32:1693-8.

[14]Dimar, *et. al.*, Clinical and Radiographic Analysis of an Optimized rhBMP-2 Formulation as an Autograft Replacement in Posterolateral Lumbar Spine Arthrodesis. J. Bone Joint Surg. Am. 2009; 91:1377-86.

[15]Dawson, *et. al.*, Recombinant Human Bone Morphogenetic Protein-2 on an Absorbable Collagen Sponge with an Osteoconductive Bulking Agent in Posterolateral Arthrodesis with Instrumentation. A Prospective Randomized Trial. J. Bone Joint Surg. Am. 2009; 91:1604-13.

[16]Medtronic believes that Concept Properties, LLC is owned by physicians including Dr. Dimar and Dr. Glassman.

[17]Medtronic believes that Inspire, LLC is owned by physicians including Dr. Transfeldt.

Medtronic *When Life Depends on Medical Technology*	**CORPORATE QUALITY, REGULATORY, CLINICAL** **Policy**	**Document: CQRC-048** **Revision: A** **Effective Date: 6 April 2006** **Page 1 of 4**
TITLE: Unapproved Uses of Approved Products		

SCOPE:

Medtronic Organizations and entities (e.g., Business Units, independent distributors who exclusively distribute for Medtronic) that distribute product information in the U.S. on Medtronic commercially available products in the U.S.

PURPOSE:

To establish consistency in the dissemination of information on unapproved or uncleared uses of Medtronic's commercially-released-approved products to non-Medtronic health care professionals or third-party payers.

POLICY:

All Medtronic Business Units and entities that distribute product information in the U.S. shall ensure that Business Unit procedures and policies prevent the promotion of approved or cleared Medtronic products for unapproved uses consistent with this Corporate Policy.

DEFINITIONS:

Affirmative Dissemination: Proactive distribution of peer-reviewed journal articles of reference texts with unapproved uses of approved products in the absence of an unsolicited request, which Business Unit Legal has determined is appropriate for distribution consistent with regulation and Corporate Legal guidance.

Responsive Information/Materials: Information and/or materials (such as unpublished studies or articles, presentations, news articles, reference texts) that reference unapproved uses of Medtronic commercially available products and are provided to a non-Medtronic health care professional or a third-party payer in direct response to an unsolicited request.

Unapproved Uses: An indication for use that is not covered by the existing regulatory approval/clearance.

Unsolicited Request: A specific and independent request for information about unapproved uses of Medtronic products made by a non-Medtronic health care professional or third-party payer that was not initiated or prompted by Medtronic personnel.

REQUIREMENTS:

1. **Office of Medical Affairs ("OMA"):** an OMA function must be established, which is: (1) a management level position that reports to BU Senior Management; (2) not subordinate to a Sales or Marketing Department or function; and (3) accountable and must have involvement on all forms of interactions and communications with the medical community

on unapproved uses, including the dissemination of articles and reference texts on unapproved uses.

2. **Affirmative Dissemination:** written procedures must address affirmative distribution of peer-reviewed articles and reference texts on unapproved uses.

3. **Unsolicited Requests:** written policies and/or procedures must provide a process for responding to unsolicited requests for responsive information or materials on unapproved uses.

4. **Medtronic-Supported Third-Party Medical Education:** written policies and/or procedures must ensure that Medtronic-supported third-party medical education is independent Business Units must have procedures to ensure third-party medical education is bona fide and independent.

5. **Medtronic-Implemented Training and Education on Medtronic Products:** written policies and/or procedures must prohibit answering unsolicited questions on unapproved uses of approved products that are posed during Medtronic-sponsored training and education on Medtronic products, except as permitted in Corporate Legal guidance. Such policies and/or procedures must prohibit the inclusion of unapproved uses in agendas and prepared content of Medtronic-sponsored training on commercially available U.S.-approved products, except as permitted for training clinical investigators in clinical studies or when a product approved for a general use cannot be demonstrated without showing a specific use.

6. **Research and Publication Strategies:** written policies and/or procedures must prohibit sales personnel involvement in the determination of funding allocation for research and publication by non-Medtronic personnel or entities on unapproved uses, including physician-sponsored studies, consistent with the requirements of Business Conduct Standards 3 and 6. Such policies/procedures may permit sales personnel to be involved in this process only to the extent necessary to supply information about researcher qualifications or interest to decision-makers, and must make clear that Sales personnel cannot decide who receives research funding.

7. **Physician Advisory Boards, Consultant Meetings, Roundtables or Discussion Groups:** written policies must prohibit the use of physician advisory boards, consultant meetings, roundtables or discussion groups to inappropriately disseminate information on unapproved uses.

8. **Notices of Availability:** Notices of Availability, which are notices to recruit clinical investigators for clinical trials, may not be used as a vehicle for promotion of a product for

unapproved uses, but may be used if there is a bona fide need for recruitment of additional clinical investigators for an open study.

9. **Training:** Business units must have procedures to address training on the Corporate and Business Unit policies and procedures at implementation, initial hiring, and annually.

10 **Exemption:** Permanent exemptions to CQRC policies shall not be granted. Business Units may be granted an annual exemption from any or all provisions of this policy by the Chief Quality and Regulatory Officer. Business Unit must provide appropriate documentation demonstrating either that a logical rationale exists for exemption from any part of the policy, or that there are currently no unapproved uses in the United States of the Business Unit's approved or cleared U.S.-commercially available products.

BIBLIOGRAPHY:

- Federal Food, Drug, and Cosmetic Act, § 360aaa; 21 C.F.R. Part 99, "Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices; Final Rule."
- *Washington Legal Foundation v. Friedman*, 13 F.Supp 2d 51 (D.DC. 1998) *extended sub. nom. Washington Legal Foundation v. Henney*, 202 F.3d. 331 (D.C. Cir. Feb. 11, 2000).
- "Decision in Washington Legal Foundation v. Henney, Notice," 65 Fed. Reg. 14286 (Mar. 16, 2000).
- FDA's Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects (March 19, 1999).
- Medtronic Business Conduct Standards 3, 6 and 8.

RESPONSIBILITY:

The Business Unit Management is responsible for implementation, training, and compliance with this policy.

Signature on File	*6 April 2006*

Susan Alpert, Ph.D., M.D. Date
Vice President
Chief Quality and Regulatory Officer

Medtronic *When Life Depends on Medical Technology*	**CORPORATE QUALITY, REGULATORY, CLINICAL** **Change History**	**Document: CQRC-048** **Revision: A** **Effective Date: 6 April 2006** **Page 4 of 4**
TITLE:	Unapproved Uses of Approved Products	

Revision	Date	Description of Change
A	6 April 2006	Initial Release

Medtronic *When Life Depends on Medical Technology*	**CORPORATE QUALITY, REGULATORY, AND CLINICAL** **Guidance**	Document: CQRC-048-G01 Revision: A Effective Date: 6 April 2006 Page 1 of 5
TITLE:	**Guidance for Unapproved Uses of Approved Products**	

SCOPE:

Medtronic Organizations who distribute product information in the USA on Medtronic commercially available products in the USA.

PURPOSE:

To establish consistency in the dissemination of information on unapproved or uncleared uses of Medtronic's commercially-release-approved products to non-Medtronic health care professional or third-party payers.

GUIDANCE:

I. Business Unit policies/procedures that address the **Office of Medical Affairs ("OMA") function** should include the following elements:

A. OMA is primarily responsible for all forms of interactions and communications with the medical community on unapproved uses, including the dissemination of articles and reference texts on unapproved uses in accordance with BU SOPs.

B. OMA will have advisory responsibility in the design and implementation of SOPs regarding provision of information on unapproved uses in other areas.

C. OMA will have input in the decision to: (1) fund third-party research requests, (2) sponsor articles by third parties, or (3) host Medtronic-consultative meetings that may include unapproved uses.

D. Business Unit Legal Counsel's review and approval is required for OMA's proposed affirmative dissemination of articles on unapproved uses, sponsorship of seminars, the grant of research funds or hosting of consultative meetings, when any of these relate to unapproved uses will require; and

E. Prohibition of all Medtronic personnel, including consultants, from using any dinner, meeting or other opportunity for the purpose of promoting products for unapproved uses.

II. Business Unit policies/procedures that address the provision of articles or other written information in response to **Unsolicited Requests** should include the following elements:

A. the written or oral request must specifically express interest in receiving materials about a particular subject or by title;

B. responsive information/materials must be issued by the OMA in a non-promotional manner and sales and marketing personnel must be prohibited from providing responsive information/materials to non-Medtronic persons; and

C. procedures must be established for fulfilling such requests that include:

i. requirements that OMA ensure that the information or materials are truthful, not misleading, and fairly balanced and have scientific and/or medical validity;

ii. requirements that written records of unsolicited requests and responses be maintained; and

iii. requirements that written materials be prominently stamped with language that:

a. states the materials contain information on unapproved uses that have not been approved/cleared by FDA;

b. states the materials are provided by Medtronic in response to an unsolicited request; and

c. discloses if Medtronic provided financial support related to the article or information.

III. Business Unit written policies and/or procedures that address **Medtronic-Supported Third-Party Medical Education** should include the following elements:

A. As a condition of support, a Medtronic-supported third-party medical education provider must disclose the financial relationships between and among Medtronic, the presenters, and the products discussed;

B. The activity must be educational in tone and nature and does not have as a predominant focus unapproved uses;

C. The third-party provider must be independent and have control over decisions regarding the content of the program and the selection of speakers, presenters, moderators and invitees;

D. All support must be documented in a written agreement; and

E. Sales personnel must not be involved in the determination of company sponsorship of third-party medical education, except as permitted under Business Conduct

Standards 3 and 8. Sales personnel may make suggestions and provide background information to decision-makers.

F. These written policies and/or procedures may also provide that a business may provide ***suggestions*** on topics, speakers, or attendees, if:

i. The Business Unit's activity is limited to responding to unsolicited requests for such suggestions;

ii. The Business Unit suggests multiple speakers and/or topics with disclosure of any relationship to Medtronic;

iii. Only OMA or a similar function outside of sales provides any suggestions; and

iv. Such requests and responses are properly documented.

IV. Business Unit written policies and/or procedures that address funding of **research and publications** on unapproved uses should include the following elements:

A. Require disclosure of Medtronic support in any publication of the results;

B. Prohibit Medtronic from requiring or compensating a researcher to speak about or broadly disseminate research findings prior to FDA approval of the unapproved uses, other than providing a report of publishable quality to Medtronic and/or a peer-reviewed journal for publication. If the researcher wishes to speak or otherwise disseminate research results without Medtronic's support, s/he may do so; and

C. Prohibit Medtronic from requiring or compensating a researcher's involvement in promotional activities related to the subject of the research before FDA approval of the unapproved use except as permitted by FDA's Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects (March 19, 1999).

D. Prohibit all Medtronic personnel from funding research or publications for the purpose of promoting products on unapproved uses.

V. Business Unit written policies and/or procedures that address **physician advisory boards, consultant meetings, or other health care professional meetings and discussion groups** on unapproved uses should provide:

A. Prior approval by BU Legal of Medtronic's dissemination of information on unapproved uses;

B. Invitees must be limited in size to those necessary to achieve the purpose; and

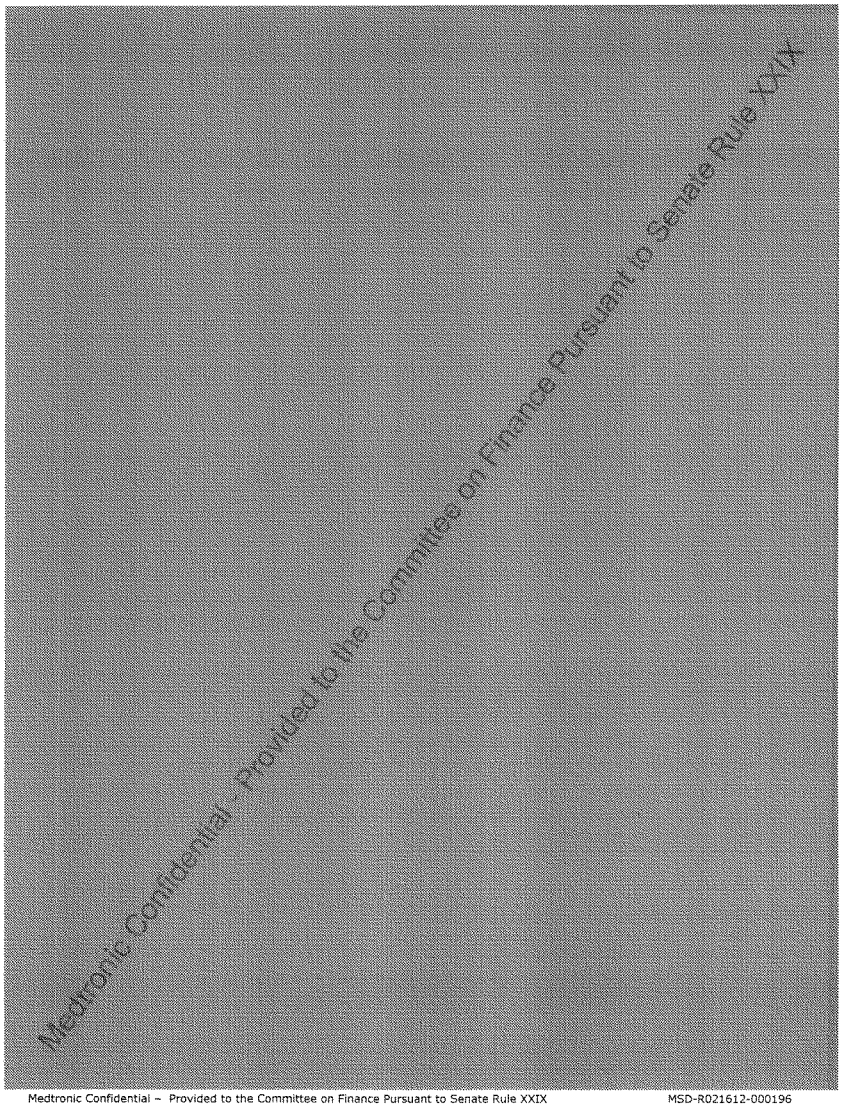
C. The purpose, activity, need for the information gathered, and intended use must be documented.

D. Prohibition of all Medtronic personnel from utilizing such meetings and groups for the purpose of promoting products on unapproved uses.

Medtronic *When Life Depends on Medical Technology*	CORPORATE QUALITY, REGULATORY, AND CLINICAL CHANGE HISTORY	Document: CQRC-048-G01 Revision: A Effective Date: 6 April 2006 Page 5 of 5

TITLE: Guidance for Unapproved Uses of Approved Products

REVISION	DATE	DESCRIPTION of CHANGE
A	6 April 2006	Initial Release


Medtronic Confidential - Provided to the Committee on Finance Pursuant to Senate Rule XXIX

Medtronic	CONFIDENTIAL	DOCUMENT/RECORD

This document/record is electronically controlled, printed copies are considered uncontrolled.

Identifier	Version	Author
048-Unapproved Uses of Approved Products	2.0	

Title: Unapproved Uses of Approved Products

APPROVALS

Signed By	Meaning of Signature	Date/Time (US Central Time)
Kerry Swanson	Initial Migration. Hard copy of signatures on file.	11/20/2006 16:38:15

Corporate Quality, Regulatory, Clinical
POLICY
Title: Unapproved Uses of Approved Products

SCOPE:

Medtronic Organizations and entities (e.g., Business Units, independent distributors who exclusively distribute for Medtronic) that distribute product information in the U.S. on Medtronic commercially available products in the U.S.

PURPOSE:

To establish consistency in the dissemination of information on unapproved or uncleared uses of Medtronic's commercially-released-approved products to non-Medtronic health care professionals or third-party payers.

POLICY:

All Medtronic Business Units and entities that distribute product information in the U.S. shall ensure that Business Unit procedures and policies prevent the promotion of approved or cleared Medtronic products for unapproved uses consistent with this Corporate Policy.

DEFINITIONS:

Affirmative Dissemination: Proactive distribution of peer-reviewed journal articles of reference texts with unapproved uses of approved products in the absence of an unsolicited request, which Business Unit Legal has determined is appropriate for distribution consistent with regulation and Corporate Legal guidance.

Responsive Information/Materials: Information and/or materials (such as unpublished studies or articles, presentations, news articles, reference texts) that reference unapproved uses of Medtronic commercially available products and are provided to a non-Medtronic health care professional or a third-party payer in direct response to an unsolicited request.

Unapproved Uses: An indication for use that is not covered by the existing regulatory approval/clearance.

Unsolicited Request: A specific and independent request for information about unapproved uses of Medtronic products made by a non-Medtronic health care professional or third-party payer that was not initiated or prompted by Medtronic personnel.

REQUIREMENTS:

1. **Office of Medical Affairs ("OMA)** an OMA function must be established, which is: (1) a management level position that reports to BU Senior Management; (2) not subordinate to a Sales or Marketing Department or function; and (3) accountable and must have involvement on all forms of interactions and communications with the medical community on unapproved uses, including the dissemination of articles and reference texts on unapproved uses.

2. **Affirmative Dissemination:** written procedures must address affirmative distribution of peer-reviewed articles and reference texts on unapproved uses.

3. **Unsolicited Requests:** written policies and/or procedures must provide a process for responding to unsolicited requests for responsive information or materials on unapproved uses.

4. **Medtronic-Supported Third-Party Medical Education:** written policies and/or procedures must ensure that Medtronic-supported third-party medical education is independent Business Units must have procedures to ensure third-party medical education is bona fide and independent.

5. **Medtronic-Implemented Training and Education on Medtronic Products:** written policies and/or procedures must prohibit answering unsolicited questions on unapproved uses of approved products that are posed during Medtronic-sponsored training and education on Medtronic products, except as permitted in Corporate Legal guidance. Such policies and/or procedures must prohibit the inclusion of unapproved uses in agendas and prepared content of Medtronic-sponsored training on commercially available U.S.-approved products, except as permitted for training clinical investigators in clinical studies or when a product approved for a general use cannot be demonstrated without showing a specific use.

6. **Research and Publication Strategies:** written policies and/or procedures must prohibit sales personnel involvement in the determination of funding allocation for research and publication by non-Medtronic personnel or entities on unapproved uses, including physician-sponsored studies, consistent with the requirements of Business Conduct Standards 3 and 6. Such policies/procedures may permit sales personnel to be involved in this process only to the extent necessary to supply information about researcher qualifications or interest to decision-makers, and must make clear that Sales personnel cannot decide who receives research funding.

7. **Physician Advisory Boards, Consultant Meetings, Roundtables or Discussion Groups:** written policies must prohibit the use of physician advisory boards, consultant meetings, roundtables or discussion groups to inappropriately disseminate information on unapproved uses.

8. **Notices of Availability:** Notices of Availability, which are notices to recruit clinical investigators for clinical trials, may not be used as a vehicle for promotion of a product for unapproved uses, but may be used if there is a bona fide need for recruitment of additional clinical investigators for an open study.

9. **Training:** Business units must have procedures to address training on the Corporate and Business Unit policies and procedures at implementation, initial hiring, and annually.

10 **Exemption:** Permanent exemptions to CQRC policies shall not be granted. Business Units may be granted an annual exemption from any or all provisions of this policy by the Chief Quality and Regulatory Officer. Business Unit must provide appropriate documentation demonstrating either that a logical rationale exists for exemption from any part of the policy, or that there are currently no unapproved uses in the United States of the Business Unit's approved or cleared U.S.-commercially available products.

BIBLIOGRAPHY:

- Federal Food, Drug, and Cosmetic Act, § 360aaa; 21 C.F.R. Part 99, "Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices; Final Rule."
- *Washington Legal Foundation v. Friedman*, 13 F.Supp 2d 51 (D.DC. 1998) *extended sub. nom. Washington Legal Foundation v. Henney*, 202 F.3d. 331 (D.C. Cir. Feb. 11, 2000).
- "Decision in Washington Legal Foundation v. Henney, Notice," 65 Fed. Reg. 14286 (Mar. 16, 2000).
- FDA's Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects (March 19, 1999).
- Medtronic Business Conduct Standards 3, 6 and 8.

RESPONSIBILITY:

The Business Unit Management is responsible for implementation, training, and compliance with this policy.

Corporate Quality, Regulatory, Clinical
POLICY
Title: Unapproved Uses of Approved Products

CHANGE HISTORY		
Revision	**Date**	**Description of Change**
A	6 April 2006	Initial Release

Owner: Susan Alpert
Department: CQRC

Medtronic	CONFIDENTIAL	DOCUMENT/RECORD

This document/record is electronically controlled, printed copies are considered uncontrolled.

Identifier	Version	Author
048-G012	2.0	

Title: Guidance for Unapproved Uses of Approved Products

APPROVALS

Signed By	Meaning of Signature	Date/Time (US Central Time)
Kerry Swanson	Initial Migration. Hard copy of signatures on file.	11/20/2008 16:13:24

SCOPE:

Medtronic Organizations who distribute product information in the USA on Medtronic commercially available products in the USA.

PURPOSE:

To establish consistency in the dissemination of information on unapproved or uncleared uses of Medtronic's commercially-release-approved products to non-Medtronic health care professional or third-party payers.

GUIDANCE:

I. Business Unit policies/procedures that address the **Office of Medical Affairs ("OMA") function** should include the following elements:

A. OMA is primarily responsible for all forms of interactions and communications with the medical community on unapproved uses, including the dissemination of articles and reference texts on unapproved uses in accordance with BU SOPs.

B. OMA will have advisory responsibility in the design and implementation of SOPs regarding provision of information on unapproved uses in other areas.

C. OMA will have input in the decision to: (1) fund third-party research requests, (2) sponsor articles by third parties, or (3) host Medtronic-consultative meetings that may include unapproved uses;

D. Business Unit Legal Counsel's review and approval is required for OMA's proposed affirmative dissemination of articles on unapproved uses, sponsorship of seminars, the grant of research funds or hosting of consultative meetings, when any of these relate to unapproved uses will require; and

E. Prohibition of all Medtronic personnel, including consultants, from using any dinner, meeting or other opportunity for the purpose of promoting products for unapproved uses.

II. Business Unit policies/procedures that address the provision of articles or other written information in response to **Unsolicited Requests** should include the following elements:

A. the written or oral request must specifically express interest in receiving materials about a particular subject or by title;

B. responsive information/materials must be issued by the OMA in a non-promotional manner and sales and marketing personnel must be prohibited from providing responsive information/materials to non-Medtronic persons; and

C. procedures must be established for fulfilling such requests that include:

i. requirements that OMA ensure that the information or materials are truthful, not misleading, and fairly balanced and have scientific and/or medical validity;

ii. requirements that written records of unsolicited requests and responses be maintained; and

iii. requirements that written materials be prominently stamped with language that:

a. states the materials contain information on unapproved uses that have not been approved/cleared by FDA;

b. states the materials are provided by Medtronic in response to an unsolicited request; and

c. discloses if Medtronic provided financial support related to the article or information.

III. Business Unit written policies and/or procedures that address **Medtronic-Supported Third-Party Medical Education** should include the following elements:

A. As a condition of support, a Medtronic-supported third-party medical education provider must disclose the financial relationships between and among Medtronic, the presenters, and the products discussed;

B. The activity must be educational in tone and nature and does not have as a predominant focus unapproved uses;

C. The third-party provider must be independent and have control over decisions regarding the content of the program and the selection of speakers, presenters, moderators and invitees;

D. All support must be documented in a written agreement; and

E. Sales personnel must not be involved in the determination of company sponsorship of third-party medical education, except as permitted under Business Conduct Standards 3 and 8. Sales personnel may make suggestions and provide background information to decision-makers.

F. These written policies and/or procedures may also provide that a business may provide ***suggestions*** on topics, speakers, or attendees, if:

i. The Business Unit's activity is limited to responding to unsolicited requests for such suggestions;

ii. The Business Unit suggests multiple speakers and/or topics with disclosure of any relationship to Medtronic;

iii. Only OMA or a similar function outside of sales provides any suggestions; and

iv. Such requests and responses are properly documented.

IV. Business Unit written policies and/or procedures that address funding of **research and publications** on unapproved uses should include the following elements:

A. Require disclosure of Medtronic support in any publication of the results;

B. Prohibit Medtronic from requiring or compensating a researcher to speak about or broadly disseminate research findings prior to FDA approval of the unapproved uses, other than providing a report of publishable quality to Medtronic and/or a peer-reviewed journal for publication. If the researcher wishes to speak or otherwise disseminate research results without Medtronic's support, s/he may do so; and

C. Prohibit Medtronic from requiring or compensating a researcher's involvement in promotional activities related to the subject of the research before FDA approval of the unapproved use except as permitted by FDA's Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects (March 19, 1999).

D. Prohibit all Medtronic personnel from funding research or publications for the purpose of promoting products on unapproved uses.

V. Business Unit written policies and/or procedures that address **physician advisory boards, consultant meetings,** or other **health** care professional **meetings and discussion groups** on unapproved uses should provide:

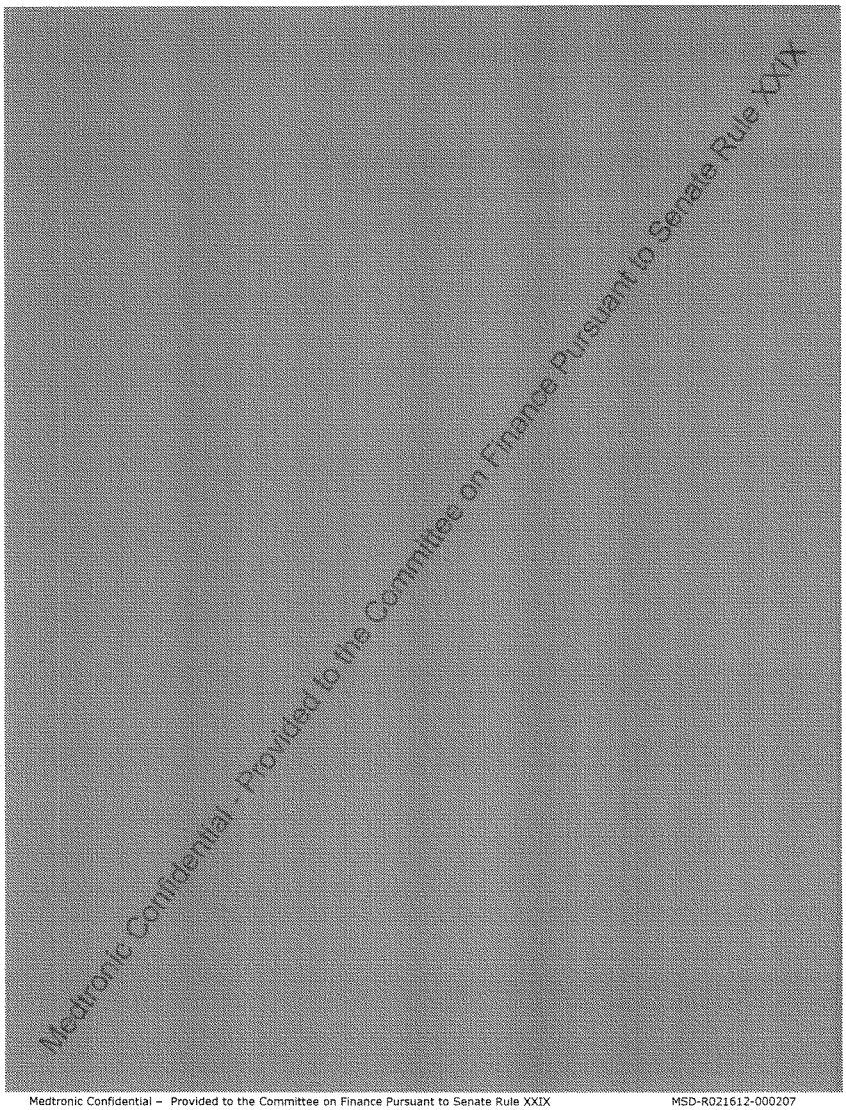
A. Prior approval by BU Legal of Medtronic's dissemination of information on unapproved uses;

B. Invitees must be limited in size to those necessary to achieve the purpose; and

C. The purpose, activity, need for the information gathered, and intended use must be documented.

D. Prohibition of all Medtronic personnel from utilizing such meetings and groups for the purpose of promoting products on unapproved uses.

CHANGE HISTORY		
REVISION	**DATE**	**DESCRIPTION of CHANGE**
A	6 April 2006	Initial Release


Medtronic Confidential - Provided to the Committee on Finance Pursuant to Senate Rule XXIX

Medtronic	CONFIDENTIAL	DOCUMENT/RECORD

This document/record is electronically controlled; printed copies are considered uncontrolled.
System of Record: Medtronic Records Control System (MRCS)

Identifier	Version	Author
048-Unapproved Uses of Approved Products	3.0	

Title: Unapproved Uses of Approved Products

APPROVALS

Signed By	Meaning of Signature	Date/Time (US Central Time)
Chip Whitacre	CQRC Operations	11/19/2009 10:23:08
Michael Morton	CQRC Regulatory	11/24/2009 15:11:03
Lisa Griffin Vincent	CQRC Clinical	11/25/2009 14:39:02
Susan Alpert	Senior Vice President, Chief Regulatory Officer	12/04/2009 09:07:13
Sandy Kalter	CQRC Legal	12/11/2009 12:02:17
Luann Pendy	CQRC Quality	12/21/2009 11:09:03

SCOPE:

Medtronic Organizations and entities (e.g., Business Units or independent distributors who exclusively distribute for Medtronic) that distribute product information in the U.S. on Medtronic commercially available products in the U.S.

PURPOSE:

To establish requirements for the dissemination of medical and scientific information on unapproved or uncleared uses of Medtronic's commercially-released-approved/cleared products or therapies to non-Medtronic health care professionals or third-party payers (collectively, "medical community").

POLICY:

All Medtronic Business Units and entities that distribute product information in the U.S. shall ensure that Business Unit procedures and policies prevent the promotion of approved or cleared Medtronic products and therapies for unapproved uses and describe the process for dissemination of medical and scientific information consistent with this Corporate Policy.

DEFINITIONS:

Affirmative Dissemination: Proactive distribution of peer-reviewed journal articles or reference texts that discuss unapproved uses of approved products in the absence of an Unsolicited Request, which Business Unit Legal has determined is appropriate for distribution consistent with this policy and Corporate Legal guidance.

Responsive Information/Materials: Information and/or materials (such as unpublished studies or articles, presentations, news articles, reference texts) that reference unapproved uses of Medtronic commercially available products and are provided to a non-Medtronic health care professional or a third-party payer *in direct response to an Unsolicited Request.*

Unapproved Uses: An indication for use that is not covered by the existing regulatory approval/clearance.

Unsolicited Request: A specific and independent request for information about unapproved uses of Medtronic products made by a non-Medtronic health care professional or third-party payer that was not initiated or prompted by Medtronic personnel.

REQUIREMENTS:

1. **Office of Medical Affairs ("OMA").**
   a. Each BU must have an OMA function that is:
      i. a management level position that reports to BU Senior Management;
      ii. not subordinate to a Sales or Marketing Department or function; and
      iii. must be authorized to review and approve all interactions and communications with the medical community on unapproved uses, including the dissemination of articles and reference texts on unapproved uses.
   b. Business Unit policies/procedures that address the OMA function should include the following elements:
      i. OMA is primarily responsible for all forms of interactions and communications with the medical community on unapproved uses, including the dissemination of articles and reference texts on unapproved uses and the response to unsolicited requests in accordance with the BU SOPs;
      ii. OMA must approve the development and implementation of SOPs regarding provision of information on unapproved uses in other functional areas;
      iii. OMA will have input in decisions to: (1) fund third-party research requests, related to unapproved uses of approved products, (2) support articles by third parties, or (3) host Medtronic-consultative meetings that discuss unapproved uses; and
      iv. A prohibition of all Medtronic personnel, including consultants, from using any dinner, meeting or other opportunity for the purpose of promoting products for unapproved uses.

2. **Affirmative Dissemination:** written procedures must address affirmative distribution of peer-reviewed articles and reference texts on unapproved uses.
   a. The procedures must require that the affirmative dissemination be conducted only in limited circumstances where such dissemination has a public health value to healthcare professionals and/or patients.
   b. The procedures must require that affirmative disseminations be documented, including the date of dissemination, the articles disseminated, and a list of recipients.
   c. Affirmative disseminations require OMA approval.
   d. Affirmative disseminations must include disclosures that: (1) states that the materials contain information on unapproved uses that have not been approved/cleared by FDA; (2) notes that insurers may or may not cover all uses described in the article and that it is advisable to confirm coverage with carriers before filing claims; and (3) discloses if Medtronic provided financial support related to the article or information.
   e. Dissemination of articles and texts on unapproved uses should be performed by OMA in a nonpromotional manner.

f. Business Unit Legal Counsel's review and approval is required for OMA's proposed affirmative dissemination of articles on unapproved uses.

3. **Unsolicited Requests:** written policies and/or procedures must provide a process for responding to Unsolicited Requests for articles or other materials on unapproved uses that include the following elements:
   a. The written or oral request must specifically express interest in receiving materials about a particular subject or by title;
   b. Responsive information/materials must be issued by the OMA in a non-promotional manner and sales and marketing personnel must be prohibited from providing responsive information/materials to medical community; and
   c. Procedures must be established for fulfilling such requests that include:
      i. Requirements that OMA ensure that the information or materials are truthful, not misleading, and fairly balanced and have scientific and/or medical validity;
      ii. Requirements that written records of Unsolicited Requests and responses be maintained;
      iii. A requirement to periodically audit the records of Unsolicited Requests and responses; and
      iv. Requirements that written materials be prominently stamped with language or include a cover letter that: (1) states that the materials contain information on unapproved uses that have not been approved/cleared by FDA; (2) states the materials are provided by Medtronic in response to an unsolicited request; (3) notes that insurers may or may not cover all uses described in the article and that it is advisable to confirm coverage with carriers before filing claims; and (4) discloses if Medtronic provided financial support related to the article or information.

4. **Medtronic-Supported Third-Party Medical Education:** written policies and/or procedures must ensure that Medtronic-supported third-party medical education involving unapproved uses is bona fide and independent and must include the following elements.
   a. As a condition of support, a Medtronic-supported third party medical education provider must disclose the financial relationships between and among Medtronic, the presenters, and the products discussed;
   b. The activity must be educational in tone and nature;
   c. The third-party provider must be independent and have control over decisions regarding the content of the program and the selection of speakers, presenters, moderators and invitees. Business Unit policies and/or procedures must address support for non-accredited third-party medical education, and require an assessment of the third-party provider's independence and control;
   d. The Business Unit must evaluate the agenda for the program, and the proportion of the program devoted to off-label uses when deciding whether or not to fund the program;
   e. The Business Unit may not provide suggestions to the CME provider on topics, speakers or attendees for the CME program, even if requested by the CME

provider, and may not review program content (other than the agenda) in advance of the program; even for factual accuracy;

f. All support must be documented in a written agreement; and
g. Sales personnel must not be involved in the determination of company sponsorship of third-party medical education, except as permitted under Business Conduct Standards 3 and 8. Accordingly, sales personnel may make suggestions and provide background information to company decision-makers.

5. **Medtronic-Implemented Training and Education on Medtronic Products:** written policies and/or procedures must
   a. Prohibit the inclusion of unapproved uses in agendas and prepared content of Medtronic-sponsored training on commercially available U.S.-approved products, except as permitted for training clinical investigators in clinical studies;
   b. Prohibit Medtronic personnel from answering unsolicited questions on unapproved uses of approved products that are posed during Medtronic-sponsored training and education on Medtronic products, except as permitted in Corporate Legal guidance. This prohibition does not apply to agendas for training clinical investigators in clinical studies or in physician training when a product approved for a general use is unable to be demonstrated without showing a specific use; and
   c. Require Business Unit Legal Counsel's review and approval for support for seminars when it relates to unapproved uses.

6. **Research and Publication Strategies:** written policies and/or procedures must explicitly prohibit sales personnel involvement in the determination of funding allocation for research and publication by non-Medtronic personnel or entities on unapproved uses, including physician-sponsored studies, consistent with the requirements of Business Conduct Standards 3 and 6. Such policies/procedures may permit sales personnel to be involved in this process only to the extent necessary to supply information about researcher qualifications or interest to decision-makers. Written policies and procedures must also include the following elements:
   a. Explicitly prohibit all Medtronic personnel from funding research or publications for the purpose of promoting products on unapproved uses;
   b. Require disclosure of Medtronic support in any publication of the results;
   c. Prohibit Medtronic from requiring or compensating a researcher to speak about or broadly disseminate research findings prior to FDA approval of the unapproved uses, other than providing a report of publishable quality to Medtronic and/or a peer-reviewed journal for publication. If the researcher wishes to speak or otherwise disseminate research results without Medtronic's support, s/he may do so;
   d. Prohibit Medtronic from requiring or compensating a researcher's involvement in promotional activities related to the subject of the research before FDA approval of the unapproved use except as permitted by FDA's *Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects* (March 19, 1999);

e. Explicitly prohibit Medtronic employees and Medtronic-contracted medical writers from providing writing assistance on publications that are on unapproved uses of approved products. This prohibition does not apply to publications on studies conducted under 21 C.F.R. Parts 312 or 812;
f. Explicitly require appropriate disclosure of an employee's or medical writer's contribution (authorship or contributorship) according to the International Committee of Medical Journal Editors (ICMJE) requirements for disclosure in publications. This includes where Medtronic funds a third party-sponsored research program (e.g., physician-sponsored) on unapproved uses to be conducted under 21 C.F.R. Parts 312 and 812 and the third party contracts with a medical writer to draft publications; and
g. Require Business Unit Legal Counsel and OMA review and approval for the proposed grant of research funds when it relates to unapproved uses.

7. **Physician Advisory Boards, Consultant Meetings, Roundtables or Discussion Groups:** written policies and/or procedures must prohibit the use of physician advisory boards, consultant meetings, roundtables or discussion groups to promote unapproved uses and must include the following elements:
   a. Require Business Unit Legal Counsel and OMA review and approval to host consultative meetings, when it relates to unapproved uses;
   b. Require Business Unit Legal Counsel and OMA review and approval of Medtronic's dissemination of information on unapproved uses in conjunction with the meeting;
   c. Invitees must be limited in number to those necessary to achieve the purpose; and
   d. The purpose of the meeting, a description of the activity, the business need for the information gathered, and intended use of the information must be documented.

8. **Notices of Availability:** Notices of Availability, which are notices to recruit clinical investigators or subjects for clinical trials, may not be used as a vehicle for promotion of a product for unapproved uses, but may be used if there is a bona fide need for recruitment of additional clinical investigators or subjects for an open study.

9. **Training:** Written policies and/or procedures must require training on the Corporate Policy and Business Unit policies and procedures and include the following elements:
   a. Training at initial hiring and annually for Sales and Marketing personnel and all other employees who interface with the medical community or have responsibility for preparing or reviewing outward-facing materials;
   b. Training at initial hiring and annually for all other personnel as determined by the BU, based on a risk assessment by the BU;
   c. Training must include product specific information, as determined by the BU, based on risk assessment;
   d. The BU must identify in the training plan a method for evaluating the effectiveness of training, *e.g.,* via a quiz or follow-up sampling; and
   e. An assessment of compliance to the training requirements of the policy and to the training plan.

10. **Exemption:** Permanent exemptions to Corporate policies shall not be granted. Business Units may be granted an annual exemption from any or all provisions of this policy by the Senior Vice President of Global Regulatory Affairs. Business Unit must provide appropriate documentation demonstrating either that a logical rationale exists for exemption from any part of the policy, or that there are currently no unapproved uses in the United States of the Business Units approved or cleared U.S.-commercially available products.

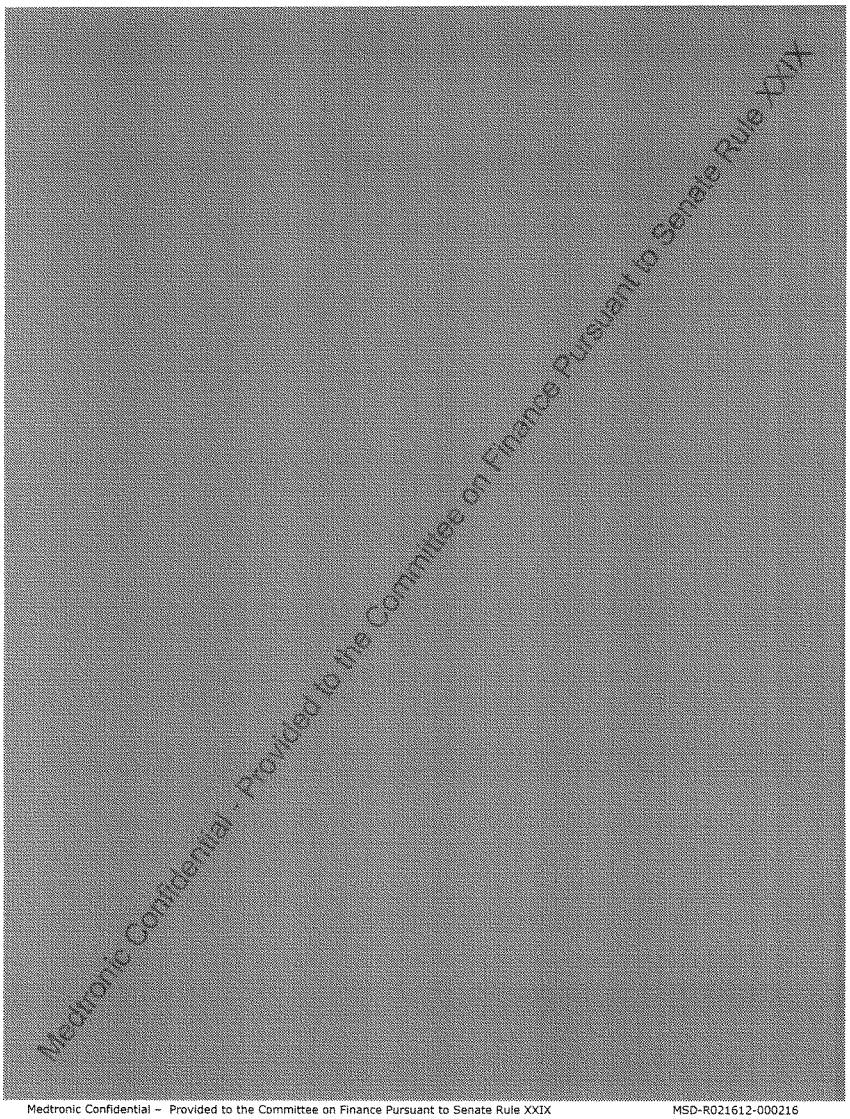
RESPONSIBILITY:

The Business Unit Management is responsible for implementation, training, and compliance with this policy.

Corporate Quality, Regulatory, Clinical
POLICY
Title: Unapproved Uses of Approved Products

CHANGE HISTORY		
Revision	**Date**	**Description of Change**
A	6 April 2006	Initial Release
2.0		Migration to MRCS
3.0		Incorporate guidance into policy, amend CME requirements to reflect ACCME revisions, stratify the training requirements, include a prohibition on employees or MDT-contracted medical writers providing medical writing assistance on UAU articles, provides parameters for affirmative dissemination, and parallels the affirmative dissemination disclosure requirements to unsolicited request disclosure requirements

Owner: Susan Alpert
Department: Corporate Regulatory Affairs


Medtronic Confidential - Provided to the Committee on Finance Pursuant to Senate Rule XXIX

Medtronic	CONFIDENTIAL	DOCUMENT/RECORD

This document/record is electronically controlled; printed copies are considered uncontrolled.
System of Record: Medtronic Records Control System (MRCS)

Identifier	Version	Author
048-Unapproved Uses of Approved Products	4.0	

Title: Unapproved Uses of Approved Products

APPROVALS

Signed By	Meaning of Signature	Date/Time (US Central Time)
Chip Whitacre	CQRC Operations	01/06/2010 16:10:27
Luann Pendy	CQRC Quality	01/06/2010 16:52:51
Susan Alpert	Senior Vice President, Chief Regulatory Officer	01/08/2010 11:49:44
Lisa Griffin Vincent	CQRC Clinical	01/08/2010 13:19:10
Sandy Kalter	CQRC Legal	01/08/2010 14:55:00
Michael Morton	CQRC Regulatory	01/13/2010 10:24:45

SCOPE:

Medtronic Organizations and entities (e.g., Business Units or independent distributors who exclusively distribute for Medtronic) that distribute product information in the U.S. on Medtronic commercially available products in the U.S.

PURPOSE:

To establish requirements for the dissemination of medical and scientific information on unapproved or uncleared uses of Medtronic's commercially-released-approved/cleared products or therapies to non-Medtronic health care professionals or third-party payers (collectively, "medical community").

POLICY:

All Medtronic Business Units and entities that distribute product information in the U.S. shall ensure that Business Unit procedures and policies prevent the promotion of approved or cleared Medtronic products and therapies for unapproved uses and describe the process for dissemination of medical and scientific information consistent with this Corporate Policy.

RESPONSIBILITY:

The Business Unit Management is responsible for implementation, training, and compliance with this policy.

DEFINITIONS:

Affirmative Dissemination: Proactive distribution of peer-reviewed journal articles or reference texts that discuss unapproved uses of approved products in the absence of an Unsolicited Request, which OMA, in consultation with Business Unit Legal, has determined is appropriate for distribution consistent with this policy and Corporate Legal guidance.

Responsive Information/Materials: Information and/or materials (such as unpublished studies or articles, presentations, news articles, reference texts) that reference unapproved uses of Medtronic commercially available products and are provided to a non-Medtronic health care professional or a third-party payer *in direct response to an Unsolicited Request.*

Unapproved Uses: An indication for use that is not covered by the existing regulatory approval/clearance.

Unsolicited Request: A specific and independent request for information about unapproved uses of Medtronic products made by a non-Medtronic health care professional or third-party payer that was not initiated or prompted by Medtronic personnel.

REQUIREMENTS:

1. **Office of Medical Affairs ("OMA").**
   a. Each BU must have an OMA function that is:
      i. a management level position that reports to BU Senior Management;
      ii. not subordinate to a Sales or Marketing Department or function; and
      iii. must be authorized to review and approve all interactions and communications with the medical community on unapproved uses, including the dissemination of articles and reference texts on unapproved uses.
   b. Business Unit policies/procedures that address the OMA function should include the following elements:
      i. OMA is primarily responsible for all forms of interactions and communications with the medical community on unapproved uses, including the dissemination of articles and reference texts on unapproved uses and the response to unsolicited requests in accordance with the BU SOPs;
      ii. OMA must approve the development and implementation of SOPs regarding provision of information on unapproved uses in other functional areas;
      iii. OMA will have input in decisions to: (1) fund third-party research requests, related to unapproved uses of approved products, (2) support articles by third parties, or (3) host Medtronic-consultative meetings that discuss unapproved uses; and
      iv. A prohibition of all Medtronic personnel, including consultants, from using any dinner, meeting or other opportunity for the purpose of promoting products for unapproved uses.

2. **Affirmative Dissemination:** written procedures must address affirmative distribution of peer-reviewed articles and reference texts on unapproved uses.
   a. The procedures must require that the affirmative dissemination be conducted only in limited circumstances where such dissemination has a public health value to healthcare professionals and/or patients.
   b. The procedures must require that affirmative disseminations be documented, including the date of dissemination, the articles disseminated, and a list of recipients.
   c. Affirmative disseminations require OMA approval.
   d. Affirmative disseminations must include disclosures that: (1) states that the materials contain information on unapproved uses that have not been approved/cleared by FDA; (2) notes that insurers may or may not cover all uses described in the article and that it is advisable to confirm coverage with carriers before filing claims; and (3) discloses if Medtronic provided financial support related to the article or information.
   e. Dissemination of articles and texts on unapproved uses should be performed by OMA in a nonpromotional manner.

f. Business Unit Legal Counsel's review and approval is required for OMA's proposed affirmative dissemination of articles on unapproved uses.

3. **Unsolicited Requests:** written policies and/or procedures must provide a process for responding to Unsolicited Requests for articles or other materials on unapproved uses that include the following elements:
   a. The written or oral request must specifically express interest in receiving materials about a particular subject or by title;
   b. Responsive information/materials must be issued by the OMA in a non-promotional manner and sales and marketing personnel must be prohibited from providing responsive information/materials to the medical community; and
   c. Procedures must be established for fulfilling such requests that include:
      i. Requirements that OMA ensure that the information or materials are truthful, not misleading, and fairly balanced and have scientific and/or medical validity;
      ii. Requirements that written records of Unsolicited Requests and responses be maintained;
      iii. A requirement to periodically audit the records of Unsolicited Requests and responses; and
      iv. Requirements that written materials be prominently stamped with language or include a cover letter that: (1) states that the materials contain information on unapproved uses that have not been approved/cleared by FDA; (2) states the materials are provided by Medtronic in response to an unsolicited request; (3) notes that insurers may or may not cover all uses described in the article and that it is advisable to confirm coverage with carriers before filing claims; and (4) discloses if Medtronic provided financial support related to the article or information.

4. **Medtronic-Supported Third-Party Medical Education:** written policies and/or procedures must ensure that Medtronic-supported third-party medical education involving unapproved uses is bona fide and independent and must include the following elements.
   a. As a condition of support, a Medtronic-supported third party medical education provider must disclose the financial relationships between and among Medtronic, the presenters, and the products discussed;
   b. The activity must be educational in tone and nature;
   c. The third-party provider must be independent and have control over decisions regarding the content of the program and the selection of speakers, presenters, moderators and invitees. Business Unit policies and/or procedures must address support for non-accredited third-party medical education, and require an assessment of the third-party provider's independence and control;
   d. The Business Unit must evaluate the agenda for the program, and the proportion of the program devoted to off-label uses when deciding whether or not to fund the program;
   e. The Business Unit may not provide suggestions to the CME provider on topics, speakers or attendees for the CME program, even if requested by the CME

provider, and may not review program content (other than the agenda) in advance of the program; even for factual accuracy;

f. All support must be documented in a written agreement; and
g. Sales personnel must not be involved in the determination of company sponsorship of third-party medical education, except as permitted under Business Conduct Standards 3 and 8. Accordingly, sales personnel may make suggestions and provide background information to company decision-makers.

5. **Medtronic-Implemented Training and Education on Medtronic Products:** written policies and/or procedures must
   a. Prohibit the inclusion of unapproved uses in agendas and prepared content of Medtronic-sponsored training on commercially available U.S.-approved products, except as permitted for training clinical investigators in clinical studies;
   b. Prohibit Medtronic personnel from answering unsolicited questions on unapproved uses of approved products that are posed during Medtronic-sponsored training and education on Medtronic products, except as permitted in Corporate Legal guidance. This prohibition does not apply to agendas for training clinical investigators in clinical studies or in physician training when a product approved for a general use is unable to be demonstrated without showing a specific use; and
   c. Require Business Unit Legal Counsel's review and approval for support for seminars when it relates to unapproved uses.

6. **Research and Publication Strategies:** written policies and/or procedures must explicitly prohibit sales personnel involvement in the determination of funding allocation for research and publication by non-Medtronic personnel or entities on unapproved uses, including physician-sponsored studies, consistent with the requirements of Business Conduct Standards 3 and 6. Such policies/procedures may permit sales personnel to be involved in this process only to the extent necessary to supply information about researcher qualifications or interest to decision-makers. Written policies and procedures must also include the following elements:
   a. Explicitly prohibit all Medtronic personnel from funding research or publications for the purpose of promoting products on unapproved uses;
   b. Require disclosure of Medtronic support in any publication of the results;
   c. Prohibit Medtronic from requiring or compensating a researcher to speak about or broadly disseminate research findings prior to FDA approval of the unapproved uses, other than providing a report of publishable quality to Medtronic and/or a peer-reviewed journal for publication. If the researcher wishes to speak or otherwise disseminate research results without Medtronic's support, s/he may do so;
   d. Prohibit Medtronic from requiring or compensating a researcher's involvement in promotional activities related to the subject of the research before FDA approval of the unapproved use except as permitted by FDA's *Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects* (March 19, 1999);

e. Explicitly prohibit Medtronic employees and Medtronic-contracted medical writers from providing writing assistance on publications that are on unapproved uses of approved products. This prohibition does not apply to publications on studies conducted under 21 C.F.R. Parts 312 or 812;
f. Explicitly require appropriate disclosure of an employee's or medical writer's contribution (authorship or contributorship) according to the International Committee of Medical Journal Editors (ICMJE) requirements for disclosure in publications. This includes where Medtronic funds a third party-sponsored research program (e.g., physician-sponsored) on unapproved uses to be conducted under 21 C.F.R. Parts 312 and 812 and the third party contracts with a medical writer to draft publications; and
g. Require Business Unit Legal Counsel and OMA review and approval for the proposed grant of research funds when it relates to unapproved uses.

7. **Physician Advisory Boards, Consultant Meetings, Roundtables or Discussion Groups:** written policies and/or procedures must prohibit the use of physician advisory boards, consultant meetings, roundtables or discussion groups to promote unapproved uses and must include the following elements:
   a. Require Business Unit Legal Counsel and OMA review and approval to host consultative meetings, when it relates to unapproved uses;
   b. Require Business Unit Legal Counsel and OMA review and approval of Medtronic's dissemination of information on unapproved uses in conjunction with the meeting;
   c. Invitees must be limited in number to those necessary to achieve the purpose; and
   d. The purpose of the meeting, a description of the activity, the business need for the information gathered, and intended use of the information must be documented.

8. **Notices of Availability:** Notices of Availability, which are notices to recruit clinical investigators or subjects for clinical trials, may not be used as a vehicle for promotion of a product for unapproved uses, but may be used if there is a bona fide need for recruitment of additional clinical investigators or subjects for an open study.

9. **Training:** Written policies and/or procedures must require training on the Corporate Policy and Business Unit policies and procedures and include the following elements:

   a. Training at initial hiring and annually for Sales and Marketing personnel and all other employees who interface with the medical community or have responsibility for preparing or reviewing outward-facing materials;
   b. Training at initial hiring and annually for all other personnel as determined by the BU, based on a risk assessment by the BU;
   c. Training must include product specific information, as determined by the BU, based on risk assessment;
   d. The BU must identify in the training plan a method for evaluating the effectiveness of training, *e.g.*, via a quiz or follow-up sampling; and
   e. An assessment of compliance to the training requirements of the policy and to the training plan.

CHANGE HISTORY		
Revision	**Date**	**Description of Change**
A	6 April 2006	Initial Release
2.0		Migration to MRCS
3.0	21 Dec 2009	Incorporate guidance into policy, amend CME requirements to reflect ACCME revisions, stratify the training requirements, include a prohibition on employees or MDT-contracted medical writers providing medical writing assistance on UAU articles, provides parameters for affirmative dissemination, and parallels the affirmative dissemination disclosure requirements to unsolicited request disclosure requirements.
4.0		Removed Exemption section because revised Corporate Policy 001 addresses an exception and deviation process.

Owner: Susan Alpert
Department: Corporate Regulatory Affairs

Medtronic

Global Policy

Scientific Publications Policy Related to MSB-Sponsored Research

Document ID: **PO004** Version: **A**

Effective Date: **8/6/10** Owner: **Lisa Griffin Vincent Ph.D.**

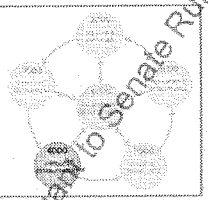


TABLE OF CONTENTS

PURPOSE 2

SCOPE 2

POLICY 3

1 General Requirements (Clinical, Pre-Clinical, and Non-Clinical Research) for Review of Requests for Publications and Publications: 3

2 MSB Employee Involvement in Publication Projects 4

3 Non-MSB Employee Participation in Publications Projects 4

4 Requirements Specific to Clinical Requests for Publications and Publications 4

5 Requirements Specific to Pre-Clinical and Non-Clinical Requests for Publications and Publications 5

DEFINITIONS 6

REFERENCES 6

REVISION HISTORY 7

Medtronic

Global Policy
Document ID: **PO004**
Version: **A**
Effective Date: **8/6/10**

Scientific Publications Policy Related to MSB-Sponsored Research

PURPOSE

The purpose of this document is to set minimum requirements for management of scientific (i.e., non-promotional) **Requests for Publications** and **Publications** related to research (clinical, pre-clinical, and non-clinical) sponsored by MSB.

SCOPE

This policy applies to all MEDTRONIC employees.

The information in this document applies to requests for Publications and Publications related to research (clinical (including health economics), pre-clinical, and non-clinical) sponsored by Medtronic Spinal & Biologics (MSB) globally. Request for Publication includes a request for research information and/or data analysis intended to be used in a future Publication.

POLICY

1 General Requirements (Clinical, Pre-Clinical, and Non-Clinical Research) for Review of Requests for Publications and Publications:

1.1 Requests for publications and publications must follow written procedures for cross-functional review and approval on scientific (i.e., non-promotional) Requests for Publications and Publications according to this Policy.

1.2 Review and approval will be required for both Requests for Publications and Publications.

1.3 Review and approval must include the following at a minimum:

- Clinical (for clinical data only) – for data accuracy, scientific rigor and contribution, technical use of product, safety and human subjects' protection, protection of confidential information, and alignment with any publication plans and processes established for a specific clinical study related to the Publication or Request.
- Research and/or Development (for pre-clinical and non-clinical data only) – for scientific rigor and contribution, technical use of product, protection of confidential information, alignment with research strategy and animal protections where applicable.
- Legal – for compliance to applicable laws and business conduct standards (BCS), protection of confidential information, and promotional claims or perception of promotional claims.
- Regulatory – for compliance to applicable regulations, unapproved use determination, protection of confidential information, promotional claims or perception of promotional claims, and consistency with regulatory filings and/or documents.
- Marketing (for clinical data only) - for alignment with business strategy and any applicable Global Strategic Publications Plan (SPP) from the Global Commercialization Process (GCP), and protection of confidential information.
- Reimbursement (for clinical data only) – for alignment with Reimbursement Strategy, and protection of confidential information.

1.4 The following information is required at a minimum to conduct a review.

1.4.1 Request for Publication:

- Requestor (e.g., employee, investigator, physician) identification information
- Description of the proposal for publication (i.e., specific publication plan)
- Publication target or use of data (i.e., journal, meeting, data use)
- Description of any data required and origin (e.g., specific studies) if applicable
- Intended participation or contribution of any MSB employees or requested services (e.g., data analysis, writing)

1.4.2 Publication: the final draft Publication document or presentation materials as applicable.

1.5 The outcome of each review should be documented.

1.6 Publications Approval on a Request for Publication or Publication will automatically be *Denied* where:

- There is evidence of improper Sales personnel involvement in the submission or review process.
- It is determined by any reviewer that the Publication would or may appear to be for the purposes of promoting unapproved uses or inducing or rewarding the use of Medtronic products, or is otherwise in violation of the BCS or any applicable laws.

1.7 Relationships to MSB must be transparent in resulting Publications, including the proper disclosure of MSB employee participation as authors or contributors. Specific relationship information and formatting should be driven by the specific journal or other publication specifications or according to International Committee of Medical Journal Editors (ICMJE) *Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the*

Conduct and Reporting of Research: Authorship and Contributorship (Guidelines, see www.ICMJE.org) where there are no identified publication specifications for transparency.

2 MSB Employee Involvement in Publication Projects

2.1 Multiple Medtronic functions including Clinical, Medical Affairs, Research, Development, Reimbursement, Communications, and Marketing, but not Sales, may initiate a Request for Publication.

2.2 Clinical, Medical Affairs, Research, or Development employees may serve as authors or contributors on Publications related to Medtronic-sponsored research according to the ICMJE Guidelines (see www.ICMJE.org):

- Employee participation must be approved as part of the review and approval process for the specific Request for Publication
- Employee participation must be transparent with proper disclosure of any conflicts of interest within resulting Publications

2.3 Marketing and Sales may not participate as authors or contributors on Publications.

2.4 Multiple Medtronic functions including Clinical, Medical Affairs, Research, Development, Reimbursement, and Marketing, but not Sales may initiate a Request for Publication

2.4.1 Marketing is accountable for the Global Strategic Publication Plan (SPP) for a MSB product/therapy in the Global Commercialization Process (GCP). International Marketing will provide input to the Publication plans; however, Clinical, Research, and Reimbursement are responsible for completion of the plans comprising the SPP:

- Clinical is responsible for clinical study Publication plans.
- Research (or Development) is responsible for pre-clinical and non-clinical publication plans, where applicable.
- Reimbursement is responsible for health economics Publications plans.

3 Non-MSB Employee Participation in Publications Projects

3.1 Non-MSB authors on Publications related to Medtronic-sponsored research must be in accordance to the ICMJE Guidelines (see www.ICMJE.org); resulting publications must include the proper disclosure of any conflicts of interest within.

3.2 A legal agreement must be in place to address the use of MSB research data and cover rights and obligations related to the Publication effort. This may be incorporated in a clinical trials agreement, research agreement or consulting agreement for other related consulting or research services. At a minimum, the agreement should address:

- Statement of the financial compensation for Publication writing or editing activities for health care professionals (HCPs) or health care organizations (HCOs), where applicable (see item 3.3. below)
- Right and obligation for MSB to review and comment on the Publication prior to **release**, for technical accuracy and protection of confidential information
- Transparency requirements on disclosure of relationship to MSB (see item 1.7. above)

3.3 MSB will not financially compensate health care professionals (HCPs) or health care organizations (HCOs) for writing or editing activities on a scientific Publications related to research sponsored by MSB. A Publication may serve as a milestone for payment in an agreement, but there must not be any financial compensation in the budget for writing or editing activities. A legal agreement (separate or incorporated into an agreement including other services) must cover the rights and obligations of the parties even though financial compensation is not provided.

4 Requirements Specific to Clinical Requests for Publications and Publications

4.1 Clinical Research and/or Medical Affairs will manage the development, review and approval process for Publications and Requests for Publications related to clinical studies independent; these individuals will be responsible for publication development and should fully meet the ICMJE criteria for authorship as discussed above.

4.2 Timing on release of clinical Publications and the specific business review process to be followed depends on the type of Publication and follows only after review and approval as described in Section 1.

4.2.1 Notice of Availability (NOA): NOAs may be released for recruitment of investigators or potential subjects and only after IDE/IND approval and registration in ClinicalTrials.gov. NOAs must be reviewed through the Clinical work instruction **CL050, Review and Approval for Clinical Data Publications** and the policy **QM21, Promotional Materials Policy**.

4.2.2 ClinicalTrials.gov Registration and Results Information: Per regulations (e.g., FDAAA 2007) and ClinicalTrials.gov requirements. Information must be reviewed through the applicable Clinical work instruction, **CL050, Review and Approval for Clinical Data Publications**.

4.2.3 Press Release:

4.2.3.1 Press releases will be allowed, but not required, following milestones of IDE/IND approval, enrollment initiation or cessation, FDA Panel review, PMA/NDA/BLA approval. Other milestones may be considered, but only as approved through the publications review process.

4.2.3.2 Press releases related to MSB IDE/IND clinical studies (investigational) involving novel products or unapproved uses for approved products will be limited to:

- Enrollment initiation,
- Announcement of publication of the overall study results in a scientific journal (or interim Publication if part of a study-specific Publication plan), and

4.2.3.3 FDA approval.

4.2.3.4 Press releases must be reviewed per **QM21, Promotional Materials Policy**.

4.2.4 Abstract/Poster: According to any publication plan and process established for a specific clinical study. Original abstracts/posters must be reviewed through **CL050, Review and Approval for Clinical Data Publications**.

4.2.5 Scientific Journal/Peer-review Article: According to a publication plan and process established for a specific clinical study. Original manuscripts must be reviewed through **CL050, Review and Approval for Clinical Data Publications**.

4.2.6 Other: (e.g., use of data in an advisory meeting, investigator meeting, congress presentations, or education program). Such publications must be reviewed through **CL050, Review and Approval for Clinical Data Publications** or **QM21, Promotional Materials Policy**.

4.2.64.2.7 In general, no Publications using data from a clinical study of a novel product or unapproved use of an approved product will be approved prior to the primary clinical study Publication unless part of a study-specific Publication plan (e.g., interim analysis, single-center data from a multi-center study, sub-study publication), driven by patient safety concerns, or other reviewed and approved data use situations.

4.3 Use of (e.g., distribution) a scientific clinical publication following initial review, approval, and release must be reviewed for the "new use" through **QM21, Promotional Materials Policy**.

5 Requirements Specific to Pre-Clinical and Non-Clinical Requests for Publications and Publications

5.1 Research and Development (R&D) will manage the development, review and approval process for Publications and Requests for Publications related to **pre-clinical and non-clinical research**.

5.2 Use of (e.g., distribution) a scientific pre-clinical or non-clinical publication following initial review, approval, and release must be reviewed for the "new use" through **QM21, Promotional Materials Policy**.

DEFINITIONS

Publication
Information and/or data released to the public in any format (written or verbal) including Notice of Availability (NOA), registration and results information posting in a public registry (e.g.. clintrials, ClinTrials.gov), press release, abstract, scientific journal article, or public presentation (e.g., script talking points, slide presentation) including, investigator or other health care provider (HCP) or other technical meetings.

Requests for Publication (Publications Requests)
Requests to initiate a specific Publication or for research information and/or data intended to be used in a future Publication (e.g., clinical study data).

Applicable Business Procedures
All applicable MSB business procedures related to review and approval of any scientific Publication as defined above.

Pre-Clinical and Non-Clinical Research
Applies to research that is not on live human subjects including, bench testing, computer modeling, laboratory, animal, and cadaver research.

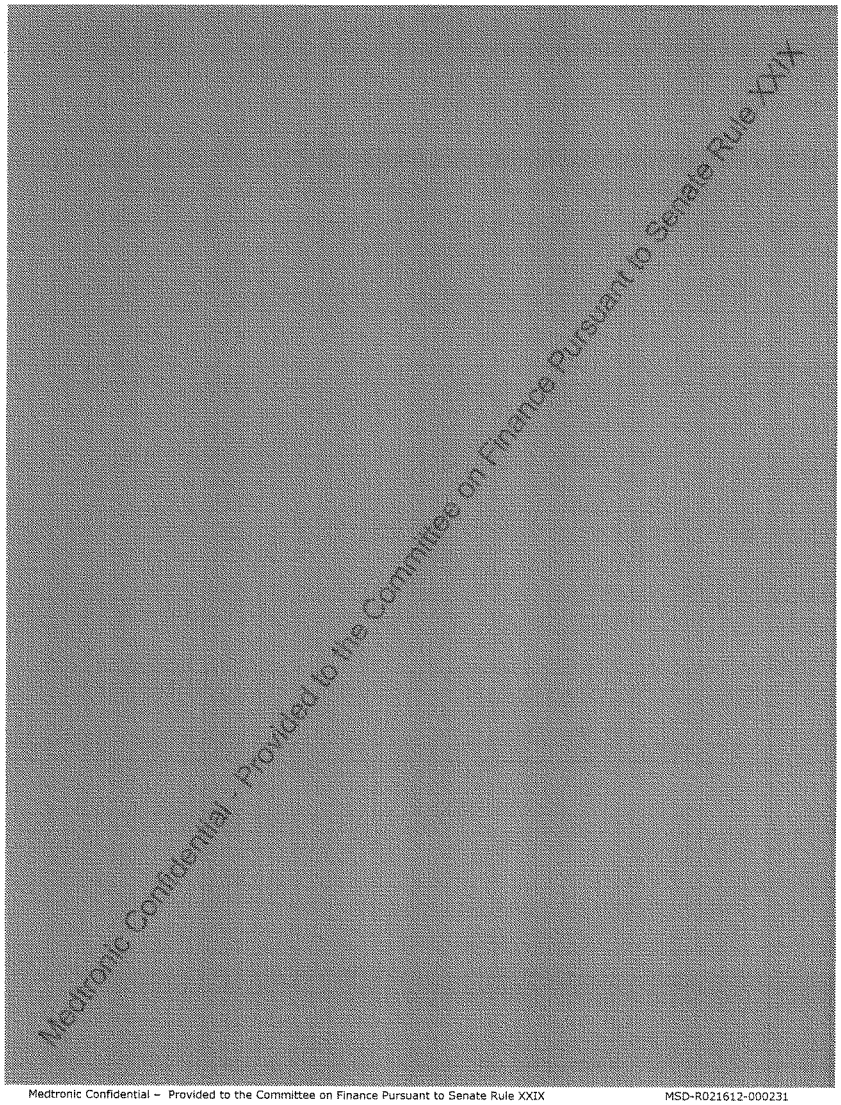
Release
Make public.

REFERENCES

CL050, Review and Approval for Clinical Data Publications 5
QM21, Promotional Materials Policy 5

REVISION HISTORY

Version	Originator	Description of Change	Date
A	Laurie Gray	Initial Release.	8/6/10


Medtronic Confidential - Provided to the Committee on Finance Pursuant to Senate Rule XXIX

Medtronic

Global Policy

Scientific Publications Policy Related to Medtronic-Sponsored Research

Document ID: P0004 Version: B

Effective Date: 11 Oct. 2011 Owner: Brian Barry

TABLE OF CONTENTS

PURPOSE 2

SCOPE 2

POLICY 3

1 General Review Requirements for (Clinical, Pre-Clinical, and Non-Clinical Research) Publications Requests & Publications: 3

2 Medtronic Employee Involvement in Publication Projects 4

3 Non-Medtronic Employee Participation in Publications Projects 4

4 Requirements Specific to Clinical Publications Requests and Publications 5

5 Requirements Specific to Pre-Clinical and Non-Clinical Publications Requests and Publications 6

DEFINITIONS 6

REFERENCES 6

REVISION HISTORY 7

Scientific Publications Policy Related to Medtronic-Sponsored Research

PURPOSE

The purpose of this document is to set minimum requirements for management of scientific (i.e., non-promotional) Publications Requests and publications related to research (clinical, pre-clinical, and non-clinical) sponsored by Medtronic.

SCOPE

This policy applies to all MEDTRONIC employees.

The information in this document applies to publications requests and publications related to research (clinical (including health economics), pre-clinical, and non-clinical) sponsored by Medtronic Spinal (Medtronic) globally. Publication requests include requests for research information and/or data analysis intended to be used in a future publication.

Scientific Publications Policy Related to Medtronic-Sponsored Research

POLICY

1 General Review Requirements for (Clinical, Pre-Clinical, and Non-Clinical Research) Publications Requests & Publications:

1.1 Publications requests and publications must follow written procedures for cross-functional review according to this policy.

1.2 Review and approval for publications requests and review of publications will be required.

1.3 Review and approval of publication requests and review of publications must include the following at a minimum:

- For Clinical Data Only:
  - Clinical Research and Biostatistics – Review for data accuracy, scientific rigor and contribution.
  - Clinical Trial Management – Review for technical use of products, safety and human subjects' protection, protection of confidential information, and alignment with any publication plans and processes established for a specific clinical study related to the publication or request.
  - Health Economics/Reimbursement – Review for alignment with Reimbursement Strategy and protection of confidential information.
- Legal – Review for compliance with applicable laws and business conduct standards (BCS), protection of confidential information, and promotional claims or perception of promotional claims.
- Medical Affairs –
  - Review for appropriate representation and communication of any unapproved use (if relevant).
  - Review for medical/clinical accuracy and fair balance.
  - Review for suitability/utility for scientific dissemination, including alignment with publication plan(s), scientific exchange strategy and business strategy.
- Regulatory – Review for compliance with applicable regulations, unapproved use determinations, protection of confidential information, promotional claims or perception of promotional claims, and consistency with regulatory filings and/or documents.
- For Pre-clinical and Non-clinical Data Only
  - Research and/or Development – for scientific rigor and contribution, technical use of product, protection of confidential information, alignment, with research strategy and animal protections, where applicable.

1.4 The following information is required at a minimum to conduct a review.

1.4.1 Request for Publications:

- Requestor (e.g., employee, investigator, physician) identification information
- Description of the proposal for publication (i.e., specific publication plan)
- Publication target or use of data (i.e., journal, meeting, data use)
- Description of any data required and origin (e.g., specific studies), if applicable
- Intended participation or contribution of any Medtronic employees or requested services (e.g., data analysis, writing)

1.4.2 Publication: the final draft publication document or presentation materials, as applicable.

1.5 The outcome of each review should be documented.

1.6 Approval for publications requests or publications will automatically be *Denied* where:

- There is evidence of improper Sales personnel involvement in the submission or review process and/or
- It is determined by any reviewer that the publication would or may appear to be for the purposes of promoting unapproved uses or inducing or rewarding the use of Medtronic products, or is otherwise in violation of the BCS or any applicable laws.

1.7 Medtronic will not provide funding or any other type of support for publications for the purpose of promoting products on unapproved uses. This prohibition does not apply to publications on studies conducted under regulatory approval (such as 21 CFR Part 312 or Part 812).

1.8 Relationships to Medtronic must be transparent in resulting publications, including the proper disclosure of Medtronic employee participation as authors or contributors. Specific relationship information and formatting

should be driven by journal or other publication specifications, or according to International Committee of Medical Journal Editors (ICMJE) *Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Authorship and Contributorship* (Guidelines, see www.ICMJE.org) where there are no identified publication specifications for transparency.

2 Medtronic Employee Involvement in Publication Projects

2.1 Clinical, Medical Affairs, Research and Development, Health Economics/Reimbursement, and Regulatory employees may serve as authors or contributors on publications related to Medtronic-sponsored research according to the ICMJE Guidelines (see www.ICMJE.org).

2.1.1 Employee participation must be approved as part of the review and approval process for the specific publication request.

2.1.2 Employee participation must be transparent with proper disclosure of any conflicts of interest within resulting publications.

2.1.3 Employees that meet authorship criteria according to ICMJE guidelines must be recognized as authors.

2.1.3.1 Ghost writing is strictly prohibited.

2.2 Employees who *are authors or contributors* on publications may review to ensure the accuracy of publications and recommend publication edits to the Background/Introductions, Methods, Results, Discussion and Conclusions.

2.3 Employees who *are not authors or contributors* on publications may review to ensure the accuracy of publications, with respect to the Background/Introduction, Methods, Conclusions, and Discussion, but may NOT contribute to the Discussion.

2.4 Medtronic Personnel in Marketing or Sales functions cannot author or contribute to publications on Unapproved Uses. Other Medtronic employees and medical writers may provide writing assistance on publications regarding unapproved uses of approved Medtronic products under the following conditions: 1) the data that is the subject of the publication is based on in vitro testing, animal testing, or human studies conducted under applicable Investigational Device Exemption (IDE) regulations (21 CFR 812) or Investigational New Drug (IND) regulations (21 CFR 312); 2) the publication is intended for submission for publication to a peer-reviewed journal; 3) the information will add to scientific knowledge (i.e., is not repetitive of existing publications; 4) the Unapproved Use discussed in the publication is the subject of a Medtronic research or evidence development effort on products/therapies; and 5) participation in the publication is consistent with other applicable corporate and business unit publication policies and procedures and any applicable disclosure standards (e.g. ICMJE) are followed. Any such writing assistance must be approved by a publications committee that includes the groups identified in section 1.3.

3 Non-Medtronic Employee Participation in Publications Projects

3.1 Non-Medtronic authors on Publications related to Medtronic-sponsored research must be in accordance with the ICMJE Guidelines (see www.ICMJE.org); resulting publications must include the proper disclosure of any conflicts of interest within.

3.2 A legal agreement must be in place to address the use of Medtronic research data and cover rights and obligations related to the publication effort. This may be incorporated in a clinical trials agreement, research agreement or consulting agreement for other related consulting or research services. At a minimum, the agreement should include/address:

- A Statement of No Financial Compensation for publication writing or editing activities for health care professionals (HCPs) or health care organizations (HCOs), where applicable (see item 3.3. below)
- The right and obligation for Medtronic to review and comment on the publication prior to its release to ensure technical accuracy and protection of confidential information
- Transparency requirements on disclosure of relationship to Medtronic (see Section 1.7).

3.3 Medtronic will not financially compensate health care professionals (HCPs) or health care organizations (HCOs) for writing or editing activities on scientific publications related to research sponsored by Medtronic. A publication may serve as a milestone for payment in an agreement, but there must not be any financial compensation in the budget for writing or editing activities.

3.3.1 *A legal agreement (separate or incorporated into an agreement including other services) must cover the rights and obligations of the parties even though financial compensation is not provided.*

4 Requirements Specific to Clinical Publications Requests and Publications

4.1 Clinical Research and/or Medical Affairs will manage the development, review and approval process for publications requests and publications related to clinical studies by establishing an independent Investigator Publication Steering Committee. The Investigator Publication Steering Committee will be responsible for publication development.

4.2 Timing on the release of clinical publications and the specific business review process to be followed depends on the type of publication and occurs only after review and approval as described in Section 1 of this policy.

4.2.1 Notice of Availability (NOA): NOAs may be released for recruitment of investigators or potential subjects and only after IDE/IND approval and registration in ClinicalTrials.gov. NOAs must be reviewed through the applicable work instructions such as **PL017, US – Investigator/Patient Recruiting Materials** and the policy **QM21, Promotional Materials Policy**.

4.2.2 ClinicalTrials.gov Registration and Results Information: Per regulations (e.g., FDAAA 2007) and ClinicalTrials.gov requirements, information must be reviewed through the procedure **SP4.23, Registration and Data Posting of Clinical Trials**.

4.2.3 Press Release:

4.2.3.1 Press releases will be allowed, but not required, following milestones of IDE/IND approval, enrollment initiation or cessation, FDA Panel review, PMA/NDA/BLA approval. Other milestones may be considered, but only as approved through the publications review process.

4.2.3.2 Press releases related to Medtronic IDE/IND clinical studies (investigational) involving novel products or unapproved uses for approved products will be limited to:

- Enrollment initiation,
- Announcement of publication of the overall study results in a scientific journal (or interim Publication, if part of a study-specific publication plan), and
- FDA approval.

4.2.3.3 Press releases must be reviewed per QM21, Promotional Materials Policy.

4.2.4 Abstract/Poster: According to any publication plan and process established for a specific clinical study. Original abstracts/posters must be reviewed through **CL050, Review and Approval for Clinical Data Publications**.

4.2.5 Scientific Journal/Peer-review Article: According to a publication plan and process established for a specific clinical study. Original manuscripts must be reviewed through **CL050, Review and Approval for Clinical Data Publications**.

4.2.5.1 Authors are expected to submit manuscripts for publication in a timely manner.

4.2.6 Other: (e.g., use of data in an advisory meeting, investigator meeting, congress presentations, or education program). Such publications must be reviewed through **CL050, Review and Approval for Clinical Data Publications** or **QM21, Promotional Materials Policy**.

4.3 In general, no publications using data from a clinical study of a novel product or unapproved use of an approved product will be approved prior to the primary clinical study publication unless it is part of a study-specific publication plan (e.g., interim analysis, single-center data from a multi-center study, sub-study publication), driven by patient safety concerns, or other such reviewed and approved data use situations.

4.3.1 Medtronic employees may not require and/or compensate researchers to speak about or broadly disseminate research findings prior to FDA approval of the unapproved uses, other than providing a report of publishable quality to Medtronic and/or a peer-reviewed journal for publication as required by **Corporate Policy 048, Unapproved Uses of Approved Products**.

4.4 Use (e.g., distribution) of a scientific clinical publication following initial review, approval, and release must be reviewed for the "new use" through **QM21, Promotional Materials Policy**.

5 Requirements Specific to Pre-Clinical and Non-Clinical Publications Requests and Publications

5.1 Research and Development (R&D) will manage the development, review and approval process for publications and Requests for Publications related to **pre-clinical and non-clinical research**.

5.2 Use (e.g., distribution) of a scientific pre-clinical or non-clinical publication following initial review, approval, and release must be reviewed for the "new use" through **QM21, Promotional Materials Policy**.

DEFINITIONS

Publication
Information and/or data released to the public in any format (written or verbal) including Notice of Availability (NOA), registration and results information posting in a public registry (e.g., clintrials, ClinTrials.gov), press release, abstract, scientific journal article, or public presentation (e.g., script talking points, slide presentation) including, investigator or other health care provider (HCP) or other technical meetings.

Requests for Publication (Publications Requests)
Requests to initiate a specific Publication or for research information and/or data intended to be used in a future Publication (e.g., clinical study data).

Applicable Business Procedures
All applicable Medtronic business procedures related to review and approval of any scientific Publication as defined above.

Pre-Clinical and Non-Clinical Research
Applies to research that is not on live human subjects including bench testing, computer modeling, laboratory, animal, and cadaver research.

Release
Make public.

REFERENCES

048, Unapproved Uses of Approved Products 5
CL050, Review and Approval for Clinical Data Publications 5
PL017, US – Investigator/Patient Recruiting Materials 5
QM21, Promotional Materials Policy 5, 6
SP4.23, Registration and Data Posting of Clinical Trials 5

Scientific Publications Policy Related to Medtronic-Sponsored Research

REVISION HISTORY

Version	Originator	Description of Change	Date
A	Laurie Gray	Initial Release.	08/06/2010
B	Jim Slaba	Updated to better align with Corporate Policy 048 §8 and §8c per recommendations made by the Spinal 048 Audit. In addition, references to MSB were removed and the company name was changed from *Medtronic Spinal and Biologics* to *Medtronic Spinal*. Inserted reference to Corporate Policy 048 §6.e.c per recommendations made by the Spinal 048 Audit. Changed owner to Brian Barry. Added Clinical Research and Biostatistics, Clinical Trial Management, and Medical Affairs functions to Section 1.3. Removed marketing function from Section 1.3. Added Section 1.7 – Medtronic will not provide funding or any other type of support for publications for the purpose of promoting precuts on unapproved uses. This prohibition does not apply to publications on studies conducted under regulatory approval (such as 21CFR Part 312 or Part 812). Deleted, former Section 2.1 – Multiple Medtronic functions including Clinical, Medical Affairs, Research, Development, Reimbursement, Communications, and Marketing, but not Sales, may initiate a Request for Publication. Added Sections 2.2 and 2.3. Changed section 2.4 to align with CQRO 048 Referenced PL017 in Section 4.2.1. Added, "Author are expected to submit manuscripts for publication in a timely manner" to Section 4.2.5. Added Tables 1&2. Added PL017, US – Investigator/Patient Recruiting Materials to the references section. Changed "Requests for Publications" to Publications Request" throughout the document.	11 Oct. 2011

Medtronic

Global Policy

Medtronic Spinal Implementation of CQRC 048, Unapproved Uses of Approved Products

Document ID: P0016 Version: A

Effective Date: 23 Aug 2011 Owner: Brian Barry

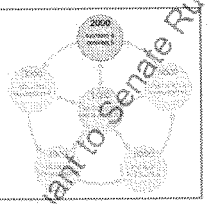


TABLE OF CONTENTS

PURPOSE 2

SCOPE 2

INTRODUCTION 2

POLICY 2

1 CQRC 048 Requirement 1: Creation of Office of Medical Affairs (OMA) 2

2 CQRC 048 Requirement 2: Affirmative Dissemination 2

3 CQRC 048 Requirement 3: Unsolicited Requests 3

4 CQRC 048 Requirement 4: Medtronic Spinal Supported Third Party Medical Education 3

5 CQRC 048 Requirement 5: Medtronic-Implemented Training and Education on Medtronic Products 3

6 CQRC 048 Requirement 6: Research and Publication Strategies 3

7 CQRC 048 Requirement 7: Physician Advisory Boards, Consultant Meetings, Roundtables, or Discussions. 3

8 CQRC 048 Requirement 8: Notices of Availability 3

9 CQRC 048 Requirement 9: Training 3

10 Additional Medtronic Spinal Policies/Procedures Addressing Prohibition of Off-Label Promotion in Relevant Subject Areas 4

DEFINITIONS 4

REFERENCES 4

REVISION HISTORY 5

Medtronic Spinal Implementation of CQRC 048, Unapproved Uses of Approved Products

PURPOSE

The purpose of this document is to provide an overview of the polices and procedures implemented by Medtronic Spinal in order to meet the requirements of Corporate policy **CQRC 048, Unapproved Uses of Approved Products.**

SCOPE

This document is designated for use at the following business locations:

- MDT Spinal and Biologics Deggendorf Manufacturing
- MDT Spinal and Biologics Humacao Manufacturing
- MDT Spinal and Biologics Memphis Headquarters
- MDT Spinal and Biologics Memphis Manufacturing
- MDT Spinal and Biologics Warsaw Manufacturing
- Spinal Graft Technologies
- Medtronic Spine, LLC (Kyphon)
- Memphis-Osteotech

INTRODUCTION

CQRC 048, Unapproved Uses of Approved Products Policy requires each Medtronic business unit to establish policies and procedures that prevent the promotion of approved or cleared Medtronic products and therapies for unapproved uses. The business unit must also establish policies and procedures describing the process for dissemination of medical and scientific information consistent with **CQRC 048.** This document serves as a map to Medtronic Spinal's policies and procedures established to meet the requirements of **CQRC 048.** The policies and procedures listed herein are located on the Medtronic Spinal Quality Sitebuilder (http://sitebuilder2/spinalbiologics/QSD/default.aspx) and/or on the Compliance MySpineTools site (http://www.myspinetools.com/compliance/).

POLICY

1 CQRC 048 Requirement 1: Creation of Office of Medical Affairs (OMA)

1.1 Medtronic Spinal shall have an Office of Medical Affairs (OMA), as required by CQRC that is a management level position reporting to Medtronic Spinal senior management. It shall not be subordinate to Sales or Marketing, and it is authorized to review and approve all interactions and communication with the medical community on unapproved uses, including the dissemination of articles and reference texts on unapproved uses. The Medtronic Spinal implementing policy for the requirement is **P0007, Dissemination of Information on Unapproved Uses of Approved_Cleared Products and Therapies.** Other policies regarding the required involvement of OMA are **P0004, Scientific Publication Policy Related to MSB-Sponsored Research** and **QM23, Group Consulting Meetings.**

2 CQRC 048 Requirement 2: Affirmative Dissemination

2.1 Medtronic Spinal has written procedures in place that address affirmative dissemination of peer-reviewed articles and references texts on unapproved uses, as required by **CQRC 048.** The policy covering Affirmative Dissemination is **P0007, Dissemination of Information on Unapproved Uses of Approved_Cleared Products and Therapies.**

3 CQRC 048 Requirement 3: Unsolicited Requests

3.1 Medtronic Spinal has written procedures in place that define a process for responding to unsolicited requests for articles or other materials on unapproved uses, as required by **CQRC 048.** The business unit policy governing response to unsolicited requests is **P0007, Dissemination of Information on Unapproved Uses of Approved_Cleared Products and Therapies.**

4 CQRC 048 Requirement 4: Medtronic Spinal Supported Third Party Medical Education

4.1 Medtronic Spinal has established procedures regarding Medtronic-sponsored third-party medical education, as required by **CQRC 048.** The procedures are **CMP001009, Healthcare Education Grants to Support Third Party Conferences** and **CMP001110, Third Party Qualifying Conference Sponsorships Committee Charter.**

5 CQRC 048 Requirement 5: Medtronic-Implemented Training and Education on Medtronic Products

5.1 Medtronic Spinal has established polices/procedures regarding Medtronic-Implemented Training and Education on Medtronic Products, as required by **CQRC 048.** The following polices/procedures address this requirement: **CMP001093, Medical Education Professional Education Unapproved Use Policy, CMP001094, Visiting Surgeon Program Unapproved Use Policy** and **MC007, Sales Rep Education Surgeon Shadowing Program-Ortho Trauma.**

6 CQRC 048 Requirement 6: Research and Publication Strategies

6.1 Medtronic Spinal has established policies/procedures which explicitly prohibit sales personnel involvement in the determination of funding allocation for research and publication by non-Medtronic personnel or entities on unapproved uses, including physician-sponsored studies, consistent with the requirements of Business Conduct Standard 3 and 6. Such policies/procedures may permit sales personnel to be involved in this process only to the extent necessary to supply information about researcher qualifications or interest to decision makers. The following policies/procedures address this requirement of **CQRC 048: P0004, Scientific Publications Policy Related to Medtronic Spinal-Sponsored Research** and **CL050, Review and Approval for Clinical Data Publication.**

7 CQRC 048 Requirement 7: Physician Advisory Boards, Consultant Meetings, Roundtables, or Discussions

7.1 Medtronic Spinal has written policies/procedures in place prohibiting the use of physician advisory boards, consultant meetings, roundtables, or discussion groups to promote unapproved uses. This requirement is covered in **QM23, Group Consulting Meetings.**

8 CQRC 048 Requirement 8: Notices of Availability

8.1 Medtronic Spinal has established policies/procedures stating that NOAs may not be used as vehicles for promotion of a product for unapproved uses, but may be used if there is a bona fide need for recruitment of additional clinical investigators or subjects for an open study. This requirement is covered in **P0004.**

9 CQRC 048 Requirement 9: Training

9.1 All Medtronic Spinal 048 implementing policies/procedures are to be communicated via notification email and/or a read and acknowledge system to individuals whose job functions require knowledge of these documents. The requirements for determining the individuals required to be trained on the policies/procedures are found in the Quality System training matrices (http://sitebuilder2/spinalbiologics/OSD/default.aspx) and/or the Medtronic Spinal Corporate Integrity Agreement found on the Compliance MySpineTools site (http://www.myspinetools.com/compliance/). The Corporate Integrity Agreement (CIA) requirements for CIA policy

and procedure communication and training are located in the Written Standards and Training and Education sections of the CIA found on pages 8 and 9.

10 Additional Medtronic Spinal Policies/Procedures Addressing Prohibition of Off-Label Promotion in Relevant Subject Areas

10.1 **QM21, Promotional Materials Policy**—Defines what constitutes promotional material; contains off-label controls for creating/distributing promotional materials.

10.2 **PL006, Control Process for Promotional Materials**—Defines the routing and approval process for promotional materials.

10.3 **P0005, Sales Reps in the Operating Room**—Defines the standards and controls related to the interaction of field representatives for the Medtronic Spinal business with healthcare professionals in the operating room (OR) setting for purposes of providing technical support for Medtronic Spinal products during surgery.

10.4 **P0006, Sales Operating Policy**—Defines what members of the sales force may do when promoting Medtronic Spinal products in an on-label manner.

10.5 **P0009, Museums Program Policy**—Defines the standards and controls related to the interaction of representatives for the Museum of Modern Spinal Surgery (Museum) at Medtronic Spinal with customers participating in promotional and/or consultative programs (Experiences).

DEFINITIONS

OMA
Office of Medical Affairs

NOA
Notice of Availability

REFERENCES

CL050, Review and Approval for Clinical Data Publication 3
CMP001009, Healthcare Education Grants to Support Third Party Conferences 3
CMP001093, Medical Education Professional Education Unapproved Use Policy 3
CMP001094, Visiting Surgeon Program Unapproved Use Policy 3
CMP001110, Third Party Qualifying Conference Sponsorships Committee Charter 3
CQRC 048, Unapproved Uses of Approved Products 1, 2
MC007, Sales Rep Education Surgeon Shadowing Program-Ortho Trauma 3
PL006, Control Process for Promotional Materials 4
P0004, Scientific Publications Policy Related to Medtronic Spinal-Sponsored Research 3
P0005, Sales Reps in the Operating Room 4
P0006, Sales Operating Policy 4
P0007, Dissemination of Information on Unapproved Uses of Approved_Cleared Products and Therapies 2, 3
P0009, Museums Program Policy 4
QM21, Promotional Materials Policy 4
QM23, Group Consulting Meetings 2, 3

Medtronic Spinal Implementation of CQRC 048, Unapproved Uses of Approved Products

REVISION HISTORY

Version	Originator	Description of Change	Date
A	Stephanie Cavender	Initial Release.	23 Aug 2011

Medtronic

Global Policy

Interactions with Health Care Professionals - General Parameters for Medtronic Spinal Product Discussions.

Document ID: P0017 Version: A

Effective Date: 11 Oct. 2011 Owner: Brad Cannon

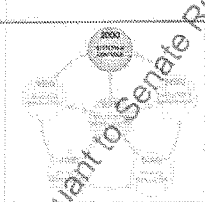


TABLE OF CONTENTS

PURPOSE 2

SCOPE 2

INTRODUCTION 2

POLICY 3

1 Interactions with HCPs in a Promotional Context 3

2 Interactions with HCPs in a Non-Promotional Context 4

3 Compliance 5

DEFINITIONS 5

REFERENCES 5

REVISION HISTORY 6

Medtronic

Global Policy
Document ID: P0017
Version: A
Effective Date: 11 Oct. 2011

Interactions with Health Care Professionals - General Parameters for Medtronic Spinal Product Discussions.

PURPOSE

The purpose of this document is to establish a policy that defines the general standards and controls relating to Medtronic Spinal employees in their interactions with external health care professionals (HCPs) with respect to discussions about the risks, benefits, performance, outcomes or specifications of a Medtronic Spinal product or technology (hereinafter referred to as "product"). More particularly, the objective of this policy is to aid such Medtronic Spinal employees in distinguishing "promotional" from "non-promotional" activities and behaviors and to provide general parameters for conduct occurring in each setting.

This policy is not intended as a description of legal or regulatory requirements.

SCOPE

This document is designated for use at the following business locations:

- MDT Spinal and Biologics Deggendorf Manufacturing
- MDT Spinal and Biologics Humacao Manufacturing
- MDT Spinal and Biologics Memphis Headquarters
- MDT Spinal and Biologics Memphis Manufacturing
- MDT Spinal and Biologics Warsaw Manufacturing
- Spinal Graft Technologies

The information in this document applies to all U.S. Medtronic Spinal employees interacting directly with external HCP customers with respect to their discussions about the risks, benefits, performance, outcomes or specifications of a Medtronic Spinal product or technology. Such employees would include, but are not limited to, sales representatives, other field representatives, marketing representatives, research and development employees, clinical and other technical specialists.

This policy does not apply to customer interactions that do not involve discussions about Medtronic products or technologies, such as discussions regarding the terms of a contract. Reimbursement discussions and conduct are also excluded from the scope of this policy as they are governed by more particularized policies and procedures relating to such activities and customer interactions. Conduct of the Office of Medical Affairs is governed by this policy, but is more specifically governed by other departmental policies and procedures.

INTRODUCTION

Consistent with the business unit's **QM21, Promotional Materials Policy**, "promotion" is defined in the following manner: "The act of furthering the growth or development of product; especially furtherance of the acceptance and sale of it through advertising publicity or discounting. A representation of the risks, benefits, performance, outcomes or specifications of a product. Promotion can be oral or written, and can occur at seminars, trade shows or during field contacts, including in-house visits or other similar settings."

Non-promotional interactions involving product - or technology - specific discussions may include references to product - or technology - specific data, outcomes, potential risks/benefits, specifications and/or other Clinical, scientific or technical aspects of the product/technology; however, such discussions should not be conducted for the purpose of furthering the acceptance and sales of merchandise. Rather, the purpose of engaging in such discussion must involve legitimate business or products, or other legitimate, documented needs for such discussion outside of the context of selling or seeking to sell, Medtronic Spinal products. Often, these discussions will occur in the context of consulting arrangements where consulting services are engaged to address documented, bona fide business needs related to product research and development, or in peer-to-peer interactions with a member of the Office of Medical Affairs (OMA).

Interactions with Health Care Professionals - General Parameters for Medtronic Spinal Product Discussions.

Examples of contexts generally deemed promotional for purposes of this policy include:

- Sales representatives detailing Medtronic Spinal products at physician offices or hospitals.
- Promotional inFOCUS meetings organized through the Museum of Modern Spinal Surgery.
- Medtronic-sponsored product exhibit booths at industry conferences.
- Medtronic-sponsored education and training events coordinated through the Medical Education group.

Examples of contexts generally deemed non-promotional for purposes of this policy include:

- The discussion and management of clinical trial activities.
- Product development discussions related to researching, engineering, and further developing an unapproved product or unapproved uses of an FDA-approved/cleared product.
- Market development discussions and research related to the understanding of future products, uses, and medical needs of targeted patient populations.
- HCP Advisory Boards conducted in accordance with QM23, Advisory Board Policy.
- HCP advice provided in the context of regulatory submissions.

POLICY

1 Interactions with HCPs in a Promotional Context

1.1 Medtronic Spinal employees who primarily engage in non-promotional activities, (e.g., OMA, Clinical, R&D, Regulatory, Compliance), should not engage in promotional discussions with HCPs.

1.1.1 Such employees may present on or discuss scientific, clinical, or technical data at promotional events, but only: (1) on an occasional basis, and not as a regular practice; (2) if the information presented is relevant to the purpose of the event; and (3) the employee is uniquely knowledgeable about the information.

1.1.2 If an OMA employee engages in a presentation or affirmative discussion at a promotional event in accordance with the content listed in the INTRODUCTION, that same employee may not respond to any unsolicited requests related to unapproved uses of approved Medtronic products raised in the context of that presentation or discussion.

1.2 Medtronic Spinal employees must not promote any products not approved or cleared by FDA.

1.3 For approved or cleared Medtronic products, Medtronic Spinal employees must know the approved indications, contraindications, warnings, and risks for all products for which they engage in promotional discussions with HCPs.

1.4 Medtronic Spinal employees must not solicit, promote, or recommend a Medtronic product for an unapproved use.

1.5 If an HCP asks an unsolicited question regarding an unapproved use of an approved Medtronic product during the course of a promotional discussion, Medtronic Spinal employees must:

- Acknowledge the question relates to an unapproved use; and
- Instruct the HCP to contact the OMA to obtain further information regarding the unapproved use.

1.6 Only promotional materials reviewed and approved through the Promotional Materials Review Process (Refer to PL006, Control Process for Promotional Material) may be used for promotional purposes. This includes promotional materials in printed or electronic format (e.g. PDFs, electronic files, internet sites). Promotional

materials include, but are not limited to, items such as product brochures, advertisements, promotional product presentations, articles, and abstracts to be distributed by the Sales or Marketing departments.

2 Interactions with HCPs in a Non-Promotional Context

2.1 Medtronic Spinal employees who primarily engage in promotional activities consistent with the definition of "promotion" in the business unit's **QM21, Promotional Materials Policy**, generally may not participate in non-promotional communications with HCPs unless prior documented specific approval is obtained from Compliance/Legal. All non-promotional interactions engaged in by such employees must occur within the scope of the approved Needs Assessment project brief. .

2.1.1 Sales employees may not engage in non-promotional discussions with HCPs outside of the Operating Room setting, with the limited exception of Sales Representatives occasionally providing additional support during Clinical Trial interactions with HCPs, as specifically designated and prior approved in writing by Clinical and Legal. Sales representatives' conduct in the Operating Room setting is governed by **P0005, Sales Reps in the Operating Room.**

2.1.2 Those Marketing representatives whose primary responsibilities involve the development and coordination of promotional materials and activities are subject to the requirement in Section 2.1. However, it is understood that Marketing personnel may speak with HCPs related to market and/or product development, in a non-promotional setting and when accounted for in a project brief reviewed and approved through the Needs Assessment process. Information and required documentation forms related to the Needs Assessment Process are located on www.MyMedtronic.com/OfficeofEthics&Compliance/Polices/MedtronicCorporatePolicyClearinghouse/BusinessConductStandards/NeedsAssessmentProcess

2.2 As with promotional discussions, non-promotional discussions may involve topics related to approved uses of approved Medtronic products.

2.3 In certain limited, controlled settings, non-promotional communications and activities may involve discussion of unapproved products or unapproved uses of approved Medtronic products; however, in such instances the following requirements apply:

- The discussion must involve legitimate "scientific exchange": peer-to-peer communication of clinical, scientific, and/or technical information.
- The information regarding unapproved products or uses in this context must be truthful, non-misleading, and fact-based.
- If the discussion relates to an unapproved use of an FDA-approved/cleared product, the FDA-approved/cleared indications must be clearly articulated.
- The discussion must be conducted in accordance with a prescribed, documented need for scientific exchange and, as appropriate, evaluated through the Needs Assessment Process.
- The participants in the discussion must represent appropriate functions (e.g., Clinical, Office of Medical Affairs, Research & Development, etc.) and be limited in number. Marketing representatives may be appropriate participants to the extent that their primary responsibilities involve the understanding and development of future product(s) and/or market(s).

2.4 Non-promotional discussions must never:

- Serve as pretext, or a guise, for furthering the acceptance and commercial sale of products for unapproved uses.

2.5 Use of Promotional Materials in a Non-Promotional Context

2.5.1 Promotional materials approved through the PMR process may be used in a non-promotional presentation or meeting for reference purposes only, i.e., if they contain factual information that is relevant to the purpose of the non-promotional program. Such materials may NOT be used for promotional purposes in this context.

2.5.2 Scientific materials may also be used for purposes of conducting the non-promotional meeting or program. Scientific materials may include, but are not limited to, items such as peer-reviewed journal articles, medical and scientific reference textbooks, clinical trial data, and/or agendas or presentations involving scientific, clinical, or technical information relevant to the specific business need identified and documented for the particular communication(s) or activity/activities.

2.5.2.1 Such materials do not require PMR approval prior to use; however, materials to be utilized during non-promotional meetings or programs that are related to an unapproved use of an FDA-approved/cleared product should be reviewed and approved by OMA and Legal in accordance with QM23, Advisory Board Policy and Corporate document, CQRC 048, Unapproved Use Policy.

2.5.2.2 These materials should be distributed only to the limited group of relevant participants.

2.5.2.3 Where applicable, these materials should be designated as "Confidential" and "Not for further distribution."

3 Compliance

3.1 Failure to follow provisions of this policy may result in disciplinary action, up to and including termination.

3.2 Compliance with this policy will be monitored periodically.

DEFINITIONS

Terminology abbreviations and acronyms are defined in the context of the document.

REFERENCES

CQRC 048, Unapproved Use Policy.....5
P0005, Sales Reps in the Operating Room.....4
QM21, Promotional Materials Policy.....2, 4
QM23. Advisory Board Policy.....3, 5

Medtronic

Global Policy
Document ID: P0017
Version: A
Effective Date: 11 Oct. 2011

Interactions with Health Care Professionals - General Parameters for Medtronic Spinal Product Discussions.

REVISION HISTORY

Version	Originator	Description of Change	Date
A	Stephanie Cavender	Initial Release	11 Oct. 2011

Corporate Quality, Regulatory, Clinical
POLICY
Title:: Policy on Standard Operating Procedures for Clinical Programs

SCOPE
Medtronic clinical groups, worldwide, that conduct clinical studies to evaluate products or indications not yet approved for commercialization or are required for regulatory purposes.

PURPOSE
The purpose of this policy is to establish requirements for a set of standard operating procedures to be developed and used by clinical groups conducting human studies for regulatory purposes.

POLICY
Clinical groups will establish and maintain written operating procedures that govern the conduct of human clinical studies used for regulatory purposes.

REFERENCE DOCUMENTS
CCRA-008 Policy on Review and Conduct of Clinical Studies
Consult laws and regulations of the countries where studies will be conducted.

DEFINITIONS AND ABBREVIATIONS
Clinical Investigational Plan (CIP) or Investigational Plan (IP) – The document(s) that encompass the components of the study and applicable regulatory requirements.
Protocol – A subsection of the IP that describes the objectives, design, methodology, statistical considerations and conduct of the studies.
SOP – Standard Operating Procedures
MDR – Medical Device Reporting

REQUIREMENTS
1. Clinical groups will establish and maintain written standard operating procedures (SOPs) for conducting studies defined in the scope of this policy. The appendices of this document provide a list of required SOP topics and required elements to be addressed in the SOPs. If the clinical group follows one or more SOP(s) authored by another functional area within the business, the adherence to the SOP must be documented.

2. SOPs will be formatted according to the style used by the business. The organization, title and specific content may vary from how they are described in this policy. However, all of the required topics and elements must be addressed in SOPs.

3. Clinical groups may develop additional SOPs and requirements beyond those listed in this policy.

4. Clinical management will ensure training of clinical personnel to their department SOPs as appropriate to their job function. Training must be documented.

5. Clinical groups will review SOPs at least every two years and update as needed.

RESPONSIBILITY:

The management for each Medtronic business is responsible for implementing, training, and complying with this policy.

CHANGE HISTORY		
REVISION	**DATE**	**DESCRIPTION OF CHANGE**
A	2/06/2003	Initial Release

Owner: Lisa Griffin Vincent
Department: Corporate Clinical

APPENDIX A – REQUIRED SOP TOPICS

Appendix	TOPIC
B	SOP Development and Revision
C	Clinical Project/Management Plan
D	Investigational Plan
E	Investigator/Site Selection
F	Site Initiation
G	Sponsor Files
H	Site Monitoring
I	Statistical Aspects of Study Development
J	Study Report Generation for Regulatory Agencies
K	Data Handling/Management
L	Data Management System
M	Study Deviation Management
N	Adverse Event Management
O	Training of Site Personnel
P	Investigator and Subject Compensation
Q	Investigational Product Accountability
R	Study Closure
S	Training of Medtronic Personnel
T	Document Control

RECOMMENDED SOP Topics: The following topics are recommended, but not required, if a clinical group engages in these activities.	
U	Preparing for Inspections by External Agencies
V	Outsourcing Activities
W	Emergency and Compassionate Use
X	Physician Advisory Committees (e.g., Data Monitoring Committee, Adverse Event Committee)
Y	Publication Policy

NOTE:

Sources – The documents cited in the appendices were used to develop the "Required Elements" and are listed only for informational purposes to assist clinical groups in developing department SOPs.

Required Documents – These documents are created as a result of following the respective SOP and are expected to be included in the department SOPs.

Required Elements – These processes or requirements are expected to be addressed in department SOPs.

Suggested Tools and Templates – These materials are provided as recommendations but are not required by clinical groups unless listed under Required Documents.

APPENDIX B

Topic: SOP Development and Revision	
Purpose: To describe the process for developing, reviewing, approving, revising and documenting deviations to SOPs.	
Sources: CQRA-015 Document Control System CQRA-020 Personnel Training Policy CQRA-028 Quality Records Policy CCRA-037 Policy on Control of Clinical Documentation	
Required Documents: Standard Operating Procedures; SOP Template	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Development process • SOP template • Version control system used	SOP template specific for the business
2. Revision process • Periodic review and update • Change control • Obsolescence	
3. Review, Approval, and Distribution • Internal review • Approval process • Effective date • Document control process • Distribution requirements	
4. Training Describe the process for determining the need for training on the new SOP and how training will be completed and documented.	Staff training matrix
5. Deviation from a SOP Describe documentation requirements for planned/unplanned deviations to SOPs: • Description of deviation • Reason or justification for deviation • Documentation requirements for prior approval	Template for reporting deviations to SOPs

APPENDIX C

Topic: Clinical Project/Management Plan	
Purpose: To describe the process for developing, reviewing and approving Clinical Project Plan.	
Sources: CFR 820.30(b) Design and Development Planning	
Required Documents: Clinical Project/Management Plan	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Development Process Describe the process to develop a Clinical Project/Management Plan. Address the following elements: • Clinical strategy and scope of study: - Purpose, duration, size and geographic location - Product description, indications for use - Medtronic and regulatory strategy and commercial release requirements by geography - Required reports • Projects risks • Study schedule • Budget & resource requirements • Training requirements for the study • Regulatory requirements for use of commercially approved products in a clinical study, including determination of investigational status, labeling, adverse event/MDR and complaint reporting Specify the point in time when the clinical project plan is required (e.g., specific phase of the product development cycle, prior to study start etc.).	Plan template Budget and Resource Plan template Study Schedule template
2. Review and approval Review and approval process for the Clinical Project Plan	Approval template
3. Revision process Requirements for updating the Clinical Project Plan	Version Control template

APPENDIX D

Topic: Investigational Plan	
Purpose: To describe the process for developing, reviewing, approving and amending an Investigational Plan.	
Sources: 21CFR 812.25 Investigational Plan; 21CFR 812.27 Report of Prior Investigations 21CFR 50 Protection of Human Subjects; 21CFR 54 Financial Disclosure 21CFR 812.43 Selecting Investigators and Monitors CCRA-008-G02 Guidance on Safety Endpoint Determination for Final Validation Clinical Studies CCRA-008-P01 Procedure on Clinical Studies Monitoring CCRA-025 Managing Clinical Study Deviations (Investigational Sites) CCRA-037 Policy on Control of Clinical Documentation CCRA-037-G01 Guideline on Example Templates for Control of Clinical Documentation CCRA-031-G01 Guideline on Investigational Plan Development and Review CCRA-036 Policy for Investigational Device/Product Accountability CCRA-036 G01 Guideline on Investigational Device/Product Accountability	
Required Documents: Investigational Plan	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Development of the Investigational Plan Specify the requirements and process for developing an IP. Include the following: • Purpose of the study • Protocol (methodology and scientific soundness) • Procedures for study conduct • Statistical Methods and Analysis • Product description, include identification of investigational and commercially-released components • Device accountability requirements • Risk analysis • Deviations • Study monitoring • Labeling • Informed consent template • IRB/EC information • Other institutions where a part of the investigation will be conducted (e.g., core laboratories, data monitoring committee) • Required records and reports (investigator and sponsor) • Report of Prior Investigations (device studies) • Investigator Brochure (drug or device studies) • Sample case report forms	IP Checklist or template (see CCRA-031-G01) Standardized definitions Consent checklist CRF templates / guidelines Report of Prior Investigations template Investigator Brochure template Investigator Agreement template (see Legal) Financial Disclosure template (see Legal)

• Confidentiality agreement, if used by study • Research/investigator Agreement • Financial Disclosure • Release/authorization of medical information, if not included in an informed consent document.	
2. Review and Approval Process Specify who will review and approve the IP and how approval documented. Address the following: • Required elements of IP checklist • Scientific soundness • Statistical aspects • Protection of human subjects • Specific geographic laws and regulations • Compliance to Medtronic policies and department SOPs • Elimination of unnecessary protocol requirements and data collection • Consistency of requirements between components • Version control	Approval Record template
3. Revision Process Process for updating the IP, including: • Review and approval of amendments (internal and external groups). • Identification of other documents affected as a result of the change.	Version Control template Change History Record template
4. Distribution and Maintenance Requirements for • Assessment of training needs • Distribution of approved documents • Records maintenance for master copies (original and revisions)	Investigator and IRB/EC letter templates for amendments

APPENDIX E

Topic: Investigator/Site Selection	
Purpose: To describe the process for identifying and selecting qualified investigators and sites.	
Sources: 21CFR 812.43(a) Selecting Investigators and Monitors	
Required Documents: Site nomination/profile form Approved list of potential investigators	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Study Criteria Require establishment of criteria that investigators/sites must meet in order to be selected for a study.	
2. Site Nomination/Identification Process to identify potential investigators/sites. Describe how information is to be collected and documented.	Site Nomination or Profile Form template with study criteria
3. Confidentiality Agreements Determine the need for confidentiality agreements.	Confidentiality Agreement template (pre-approved by Legal)
4. FDA Sanctions (US Investigators only) Verify that nominated/identified investigators are not on the FDA list of investigators who have been disqualified, restricted or debarred from conducting clinical studies. See FDA websites.	
5. Site Selection Process for reviewing and deciding who will participate in the study.	
6. Investigator List Documentation and maintenance of Investigator list.	Approved list of potential investigators

APPENDIX F

Topic: Site Initiation	
Purpose:	To describe the process for activating an investigational site.
Sources:	21CFR 812.40 General Responsibilities of Sponsors 21CFR 812.42 FDA and IRB Approval 21CFR 812.43(c) Selecting Investigators and Monitors – Obtaining Agreements 21CFR 812.140 Records
Required Documents:	Site activation record with required documentation Regulatory approval in the country where study is to be conducted
Required SOP Elements	**Suggested Tools/Templates**
1. Describe the process for developing, collecting and tracking required site activation documents • Clinical study agreement • Compensation agreement, if separate from study agreement • Confidentiality agreement, if required by business • Financial disclosure for investigators, if required by regulations • IRB/EC approval • IRB/EC/MDT approved informed consent • IRB/EC chairman (IDE sites only) • IRB/EC roster or letter of compliance (optional) • Investigator curriculum vitae • Investigator delegation or task authorization form (recommended, but optional for device studies) • Site training documentation • Regulatory agency approval	Site tracking system and site activation checklist Template for investigator delegation or task authorization form
2. Study Material Define required study materials to be provided to each site.	

APPENDIX G

Topic: Sponsor Files	
Purpose: To describe the requirements for sponsor files.	
Sources: 21CFR 812.140b Sponsor Records 21CFR 812.140d Retention Period 21CFR 812.140e Records Custody CQRA-028 Quality Records Policy	
Required Documents: None	
Required SOP Elements:	**Suggested Tools/Templates:**
1. File Requirements Documents required by regulation, business, and corporate policies and procedures must be maintained. Describe requirements for file contents and organization, such as: • Clinical Project File • Inv estigator records • Subject data records • Monitoring records • Compensation records	Checklist of required contents
2. Filing Procedures Describe requirements for maintaining and filing study documents in the sponsor files. Include the following: • Person or job title responsible for filing study documents • Location to be utilized for filing documents • Procedure for maintaining files (electronic and/or paper documents) • Process for ensuring subject confidentiality	
3. Record Retention Describe the process for archiving sponsor files at study closure. Include: • Retention period & records custody	

APPENDIX H

Topic: Site Monitoring	
Purpose:	To describe the process for defining, documenting and implementing site monitoring activities for clinical studies.
Sources:	21CFR 812.46 Monitoring Investigations 21CFR 812.140(a) Investigator Records CCRA-008-P01 Procedure For Clinical Studies Monitoring CCRA-008-G01 Guidance on Implementing a Monitoring Program CAPA Process
Required Documents:	Monitoring Plan or written procedures if different from SOP Documentation of training/qualification of monitors Monitoring report Monitoring visit log

Required SOP Elements:	**Suggested Tools/Templates:**
1. Monitoring plan or written procedure Describe the requirements for developing a monitoring plan. The monitoring plan will include: • Who will perform monitoring and required qualifications • Criteria for determining the timing and frequency of visits • Regulatory and study management documents to be reviewed • Amount of subject data to be monitored • CRF data requiring source document verification • Define tools used for monitoring (e.g., checklists, logs, reports, communications) • Outsourcing, if used Note: Monitoring Plans or other written procedures are required when there are significant study specific details that cannot be described in a SOP.	Monitoring Plan template
2. Monitor Qualification Address documenting qualifications of monitors Identify required skills and training	

3. Monitoring Procedure Describe the following processes: • Notifying the study site prior to visit • Conducting the monitoring visit • Review of regulatory and study management documents • Data elements requiring source document verification • Documenting the monitoring visit • Notifying investigators and site personnel of observations • Documenting protocol deviations • Internal review and sign-off of monitoring reports • A "closed-loop" system to verify that issues identified during monitoring are addressed and closed	Monitoring Report template Monitoring Visit Log template Letter templates
4. Periodic Review Address requirements for documented periodic reviews of monitor findings. Include: • Trend analysis on action items associated with the monitoring reports • Management review of corrective and preventive (CAPA) items	Review templates

APPENDIX I

Topic: Statistical Aspects of Study Development	
Purpose:	To describe the elements of the statistical section of a protocol, the process for validating computer programs used for statistical analyses and the process for generating randomization schedules.
Sources:	21CFR 812.25(b) Protocol Methodology and Scientific Soundness 21CFR 11.10(a) Validation of systems CCRA-031-G01 Guideline on Investigational Plan Development and Review CCRA-008-G02 Guidance on Safety Endpoint Determination for Final Validation Clinical Studies
Required Documents:	Statistical Section of Protocol Statistical Program Validation Report Randomization Schedules
Required SOP Elements:	**Suggested Tools/Templates:**
1. Statistical Design and Analysis Address requirements for: • Identifying the statistical hypotheses to be tested and/or statistical parameters to be estimated • Sample size calculation • Statistical analysis • Identifying subjects for analysis • Presenting statistical results • Review and approval of the statistical methods • Revising the statistical methods	Statistical analysis checklist (See also IP checklist)
2. Validation of Statistical Programs Address requirements for: • Validating a statistical program • Ensuring the integrity and protection of the program • Reviewing, approving and revising the program	Validation Plan
3. Randomization Address requirements for: • Generating randomization assignments • Deploying the randomization assignments • Protecting the randomization assignments • Tracking compliance to the randomization assignments • Unblinding a randomization assignment in case of an emergency	Validated statistical program

APPENDIX J

Topic: Study Report Generation for Regulatory Agencies	
Purpose: To define the process for developing, reviewing, approving and revising study reports.	
Sources: 21CFR 812.36(f) Treatment Use of an Investigational Device 21CFR 812.150 Reports 21CFR 814.84 Reports	
Required Documents: Documentation of Report Approval	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Report Development Process Identify type of report and required elements (e.g., progress, PMA(s), final, or post-approval reports).	Report templates with required elements
2. Report dataset Define the requirements for creating report dataset, include: • Schedule • Database cut-off • Discrepancies resolution • Freeze/store dataset • Statistical analysis • Other requirements based on department process	
3. Report Approval Address requirements for: • Review and approval of reports (identify reviewers/approvers by functional roles) • Approval documentation requirements	Report approval template
4. Report Distribution Identify requirements for internal and external distribution.	
5. Report Revisions Define process for managing report revisions subsequent to initial distribution.	

APPENDIX K

Topic: Data Handling/Management	
Purpose: To describe the process to be followed for managing study data.	
Sources: 21CFR 50.25 (a)(5) Elements of Informed Consent 45CFR 160 and 164 ("HIPAA Final Rule ")	
Required Documents: None	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Requirements Address the following: • Process for maintaining confidentiality of information about each subject • Process to allow changes to CRF data to be made only by authorized personnel, initialed and dated, and the original entry retained for comparison • Describe how data is collected, processed and maintained in-house • Process for identifying and resolving missing or questionable data • Procedures for database management, data archiving, and retention period (see Appendix L)	Template for data clarification forms
2. Data Management Plan (DMP) - Optional If a separate data management plan is used, require the following: • Development of the plan • Required content • Internal review and approval • Revising or updating the DMP • Distribution (e.g., identify by functional role)	

APPENDIX L

Topic: Data Management System	
Purpose:	To describe the process of developing, validating and maintaining a clinical data management system (DMS).
Sources:	21CFR 11 Electronic Records and Electronic Signatures MIT-001 System Development and Validation Life Cycle Policy (SVDLC) Guidance for Industry, Computerized Systems Used in Clinical Trials, April 1999; US Food And Drug Administration
Required Documents:	Data Management System Requirements Document Validation Plan and Test Report Change Control Management Records
Required SOP Elements:	**Suggested Tools/Templates:**
1. Study Requirements Process for establishing database specifications and developing a Data Management System (DMS) Requirements Document that includes the following elements: • Data points to be captured, e.g., data point on the CRF, data points captured by the device, data points maintained by the core lab • Data validation checks, e.g., required fields, range checks, intra/inter CRF checks • Data extract requirements, e.g., requirements for the statisticians such as SAS variable names, etc.	DMS requirements document template
2. DMS Development Address development of the DMS application, including: • Selection of hardware and software requirements • Construction of the DMS application for a new study • Validation plan, testing and approval (e.g., peer review, and user acceptance) • Required documentation • Release for production use	Software specific work instructions Template for validation plan and report
3. Training Address the need for training the study team and end users and how training is be documented.	
4. Report Generation Process for developing and validating reports derived from the database for study management.	
5. System Maintenance Describe procedures to be followed for system maintenance. Include: • Periodic back-up • Security measures • Change control procedures • Disaster contingency plan	

APPENDIX M

Topic: Study Deviation Management	
Purpose:	To describe the process for defining, documenting, reviewing, reporting and maintaining records of study deviations that occur at investigational sites.
Sources:	CCRA-025 Managing Clinical Study Deviations (Investigational Sites) CCRA-008-G01 Guidance on Implementing a Monitoring Program CAPA Process 21CFR 812.150(a)(4) Deviations From the Investigational Plan 21CFR 812.46 (a) Securing Compliance
Required Documents:	Deviation Report Form (may be part of a CRF or separate form)
Required SOP Elements:	**Suggested Tools/Templates:**
1. Definition Provide the definition of a study deviation and examples of typical study deviations. Define any classification system used by the clinical group.	See CCRA-025
2. Records Describe how information on deviations will be collected and recorded. Include: • Required information • Investigator review and acknowledgement • Data management system (e.g., forms, database)	Deviation Report Form Template (may be part of a CRF or a separate document)
3. Internal Review Describe the process for internal review of deviation: • Upon discovery • Follow-up and resolution (CAPA) • Management review – trending and analysis	
4. Reporting Define the process for external reporting of deviations to regulatory agencies, investigator sites, and IRB/EC required by geographic regulations. Require periodic site-specific reports summarizing deviations to be provided to investigators.	
5. Prior Approval Describe the process for obtaining and documenting clinical study management approval prior to the investigator initiating changes in or deviations from the investigational plan or protocol.	Deviation "prior approval form" template
6. Securing Compliance Describe the process to secure compliance or suspend/terminate the investigator if not compliant.	

APPENDIX N

Topic: Adverse Event Management	
Purpose: To describe the process for identifying, defining, classifying, reviewing, and reporting adverse events (AE) during a clinical study.	
Sources: 21CFR 812.3(s) Unanticipated Adverse Device Effects 21CFR 812.150 (a)(1), (b)(1) Reports	
Required Documents: Adverse Event Reporting Form (e.g., CRF)	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Identifying and defining adverse events Define key types of events and classification systems, if used. For instance: • Anticipated adverse event • Unanticipated adverse device effect (UADE) • Device-related adverse event	Matrix of reporting requirements by geography Standardized definitions and classifications based on therapeutic area
2. Investigator Reporting Address information to be provided in study materials (e.g., protocol, CRFs). Include the following: • List of anticipated AEs • Types AEs requiring reporting (e.g., every adverse event vs. a subset of product or study-related events) • Methods to report AEs • Obligations for reporting events (e.g., IRB/EC, sponsor, regulatory authority) • Information required by sponsor (E.g., event description, date of onset, severity or AE classification, outcome or resolution status) • Time frame for investigator reporting	Template for standard protocol language
3. Adverse Event Review Describe the internal review process for: • Ev ent classification • Who is responsible for reviewing (monitor, study team, regulatory) • Time frames for review • Documentation requirements • Trend -analysis to allow prompt knowledge of potential safety issues Describe the external review process, if used (e.g., adverse event committee, data monitoring committee)	Flowchart for AE reporting Guidelines for a Data Safety Committee or Adverse Events Committee
4. Unanticipated Adverse Device Effects Describe specific procedures for reviewing and reporting unanticipated adverse device effects	
5. External Reporting Define requirements for: • Expedited and routine reporting to regulatory agencies • Reporting to IRB/EC and investigators	

Note: Consult laws and regulations of the countries where studies are to be conducted for geography-specific requirements.

APPENDIX O

Topic: Training of Site Personnel	
Purpose: To describe the process for developing, implementing and documenting study-specific training of site personnel involved in clinical studies.	
Sources: 21CFR 812.43(a) Selecting Investigators 21CFR 812.45 Informing Investigators	
Required Documents: Training Documentation Form	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Developing Training Requirements Address the following elements: • Topics and materials to be covered • Study-specific training needs (e.g., protocol, product) • Personnel to be trained based on responsibility in the study • Methods of training (i.e., investigator/coordinator meeting, conference call, on-site) • Timing and frequency of training • Identification of trainers by functional role	
2. Required Training Components Training materials will include the following: • Technical overview of product(s) • Protocol overview • Study procedures • Managing investigational product disposition • Investigational device/product accountability procedures • Procedures for returning unused/explanted product(s) • CRF completion and management • Investigator's responsibilities • Sponsor's responsibilities • Procedures for obtaining informed consent • IRB/EC role • Procedures for adverse event reporting • Procedures for study deviation reporting • Monitoring requirements and expectations • Potential for regulatory inspection • Site record maintenance and retention • Reimbursement information (based on geographic regulation) • Regulatory requirements for commercially approved products used in a clinical study, including adverse event and complaint	Training materials checklist

reporting • Other regulatory requirements not listed above such as geography-specific regulations.	
3. Documentation of Training Describe the process for documenting training. The following items must be included on training documentation form(s) used: • Study name or meeting title • Attendees name, signature and date of training • Name and signature of trainer(s) • General nature of training (e.g., protocol, product technology, regulations, etc.) • Maintain a copy of training materials	Training documentation form
4. On-going Study Training Process for identifying and training new site personnel when staff changes occur during a study.	

APPENDIX P

Topic: Investigator and Subject Compensation	
Purpose: To describe the process and requirements for issuing investigator and subject compensation.	
Sources: FDA Information Sheet "Payment to Research Subjects"	
Required Documents: Fully executed investigator compensation agreement Subject compensation information in consent document	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Investigator/Site Compensation Process for issuing investigator/site compensation. Include the following: • Fully executed investigator compensation agreement is available, included the amount and schedule of payments • General criteria for determining when payments are due • Internal payment authorization and check requests • Requirements for correspondence accompanying investigator compensation • Documentation required for record retention	Payment/Check Request Form Study compensation letter template
2. Subject Compensation Describe the process for payments to study subjects if applicable to a study. Include the following: • Process to determine if payment is appropriate for study • The amount and schedule of payments must be set forth in the informed consent document • Internal payment authorization and check requests • Requirements for correspondence accompanying subject compensation • Documentation required for record retention	Payment/Check Request Form Study compensation letter template

APPENDIX Q

Topic: Investigational Product Accountability	
Purpose: To establish the requirements for investigational product accountability and tracking.	
Sources: 21CFR 812.100 General Responsibilities of Investigators 21CFR 812.110 Specific Responsibilities of Investigators 21CFR 812.140 Records CCRA-036 Policy for Investigational Device/Product Accountability CCRA-036-G01 Guideline on Investigational Device/Product Accountability	
Required Documents: List of sites authorized to receive investigational product Investigational Product Disposition Log	
Required SOP Elements	**Suggested Tools/Templates**
1. Product storage at sponsor If investigational product is stored by clinical personnel, specify the procedures for secure storage and access by only authorized personnel.	
2. Authorizing shipment Define process for authorizing shipment to investigational sites, field and clinical personnel. Identify method to track on-going site status for receiving investigational product.	Checklist for shipment authorization Shipping request form template
3. Inventory tracking Define requirements for a product tracking system and traceability documentation. Include provisions for determining when commercially released product enters the clinical study and is considered to be investigational.	
4. Inventory management at investigational sites Describe how investigational product will be maintained and tracked at sites. Include the following: • Inventory storage requirements, security • Product disposition log • Documentation required for disposal of investigational product	Product disposition log
5. Returned Product Describe the process for return and receipt of investigational product by the sponsor.	Investigational product return form template
6. Inventory Reconciliation Describe the process for inventory reconciliation, including all investigational products shipped from finished goods, field and consignment inventory, and end/use disposition.	Template for reconciliation report

APPENDIX R

Topic: Study Closure	
Purpose: To describe the process to close a completed study or to prematurely suspend or terminate a clinical study at the site, at the sponsor, and with the regulatory agencies.	
Sources: 21CFR 812.150 Reports 21CFR 812.30 FDA Action on Applications CCRA-008-P01 Procedure for Clinical Studies Monitoring CQRA-028 Quality Records Policy	
Required Documents: Notification to regulatory agencies	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Types of study or site closure Define the types of study or site closure: • Completed Site/Study – When sponsor and/or regulatory requirements have been satisfied per the investigational plan and/or decision of the business • Suspended Site/Study – Temporarily postponement of study activities related to enrollment and distribution of the investigational product • Terminated Site/Study – Discontinuation by sponsor or by withdrawal of IRB/EC or FDA approval of an investigation before completion	
2. Completed Site/Study Describe the process for closing a completed study. Identify responsibilities, procedures, and required documentation to close the study at the site, at the Sponsor, and with regulatory agencies. Include: • Identify who is involved in the decision making process and required documentation (e.g., rationale, approvals) • Notification to regulatory agencies • Investigator notification requirements (e.g., study closure date, rationale for closure, discontinuation of data requirements, and disposition of products, record retention requirements, IRB/EC notification • See closure activities below	Checklist for investigator notification requirements
3. Suspended Site/Study Describe the process for suspending a clinical study or site: • Identify who is involved in the decision making process and required documentation (e.g., rationale, approvals) • Procedure to notify the sites, IRB/EC and regulatory agencies • Identify the process for reactivating or terminating the study or site • Address follow-up for existing patients	Checklist for investigator notification requirements

4. Terminated Site/Study Describe the process for prematurely stopping a clinical study or site: • Identify who is involved in the decision making process and required documentation (e.g., rationale, approvals) • Identify the procedure to notify the sites, IRB/EC • Require regulatory agency notification • Identify the closure activities at the site and at the sponsor that will be required (see below) • Address follow-up for existing patients	Checklist for investigator notification requirements
5. Site closure activities Define the activities to be performed at an investigational site during a study closure visit for a "completed" study and a "permanently terminated" study. Include the following: • Investigator/study files are complete and accurate • All CRFs, clarification and missing data received • Annual and interim reports (as required by regulation) are up to date • Deficiencies resolved or closed (e.g., administrative binder) • Investigational product accountability is complete • Equipment to be returned to sponsor • Record retention requirements agreed by investigator • Obligation for final reports to be submitted by investigators as required by regulations • Other activities defined by the sponsor or protocol	Checklist with study closure monitoring report
6. Sponsor closure activities Describe the process for study closure at the Sponsor. Include the following: • Project, subject, and site files are complete and accurate • Reconciliation of unused, used or explanted investigational-labeled products • Final compensation and contractual obligations • Complete the final report for submission to sites, IRB/EC and regulatory agencies • Record retention procedures • Process to track financial disclosure after study closure (as required by regulation)	Close-out checklist (sponsor) Template for final clinical report

APPENDIX S

Topic: Training of Medtronic Personnel	
Purpose: To describe the process for training and documenting training of Medtronic personnel involved in a clinical study.	
Sources: 21CFR 812.43 Selecting Monitors CQRA-020 Personnel Training Policy	
Required Documents: Training Plan, Training Record	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Definitions **Department Training File** – A central file for each Clinical Department containing training records, such as, department training attendance rosters and presentations. In the US, the files may also contain the individual employee training record, job description, and CV/resume. **Training Plan** – A document that outlines the specific training an employee needs and will receive in order to perform his/her job function. The Training Plan may be a separate document or part of the Individual Plan (IDP). **Training Record** – A record (hard copy or electronic) used to document training received.	
2. Training requirements – clinical personnel Identify training requirements and frequency based on functional role (include both employee and contractor).	Job/training matrix
3. New hire assessment Address requirements to assess new employee skills and needs.	Training plan template
4. Documentation Describe how training will be documented and how records will be maintained.	Training record template

APPENDIX T

Topic: Document Control	
Purpose: To describe the process for the approval, revision and maintenance of controlled clinical documents and records.	
Sources: CQRA 015 Document Control System CCRA 037 Policy on Control of Clinical Documentation CCRA-037-G01 Example Templates for Control of Clinical Documentation 21CFR 820.40 Document Controls, Quality System Regulation	
Required Documents: Approval Documentation Change History Documentation	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Draft Documents Identify document control procedures to create, review and edit new documents. Address requirements for draft. Identify system used to track routing of documents.	Routing Sheet template
2. Approval Process for document approval, including documentation, effective date, and initiation of change history records.	Approval Record template Change History Record template
3. Version Control Format Describe document requirements for version control (e.g., footer, pagination, etc).	
4. Document Maintenance and Retention Describe where the original master will be maintained in a secure location.	
5. Training Determine the need for training on the new or modified document and how this training will be completed and documented.	
6. Distribution Identify requirements for document distribution and traceability.	
7. Revisions Describe the process and requirements for initiating changes to approved documents: • Draft, review, and edit process • Updating the change history records • Document approval • Identification of affected documents • Document maintenance, retention, training, and distribution (see above) • Disposition of retired documents	Document Change Order template

APPENDIX U

Topic: Preparing for Inspections by External Agencies	
Purpose: To describe the process for preparing and managing inspections performed by external parties.	
Sources: CQRA-029 Regulatory Inspection Policy Corporate Directive: Dotted Line Relationship Between Corporate and Business/Geography Clinical Heads 21CFR 812.145 Inspections	
Required Documents: None	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Preparation for sponsor inspection. Include the following requirements: • Identify qualified individual(s) to serve as the clinical representative or clinical inspection coordinator • Identify who to contact when notice of an inspection is received. Include notification to business management and Corporate Regulatory Affairs and Compliance • Identify other team members to prepare and assist with the inspection • Describe the process to train personnel to be involved in inspections	Preparation checklist
2. During the sponsor inspection Describe requirements to be followed during the inspection, such as: • A list of documents and copies provided to the inspector(s) • Notes on each day's progress • Informing Corporate and business management on major non-compliance issues, unreasonable requests, prolonged delays, or other unusual development before or during the inspection	
3. Upon completion of the sponsors inspection • Identify who will be notified of the results of the inspections. Corporate review is mandatory. • Provision to forward Corporate the following documents: - Notice of Inspection (482) - Observations (483) - Draft and final responses to observations and exhibits or attachments - Establishment Inspection Report (EIR) - Warning or untitled letters and responses	
4. Investigator, IRB/EC inspections (study related) Describe the process to be followed for an intended inspection by a regulatory agency. Include the following: • Clinical and other sponsor personnel to be notified	Preparation checklist Standard training information

• Medtronic inspection contact • Site training • Investigator/site support during inspection, if requested • Reporting observations and response (see Item 3 above)	
5. CRO inspections (study related) Describe the process to be followed for an intended inspection by a regulatory agency. Include the following: • Clinical and other sponsor personnel to be notified • Medtronic inspection contact • CRO support during inspection • Reporting observations & response to sponsor (see item 3 above)	

APPENDIX V

Topic: Outsourcing Activities	
Purpose: To describe the process for selecting, managing, training and communicating with outsourcing vendors used for clinical studies.	
Sources: 21CFR 312.52 Transfer of Obligations to a Contract Resource Organization No specific regulation for outsourcing requirements in device studies	
Required Documents: Qualification/evaluation checklist Confidentiality agreement for proprietary information Fully executed contract or agreement Qualification, CVs or resumes of subcontractors and professional services	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Outsourcing Plan Define how decision will be made to pursue outsourcing activities.	
2. Confidentiality Agreement Require confidentiality agreement for proprietary information.	Template from legal
3. Qualification of Outsourcing Vendor Describe the process for identifying outsourcing candidates and the process for documenting the screening and qualification of each. Include a process for evaluating vendor SOPs to be used for the study. This review will be documented.	Evaluation checklist CVs or resumes of prospective candidates
4. Selection of Outsourcing Vendor Describe the process for reviewing outsourcing candidates and final selection.	
5. Contract/Project Agreement Describe the process for drafting and executing the contracts or agreements.	Example work order checklist or legal template
6. Training of Outsourcing Personnel Describe how outsourcing personnel will be trained and managed (may refer to clinical management plan/monitoring plan for study specific details).	Training logs
7. Evaluating Performance Describe requirements for evaluating the activities performed by the outsourcing vendor. Document the evaluation.	
8. Corrective and Preventive Action Describe a process for communicating and documenting issues and corrective actions.	

APPENDIX W

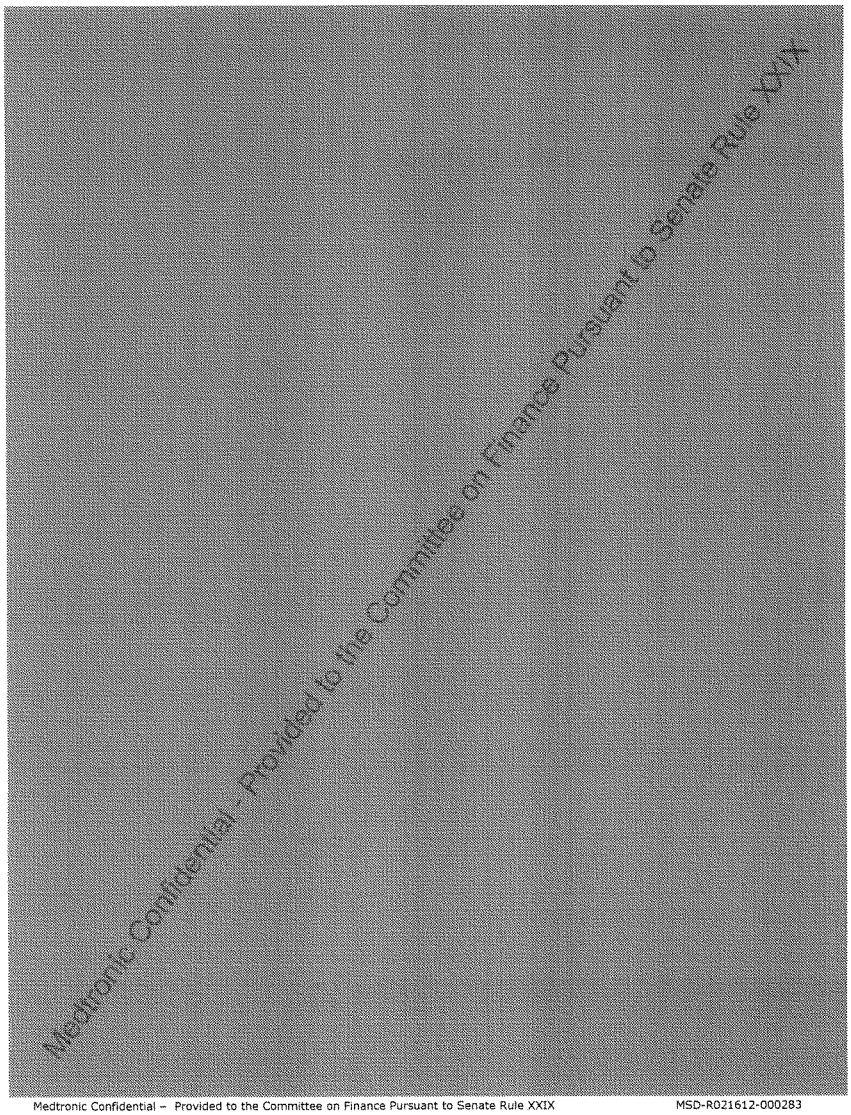
Topic: Emergency and Compassionate Use	
Purpose: To describe the procedures to be followed for emergency and compassionate use of an investigational device (US regulations).	
Sources: 21CFR 812.35(a) Supplemental applications FDA Guidance on IDE Policies and Procedures (January 20, 1998), Chapter III - Expanded Access to Unapproved Devices, Emergency Use of Unapproved Medical Devices	
Required Documents: None	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Definitions: Emergency Use -- Use of an investigational device in a patient that has a life-threatening condition that needs immediate treatment and: (a) no generally acceptable alternative treatment for the condition exists and (b) because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use. **Compassionate Use** -- Use of an investigational device in a patient with a serious, but not life threatening condition.	
2. Emergency Use Describe the requirements and process relating to: • Required documentation from physician and hospital/institution • Sponsor and regulatory review and pre-approval when possible (e.g., investigational product release) • Communicating physician obligations after emergency use • Consideration for including a site or a patient in the clinical study, the extent to which the protocol will be followed and how patient data will be reported • Documenting relevant physician/site training • Notifying FDA of the emergency use • Internal review of patient data and status	Emergency Use requirements checklist Emergency Use consent template
3. Compassionate Use Describe the requirements and process relating to: • Required documentation from physician and hospital/institution • Sponsor review and pre-approval • FDA pre-approval on a case-by-case basis or implementation of a compassionate use protocol • Communicating physician obligations after compassionate use • Consideration for including the site or patient in the clinical study, the extent to which the protocol will be followed and how patient data will be reported • Documenting relevant physician/site training • Internal review of patient data and status	Compassionate Use requirements checklist Compassionate Use consent template

APPENDIX X

Topic: Physician Advisory Committees	
Purpose: To describe the process for identifying and selecting members for physician committees used for activities such as adverse event review, data monitoring and study oversight.	
Sources: FDA Draft guidance: On the Establishment and Operation of Clinical Trial Data Monitoring Committees	
Required Documents: Membership roster, meeting documentation	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Committee Role Describe the purpose and role of the committee. Indicate when this committee is used. Examples of physician advisory committees include: • Adverse event committee • Data monitoring committee • Physician steering committee	
2. Membership Criteria • Establish criteria that individuals must meet in order to be selected as a committee member • Committee composition, including chair • Requirements for confidentiality and consulting agreements	
3. Committee Procedures • Specific processes to be followed by committee • Frequency and format of meetings • Requirements for documenting and filling meeting minutes	Guideline for committee operations

APPENDIX Y

Topic: Publication Policy	
Purpose: To establish requirements governing the publication of study data	
Sources: None	
Required Documents: None	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Publication Strategy Establish requirements for creating study publication plans/strategy. Consider the following: • Determine the need for a formal publication plan • Whether preliminary study results can be released prior to study completion • Extent to which study results will be offered for publication to investigators and non-investigators • Use of a publication committee, if desired • Process for identifying and selecting authors • Sponsor guidelines provided to investigators • Expected timelines for manuscript submissions • Process for identifying Medtronic personnel to assist the author(s) and their responsibilities	Standardized publication guidelines
2. Review, Approval & Submission • Process for identifying and selecting individuals to review publications • Process for reviewing and documenting approval • Expected timelines for reviewing, approving and submitting publications • Process for submitting publications, including who will be notified of publications (Medtronic personnel and others)	Publication/abstract approval form
3. Ad Hoc Requests Describe the process for approving and responding to ad hoc data requests that are outside of a previously defined publication plan. Consider internal and external requests.	


Medtronic Confidential - Provided to the Committee on Finance Pursuant to Senate Rule XXIX

Medtronic	CONFIDENTIAL	DOCUMENT/RECORD

This document/record is electronically controlled, printed copies are considered uncontrolled.

Identifier	Version	Author
031-Policy on Standard Operating Procedures for Clinical Programs	3.0	Barb Westrum

Title: Policy on Standard Operatong Procedures for Clinical Programs

APPROVALS

Signed By	Meaning of Signature	Date/Time (US Central Time)
Lisa Griffin Vincent	CQRC Clinical	01/04/2007 16:39:39
Susan Alpert	Chief Quality and Regulatory Officer	01/05/2007 08:06:20
Chip Whitacre	CQRC Operations	01/10/2007 10:09:27
Michael Morton	Corporate Regulatory Affairs	01/10/2007 17:22:51
Kenneth Kopesky	CQRC Quality	01/18/2007 14:41:11
Sandy Kalter	CQRC Legal	01/24/2007 16:12:36

Corporate Quality, Regulatory, Clinical
POLICY
Title: Policy on Standard Operating Procedures for Clinical Studies

SCOPE

Medtronic Worldwide

PURPOSE

The purpose of this policy is to establish requirements for written standard operating procedures (SOPs) for conducting human clinical studies when study data will be submitted to a regulatory authority. For other types of studies, this document may be used as guidance in developing SOPs.

POLICY

Businesses and geographies will establish and maintain written operating procedures that govern the conduct of human clinical studies when study data will be submitted to a regulator authority This includes both pre- and post-market studies. Such procedures will be designed to reflect Medtronic's responsibility for protecting the rights, safety and welfare of study subjects and for ensuring the integrity of study data.

DEFINITIONS AND ABBREVIATIONS

Clinical Investigation Plan (CIP) or Investigation Plan (IP) – The document(s) that encompass the components of the study and applicable regulatory requirements. (Also known as *Investigational plan*)

Protocol – A subsection of the IP that describes the objectives, design, methodology, statistical considerations and conduct of the studies.

SOP – Standard Operating Procedures

MDR – Medical Device Reporting

REQUIREMENTS

1. Medtronic businesses and geographies will establish and maintain written standard operating procedures (SOPs) for conducting studies as defined the policy statement The appendices of this document provide a list of required SOP topics and required elements to be addressed in the SOPs. SOP(s) authored by another group or functional area may be used and the required adherence to such SOP(s) must be documented.

2. SOPs may be formatted according to the style used by the Medtronic entity. The organization, title and specific content may vary from how they are described in this policy. However, all of the required topics and elements must be addressed in SOPs.

3. Additional SOPs and requirements may be developed beyond those listed in this policy.

4. Management will ensure training of personnel to their department SOPs and other applicable documents as appropriate to their job function. Training must be documented.

5. SOPs will be reviewed at least every two years and updated as needed.

RESPONSIBILITY:

The management for each Medtronic business and geography is responsible for implementing, training, and complying with this policy.

APPENDIX A – REQUIRED SOP TOPICS

Appendix	Topic
B	SOP Development and Revision
C	Clinical Project/Management Plan
D	Investigation Plan and Related Documents
E	Investigator/Site Selection
F	Site Initiation
G	Sponsor Files
H	Site Monitoring
I	Statistical Aspects of Study Development
J	Study Report Generation for Regulatory Authorities
K	Data Handling/Management
L	Data Management System
M	Study Deviation Management
N	Adverse Event Management
O	Training of Investigation Site Personnel
P	Investigator and Subject Compensation
Q	Investigational Product Accountability
R	Study Closure
S	Training of Medtronic Personnel
T	Document Control
U	Preparing for Inspections by External Agencies
V	Outsourcing Activities
W	Emergency and Compassionate Use/ Humanitarian

RECOMMENDED SOP Topics: The following topics are recommended, but not required, if a clinical group engages in these activities.	
X	Advisory Committees (e.g., Data Monitoring Committee, Adverse Event Committee)
Y	Publication Policy

NOTE:

Required Documents – These documents are created as a result of following the respective SOP and are expected to be included in the department SOPs.

Required Elements – These processes or requirements are expected to be addressed in department SOPs.

Suggested Tools and Templates – These materials are provided as recommendations but are not required unless listed under Required Documents.

APPENDIX B

Topic: SOP Development and Revision	
Purpose: To describe the process for developing, reviewing, approving, revising and documenting deviations to SOPs.	
Related Corporate Policy, Procedure, or Guidance: CQRC-015 Document Control System CQRC-020 Personnel Training Policy CQRC-028 Quality Records Policy CCRA-037 Policy on Control of Clinical Documentation	
Required Documents: Standard Operating Procedures; SOP Template	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Development process • SOP template • Version control system used	SOP template specific for the business
2. Revision process • Periodic review and update • Change control • Obsolescence	
3. Review, Approval, and Distribution • Internal review • Approval process • Effective date • Document control process • Distribution requirements	
4. Training Describe the process for determining the need for training on the new SOP and how training will be completed and documented.	Staff training matrix
5. Deviation from a SOP Describe documentation requirements for planned/unplanned deviations to SOPs: • Description of deviation • Reason or justification for deviation • Documentation requirements for prior approval	Template for reporting deviations to SOPs

APPENDIX C

Topic: Clinical Project/Management Plan	
Purpose: To describe the process for developing, reviewing approving and revising a Clinical Project Plan.	
Related Corporate Policy, Procedure, or Guidance:	
Required Documents: Clinical Project/Management Plan. This document may also be known as a "Clinical Strategy Plan" or be part of an overall product development process.	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Development Process Describe the process to develop a Clinical Project/Management Plan. Address the following elements: • Clinical strategy and scope of study: - Purpose, duration, size and geographic location - Justification for the study - Product description, indications for use - Regulatory strategy and Medtronic commercial release requirements by geography - Required reports • Project risks (Identification of potential issues that could have significant impact the project, including budget, schedule, and resources.) • Study schedule • Budget & resource requirements • Training requirements for the study • Regulatory requirements for use of commercially approved products in a clinical study, including determination of investigational status, labeling, adverse event/MDR and complaint reporting • Specify the point in time when the clinical project plan is required (e.g., specific phase of the product development cycle, prior to study start etc.). •	Plan template Budget and Resource Plan template Study Schedule template Roles and Responsibility Matrix
2. Review and approval Review and approval process for the Clinical Project Plan	Approval template
3. Revision process Requirements for updating the Clinical Project Plan	Version Control template

APPENDIX D

Topic: Investigation Plan and Related Documents	
Purpose: To describe the process for developing, reviewing, approving and amending an Investigation Plan.	
Related Corporate Policy, Procedure, or Guidance: CQRC-008 Policy on Conduct and Review of Clinical Studies CQRC-008-P01 Procedure on Clinical Studies Monitoring CRRC-009 Policy on Adverse Event Reporting to Regulatory Authorities CCRA-025 Managing Clinical Study Deviations (Investigational Sites) CCRA-031-G01 Guideline on Investigational Plan Development and Review CQRC-036 Policy for Investigational Device/Product Accountability CQRC-036 G01 Guideline on Investigational Device/Product Accountability CCRA -037 Policy on Control of Clinical Documentation CQRC-037-G01 Guideline on Example Templates for Control of Clinical Documentation	
Required Documents: Investigation Plan Change History Record	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Development of the Investigation Plan Specify the requirements and process for developing an IP. Include the following: • Purpose of the study • Objectives and duration of the study • Hypotheses and endpoints • Protocol design, methodology, and scientific soundness • Procedures for study conduct • Data Management • Statistical Methods and Analysis • Product description, include identification of investigational and commercially-released components • Device accountability requirements • Justification for the study • Risk analysis • Adverse event definitions and requirements for reporting • Deviation reporting	IP Checklist or template (see CCRA-031-G01) Standardized definitions

• Sponsor identification • Study monitoring procedures • IRB/Ethics Committee information • Other institutions where a part of the investigation will be conducted (e.g., core laboratories, data monitoring committee) • Required records and reports (investigator and sponsor) • Investigation plan amendments • Publication policy	
2. Global Regulatory Requirements for Clinical Studies and Clinical Data. Address a process to identify unique requirements for the countries where: • the study is conducted • the product is in market use • the product is intended to be marketed (eg, data will be used to support future regulatory submissions) Such country-specific requirements may include (but are not limited to) the following: • regulatory authority notification or approval • reports of clinical experience outside of the current study • adverse event reporting requirements and timeframes • data integrity assurance procedures • subject protection provisions	CQRC-009 Policy on Adverse E vent Reporting To Regulatory Authorities
3. Related Documents • Informed consent template • Report of Prior Investigations, if used • Literature review • Preclinical and laboratory testing • Previous clinical experience • Investigator Brochure, if used • Instructions for use • Investigational Labeling • Case report forms • Confidentiality agreement, if used • Investigator agreement • Financial Disclosure	Consent checklist CRF templates / guidelines Report of Prior Investigations template Investigator Brochure template Investigator Agreement template (see Legal) Financial Disclosure template (see Legal)

• Release/authorization of medical information, if not included in an informed consent document.	
4. Review and Approval Process Specify who will review and approve the IP and related documents, and how approval is documented. Address the following: • Required elements of IP checklist • Scientific soundness • Statistical aspects • Protection of human subjects • Regulatory review • Specific geographic laws and regulations • Compliance to Medtronic policies and department SOPs • Legal review • Elimination of unnecessary protocol requirements and data collection • Consistency of requirements between components • Document control procedures • External review and approval process	Approval Record template
5. Revision Process Process for updating the IP and related documents, including: • Review and approval of amendments (internal and external groups). • Identification of other documents affected as a result of the change.	Version control template Change History Record template
6. Distribution and Maintenance Requirements for • Assessment of training needs • Distribution of approved documents • Records maintenance for master copies (original and revisions)	Investigator and IRB/EC letter templates for amendments

APPENDIX E

Topic: Investigator/Site Selection	
Purpose: To describe the process for identifying and selecting qualified investigators and sites.	
Related Corporate Policy, Procedure, or Guidance:	
Required Documents: Approved list of potential investigators	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Study Criteria Require establishment of criteria that investigators/sites must meet in order to be selected for a study.	
2. Site Nomination/Identification Process to identify potential investigators/sites. Describe how information is to be collected and documented.	Site Nomination or Profile Form template with study criteria
3. Confidentiality Agreements Determine the need for confidentiality agreements.	Confidentiality Agreement template (pre-approved by Legal)
4. FDA Sanctions Verify that nominated/identified investigators are not on the FDA lists of investigators who have been disqualified, restricted or debarred from conducting clinical studies.	See FDA website: http://www.fda.gov/oc/gcp/clinenforce.html
5. Site Selection Process for reviewing and deciding who will participate in the study. As appropriate, communicate confirmation back to the nominators, study team, and business management as to which sites will be invited to participate in the study or are intended to be activated.	
6. Investigator List Documentation and maintenance of Investigator list.	Approved list of potential investigators

APPENDIX F

Topic: Site Initiation	
Purpose: To describe the process for activating an investigation site.	
Related Corporate Policy, Procedure, or Guidance:	
Required Documents: Site activation record with required documentation Regulatory approval/clearance/notification as required by regulations in the country where study is to be conducted	
Required SOP Elements	**Suggested Tools/Templates**
1. Describe the process for developing, collecting and tracking required site activation documents • Investigator agreement • Compensation agreement, if separate from investigator agreement • Confidentiality agreement, if required by business • Financial disclosure for investigators, if required by regulations • IRB/EC approval • IRB/EC/MDT approved informed consent • IRB/EC chairman (IDE sites only) • IRB/EC roster or letter of compliance (optional) • Investigator curriculum vitae • Investigator delegation or task authorization form (recommended, but optional for device studies) • Site training documentation • Regulatory authority approval, clearance, or notification as required by regulations.	Site tracking system and site activation checklist Template for investigator delegation or task authorization form

2. Study Material Define required study materials to be provided to each site. (A general list can be defined along with flexibility to tailor to individual studies as needed.)	Examples: Study Documents Binder • Contact information • Screening logs (if used) • Protocol • Authorized (current) Informed consent. • Correspondence • Delegated task list (if used) • Etc. Patient Data Binders with CRFs

APPENDIX G

Topic: Sponsor Files	
Purpose: To describe the requirements for sponsor files.	
Related Corporate Policy, Procedure, or Guidance: CQRC-028 Quality Records Policy	
Required Documents: None	
Required SOP Elements:	**Suggested Tools/Templates:**
1. File Requirements Documents required by regulation, business, and corporate policies and procedures must be maintained. Describe requirements for file contents and organization, such as: • Clinical Project File • Investigator records • Subject data records • Monitoring records • Compensation records	Checklist of required contents
2. Filing Procedures Describe requirements for maintaining and filing study documents in the sponsor files. Include the following: • Procedure for maintaining files (electronic and/or paper documents) • Process for ensuring subject confidentiality	
3. Record Retention Describe the process for archiving sponsor files at study closure. Include: • Retention period & records custody	See CCRC-028 Quality Records Policy

APPENDIX H

Topic: Site Monitoring	
Purpose: To describe the process for defining, documenting and implementing site monitoring activities for clinical studies.	
Related Corporate Policy, Procedure, or Guidance: CQRC-008-P01 Procedure For Clinical Studies Monitoring CQRC-008-G01 Guidance on Implementing a Monitoring Program CAPA Process	
Required Documents: Monitoring Plan or written procedures if different from SOP Documentation of training/qualification of monitors Monitoring report Monitoring visit log	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Monitoring plan or written procedure Describe the requirements for developing a monitoring plan. The monitoring plan will include: • Who will perform monitoring and required qualifications • Criteria for determining the timing and frequency of visits • Regulatory and study management documents to be reviewed • Amount of subject data to be monitored • CRF data requiring source document verification • Define tools used for monitoring (e.g., checklists, logs, reports, communications) • Outsourcing, if used Note: Monitoring Plans or other written procedures are required when there are significant study specific details that cannot be described in a SOP.	Monitoring Plan template
2. Monitor Qualification Identify required skills and training Document qualifications of monitors Document training completion	See CQRC 008-P01 for training elements

3. Monitoring Process Describe the following processes: • Notifying the study site prior to visit • Conducting the monitoring visit • Review of regulatory and study management documents • Data elements requiring source document verification • Documenting the monitoring visit • Notifying investigators and site personnel of observations • Documenting protocol deviations • Internal review and sign-off of monitoring reports • A "closed-loop" system to veri fy that issues identified during monitoring are addressed and closed	Monitoring Report template Monitoring Visit Log template Letter templates
4. Periodic Review Address requirements for documented periodic reviews of monitor findings. Include: • Trend analysis on action items associated with the monitoring reports • Clinical study management review of corrective and preventive (CAPA) items	Review templates

APPENDIX I

Topic: Statistical Aspects of Study Development	
Purpose: To describe the elements of the statistical section of a protocol, the process for validating computer programs used for statistical analyses and the process for generating randomization schedules.	
Related Corporate Policy, Procedure, or Guidance: CCRA-031-G01 Guideline on Investigation Plan Development and Review	
Required Documents: Statistical Section of Protocol Statistical Program Validation Report Randomization Schedules	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Statistical Design and Analysis (for powered studies) Address requirements for: • Identifying the statistical hypotheses to be tested and/or statistical parameters to be estimated • Sample size calculation • Statistical analysis • Identifying subjects for analysis • Presenting statistical results • Review and approval of the statistical methods • Revising the statistical methods	Statistical analysis checklist (See also IP checklist)
2. Validation of Statistical Programs Address requirements for: • Validating a statistical program • Ensuring the integrity and protection of the program • Reviewing, approving and revising the program	Validation Plan
3. Randomization Process (for randomized studies) Address requirements for: • Generating randomization assignments • Deploying the randomization assignments • Protecting the randomization assignments • Tracking compliance to the randomization assignments • Unblinding a randomization assignment in case of an emergency	Validated statistical program

APPENDIX J

Topic: Study Report Generation	
Purpose: To define the process for developing, reviewing, approving and revising study reports	
Related Corporate Policy, Procedure, or Guidance:	
Required Documents: Documentation of Report Approval	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Report Development Process Identify type of report and required elements (e.g., internal report, progress report, PMA(s), final, or post-approval reports, etc.).	Report templates with required elements
2. Report dataset Define the requirements for creating report dataset, include: • Schedule • Database cut-off • Discrepancies resolution • Freeze/store dataset • Statistical analysis	
3. Report Approval Address requirements for: • Review and approval of reports (identify reviewers/approvers by functional roles) • Approval documentation requirements	Report approval template
4. Report Distribution Identify requirements for internal and external distribution.	
5. Document Control • Address requirements for document control • Define process for managing report revisions subsequent to initial distribution. • Describe the process for archiving the data set and report(s). Include retention period and records custody.	See CCRC-028 Quality Records Policy

APPENDIX K

Topic: Data Handling/Management	
Purpose: To describe the process to be followed for managing study data	
Related Corporate Policy, Procedure, or Guidance:	
Required Documents: None	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Requirements Address the following: • Process for maintaining confidentiality of information about each subject • Process to allow changes to CRF data to be made only by authorized personnel, initialed and dated, and the original entry retained for comparison • Describe how data is collected, processed and maintained • Process for identifying and resolving missing or questionable data • Procedures for database management, data archiving, and retention period (see Appendix L)	Template for data clarification forms
2. Data Management Plan (DMP) - Optional If a separate data management plan is used, require the following: • Development of the plan • Required content • Internal review and approval • Revising or updating the DMP • Distribution (e.g., identify by functional role)	

APPENDIX L

Topic: Data Management System	
Purpose: To describe the process of developing, validating and maintaining a clinical data management system (DMS).	
Related Corporate Policy, Procedure, or Guidance: MIT-001 System Development and Validation Life Cycle Policy (SDVLC)	
Required Documents: Data Management System Requirements Document Validation Plan and Test Report Change Control Management Records	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Study Requirements Process for establishing database specifications and developing a Data Management System (DMS) Requirements Document that includes the following elements: • Data points to be captured, e.g., data point on the CRF, data points captured by the device, data points maintained by the core lab • Data validation checks, e.g., required fields, range checks, intra/inter CRF checks • Data extract requirements, e.g., requirements for the statisticians such as SAS variable names, etc.	DMS requirements document template
2. DMS Development Address development of the DMS application, including: • Selection of hardware and software requirements • Construction of the DMS application for a new study • Validation plan, testing and approval (e.g., peer review, and user acceptance) • Required documentation • Release for production use	Software specific work instructions Template for validation plan and report
3. Training Address the need for training the study team and end users and how the training is to be documented.	
4. Report Generation Process for developing and validating reports derived from the database for study management.	
5. System Maintenance Describe procedures to be followed for system maintenance.	

Include: • Periodic back-up • Security measures • Change control procedures • Disaster contingency plan • Archiving data and retention period, if not covered elsewhere	

APPENDIX M

Topic: Study Deviation Management	
Purpose: To describe the process for defining, documenting, reviewing, reporting and maintaining records of study deviations that occur at investigation sites.	
Related Corporate Policy, Procedure, or Guidance: CCRA-025 Managing Clinical Study Deviations (Investigational Sites) CQRC-008-G01 Guidance on Implementing a Monitoring Program CAPA Process	
Required Documents: Deviation Report Form (may be part of a CRF or separate form)	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Definition Provide the definition of a study deviation and examples of potential study deviations. Define any classification system used for the study.	See CCRA-025
2. Records Describe how information on deviations will be collected and recorded. Include: • Required information • Investigator review and acknowledgement • Data management system (e.g., forms, database)	Deviation Report Form Template (may be part of a CRF or a separate document)
3. Internal Review Describe the process for internal review of deviation: • Upon discovery • Follow-up and resolution (e.g., monitoring CAPA process) • Comprehensive summary review by clinical study management and the clinical study team on a periodic basis. •	
4. Reporting Define the process for external reporting of deviations to regulatory authorities, investigators, and IRB/EC required by geographic regulations. Require periodic site-specific reports summarizing deviations to be provided to investigators.	

5. Prior Approval Describe the process for obtaining and documenting clinical study management approval prior to the investigator initiating changes in or deviations from the investigation plan or protocol.	Deviation "prior approval form" template
6. Deviations resulting from emergency situations Describe the process for documenting and reporting deviations from the investigation plan to protect the life or physical well-being of a subject in an emergency.	
7. Securing Compliance Describe the process to secure compliance or suspend/terminate the investigator if not compliant.	

APPENDIX N

Topic: Adverse Event Management	
Purpose: To describe the process for identifying, defining, classifying, reviewing, and reporting adverse events (AE) during a clinical study.	
Related Corporate Policy, Procedure, or Guidance: CQRC-009 Policy on Adverse Event Reporting to Regulatory Authorities CQRC-009-P01 Clinical Adverse Event Reporting in Japan	
Required Documents: Adverse Event Reporting Form (e.g., CRF)	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Identifying and defining adverse events Define classification systems For instance: • Anticipated/expected and Unanticipated/unexpected • Device/procedure relatedness • Seriousness of event	Matrix of reporting requirements by geography Standardized definitions and classifications based on therapeutic area
2. Investigator Reporting Address information to be provided in study materials (e.g., protocol, CRFs). Include the following: • List of anticipated/expected AEs • Types of AEs requiring reporting (e.g., every adverse event vs. a subset of product or study-related events) • Methods to report AEs • Obligations for reporting events (e.g., IRB/EC, sponsor, regulatory authority) • Information required by sponsor (E.g., event description, date of onset, severity or AE classification, actions taken, outcome or resolution status) • Time frame for investigator reporting	Template for standard protocol language
3. Adverse Event Review Describe the internal review process for: • Event classification • Who is responsible for reviewing (monitor, study team, regulatory) • Time frames for review • Documentation requirements • Trend -analysis to allow prompt knowledge of potential safety issues	Flowchart for AE reporting Guidelines for a Data Safety Committee or Adverse Events Committee

Describe the external review process, if used (e.g., adverse event committee, data monitoring committee)	
4. Internal Reporting Describe procedures for reporting adverse event information to Product Assurance groups or other functional groups required by the business. Consider the following: - AEs associated with the investigational device/study - AEs associated with commercially released product - Product complaints that may represent AEs	
5. External Reporting Define requirements for: • Expedited and routine reporting to regulatory authorities • Reporting to IRB/EC and investigators	CQRC-009 Policy on Adverse Event Reporting to Regulatory Authorities

Note: Consult laws and regulations of the countries where studies are to be conducted for geography-specific requirements.
For example:

- EMEA requirements, forms, and templates – see BRC quality website http://intranet.brc.medtronic.com/quality/qdocum/forms/clin_gen/forms/clinical.htm
- Japan requirements – See CQRC-009-P01

APPENDIX O

Topic: Training of Investigation Site Personnel	
Purpose: To describe the process for developing, implementing and documenting study-specific training of investigation site personnel involved in clinical studies.	
Related Corporate Policy, Procedure, or Guidance:	
Required Documents: Training Documentation Form	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Developing Training Requirements Address the following elements: • Topics and materials to be covered • Study-specific training needs (e.g., protocol, product) • Personnel to be trained based on responsibility in the study • Methods of training (i.e., investigator/coordinator meeting, conference call, on-site) • Timing and frequency of training • Identification of trainers by functional role	Site Training plan
2. Required Training Components Training materials will include the following: • Technical overview of product(s) • Protocol overview • Study procedures • Managing investigational product disposition • Investigational device/product accountability procedures • Procedures for returning unused/explanted product(s) • CRF completion and management • Investigator's responsibilities • Sponsor's responsibilities • Procedures for obtaining informed consent • IRB/EC role • Procedures for adverse event reporting • Procedures for study deviation reporting • Monitoring requirements and expectations • Potential for regulatory inspection and audit by sponsor • Site record maintenance and retention	Training materials checklist

• Reimbursement information (based on geographic regulation) • Regulatory requirements for commercially approved products used in a clinical study, including adverse event and complaint reporting • Other regulatory requirements not listed above such as geography-specific regulations.	
3. Documentation of Training Describe the process for documenting training. The following items must be documented: • Study name or training title • Date of training • Attendees name • Name of trainer(s) • General nature of training (e.g., protocol, product technology, regulations, etc.) • Maintain a copy of training materials	Training documentation form
4. On-going Study Training Process for identifying and training new site personnel when staff changes occur during a study.	

APPENDIX P

Topic: Investigator and Subject Compensation	
Purpose: To describe the process and requirements for issuing investigator and subject compensation.	
Related Corporate Policy, Procedure, or Guidance:	
Required Documents: Fully executed investigator compensation agreement Subject compensation information in consent document	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Investigator/Site Compensation Process for issuing investigator/site compensation. Include the following: • Fully executed investigator compensation agreement is available, included the amount and schedule of payments • General criteria for determining when payments are due • Internal payment authorization and check requests • Requirements for correspondence accompanying investigator compensation • Documentation required for record retention	Payment/Check Request Form Study compensation letter template
2. Subject Compensation Describe the process for payments to study subjects if applicable to a study. Include the following: • Process to determine if payment is appropriate for study • The amount and schedule of payments must be set forth in the informed consent document • Internal payment authorization and check requests • Requirements for correspondence accompanying subject compensation • Documentation required for record retention	Payment/Check Request Form Study compensation letter template
3. Business Conduct Standards Require all investigator and patient compensation to adhere to Medtronic Business Conduct Standards.	

APPENDIX Q

Topic: Investigational Product Accountability	
Purpose: To establish the requirements for investigational product accountability and tracking.	
Related Corporate Policy, Procedure, or Guidance: CQRC-036 Policy for Investigational Device/Product Accountability CQRC-036-G01 Guideline on Investigational Device/Product Accountability	
Required Documents: List of sites authorized to receive investigational product Investigational Product Disposition Log	
Required SOP Elements	**Suggested Tools/Templates**
1. Product storage at sponsor If investigational product is stored by clinical personnel, specify the procedures for secure storage and access by only authorized personnel.	
2. Authorizing shipment Define process for authorizing shipment to investigation sites, field and clinical personnel. Identify method to track on-going site status for receiving investigational product.	Checklist for shipment authorization Shipping request form template
3. Inventory tracking Define requirements for a product tracking system and traceability documentation. Include provisions for determining when commercially released product enters the clinical study and is considered to be investigational.	
4. Inventory management at investigational sites Describe how investigational product will be maintained and tracked at sites. Include the following: • Inventory storage requirements, security • Product disposition log • Documentation required for disposal of investigational product	Product disposition log
5. Returned Product Describe the process for return and receipt of investigational product by the sponsor.	Investigational product return form template

6. Inventory Reconciliation Describe the process for inventory reconciliation, including all investigational products shipped from finished goods, field and consignment inventory, and end/use disposition.	Template for reconciliation report

APPENDIX R

Topic: Study Closure	
Purpose: To describe the process to close a completed study or to prematurely suspend or terminate a clinical study at the site, at the sponsor, and with the regulatory authorities.	
Related Corporate Policy, Procedure, or Guidance: CQRC-008-P01 Procedure for Clinical Studies Monitoring CQRC-028 Quality Records Policy	
Required Documents: Notification to regulatory authorities	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Types of study or site closure Define the types of study or site closure: • Completed Site/Study – When sponsor and/or regulatory requirements have been satisfied per the investigation plan and/or decision of the business • Suspended Site/Study – Temporarily postponement of study activities related to enrollment and distribution of the investigational product • Terminated Site/Study – Discontinuation by sponsor or by withdrawal of IRB/EC or regulatory approval of an investigation before completion	
2. Completed Site/Study Describe the process for closing a completed study. Identify responsibilities, procedures, and required documentation to close the study at the site, at the Sponsor, and with regulatory authorities. Include: • Identify who is involved in the decision making process and required documentation (e.g., rationale, approvals) • Notification to regulatory authorities • Investigator notification requirements (e.g., study closure date, rationale for closure, discontinuation of data requirements, and disposition of products, record retention requirements, IRB/EC notification • See closure activities below	Checklist for investigator notification requirements
3. Suspended Site/Study Describe the process for suspending a clinical study or site: • Identify who is involved in the decision making process and required documentation (e.g., rationale, approvals)	Checklist for investigator notification requirements

• Procedure to notify the sites, IRB/EC and regulatory authorities • Identify the process for reactivating or terminating the study or site • Address follow-up for existing patients	
4. Terminated Site/Study Describe the process for prematurely stopping a clinical study or site: • Identify who is involved in the decision making process and required documentation (e.g., rationale, approvals) • Identify the procedure to notify the sites, IRB/EC • Require regulatory authority notification • Identify the closure activities at the site and at the sponsor that will be required (see below) • Address follow-up for existing patients	Checklist for investigator notification requirements
5. Site closure activities Define the activities to be performed at an investigation site during a study closure visit for a "completed" study and a "permanently terminated" study. Include the following: • Investigator/study files are complete and accurate • All CRFs, clarification and missing data received • Annual and interim reports (as required by regulation) are up to date • Deficiencies with the administrative (or regulatory) binder are resolved or closed • Investigational product accountability is complete • Equipment to be returned to sponsor • Record retention requirements agreed by investigator • Obligation for final reports to be submitted by investigators as required by regulations • Other activities defined by the sponsor or protocol	Checklist with study closure monitoring report
6. Sponsor closure activities Describe the process for study closure at the Sponsor. Include the following: • Project, subject, and site files are complete and accurate • Reconciliation of unused, used or explanted investigational-labeled products • Final compensation and contractual obligations • Complete the final report for submission to sites, IRB/EC	Close-out checklist (sponsor) Template for final clinical report

and regulatory authorities • Record retention procedures • Process to track financial disclosure after study closure (as required by regulation)	

APPENDIX S

Topic: Training of Medtronic Personnel	
Purpose: To describe the process for training and documenting training of Medtronic personnel involved in a clinical study.	
Related Corporate Policy, Procedure, or Guidance: CQRC-020 Personnel Training Policy	
Required Documents: Training Plan, Training Record	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Definitions **Department Training File** – A central file for each Clinical Department containing training records, such as, department training attendance rosters and presentations. Files may also contain the individual employee training record, job description, and CV/resume. **Training Plan** – A document that outlines the specific training an employee needs and will receive in order to perform his/her job function. The Training Plan may be a separate document or part of the Individual Development Plan (IDP). **Training Record** – A record (hard copy or electronic) used to document training received.	
2. Training requirements – clinical personnel Identify training requirements and frequency based on functional role (include both employee and contract labor). Note: For outsourcing (eg, CRO) training requirements see Appendix V.	Job/training matrix
3. New hire assessment Address requirements to assess new employee skills and needs.	Training plan template
4. Documentation Describe the process for documenting training. The following items must be documented: • Study name or training title • Date of training • Attendees name • Name of trainer(s) • General nature of training (e.g., protocol, product technology, regulations, etc.)	Training record template

APPENDIX T

Topic: Document Control	
Purpose: To describe the process for the approval, revision and maintenance of controlled clinical documents and records.	
Related Corporate Policy, Procedure, or Guidance: CQRC-015 Document Control System CCRA-037 Policy on Control of Clinical Documentation CQRC-037-G01 Example Templates for Control of Clinical Documentation	
Required Documents: Approval Documentation Change History Documentation	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Documents requiring document control Identify documents that are subject to document control procedures.	CQRC 037 Policy on Control of Clinical Documentation
2. Review of Draft Documents Identify document control procedures to create, review and edit new documents. Draft documents should be clearly identified as such. Identify system used to track routing of documents.	Routing Sheet template
3. Approval Process for document approval, including documentation, effective date, and change history record.	Approval Record template Change History Record template
4. Version Control Format Describe document requirements for version control (e.g., footer, pagination, etc).	CQRC-037-G01 Example Templates for Control of Clinical Documentation
5. Document Maintenance and Retention Describe where the original master will be maintained in a secure location.	
6. Training Determine the need for training on the new or modified document and how this training will be completed and documented.	
7. Distribution Identify requirements for document distribution and traceability.	

8. Revisions Describe the process and requirements for initiating changes to approved documents: • Draft, review, and edit process • Updating the change history records • Document approval • Identification of affected documents • Document maintenance, retention, training, and distribution (see above) • Disposition of retired documents	Document Change Order template
9, Records Retention Describe the process for archiving study records, including Retention period & records custody	See CCRC-028 Quality Records Policy

APPENDIX U

Topic: Preparing for Inspections by External Agencies	
Purpose: To describe the process for preparing and managing inspections performed by external parties.	
Related Corporate Policy, Procedure, or Guidance: CQRC-029 Regulatory Inspection Policy	
Required Documents: None	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Preparation for sponsor inspection. Include the following requirements: • Identify qualified individual(s) to serve as the clinical representative or clinical inspection coordinator • Identify who to contact when notice of an inspection is received. Include notification to business management and Corporate Quality, Regulatory and Clinical (CQRC) • Identify other team members to prepare and assist with the inspection • Describe the process to train personnel to be involved in inspections	Preparation checklist
2. During the sponsor inspection Describe requirements to be followed during the inspection, such as: • A list of documents and copies provided to the inspector(s) • Notes on each day's progress • Informing Corporate and business management on major non-compliance issues, unreasonable requests, prolonged delays, or other unusual development before or during the inspection	

3. Upon completion of the sponsors inspection • Identify who will be notified of the results of the inspections. Corporate review is mandatory. • Provision to forward Corporate the following documents if available: - Notice of Inspection (482) - Observations (483) - Draft and final responses to observations and exhibits or attachments - Establishment Inspection Report (EIR) - Warning or untitled letters and responses	
4. Investigator, IRB/EC inspections (study related) Describe the process to be followed for an intended inspection by a regulatory authority. Include the following: • Clinical and other sponsor personnel to be notified • Medtronic inspection contact • Site training • Investigator/site support during inspection, if requested • Reporting observations and response (see item 3 above)	Preparation checklist Standard training information
5. CRO inspections (study related) Describe the process to be followed for an intended inspection by a regulatory authority. Include the following: • Clinical and other sponsor personnel to be notified • Medtronic inspection contact • CRO support during inspection • Reporting observations & response to sponsor (see item 3 above)	

APPENDIX V

Topic: Outsourcing Activities	
Purpose: To describe the process for selecting, managing, training and communicating with outsourcing vendors used for clinical studies.	
Related Corporate Policy, Procedure, or Guidance:	
Required Documents: Qualification/evaluation checklist Confidentiality agreement for proprietary information Fully executed contract or agreement Qualification, CVs or resumes of subcontractors and professional services	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Outsourcing Plan Define how decision will be made to pursue outsourcing activities.	
2. Confidentiality Agreement Require confidentiality agreement for proprietary information.	Template from legal
3. Qualification of Outsourcing Vendor Describe the process for identifying outsourcing candidates and the process for documenting the screening and qualification of each. Include a process for evaluating vendor SOPs to be used for the study. This review will be documented.	Evaluation checklist CVs or resumes of prospective candidates
4. Selection of Outsourcing Vendor Describe the process for reviewing outsourcing candidates and final selection.	
5. Contract/Project Agreement Describe the process for drafting and executing the contracts or agreements.	Example work order checklist or legal template
6. Training of Outsourcing Personnel Describe how outsourcing personnel will be trained and managed (may refer to clinical management plan/monitoring plan for study specific details).	Training logs
7. Evaluating Performance Describe requirements for evaluating the activities performed by the outsourcing vendor. Document the evaluation.	

8. Corrective and Preventive Action Describe a process for communicating and documenting issues and corrective actions.	

APPENDIX W

Topic: Emergency and Compassionate Use/Humanitarian	
Purpose: To describe the procedures to be followed in special circumstances when an investigational product is used outside of the approved investigation plan/protocol. Examples include (but not limited to): emergency use (FDA), compassionate use (FDA), and Humanitarian (EU).	
Related Corporate Policies, Procedures, Guidance	
Required Documents: Required documentation from physician, IRB/Ethics Committee and regulatory authorities	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Definitions: Consult applicable country regulations, for example: • Emergency Use: (FDA) • Compassionate Use (FDA) • Humanitarian Use (EU) • Others, as appropriate to product and geography	
2. Regulatory Requirements Identify specific regulatory requirements and describe procedures for each category of use. Consider the following: • Required documentation from physician • Documentation of patient condition supporting use of the investigational product • Regulatory authority notification or pre-approval • IRB or Ethics committee notification or pre-approval • Sponsor notification or pre-approval, • Sponsor process for release of investigational product • Documentation of relevant physician/site training • Communication of physician obligations after use, such as follow-up care and reporting patient status • Consideration of including the site and patient data in the clinical study. This includes the extent to which a protocol will be followed and how patient data will be reported to the sponsor. • Informed consent and data release • Internal (sponsor) review of patient status • Inclusion of data in clinical reports and regulatory submissions	Checklist of requirements applicable to specific category of use Sponsor approval form applicable to specific category of use Informed consent template specific to category of use and addressing clinical study if applicable.

APPENDIX X

Topic: Advisory Committees	
Purpose: To describe the process for identifying and selecting members for advisory committees used for activities such as adverse event review, data monitoring and study oversight.	
Related Corporate Policy, Procedure, or Guidance:	
Required Documents: Membership roster, meeting documentation, confidentiality and consulting agreements	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Committee Role Describe the purpose and role of the committee. Indicate when this committee is used. Examples of advisory committees include: • Adverse event committee • Data monitoring committee • Study steering committee • Publication committee	
2. Membership Criteria • Establish criteria that individuals must meet in order to be selected as a committee member. • Committee composition, including chair • Requirements for confidentiality and consulting agreements	confidentiality and consulting agreements
3. Committee Procedures • Role of the sponsor • Specific processes to be followed by committee • Frequency and format of meetings • Requirements for documenting and filling meeting minutes	Guideline for committee operations

APPENDIX Y

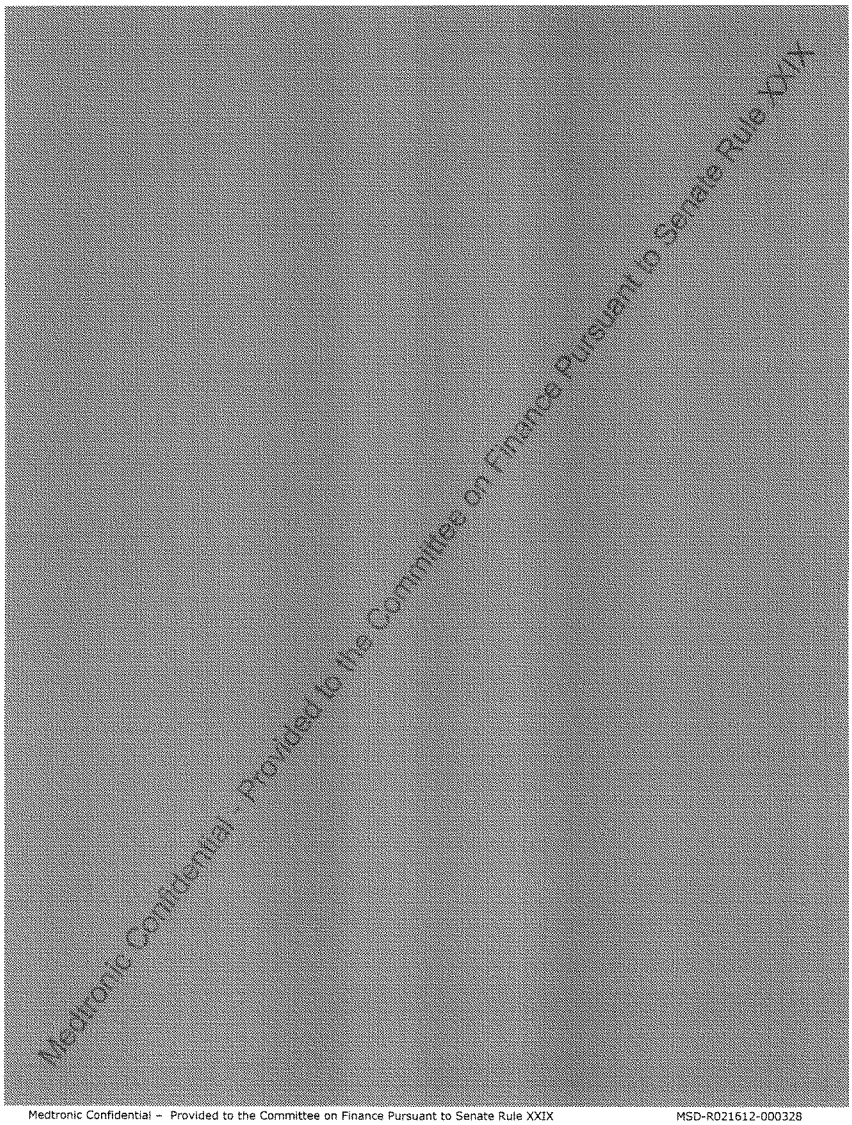
Topic: Publication Policy	
Purpose: To establish requirements governing the publication of study data	
Related Corporate Policy, Procedure, or Guidance:	
Required Documents: None	
Required SOP Elements:	**Suggested Tools/Templates:**
1. Publication Strategy Establish requirements for creating study publication plans/strategy. Consider the following: • Determine if prior registration in a public study registry is required and desirable • Determine the need for a formal publication plan • Determine how the publication strategy will be communicated to investigators (eg, explained in the protocol, investigator agreement or another document) • Whether preliminary study results can be released prior to study completion • Extent to which study results will be offered for publication to investigators and non-investigators • Use of a publication committee, if desired • Process for identifying and selecting authors • Sponsor guidelines provided to investigators • Expected timelines for manuscript submissions • Process for identifying Medtronic personnel to assist the author(s) and their responsibilities	Publication guidelines and standards (www.icmje.org)
2. Review, Approval & Submission of Publications • Process for identifying and selecting individuals to review publications • Process for reviewing and documenting approval • Expected timelines for reviewing, approving and submitting publications • Process for submitting publications, including who will be notified of publications (Medtronic personnel and others)	Publication/abstract approval form

3. Ad Hoc Requests Describe the process for approving and responding to ad hoc data requests that are outside of a previously defined publication plan. Consider internal and external requests.	

- End of Document

CHANGE HISTORY		
REVISION	**DATE**	**DESCRIPTION of CHANGE**
A	Feb 6, 2003	Initial Release
3.0		Periodic Update 1. Scope Change – Medtronic Worldwide 2. Applicability – Studies where data will be submitted to regulatory authorities. *This includes both pre- and post-market studies.* 3. Global focus – not regulatory specific 4. Three topics upgraded from "recommended" to "required" • Preparing for Inspections by External Agencies • Outsourcing Activities • Emergency and Compassionate Use/ Humanitarian 5. General update and editing throughout document

Owner: Lisa Griffin Vincent
Department: Corporate Clinical


Medtronic Confidential - Provided to the Committee on Finance Pursuant to Senate Rule XXIX

Medtronic	CONFIDENTIAL	DOCUMENT/RECORD

This document/record is electronically controlled, printed copies are considered uncontrolled.

Identifier	Version	Author
031-Policy on Standard Operating Procedures for Clinical Programs	4.0	Barb Westrum

Title: Policy on Standard Operatong Procedures for Clinical Programs

APPROVALS

Signed By	Meaning of Signature	Date/Time (US Central Time)
Lisa Griffin Vincent	CQRC Clinical	10/11/2007 09:55:43
Susan Alpert	Chief Quality and Regulatory Officer	10/23/2007 09:22:39
Michael Morton	CQRC Regulatory	10/29/2007 16:50:50
Chip Whitacre	CQRC Operations	11/01/2007 12:09:49
Sandy Kalter	CQRC Legal	11/05/2007 16:30:01

Corporate Quality, Regulatory, Clinical
POLICY 031
Title: Policy on Standard Operating Procedures for Clinical Studies

SCOPE: Medtronic Worldwide

PURPOSE
The purpose of this policy is to establish content requirements for written standard operating procedures (SOPs) that govern the conduct of Medtronic-sponsored clinical studies involving human subjects. Written operating procedures are required regardless of the functional area initiating the study.

This policy covers all types of Medtronic-sponsored clinical studies, including basic research, product development, pre-market, and post-market studies. A clinical study is defined as an investigation that involves one or more human subjects about whom an investigator conducting research obtains:

1. Data through intervention or interaction with the individual, or
2. Identifiable private information.

Written standard operating procedures will be designed to reflect Medtronic's responsibility for protecting the rights, safety and welfare of study subjects, ensuring the integrity of study data, meeting regulatory obligations where applicable, and protecting Medtronic business practices.

POLICY
Businesses and geographies will establish and maintain written operating procedures that govern the conduct of Medtronic-sponsored clinical studies.

Note: Nothing in this policy is intended to contradict local laws, regulations or other Medtronic Policies. In cases of conflicting direction, local laws and regulations where the study is being conducted have precedence.

REQUIREMENTS

1. Medtronic businesses and geographies will establish and maintain written standard operating procedures (SOPs) for conducting Medtronic-sponsored clinical studies. The appendices of this document provide the required topics and elements to be addressed in the SOPs. SOP(s) authored by another group, entity, or functional area may be used if the decision, required training, and adherence to such SOP(s) is documented.

2. SOPs may be formatted according to the style used by the Medtronic entity. The organization, title and specific content may vary from how they are described in this policy. However, all of the required topics and elements must be addressed in SOPs.

3. Additional SOPs and requirements may be developed beyond those listed in this policy.

4. Business or geography management will ensure training of personnel to their relevant SOPs and other applicable documents as appropriate to their job function. Training must be documented.

5. SOPs will be reviewed at least every two years and updated as needed.

6. If a business or geography does not engage in a specific SOP topic listed in this policy (see Appendix A), it need not maintain procedures for that activity. Each business or geography must keep a list of those SOP topics for which it does not have procedures and document the rationale for why they are not needed. The following conventions are used in the appendices:

SOP Deliverables (header) – required documents that are created as a result of following the respective SOP.

Required SOP Elements (left column) – processes and elements that are required to be addressed in SOPs unless otherwise noted (See requirement 6). Common processes may be used across studies or alternatively, tailored to specific types of studies.

Suggested Tools and Templates (right column) – items are provided as recommendations and are not required.

RESPONSIBILITY:
The management for each Medtronic business and geography is responsible for implementing, training, and complying with this policy.

APPENDIX A – SOP TOPICS

Appendix	SOP Topic
B	SOP Development and Revision
C	Clinical Project/Management Plan
D	Investigation Plan and Related Documents
E	Investigator/Site Selection
F	Site Initiation
G	Sponsor Files
H	Site Monitoring
I	Statistical Aspects of Study Development
J	Study Report Generation
K	Data Handling/Management
L	Data Management System
M	Study Deviation Management
N	Adverse Event Management
O	Training of Investigation Site Personnel
P	Investigator and Subject Compensation
Q	Investigational Product Accountability
R	Study Closure
S	Training of Medtronic Personnel
T	Document Control
U	Preparing for Inspections by External Agencies
V	Outsourcing Activities
W	Emergency Use, Compassionate Use, and Humanitarian Use
X	External Advisory Committees
Y	Publication Policy

APPENDIX B

Topic: SOP Development and Revision
Purpose: To describe the process for developing, reviewing, approving, revising and documenting deviations to SOPs.
Related Corporate Policy, Procedure, or Guidance: CQRC-015 Document Control System CQRC-020 Personnel Training Policy CQRC-028 Quality Records Policy CCRA-037 Policy on Control of Clinical Documentation
SOP Deliverables: • Standard Operating Procedures

Required SOP Elements:	**Suggested Tools/Templates:**
1. Development process a. SOP template b. Version control system used	SOP template specific for the business
2. Revision process a. Periodic review and update b. Change control c. Obsolescence	
3. Review, Approval, and Distribution a. Internal review b. Approval process c. Effective date d. Document control process e. Distribution requirements	
4. Training Describe the process for determining the need for training on the new SOP and how training will be completed and documented.	Staff training matrix
5. Deviation from a SOP Describe documentation requirements for planned/unplanned deviations to SOPs: a. Description of deviation b. Reason or justification for deviation c. Documentation requirements for prior approval	Template for reporting deviations to SOPs

APPENDIX C

Topic: Clinical Project/Management Plan
Purpose: To describe the process for developing, reviewing approving and revising a Clinical Project/Management Plan.
Related Corporate Policy, Procedure, or Guidance: CQRC-002 Commercial Release Policy
SOP Deliverables: • Clinical Project/Management Plan. This document may also be part of a "Clinical Strategy Plan" or an overall product development process.

Required SOP Elements:	**Suggested Tools/Templates:**
1. Development Process Describe the process to develop a Clinical Project/Management Plan. Address the following elements: a. Clinical strategy and scope of study: 1. Purpose, duration, size and geographic location 2. Justification for the study, including factors related to • use of human subjects • scientific soundness, • alignment with business strategy (e.g., strategic interest in therapy or R&D and/or therapy development opportunities) • clinical evidence planning (including cost-effectiveness) 3. Product description, indications for use 4. Global Regulatory strategy and Medtronic commercial release requirements.** Address requirements for the countries where: • the study is conducted • the product is marketed • the product is intended to be marketed (e.g., data will be used to support future regulatory submissions) 5. Reimbursement strategy by geography**, including • reimbursement considerations during clinical study (i.e., considerations of applicable laws or policies by government and other third party payors) • requirements for clinical evidence upon market release (e.g., clinical and cost effectiveness data needed to support reimbursement decisions by government and other third party payors) 6. Required reports (e.g., interim and/or final report) **If the strategy is completed in a separate document, then it is appropriate to reference the strategy document.	Plan template Budget and Resource Plan template Study Schedule template Roles and Responsibility Matrix CQRC-009 Policy on Adverse Event Reporting To Regulatory Authorities

Required SOP Elements:	Suggested Tools/Templates:
b. Project risks (Identification of potential issues that could have significant impact the project, including budget, schedule, and resources. c. Study schedule d. Budget & resource requirements e. Expectations for device/product reimbursement during study f. Training requirements for the study g. Regulatory requirements for use of commercially approved products in a clinical study, including determination of investigational status, labeling, adverse event and complaint reporting h. Specify the point in time when the clinical project plan is required (e.g., specific phase of the product development cycle, prior to study start)	
2. Review and approval a. Documented review and approval process for the Clinical Project/ Management Plan. b. Documented review and approval process for decision to fund and initiate the study.	Approval template
3. Revision process Requirements for updating the Clinical Project/Management Plan.	Version Control template

Corporate Quality, Regulatory, Clinical
POLICY 031
Title: Policy on Standard Operating Procedures for Clinical Studies

APPENDIX D

Topic: Investigation Plan (IP) and Related Documents
Purpose: To describe the process for developing, reviewing, approving and amending an Investigation Plan.
Related Corporate Policy, Procedure, or Guidance: CQRC-008 Policy on Conduct and Review of Clinical Studies CQRC-008-P01 Procedure on Clinical Studies Monitoring CRRC-009 Policy on Adverse Event Reporting to Regulatory Authorities CQRC-025 Managing Clinical Study Deviations (Investigational Sites) CQRC-031-G01 Guideline on Investigational Plan Development and Review CQRC-036 Policy for Investigational Device/Product Accountability CQRC-036 G01 Guideline on Investigational Device/Product Accountability CQRC-037 Policy on Control of Clinical Documentation CQRC-037-G01 Guideline on Example Templates for Control of Clinical Documentation
SOP Deliverables: • Investigation Plan with Change History Record

Required SOP Elements:	**Suggested Tools/Templates:**
1. Development of the Investigation Plan Specify the requirements and process for developing an IP. Include the following: a. Purpose and objective of the study clearly specifying the research question b. Duration of the study c. Hypotheses and endpoints d. Protocol design, methodology, and scientific soundness e. Procedures for study conduct f. Data management, including identification of steps where a computerized system will be used to create, modify, maintain, archive, retrieve, or transmit source data. g. Statistical methods and analysis h. Product description, include identification of investigational and commercially-released components i. Investigational device/product accountability requirements j. Justification for the study k. Risk analysis l. Adverse event definitions and requirements for reporting m. Data Monitoring Committee (DSMB), Clinical Events committee (CEC),or other advisory group if used for study n. Deviation reporting o. Sponsor identification p. Study monitoring procedures q. IRB/Ethics Committee requirements r. Other institutions where a part of the investigation will be conducted (e.g., core laboratories, data monitoring committee) s. Required records and reports (investigator and sponsor) t. Investigation plan amendments u. Publication policy	Plan checklist (see CCRA-031-G01) Plan template Standardized definitions

Required SOP Elements:	Suggested Tools/Templates:
2. Global Regulatory Requirements Pertaining to the Study. Such country-specific requirements may include (but are not limited to) the following: a. regulatory authority notification or approval b. reports of clinical experience outside of the current study c. adverse event reporting requirements and timeframes d. data integrity assurance procedures e. subject protection provisions	
3. Related Documents Specify the requirements and process for developing the following: a. Informed consent template b. Report of Prior Investigations, if any c. Literature review d. Preclinical and laboratory testing e. Previous clinical experience related to the product and study objectives f. Investigator Brochure, if any g. Instructions for use h. Investigational device/product labeling i. Case report forms j. Confidentiality agreement, if used k. Investigator/site agreement l. Financial Disclosure (If required by regulations) m. Release/authorization of medical information, if not included in an informed consent document.	Consent checklist CRF templates / guidelines Report of Prior Investigations template Investigator Brochure template Investigator/Site Agreement template (see Legal) Financial Disclosure template (see Legal)
4. Review and Approval Process Specify who will review and approve the IP and related documents, and how approval is documented. Address the following: a. Required elements of IP checklist b. Scientific soundness c. Statistical aspects d. Data handling/management e. Protection of human subjects f. Regulatory review g. Specific geographic laws and regulations h. Compliance to Medtronic policies and department SOPs i. Legal review j. Elimination of unnecessary protocol requirements and data collection k. Consistency of requirements between components l. Document control procedures m. External review and approval process	Approval Record template Investigator and IRB/EC letter templates for review and approval for initial submission and amendments
5. Revision Process Process for updating the IP and related documents, including:	Version control template

Required SOP Elements:	Suggested Tools/Templates:
a. Review and approval of amendments (internal and external groups). b. Identification of other documents affected as a result of the change	Change History Record template
6. Distribution and Maintenance Requirements for: a. Assessment of training needs b. Distribution of approved documents c. Records maintenance for master copies (original and revisions)	Investigator and IRB/EC letter templates for amendments

Corporate Quality, Regulatory, Clinical
POLICY 031
Title: Policy on Standard Operating Procedures for Clinical Studies

APPENDIX E

Topic: Investigator/Site Selection
Purpose: To describe the process for identifying and selecting qualified investigators and sites.
Related Corporate Policy, Procedure, or Guidance: **Business Conduct Standards**
SOP Deliverables: • Investigator/site list

Required SOP Elements:	**Suggested Tools/Templates:**
1. Study Criteria for Investigator/Site Selection Require establishment of criteria that investigators/sites must meet in order to be selected for a study. Include factors related to: • investigator's qualifications, education and experience • interest in product/disease • patient population/referral base • administrative support and facilities • past experience in conducting clinical studies • study specific requirements as determined by the investigational plan.	
2. Investigator/Site Nomination /Identification a. Process to identify potential investigators/sites. b. Describe how information is to be collected and documented in accordance with Medtronic Business Conduct Standards (eg, role of sales limited to providing information regarding interest and qualification of investigators and sites.)	Site Nomination or Profile Form template with study criteria
3. Confidentiality Agreements Determine the need for confidentiality agreement.	Confidentiality Agreement template (pre-approved by Legal)
4. Government Sanctions Verify that investigators have no restrictions on their clinical research activities imposed by a government agency. Examples: • FDA List - disqualified, restricted or debarred from conducting clinical studies • HHS (OIG) List - Excluded from participation in all Federal Health Care programs (e.g., Medicare, M Card)	See FDA website: http://www.fda.gov/oc/gcp/clinenforce.html and http://www.fda.gov/ora/compliance_ref/debar/ See HHS website: http://exclusions.oig.hhs.gov/
5. Investigator/Site Selection a. Process for reviewing and deciding who will be invited to participate in the study. b. As appropriate, communicate confirmation back to the nominators, study team, and business management as to which sites will be invited to participate in the study or are intended to be activated.	

Required SOP Elements:	Suggested Tools/Templates:
6. Investigator/Site List Documentation and maintenance of Investigator list.	

APPENDIX F

Topic: Site Initiation
Purpose: To describe the process for activating an investigation site.
Related Corporate Policy, Procedure, or Guidance
SOP Deliverables: • Site activation record with required documentation • IRB/EC approval as required by regulations • Regulatory approval/clearance/notification

Required SOP Elements:	**Suggested Tools/Templates**
1. Describe the process for developing, collecting and tracking required site activation documents, including: a. Investigator agreement b. Investigator/site compensation agreement, if separate from investigator/site agreement c. Confidentiality agreement, if required by the business d. Financial disclosure for investigators, if required by regulations e. IRB/EC approval of the study and related materials, or documentation of IRB/EC determination if approval is not required. Include the following when used for the study • Study protocol or investigational plan • MDT approved informed consent form or medical information release if a consent document is not used. • Investigator's brochure • Materials to be used to recruit subjects • Materials to be provided to subjects. • Provision (if any) for payments to be made to subjects, such as reimbursement of expenses, f. Name of IRB/EC chair (if required by regulation) g. IRB/EC roster or letter of compliance (if available) h. Investigator curriculum vitae i. Investigator delegation or task authorization form j. Site training documentation k. Regulatory authority approval, clearance, or notification as required by regulations.	Site tracking system and site activation checklist Template for investigator delegation or task authorization form Template to obtain permission for access and use of medical information (medical information release).
2. Study Material Define required study materials to be provided to each site. (A general list can be defined along with flexibility to tailor to individual studies as needed.)	Study Documents Binder • Contact information • Screening log • Protocol • Authorized (current) Informed consent or medical information release template (if used)

Required SOP Elements:	Suggested Tools/Templates
	• Correspondence • Delegated task list Patient Data Binders with CRFs

APPENDIX G

Topic: Sponsor Files
Purpose: To describe the requirements for sponsor files.
Related Corporate Policy, Procedure, or Guidance: CQRC-028 Quality Records Policy
SOP Deliverables: None

Required SOP Elements:	**Suggested Tools/Templates:**
1. File Requirements Documents required by regulation, business, and corporate policies and procedures must be maintained. Describe requirements for file contents and organization, such as: a. Clinical project file b. Investigator records c. Subject data records d. Monitoring records e. Compensation records	Checklist of required contents
2. Filing Procedures Describe requirements for maintaining and filing study documents in the sponsor files. Include the following: a. Procedure for maintaining files (electronic and/or paper documents) b. Process for ensuring subject confidentiality	
3. Record Retention Describe the process for archiving sponsor files at study closure. Include retention period and records custody	See CCRC-028 Quality Records Policy

APPENDIX H

Topic: Site Monitoring
Purpose: To describe the process for defining, documenting and implementing site monitoring activities for clinical studies. Note: Monitoring Plans are required when there are significant study specific details that cannot be described in a SOP.
Related Corporate Policy, Procedure, or Guidance: CQRC-008-P01 Procedure For Clinical Studies Monitoring CQRC-008-G01 Guidance on Implementing a Monitoring Program CAPA Process
SOP Deliverables: • Monitoring Plan • Monitoring report and monitoring visit log • Documentation of training/qualification of monitors

Required SOP Elements:	**Suggested Tools/Templates:**
1. Monitoring plan or written procedure Describe the requirements for developing a monitoring plan. The monitoring plan will include: a. Who will perform monitoring and required qualifications b. Criteria for determining the timing and frequency of visits c. Regulatory and study management documents to be reviewed d. Amount of subject data to be monitored e. CRF data requiring source document verification f. Define tools used for monitoring (e.g., checklists, logs, reports, communications) g. Outsourcing, if used	Monitoring Plan template
2. Monitor Qualification a. Identify required skills and training b. Document qualifications of monitors c. Document training completion	See CQRC 008-P01 for training elements
3. Monitoring Visit Process a. Describe the following processes: b. Notifying the site c. Conducting the monitoring visit d. Review of regulatory and study management documents e. Data elements requiring source document verification f. Monitoring visit documentation g. Notifying investigators and site personnel of observations h. Documenting protocol deviations i. Internal review and sign-off of monitoring reports j. A "closed-loop" system to verify that issues identified during monitoring are addressed and closed	Monitoring Report template Monitoring Visit Log template Letter templates

Required SOP Elements:	Suggested Tools/Templates:
4. Periodic Review Address requirements for documented periodic reviews of monitor findings. Include: a. Trend analysis on action items b. Corrective and preventive actions (CAPA)	Review templates

APPENDIX I

Topic: Statistical Aspects of Study Development
Purpose: To describe the elements of the statistical section of a protocol, the process for validating computer programs used for statistical analyses and the process for generating randomization schedules. Note: All studies should have a statistical plan (even if the plan is limited to descriptive statistics) to identify how the data will be used and analyzed, and the results presented.
Related Corporate Policy, Procedure, or Guidance: CCRA-031-G01 Guideline on Investigation Plan Development and Review
SOP Deliverables: • Statistical Section of Protocol (and/or Statistical Analysis Plan) • Statistical Program Validation Report • Master Randomization Schedule

Required SOP Elements:	**Suggested Tools/Templates:**
1. Statistical Design and Analysis Address requirements for: a. Identifying the statistical hypotheses to be tested and/or statistical parameters to be estimated b. Sample size calculation and justification c. Statistical analysis d. Identifying subjects for analysis e. Presenting statistical results f. Review and approval of the statistical methods g. Revising the statistical methods	Statistical analysis checklist (See also IP checklist)
2. Validation of Statistical Programs Address requirements for: a. Validating a statistical program b. Ensuring the integrity and protection of the program c. Reviewing, approving and revising the program	Validation Plan
3. Randomization Process Address requirements for: a. Generating randomization assignments b. Deploying the randomization assignments c. Protecting the randomization assignments d. Tracking compliance to the randomization assignments e. Unblinding a randomization assignment in case of an emergency	Validated Statistical Program

APPENDIX J

Topic: Study Report Generation
Purpose: To define the process for developing, reviewing, approving and revising study reports
Related Corporate Policy, Procedure, or Guidance: CQRC 011 - Submission Integrity Policy
SOP Deliverables: • Study report(s) with documentation of approval **Note:** A final internal report is required at a minimum, regardless of the type of study.

Required SOP Elements:	**Suggested Tools/Templates:**
1. Report Development Process Identify type of report and required elements (e.g., internal report, progress report, PMA(s), final, or post-approval reports).	Report templates with required elements
2. Report dataset Define the requirements for creating report dataset, including: a. Schedule b. Database cut-off c. Discrepancies resolution d. Freeze/store dataset e. Statistical analysis	
3. Report Approval Address requirements for: a. Review and approval of reports (identify reviewers/approvers by functional roles) b. Approval documentation requirements	Report approval template
4. Report Distribution Identify requirements for internal and external distribution.	
5. Document Control a. Address requirements for document control b. Define process for managing report revisions subsequent to initial distribution c. Describe the process for archiving the data set and report(s). Include retention period and records custody.	See CCRC-028 Quality Records Policy

APPENDIX K

Topic: Data Handling/Management
Purpose: To describe the process to be followed for managing study data and responding to ad hoc requests for access to data
Related Corporate Policy, Procedure, or Guidance:
SOP Deliverables:

Required SOP Elements:	**Suggested Tools/Templates:**
1. Requirements Address the following: a. Process for maintaining confidentiality of information about each subject b. Process to allow changes to CRF data to be made only by authorized personnel, initialed and dated, and the original entry retained for comparison c. Describe how data is collected, processed and maintained d. Process for identifying and resolving missing or questionable data e. Procedures for database management, data archiving, and retention period (see Appendix L) f. Training requirements for internal staff and investigation sites	Template for data clarification forms
2. Data Management Plan (DMP) If a separate data management plan is used to supplement SOPs due to study-specific requirements, require the following: a. Development of the plan b. Required content c. Internal review and approval d. Revising or updating the DMP e. Distribution (e.g., identify by functional role)	Template for DMP
3. Ad Hoc Requests for Study Data Describe the process for responding to ad hoc requests for study data from internal (Medtronic) and external (investigators, regulatory authorities) sources. Address requirements for the following: a. Guidelines regarding access to raw and summary data • Ensure integrity of study is not jeopardized (e.g., pre-mature release) • Procedures to maintain subject confidentiality • Ensure use within permission given by subjects regarding private medical information • Alignment with businesses objectives b. Formal written request for purposes outside of normal study-related activities	Access to Data Request Form

Required SOP Elements:	Suggested Tools/Templates:
• Description of data or analysis requested • Proposed use of data c. Documented review and approval of requests d. Require confidential disclosure agreement e. Identification of Medtronic resources to assist with the request f. Development of data set.(e.g., data cleaning, freeze, export) g. Documented review and approval of dataset	

APPENDIX L

Topic: Data Management System
Purpose: To describe the process of developing, validating and maintaining a clinical data management system (DMS).
Related Corporate Policy, Procedure, or Guidance: MIT-001 System Development and Validation Life Cycle Policy (SDVLC)
SOP Deliverables: • Data Management System Requirements Document • Validation Plan and Test Report • Change Control Management Records

Required SOP Elements:	**Suggested Tools/Templates:**
1. Study Requirements Process for establishing database specifications and developing a Data Management System Requirements Document that includes the following elements: a. Data points to be captured, e.g., data point on the CRF, data points captured by the device, data points maintained by the core lab b. Data validation checks, e.g., required fields, range checks, intra/inter CRF checks c. Data extract requirements, e.g., requirements for the statisticians such as SAS variable names	DMS requirements document template
2. Data Management System Development Address development of the DMS application, including: a. Selection of hardware and software requirements b. System set-up/installation (including the description and specific use of software, hardware, and physical environment and the relationship) c. System operating manual d. Data collection and handling (including audit trail, and risk assessment) e. Construction of the DMS application for a new study f. Validation and functionality testing and approval (e.g., peer review, and user acceptance) g. Required documentation h. Release for production use i. Roles and responsibilities of sponsors, clinical sites and other parties with respect to the use of computerized systems in clinical trials. j. Regulatory requirements (e.g., FDA Part II)	Software specific work instructions Template for validation plan and report
3. Training Address the need for training the study team and end users and how the training is to be documented.	
4. Report Generation	

Required SOP Elements:	Suggested Tools/Templates:
Process for developing and validating reports derived from the database for study management.	
5. System Maintenance Describe procedures to be followed for system maintenance. Include: a. Security measures b. Change control procedures c. Periodic back-up and recovery d. Alternative recording methods (in case of system unavailability) e. Disaster contingency plan f. Archiving data and retention period, if not covered elsewhere g. System decommissioning	

APPENDIX M

Topic: Study Deviation Management
Purpose: To describe the process for defining, documenting, reviewing, reporting and maintaining records of study deviations that occur at investigation sites.
Related Corporate Policy, Procedure, or Guidance: CCRA-025 Managing Clinical Study Deviations (Investigational Sites) CQRC-008-G01 Guidance on Implementing a Monitoring Program CAPA Process
SOP Deliverables: • Deviation Report Form (may be part of a CRF or separate form)

Required SOP Elements:	**Suggested Tools/Templates:**
1. Definition a. Provide the definition of a study deviation and examples of potential study deviations. b. Define any classification system used for the study.	See CCRA-025
2. Records Describe how information on deviations will be collected and recorded. Include: a. Required information b. Investigator review and acknowledgement c. Data management system (e.g., forms, database)	Deviation Report Form Template (may be part of a CRF or a separate document)
3. Internal Review Describe the process for internal review of deviation: a. Upon discovery b. Follow-up and resolution (e.g., monitoring CAPA process) c. Comprehensive summary review by clinical study management and the study team on a periodic basis.	
4. Reporting a. Define the process for external reporting of deviations to regulatory authorities, investigators, and IRB/EC required by geographic regulations. b. Require periodic site-specific reports summarizing deviations to be provided to investigators.	
5. Prior Approval Describe the process for obtaining and documenting clinical study management approval prior to the investigator initiating changes in or deviations from the investigation plan or protocol.	Deviation "prior approval form" template
6. Deviations resulting from emergency situations Describe the process for documenting and reporting deviations from the investigation plan to protect the life or physical well-being of a subject in an emergency.	

Required SOP Elements:	Suggested Tools/Templates:
7. Securing Compliance a. Describe the process to secure compliance or suspend/terminate the investigator if not compliant. b. Address process if fraud or fraudulent misconduct is discovered, include legal counsel involvement.	

APPENDIX N

Topic: Adverse Event Management
Purpose: To describe the process for identifying, defining, classifying, reviewing, and reporting adverse events (AE) during a clinical study.
Related Corporate Policy, Procedure, or Guidance: CQRC-009 Policy on Adverse Event Reporting to Regulatory Authorities CQRC-009-P01 Clinical Adverse Event Reporting in Japan
SOP Deliverables: • Adverse Event Reporting Form (e.g., CRF)

Required SOP Elements:	**Suggested Tools/Templates:**
1. Identifying and defining adverse events Define classification systems For instance: a. Anticipated/expected and Unanticipated/unexpected b. Device/procedure relatedness c. Seriousness of event d. Product complaints	Standardized definitions and classifications based on therapeutic area
2. Investigator Reporting Address information to be provided in study materials (e.g., protocol, CRFs). Include the following: a. List or statement of anticipated/expected AEs b. Types of AEs requiring reporting (e.g., every adverse event vs. a subset of product or study-related events) c. Methods to report AEs d. Obligations for reporting events (e.g., IRB/EC, sponsor, regulatory authority) e. Information required by sponsor (E.g., event description, date of onset, severity or AE classification, actions taken, outcome or resolution status) f. Time frame for investigator reporting	Template for standard protocol language Template for standard CRF elements for AE reporting
3. Adverse Event Review Describe the internal review process for: Event classification Who is responsible for reviewing (monitor, study team, regulatory) a. Time frames for review b. Documentation requirements c. Trend analysis to allow prompt knowledge of potential safety issues Describe any external review process (e.g., clinical event committee, data monitoring committee)	Flowchart for AE reporting Guidelines for a Data Safety Committee or Adverse Events Committee
4. Internal Reporting Describe procedures for reporting adverse event information to Product Assurance groups or other functional groups required by the business. Include the following: • AEs associated with the investigational device/study	

Required SOP Elements:	Suggested Tools/Templates:
• AEs associated with commercially released product • AEs that may represent product complaints	
5. External Reporting Define the process and requirements for: a. Expedited and routine reporting to regulatory authorities b. Reporting to IRB/EC and investigators c. Post-market or vigilance reporting d. Reporting AEs from other clinical studies or complaints from all countries for the product or therapy being evaluated Note: Consult laws and regulations of the countries where studies are to be conducted for geography-specific requirements	CQRC-009 Policy on Adverse Event Reporting to Regulatory Authorities Matrix of reporting requirements by geography

APPENDIX O

Topic: Training of Investigation Site Personnel
Purpose: To describe the process for developing, implementing and documenting study-specific training of investigation site personnel involved in clinical studies.
Related Corporate Policy, Procedure, or Guidance:
SOP Deliverables: • Training Documentation Form

Required SOP Elements:	**Suggested Tools/Templates:**
1. Developing Training Requirements Address the following elements: a. Topics and materials to be covered b. Study-specific training needs (e.g., protocol, product) c. Personnel to be trained based on responsibility in the study d. Methods of training (i.e., investigator/coordinator meeting, conference call, on-site) e. Timing and frequency of training f. Identification of trainers by functional role	Site Training plan
2. Required Training Components Training materials will include the following: a. Technical overview of product(s) b. Protocol overview c. Study procedures d. Managing investigational product disposition e. Investigational device/product accountability procedures f. Procedures for returning unused/explanted product(s) g. CRF completion and management h. Investigator's responsibilities i. Sponsor's responsibilities j. Procedures for obtaining informed consent k. IRB/EC requirements l. Procedures for adverse event reporting m. Procedures for study deviation reporting n. Monitoring requirements and expectations o. Potential for regulatory inspection and audit by sponsor p. Site record maintenance and retention q. Device/product reimbursement information (based on geographic regulation) r. Investigation site and subject compensation s. Regulatory requirements for commercially approved products used in a clinical study, including adverse event and complaint reporting t. Other regulatory requirements not listed above such as geography-specific regulations.	Training materials checklist

Required SOP Elements:	Suggested Tools/Templates:
3. Documentation of Training Describe the process for documenting training. The following items must be documented: a. Study name or training title b. Date of training c. Attendees name d. Name of trainer(s) e. General nature of training (e.g., protocol, product technology, regulations) f. Maintain a copy of training materials	Training documentation form
4. On-going Study Training Process for identifying and training new site personnel when staff changes occur during a study.	

APPENDIX P

Topic: Investigator and Subject Compensation
Purpose: To describe the process and requirements for issuing investigator and subject compensation.
Related Corporate Policy, Procedure, or Guidance: **Medtronic Business Conduct Standards**
Required Documents (Deliverable as a result of following SOPs) **SOP Deliverables:** • Fully executed investigator/site compensation agreement • Subject compensation information in consent document

Required SOP Elements:	**Suggested Tools/Templates:**
1. Investigator/Site Compensation Process for issuing investigator/site compensation. Include the following: a. Fully executed investigator/site compensation agreement is available, including the amount and schedule of payments b. General criteria for determining when payments are due c. Determination of general market rate or fair market value for the work product and services performed d. Internal payment request and authorization e. Requirements for correspondence accompanying investigator compensation f. Documentation required for record retention	Payment/Check Request Form Study compensation letter template
2. Subject Compensation or reimbursement Describe the process for payments to study subjects if applicable to a study. Include the following: a. Process to determine if payment is appropriate for study, such as provision (if any) for payments to be made to subjects for reimbursement of expenses (e.g., travel, lodging, mileage, food, etc.) b. The amount and schedule of payments must be set forth in the informed consent document c. Internal payment authorization and check requests d. Requirements for correspondence accompanying subject payments e. Documentation required for record retention	Payment/Check Request Form Study compensation letter template
3. Business Conduct Standards Require all investigator and patient compensation to adhere to Medtronic Business Conduct Standards.	

APPENDIX Q

Topic: Investigational Product Accountability
Purpose: To establish the requirements for investigational product accountability and tracking. **Note:** Device/product accountability procedures are required for investigational products as defined in the policy CQRC-036, regardless of the type of study
Related Corporate Policy, Procedure, or Guidance: CQRC-036 Policy for Investigational Device/Product Accountability CQRC-036-G01 Guideline on Investigational Device/Product Accountability
SOP Deliverables: • List of sites authorized to receive investigational product • Investigational Product Disposition Log

Required SOP Elements:	**Suggested Tools/Templates**
1. Product storage at sponsor If investigational product is stored by clinical personnel, specify the procedures for secure storage and access by only authorized personnel.	
2. Authorizing shipment a. Define process for authorizing shipment to investigation sites, field and clinical personnel. b. Identify method to track on-going site status for receiving investigational product.	Checklist for shipment authorization Shipping request form template
3. Inventory tracking Define requirements for a product tracking system and traceability documentation. Include provisions for determining when commercially released product enters the clinical study and is considered to be investigational.	
4. Labeling Clinical Product "Caution, Federal law limits this product to investigational use."	
4. Inventory management at investigational sites Describe how investigational product will be maintained and tracked at sites. Include the following: a. Inventory storage requirements, security b. Product disposition log c. Documentation required for return of investigational product d. Documentation required for disposal of investigational product (eg, documented method of disposal)	Product disposition log

Required SOP Elements:	Suggested Tools/Templates
5. Returned Product Describe the process for return and receipt of investigational product by the sponsor.	Investigational product return form template
6. Inventory Reconciliation Describe the process for inventory reconciliation, including all investigational products shipped from finished goods, field and consignment inventory, and end/use disposition.	Template for reconciliation report

APPENDIX R

Topic: Study Closure	
Purpose:	To describe the process to close a completed study or to prematurely suspend or terminate a clinical study at the site, at the sponsor, and with the regulatory authorities.
Related Corporate Policy, Procedure, or Guidance: CQRC-008-P01 Procedure for Clinical Studies Monitoring CQRC-028 Quality Records Policy	
SOP Deliverables: • Notification to regulatory authorities	

Required SOP Elements:	**Suggested Tools/Templates:**
1. Types of study or site closure Define the types of study or site closure: a. Completed Site/Study – When sponsor and/or regulatory requirements have been satisfied per the investigation plan and/or decision of the business b. Suspended Site/Study – Temporarily postponement of study activities related to enrollment or distribution of the investigational product c. Terminated Site/Study – Discontinuation by sponsor or by withdrawal of IRB/EC or regulatory approval of an investigation prior to completion.	
2. Completed Site/Study Describe the process for closing a completed study. Identify responsibilities, procedures, and required documentation to close the study at the site, at the Sponsor, and with regulatory authorities. Include the following: a. Identify who is involved in the decision making process and required documentation (e.g., rationale, approvals) b. Regulatory authorities notification, if required by regulations c. Investigator notification requirements (e.g., study closure date, rationale for closure, discontinuation of data requirements, and disposition of investigational products, record retention requirements, IRB/EC notification d. See closure activities below	Checklist for investigator notification requirements
3. Suspended Site/Study Describe the process for suspending a clinical study or site: a. Identify who is involved in the decision making process and required documentation (e.g., rationale, approvals) b. Procedure to notify the sites, IRB/EC if required by regulation or institutional policy c. Regulatory authority notification, if required by regulations d. Identify the process for reactivating or terminating the study or site	Checklist for investigator notification requirements

Required SOP Elements:	Suggested Tools/Templates:
e. Address follow-up for existing patients	
4. Terminated Site/Study Describe the process for prematurely stopping a clinical study or site: a. Identify who is involved in the decision making process and required documentation (e.g., rationale, approvals) b. Identify the procedure to notify the sites, IRB/EC, if required by regulation or institutional policy c. Regulatory authority notification, if required by regulations d. Identify the closure activities at the site and at the sponsor that will be required (see below) e. Address follow-up for existing patients	Checklist for investigator notification requirements
5. Site closure activities Define the activities to be performed at an investigation site during a study closure visit for a "completed" study and a "permanently terminated" study. Include the following: a. Investigator/study files are complete and accurate b. All CRFs, clarification and missing data received c. Annual and interim reports (as required by regulation) are up to date d. Deficiencies with the administrative (or regulatory) binder are resolved or closed e. Investigational product accountability is complete f. Equipment to be returned to sponsor g. Record retention requirements agreed by investigator h. Obligation for final reports to be submitted by investigators as required by regulations i. Other activities defined by the sponsor or protocol	Checklist with study closure monitoring report
6. Sponsor closure activities Describe the process for study closure at the Sponsor. Include the following: a. Project, subject, and site files are complete and accurate b. Reconciliation of unused, used or explanted investigational-labeled products c. Final compensation and contractual obligations d. Complete the final report for submission to sites, IRB/EC and regulatory authorities e. Record retention procedures f. Process to track financial disclosure after study closure (if required by regulation)	Close-out checklist (sponsor) Template for final clinical report

APPENDIX S

Topic: Training of Medtronic Personnel
Purpose: To describe the process for training and documenting training of Medtronic personnel involved in a clinical study.
Related Corporate Policy, Procedure, or Guidance: CQRC-020 Personnel Training Policy
SOP Deliverables: • Training Plan • Training Record

Required SOP Elements:	**Suggested Tools/Templates:**
1. Definitions **Training Plan** – A document that outlines the specific training an employee needs and will receive in order to perform his/her job function. The Training Plan may be a separate document or part of the Individual Development Plan (IDP). **Training Record** – A record (hard copy or electronic) used to document training received.	
2. Training Plan Identify and document training requirements and frequency based on functional role (include both employee and contract labor) as part of an overall training plan. Note: For outsourcing (e.g., CRO) training requirements see Appendix V.	Job/training matrix
3. New hire assessment Address requirements to assess new employee skills and needs as part of an overall training plan.	Training plan template
4. Training Record Describe the process for documenting training in the department training file. The following items must be documented in the training record a. Study name or training title b. Date of training c. Attendees name d. Name of trainer(s) e. General nature of training (e.g., protocol, product technology, regulations)	Training record template

APPENDIX T

Topic: Document Control
Purpose: To describe the process for the approval, revision and maintenance of controlled clinical documents and records.
Related Corporate Policy, Procedure, or Guidance: CQRC-015 Document Control System CCRA-037 Policy on Control of Clinical Documentation CQRC-037-G01 Example Templates for Control of Clinical Documentation
SOP Deliverables: • Approval and Change History Documentation

Required SOP Elements:	**Suggested Tools/Templates:**
1. Documents requiring document control Identify documents that are subject to document control procedures.	CQRC 037 Policy on Control of Clinical Documentation
2. Review of Draft Documents a. Identify document control procedures to create, review and edit new documents. b. Draft documents should be clearly identified as such. c. Identify system used to track routing of documents.	Routing Sheet template
3. Approval Process for document approval, including documentation, effective date, and change history record.	Approval Record template Change History Record template
4. Version Control Format Describe document requirements for version control (e.g., footer, pagination, control number).	CQRC-037-G01 Example Templates for Control of Clinical Documentation
5. Document Maintenance and Retention Describe where the original master will be maintained in a secure location.	
6. Training Determine the need for training on the new or modified document and how this training will be completed and documented.	
7. Distribution Identify requirements for document distribution and traceability.	
8. Revisions Describe the process and requirements for initiating changes to approved documents: a. Draft, review, and edit process b. Updating the change history records c. Document approval	Document Change Order template

Required SOP Elements:	Suggested Tools/Templates:
d. Identification of affected documents e. Document maintenance, retention, training, and distribution (see above) f. Disposition of retired documents	
9. Records Retention Describe the process for archiving study records, including Retention period & records custody	See CCRC-028 Quality Records Policy

APPENDIX U

Topic: Preparing for Inspections by External Agencies
Purpose: To describe the process for preparing and managing inspections performed by external parties. **Note:** For low risk situations, this may be a statement or reference to the organization's general procedure.
Related Corporate Policy, Procedure, or Guidance: CQRC-029 Regulatory and Enforcement Policy
SOP Deliverables: None

Required SOP Elements:	**Suggested Tools/Templates:**
1. Preparation for a study-related sponsor inspection Include the following requirements: a. Identify qualified individual(s) to serve as the clinical representative or clinical inspection coordinator b. Identify who to contact when notice of an inspection is received. Include notification to business management and Corporate Quality, Regulatory and Clinical (CQRC) c. Identify other team members to prepare and assist with the inspection d. Describe the process to train personnel to be involved in inspections	Preparation checklist
2. During the sponsor inspection Describe requirements to be followed during the inspection, such as: a. A list of documents and copies provided to the inspector(s) b. Notes on each day's progress c. Informing Corporate (CQRC) and business management on major non-compliance issues, unreasonable requests, prolonged delays, or other unusual development before or during the inspection	
3. Upon completion of the sponsor inspection a. Identify who will be notified of the results of the inspections. Corporate (CQRC) review is mandatory. b. Provision to forward Corporate (CQRC) the following documents if available: • Notice of Inspection • Observations • Draft and final responses to observations and exhibits or attachments • Establishment Inspection Report (US) • Warning or untitled letters and responses	
4. Investigator, IRB/EC inspections (study related)	Preparation checklist

Required SOP Elements:	Suggested Tools/Templates:
Describe the process to be followed for an intended inspection by a regulatory authority. Include the following: a. Clinical and other sponsor personnel to be notified b. Medtronic inspection contact c. Site training d. Investigator/site support in preparation for or during inspection, if requested e. Reporting observations and response (see Item 3 above)	Standard training information
5. CRO inspections (study related) Describe the process to be followed for an intended inspection by a regulatory authority. Include the following: a. Clinical and other sponsor personnel to be notified b. Medtronic inspection contact c. CRO support in preparation for or during inspection d. Reporting observations & response to sponsor (see item 3 above)	

APPENDIX V

Topic: Outsourcing Activities
Purpose: To describe the process for selecting, managing, training and communicating with outsourcing vendors used for clinical studies.
Related Corporate Policy, Procedure, or Guidance:
SOP Deliverables: • Confidentiality agreement-for proprietary information • Fully executed contract or agreement • Documented qualifications of subcontractors and professional services

Required SOP Elements:	**Suggested Tools/Templates:**
1. Outsourcing Plan Define how decisions will be made to pursue outsourcing activities.	Plan template
2. Confidentiality Agreement Require confidentiality agreement for proprietary information.	Template from legal
3. Qualification of Outsourcing Vendor Describe the process for a. identifying outsourcing candidate(s) b. documented screening and qualification c. documented evaluation of vendor SOPs to be used for the study	Evaluation checklist CVs or resumes of prospective candidates
4. Selection of Outsourcing Vendor Describe the process for reviewing outsourcing candidate(s) and final selection.	
5. Contract/Project Agreement Describe the process for drafting and executing the contracts or agreements.	Example work order checklist or legal template
6. Training of Outsourcing Personnel Describe how outsourcing personnel will be trained and managed (may refer to clinical management plan/monitoring plan for study specific details)	Training logs
7. Evaluating Performance Describe requirements for evaluating the activities performed by the outsourcing vendor. Document the evaluation.	
8. Corrective and Preventive Action Describe a process for communicating and documenting issues and corrective actions.	

APPENDIX W

Topic: Emergency Use, Compassionate Use, and Humanitarian Use
Purpose: To describe the procedures to be followed in special circumstances when an investigational product is used outside of the approved investigation plan/protocol. Examples include (but not limited to): Emergency Use (FDA), Compassionate Use (FDA), and Humanitarian Use (EU, FDA).
Related Corporate Policies, Procedures, Guidance
SOP Deliverables: • Required documentation from physician • IRB/Ethics Committee and regulatory authorities

Required SOP Elements:	**Suggested Tools/Templates:**
1. Definitions: Consult applicable country regulations, for example: a. Emergency Use: (FDA) b. Compassionate Use (FDA) c. Humanitarian Use (EU, FDA) d. Others, as appropriate to product and geography	
2. Regulatory Requirements Identify specific regulatory requirements and describe procedures for each category of use. Address the following: a. Required documentation from physician b. Documentation of patient condition supporting use of the investigational product c. Regulatory authority notification or pre-approval d. IRB or Ethics committee notification or pre-approval e. Sponsor notification or pre-approval f. Sponsor process for release of investigational product g. Documentation of relevant physician/site training h. Communication of physician obligations after use, such as follow-up care and reporting patient status i. Consideration of including the site and patient data in the clinical study. This includes the extent to which a protocol will be followed and how patient data will be reported to the sponsor. j. Informed consent and data release k. Internal (sponsor) review of patient status l. Inclusion of data in clinical reports and regulatory submissions	Checklist of requirements applicable to specific category of use Sponsor approval form applicable to specific category of use Informed consent template specific to category of use and addressing clinical study if applicable.

APPENDIX X

Topic: External Advisory Committees
Purpose: To describe the process for identifying and selecting members for external advisory committees used for activities such as adverse event review, data monitoring and study oversight. **Note:** Corporate Policy does not require the use of Advisory Committees. However, if such committees are used, SOPs must address the following elements.
Related Corporate Policy, Procedure, or Guidance: Medtronic Business Conduct Standards
SOP Deliverables: • Membership roster and meeting documentation • Confidentiality and consulting agreements

Required SOP Elements:	**Suggested Tools/Templates:**
1. Committee Role Describe the purpose and role of the committee. Indicate when this committee is used. Examples of advisory committees include: a. Adverse event committee b. Data monitoring committee c. Study steering committee d. Publication committee	
2. Membership Criteria a. Establish criteria that individuals must meet in order to be selected as a committee member b. Committee composition, including chair c. Requirements for confidentiality and consulting agreements d. Arrangements for Compensation	Confidentiality and consulting agreements See MDT Business Conduct Standards
3. Committee Procedures a. Role of the sponsor b. Specific processes to be followed by committee c. Frequency and format of meetings d. Requirements for documenting and filling meeting minutes	Guideline for committee operations

APPENDIX Y

Topic: Publication Policy
Purpose: To establish requirements governing the publication of study data.
Related Corporate Policy, Procedure, or Guidance:
SOP Deliverables: • Study publication plan (may be part of another document)

Required SOP Elements:	**Suggested Tools/Templates:**
1. Publication Strategy Establish requirements for creating study publication plans. Address the following: a. Determine if prior registration and/or results posting in a public database is required by regulation, Medtronic policy or from a business strategy perspective. b. Process to ensure that clinical trial outcomes, whether positive or negative, will be made public in an appropriate manner.(e.g., scientific literature, key therapeutic meetings, public database of trial outcomes information) c. Determine the need for a publication governance committee. d. Determine the need for a formal publication plan that is separate from other study documentation (see #2 below) e. Determine how the publication plan will be communicated to investigators (e.g., explained in the protocol, investigator agreement or another document). f. Determine the process for Medtronic review and approvals required for release of any study information into the public domain, including registration in a public study registry.	Publication guidelines and standards: www.icmje.org World Health Organization International clinical Trials Registry Platform www.who.int/ictrp/en/ NIH (FDA)database www.clinicaltrials.gov
2.Publication Plan Content Address the following: a. Objectives of the publication(s) b. Targeted audiences, recommended journals, medical congresses and timing of these activities. c. Whether preliminary study results can be released prior to study completion. d. Extent to which study results will be offered for publication to investigators and non-investigators. e. Study policy regarding publications based on a single-center experience or other subsets of the full data set. f. Process for identifying and selecting authors (e.g., authorship criteria). g. Sponsor guidelines provided to investigators, including the requirement for outcomes to be presented without bias and with full disclosure. h. Expected timelines for manuscript submissions.	

Required SOP Elements:	Suggested Tools/Templates:
i. Process for identifying Medtronic personnel to assist the author(s) and their responsibilities	
3. Review, Approval & Submission of Publications a. Process for identifying and selecting individuals to review publications b. Process for reviewing and documenting approval c. Expected timelines for reviewing, approving and submitting publications d. Process for submitting publications, including who will be notified of publications (Medtronic personnel and others) e. Tracking of requests, draft manuscripts and progress toward publication.	Publication/abstract approval form
4. Ad Hoc Publication Proposal Requests Describe the process for approving and responding to ad hoc publication proposals that are outside of a previously defined publication plan. Address the following for internal (Medtronic) and external requests. a. Formal written requests, including the following: • Type of publication (e.g., abstracts, poster, manuscript) • Objective of the analysis • References or supporting articles • Targeted journals • Timelines to meet publication goals • Data to be provided • Medtronic resource needs, if any b. Documented review and approval of request c. Procedures regarding access to data (see also Appendix K).	Publication Proposal Form Access to Data Request Form

CHANGE HISTORY		
REVISION	**DATE**	**DESCRIPTION of CHANGE**
A	Feb 6, 2003	Initial Release
1.0 – 2.0		Conversion to MCRS Document Control System. No changes made.
3.0	Jan 24, 2007	Periodic Update 1. Scope Change – Medtronic Worldwide 2. Applicability – Studies where data will be submitted to regulatory authorities. This includes both pre- and post-market studies. 3. Global focus – not regulatory specific 4. Three topics upgraded from "recommended" to "required" • Preparing for Inspections by External Agencies • Outsourcing Activities • Emergency and Compassionate Use/ Humanitarian 5. General update and editing throughout document
4.0		1. Expanded policy to cover all types of studies 2. Changed title to "Policy On Standard Operating Procedures For Clinical Studies" 3. Change in Purpose and Policy 4. Added requirement #6 and #7 5. Deleted Definitions and Abbreviations per Corporate format 6. Changed "Required Documentation" to "SOP Deliverables" 7. Added reimbursement strategy to Appendix C 8. Added BSC considerations to Appendix C & E 9. Added sections on data access to Appendices K &Y 10. Expanded elements for publication policy 11. Expanded elements for electronic databases 12. Two topics upgraded from "recommended" to "required" X. External Advisory Committees Y. Publication Policy 13. Extensive editing though out document

TITLE: Policy on Medtronic Clinical Trial Principles

SCOPE: Medtronic Worldwide

PURPOSE: To establish common principles that guide the design, conduct and reporting of Medtronic-sponsored clinical trials.

POLICY: The Medtronic Clinical Trial Principles will be used to guide the design, conduct and reporting of Medtronic-sponsored clinical trials.

REQUIREMENTS:

A. All Medtronic businesses and geographies will incorporate the Medtronic Clinical Trial Principles into standard operating procedures for clinical trials.

B. Clinical trials include Medtronic-sponsored human clinical studies that are prospectively designed to develop safety and efficacy data that will directly impact clinical practice.

C. The Medtronic Clinical Trial Principles:

1) Medtronic clinical trials will be conducted to provide relevant data in order to help answer important open questions pertaining to product safety, efficacy, cost-effectiveness and appropriate utilization.

2) Medtronic clinical trials will be designed without bias and with the necessary scientific rigor to ensure that results are statistically meaningful and defensible.

3) Medtronic clinical trials will be conducted in compliance with all governing laws and regulations, and with adequate oversight to ensure that outcomes are valid and appropriately documented.

4) Medtronic clinical trial outcomes, whether positive or negative, will be made public in an appropriate manner.

5) Medtronic clinical trial outcomes will be presented without bias and with full disclosure.

6) Individuals and institutions involved in designing and conducting Medtronic clinical trials and presenting clinical data from them will be compensated fairly and equitably, taking into account all circumstances surrounding the particular trial, including general market rates for similar trials as well as market compensation paid to the individuals and institutions by other parties (in this regard, Medtronic stock or stock options will not be used as compensation).

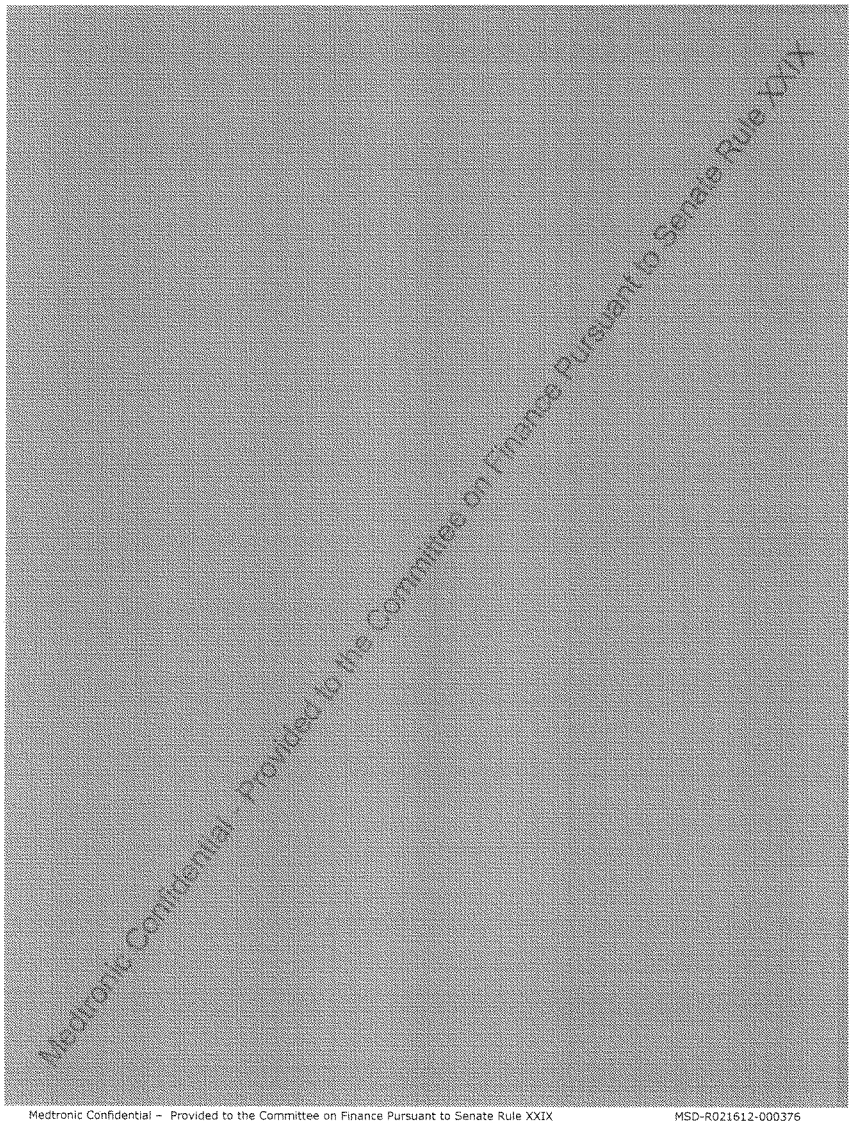
7) All consultation with Medtronic that is provided by an investigator will comply with the "Medtronic Business Conduct Standards" on consulting, research, and advisory arrangements that establish work product and compensation rates.

8) A listing of all pivotal Medtronic clinical trials will be maintained and made public, including required registration on official public databases.

RESPONSIBILITY:
The management for each Medtronic business and geography is responsible for implementation of and training, and compliance with this policy.

CHANGE HISTORY	
VERSION	**SUMMARY OF CHANGES**
2.0 New	Policy

Owner: Lisa Griffin Vincent
Department: Corporate Clinical



Medtronic	CONFIDENTIAL	DOCUMENT/RECORD

This document/record is electronically controlled, printed copies are considered uncontrolled.

Name	Version	Author
032-Medtronic Clinical Trials Principles	3.0	Debra Pederson

Title: Medtronic Clinical Trials Principles

Approvals

Signed By	Meaning of Signature	Date/Time (GMT)
Lisa Griffin Vincent	CQRC Clinical	02/15/2008 17:34:17
Chip Whitacre	CQRC Operations	02/19/2008 22:02:15
Michael Morton	CQRC Regulatory	02/22/2008 19:33:03
Sandy Kalter	CQRC Legal	03/05/2008 19:19:58
Susan Alpert	Chief Quality and Regulatory Officer	05/22/2008 13:27:40

TITLE: Policy on Medtronic Clinical Trial Principles

SCOPE: Medtronic Worldwide

PURPOSE: To establish common principles that guide the design, conduct and reporting of Medtronic-sponsored clinical trials.

POLICY: The Medtronic Clinical Trial Principles will be used to guide the design, conduct and reporting of Medtronic-sponsored clinical trials.

REQUIREMENTS:

A. All Medtronic businesses and geographies will incorporate the Medtronic Clinical Trial Principles into standard operating procedures for clinical trials.

B. Clinical trials include Medtronic-sponsored human clinical studies that are prospectively designed to develop safety and efficacy data that will directly impact clinical practice.

C. The Medtronic Clinical Trial Principles:

1) Medtronic clinical trials will be conducted to provide relevant data in order to help answer important open questions pertaining to product safety, efficacy, cost-effectiveness and appropriate utilization.

2) Medtronic clinical trials will be designed without bias and with the necessary scientific rigor to ensure that results are statistically meaningful and defensible.

3) Medtronic clinical trials will be conducted in compliance with all governing laws and regulations, and with adequate oversight to ensure that outcomes are valid and appropriately documented.

4) Medtronic clinical trial outcomes, whether positive or negative, will be made public in an appropriate manner.

5) Medtronic clinical trial outcomes will be presented without bias and with full disclosure.

6) Individuals and institutions involved in designing and conducting Medtronic clinical trials and presenting clinical data from them will be compensated fairly and equitably, taking into account all circumstances surrounding the particular trial, including general market rates for similar trials as well as market compensation paid to the individuals and institutions by other parties. In this regard, Medtronic stock or stock options will not be used as compensation.

7) All consultation with Medtronic that is provided by an investigator will comply with the "Medtronic Business Conduct Standards" on consulting, research, and advisory arrangements that establish work product and compensation rates.

8) A listing of all pivotal Medtronic clinical trials will be maintained and made public*, including required registration on official public databases.

*posted on www.MedtronicTrials.com

RESPONSIBILITY:
The management for each Medtronic business and geography is responsible for implementation of and training, and compliance with this policy.

CHANGE HISTORY	
VERSION	**SUMMARY OF CHANGES**
2.0	New Policy
3.0	1. Item #6 – Removed statement from parentheses and made into a sentence. ("In this regard, Medtronic stock or stock options will not be used as compensation.") 2. Item #8 – Added asterisk and explanation: "*posted on www.MedtronicTrials.com"

Owner: Lisa Griffin Vincent
Department: Corporate Clinical

Medtronic **Memphis Headquarters Local Instruction**

Review and Approval for Clinical Data Publication

Document ID: **CL050** Version: **A**

Effective Date: **12/10/2007** Owner: **Barry Paller**

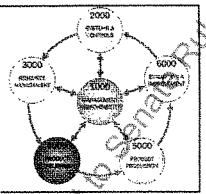


TABLE OF CONTENTS

PURPOSE 3

SCOPE 3

RESPONSIBILITIES 3

INSTRUCTION 5

1 Publication of Data from Single Investigator Site [A] [B] [C] [D] [E] [F] [G] 5

2 Publication of Data from Multiple Investigator Sites of Pivotal Trial or Data from Entire Cohort of Pilot Trial [A] [B] [C] [D] [E] [F] [G] 6

3 Publication of Data from Entire Pivotal Clinical Study or Combined Data from Multiple Studies [A] [B] [C] [D] [E] [F] [G] 7

4 Publication of Subgroup Analysis of Pivotal Trial [A] [B] [C] [D] [E] [F] [G] 8

5 Dissemination of Regulatory Progress Reports of Clinical Trial [A] [B] [C] [D] [E] [F] [G] 8

6 Data Mining of Regulatory Clinical Trial Data [A] [B] [C] [D] [E] [F] 9

7 Access to Clinical Raw Data [A] [B] [C] [D] [E] [F] [G] 9

8 Approval Through E-mails [E] [F] 10

RECORDS 10

DEFINITIONS 11

REFERENCES 11

REVISION HISTORY 12

Medtronic

Review and Approval for Clinical Data Publication

PURPOSE

The purpose of this document is to establish a review and approval process for the publication of clinical data. The procedure is intended to ensure a high level of scientific standards, to guarantee the accuracy of data, and to maintain the integrity of Medtronic study publications, as well as to reduce the impact of publications of clinical data on the worldwide regulatory approval process of the product under investigation.

SCOPE

The information in this document applies to all requests for clinical data and the development of publications that utilize data from the clinical studies sponsored, initiated, and conducted by the clinical /regulatory departments at Medtronic's Spinal and Biologics Business. These studies include, but are not limited to, those conducted under the FDA (IDE or IND) and other governmental regulations. Submissions of clinical trial data to governmental, regulatory, insurance, or other agencies inside or outside the United States to seek product approval, support continued clinical use, or support reimbursement/coverage decision are not covered under this procedure.

RESPONSIBILITIES

Indicator [1]	Function or Role	Summary of Responsibilities
[A]	Publication Coordinator	A Medtronic employee who is charged to coordinate a specific publication project.
[B]	Investigator/author	Site investigator/author who is requesting to publish clinical data responsible for adhering to the signed investigator agreement for the study and this policy.
[C]	Clinical Affairs staff	Medtronic clinical affair employees responsible for assisting with the request to publish clinical data.
[D]	Regulatory staff	Medtronic regulatory employees responsible for assisting with the request to publish clinical data.
[E]	Biostatistics and Strategic Research	Medtronic biostatistics and strategic research employees responsible for assisting with the request to publish clinical data.
[F]	Study Statistician/Analyst	Medtronic biostatistical and analytical employee who gathers data, documents the executed request, and saves all the datasets used, programs, and output.
[G]	Publication Committee	Medtronic employees who develop publication strategy and schedule, if necessary, make decisions on requests for publishing clinical data, and review all forms of publications for a specific device, clinical study, or project. The Publication Committee may include, but is not limited to, qualified individuals representing areas of clinical affairs, biostatistics, marketing/product development, health-economics/reimbursement, and regulatory. The head of Biostatistics and Strategic Research or his/her designee will work with various groups to set up the committee membership and notify each member via a memorandum.

[1] **Responsibility Indicators** are used throughout this document to highlight responsibilities for each affected function or role.

Review and Approval for Clinical Data Publication

INSTRUCTION

1 Publication of Data from Single Investigator Site [A] [B] [C] [D] [E] [F] [G]

1.1 An investigator can publish pilot and pivotal clinical study results specific to his/her clinical site when desired.

1.2 In advance, Medtronic must be notified of this in accordance with the signed investigator agreement for the study.

1.3 The final draft of the abstract, manuscript, or any other form of publication should be forwarded to Medtronic for review.

1.4 The publication coordinator will submit the manuscript to the publication committee for review, and send comments, if any, back to the investigator.

1.5 Medtronic reserves its right to delay such a publication until the full study results are published.

1.6 Through the publication coordinator, the investigator should supply a copy of the published abstract or article to Medtronic for documentation.

1.7 With the assistance and support of the publication coordinator, the Biostatistics and Strategic Research staff will use the CLF050-02, Clinical Data Publication Tracking Form to document the publication notification and review, along with a copy of the final publication.

1.8 If Medtronic is requested to provide summary and/or statistical analysis of clinical data, including summary data manually prepared, the Biostatistics and Strategic Research staff will work with the publication coordinator to prepare the CLF050-01, Clinical Data Publication Request Form and to seek the approvals from management responsible for the study from the Regulatory, Clinical Affairs, and Biostatistics and Strategic Research groups,.

1.9 According to the approved request, the Study Statistician/Analyst and/or other clinical staff complete the request and after appropriate internal reviews, send the results to the publication coordinator and/or directly to the investigator, as well as those who approved the request.

1.10 The Study Statistician/Analyst or other clinical staff should document the executed request and save all the datasets used, programs, and output. Other clinical staff will also make appropriate documentation if they have provided information for the publication.

1.11 For major data update of the publication, repeat Steps 1.2 to 1.10.

2 Publication of Data from Multiple Investigator Sites of Pivotal Trial or Data from Entire Cohort of Pilot Trial [A] [B] [C] [D] [E] [F] [G]

2.1 Investigators can publish results from a whole pilot study cohort and pooled pivotal clinical study results specific to their clinical sites when desired as long as the patient cohort size represents less than 50% of the total patient population for the pivotal study. Further, for pivotal studies with more than one treatment group, the patient cohort size for each treatment group being discussed cannot exceed 50% of the total number of patients per group.

2.2 In advance, Medtronic must be notified of this in accordance with the signed investigator agreement for the study.

2.3 For these types of publications, Medtronic is usually requested to provide summary and/or statistical analysis of clinical data. The Biostatistics and Strategic Research staff will work with the publication coordinator to prepare the CLF050-01, Clinical Data Publication Request Form and to seek the approvals from the publication committee.

2.4 According to the approved request, the Study Statistician/Analyst and/or other clinical staff complete the request and after appropriate internal reviews, send the results to the publication coordinator and/or directly to the investigator(s)/author(s), as well as those who approved the request.

2.5 The Study Statistician/Analyst should document the executed request and save all the datasets used, programs, and output. Other clinical staff will also make appropriate documentation if they have provided information for the publication.

2.6 The final draft of the abstract, manuscript, or any other form of publication should be forwarded to Medtronic for review.

2.7 The publication coordinator will seek the publication committee for review, and send comments, if any, back to the leading investigator/author.

2.8 Medtronic reserves its right to delay such a publication until the full study results are published.

2.9 Through the publication coordinator, the investigator should supply a copy of the published abstract or article to Medtronic for documentation.

2.10 With the assistance and support of the publication coordinator, the Biostatistics and Strategic Research staff will use the CLF050-02, Clinical Data Publication Tracking Form to document the publication notification and review, along with a copy of the final publication.

2.11 For major data update of the publication, repeat Steps 2.2 to 2.10.

3 Publication of Data from Entire Pivotal Clinical Study or Combined Data from Multiple Studies [A] [B] [C] [D] [E] [F] [G]

3.1 For each such publication project, the Publication Committee will develop appropriate publication strategy and schedule in advance, if necessary and be responsible for reviewing and approving for such publications.

3.2 Investigators cannot publish any preliminary or final results for an entire pivotal clinical study without prior approval from Medtronic. The initial publication of the final results cannot precede:

3.2.1 a pre-approval public presentation of the results for regulatory purposes, such as at an FDA Advisory Panel meeting,

3.2.2 the receipt of an approvable letter from a regulatory agency if a prior pre-approval public presentation is not required, or

3.2.3 a decision not to pursue regulatory approval(s) of the product or technology.

Because of the usual time lapse from submitting to publishing, a manuscript can be submitted before the aforementioned events, but should be reasonably expected to be published after one of these events.

3.3 The amassing of final clinical results from more than one pivotal clinical study for a publication is not permissible without prior approval from Medtronic. The considerations from Step 3.2 above apply to this situation and every involved study must meet the criteria.

3.4 Any exception to the criteria outlined in Steps 3.2 and 3.3 should be approved by the Publication Committee, with the justification specified on the CLF050-01, Clinical Data Publication Request Form. An example for such an exemption is to publish results of auxiliary study data that are neither primary nor secondary study endpoints as defined in the study protocol. Company's strategic need may also justify such an exemption.

3.5 Even if one or more of these criteria are met, Medtronic may deny a publication request based on strategic regulatory considerations such as pending approval in more than one country.

3.6 A request to publish the final results for the entire pivotal clinical study or the combined final results must be reviewed and approved by the Publication Committee. The request is documented on the CLF050-01, Clinical Data Publication Request Form. The Biostatistics and Strategic Research staff will prepare the CLF050-01, Clinical Data Publication Request Form and seek the approvals from the Publication Committee.

3.7 The Study Statistician/Analyst should document the executed request and save all the datasets used, programs, and output. Other clinical staff will also make appropriate documentation if they have provided information for the publication.

3.8 If the need arises, Medtronic staff or external consultant can develop and provide the study results, along with the description of study methodologies, via a publication template, including tables and graphs suitable for the publication, to ensure the accuracy and improve the efficiency.

3.9 The publication coordinator will send the study results and/or a template to the investigator(s)/author(s) and coordinate activities and communications for completing the publication draft.

3.10 The final draft of the abstract, manuscript, or any other form of publication should be forwarded to Medtronic for review.

3.11 The publication coordinator will seek the publication committee for review, and send comments, if any, back to the lead investigator/author.

3.12 Through the publication coordinator, the lead investigator/author should supply a copy of the published abstract or article to Medtronic for documentation.

3.13 With the assistance and support of the publication coordinator, the Biostatistics and Strategic Research staff should use the CLF050-02, Clinical Data Publication Tracking Form to document the publication notification and review, along with a copy of the final publication.

3.14 For major data update of the publication, repeat Steps 3.6 to 3.13.

4 Publication of Subgroup Analysis of Pivotal Trial [A] [B] [C] [D] [E] [F] [G]

4.1 Subgroup analyses that are not pre-specified in the study protocol are exploratory by nature. Publication of subgroup analysis results may also jeopardize the regulatory approval of the product under investigation, because of the issues associated with pooling data over various subgroups. If pooling data is not justified, the statistical power for assessing primary and secondary study hypotheses will be greatly decreased and thus the probability to meet the study objectives will be drastically decreased. It may also restrict the indications for the product use.

4.2 Therefore, publication of subgroup analysis results is not permissive before the criteria described in Steps 3.2 and 3.3 are met.

4.3 Any publication of subgroup analyses, regardless of patient cohort, should be subject to the same level of scrutiny described in Section 3 for review and approval.

4.4 Some examples of subgroup analyses that may impact the regulatory approval process are: comparing smoking patients with non-smoking patients, patients with worker's compensation with those without worker's compensation, radiculopathy patients with myelopathy patients, patients treated at one levels with those treated at two levels, and comparing patients treated at different spinal levels (e.g., L4-L5 versus L5-S1).

5 Dissemination of Regulatory Progress Reports of Clinical Trial [A] [B] [C] [D] [E] [F] [G]

5.1 Regulatory progress reports of a clinical trial, such as annual reports to FDA, are periodically distributed to individual investigators and their Institutional Review Boards (IRBs) according to the regulations. Such reports and other summaries of data may also be distributed inside or outside of Medtronic. Nevertheless, the use of such summary information and reports for any form of publications is subject to the procedures outlined above.

5.2 Use of US IDE trial data for international regulatory submissions or other purposes at any stages of the trial should have a separate review and approval process that at minimum involves the Regulatory, Clinical Affairs, Biostatistics and Strategic Research, and Global Healthcare Economics functions.

6 Data Mining of Regulatory Clinical Trial Data [A] [B] [C] [D] [E] [F]

6.1 Requests for analyses of IDE or other regulatory trial data for publications will in principle be limited to the trial investigator(s). Requests from other key opinion leaders (KOLs) or non-investigator surgeons for Medtronic may also be considered, if

6.1.1 The KOL/non-investigator surgeon has an effective confidentiality agreement with Medtronic;

6.1.2 There is no issue for complying all the relevant policies and codes of Medtronic business conduct; and

6.1.3 The request meets strategic research needs of the company.

6.2 In preparing for such a request, the publication coordinator should first seek the input from the marketing/product development group who sponsored the initial clinical study to align various publication interests and strategy.

6.3 The publication coordinator should work with the executive who is responsible for clinical affairs or his/her designee(s) to determine whether or not the request meets strategic research needs of the company.

6.4 The publication coordinator is charged with the responsibilities to ensure that the conditions in Section 6.1 are met by approving the data request form.

6.5 All such requests will follow the procedure defined in this document and other relevant company procedures.

7 Access to Clinical Raw Data [A] [B] [C] [D] [E] [F] [G]

7.1 Because the sensitivity of health information and related regulations, Medtronic will not provide complete raw datasets of a clinical study to any non-Medtronic employee for non-regulatory purposes, unless the Executive Management responsible for Clinical Affairs approves the exemption. Any provision of raw data will be subject to legal review to ensure compliance with all applicable privacy laws. Specific queries of data such as description of adverse events of a particular type can be provided to the individuals who work on a particular publication project that is approved by Medtronic.

7.2 For publication purposes, Medtronic will assist in summarizing and analyzing the clinical data and provide the author(s) with necessary summary information.

7.3 In any case where the supply of raw datasets of a clinical study to any non-Medtronic employee for non-regulatory purposes is deemed necessary and approved by the Executive Management and reviewed by legal, the Medtronic employee who sends the datasets is responsible for ensuring that the recipient of the datasets is under a confidentiality contract with Medtronic. Any (hard copy or electronic) form of the raw data should either be returned to Medtronic or verified as destroyed after the completion of an intended project.

8 Approval Through E-mails [E] [F]

8.1 All the approvals aforementioned in this procedure can be communicated via e-mail and documented by the Biostatistics and Strategic Research staff.

RECORDS

The following records will be maintained according to the retention standards defined by regulatory agencies, applicable Medtronic Corporate Policies, and record retention procedures:

- CLF052-01
- CLF052-02
- E-mail approval documentation

Review and Approval for Clinical Data Publication

DEFINITIONS

Clinical raw data
By-subject data collected from clinical studies and stored/presented in either an electronic format or a hard-copy format. Any provision of raw data will be subject to legal review to ensure compliance with all applicable privacy laws.

Pilot clinical study
A small-scale clinical study typically having fewer than 50 patients. A pilot study is considered to be the same as a feasibility study.

Pivotal clinical study
A large-scale clinical study with hypothesis testing and a sample size based on statistical considerations. The results from the study are often intended to serve as primary support for regulatory approval(s).

Publish
This term encompasses all modes of public data conveyance including, but not limited to, journal articles, books, and abstracts.

REFERENCES

CLF050-01, Clinical Data Publication Request Form 3, 4
CLF050-02, Clinical Data Publication Tracking Form 3, 4, 5

Medtronic

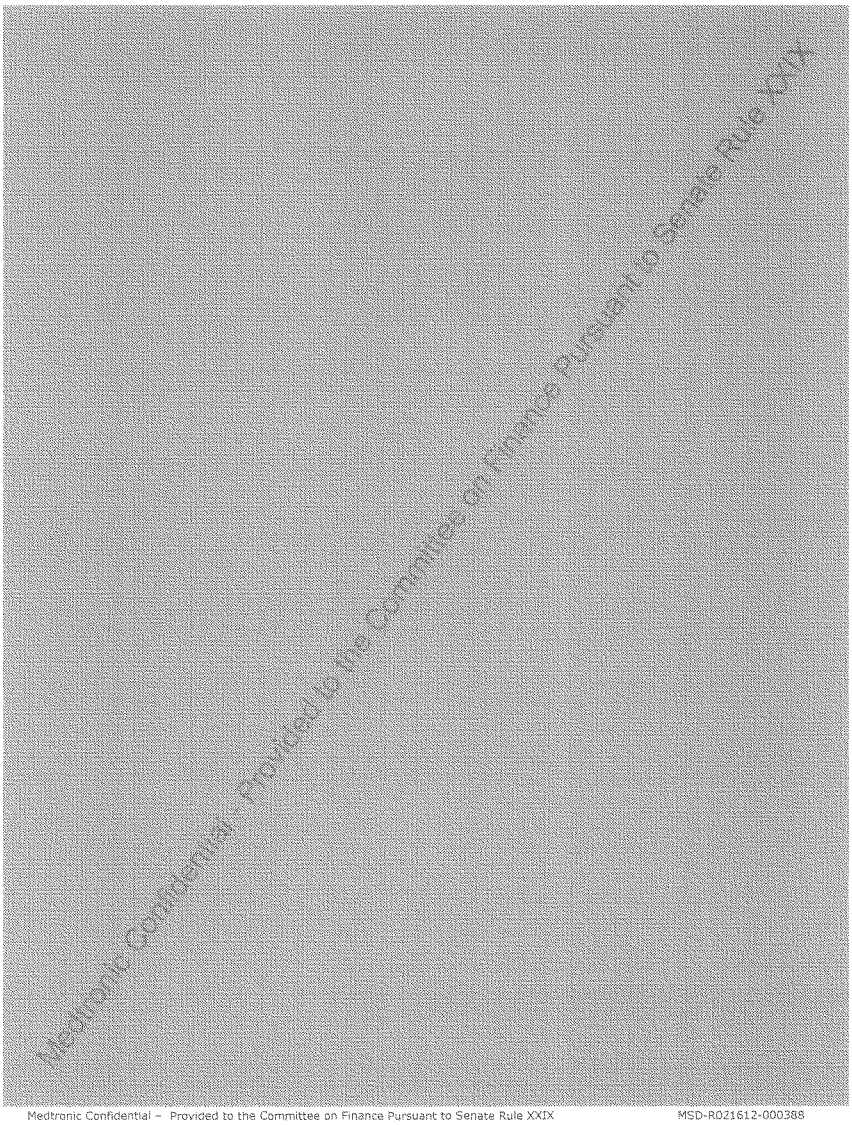
Memphis Headquarters Local Instruction

Document ID: CL050
Version: A
Effective Date: 12/10/2007

Review and Approval for Clinical Data Publication

REVISION HISTORY

Version	Originator	Description of Change	Date
A	Guorong Ma	Initial release.	12/10/07



Medtronic

Memphis Headquarters Local Instruction

Review and Approval for Clinical Data Publication

Document ID: **CL050** Version: **B**

Effective Date: **7/7/2008** Owner: **Barry Paller**

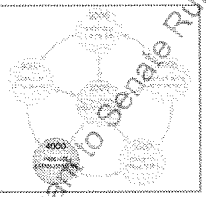


TABLE OF CONTENTS

PURPOSE 2

SCOPE 2

RESPONSIBILITIES 2

INSTRUCTION 3

1 Publication of Data from Single Investigator Site [A] [B] [C] [D] [E] [F] [G] 3

2 Publication of Data from Multiple Investigator Sites of Pivotal Trial or Data from Entire Cohort of Pilot Trial [A] [B] [C] [D] [E] [F] [G] 3

3 Publication of Data from Entire Pivotal Clinical Study or Combined Data from Multiple Studies [A] [B] [C] [D] [E] [F] [G] 4

4 Publication of Subgroup Analysis of Pivotal Trial [A] [B] [C] [D] [E] [F] [G] 5

5 Dissemination of Regulatory Progress Reports of Clinical Trial [A] [B] [C] [D] [E] [F] [G] 5

6 Data Mining of Regulatory Clinical Trial Data [A] [B] [C] [D] [E] [F] 5

7 Access to Clinical Raw Data [A] [B] [C] [D] [E] [F] [G] 6

8 Approval Through E-mails [E] [F] 6

9 Unapproved Uses [A] [C] [D] [G] 6

RECORDS 6

DEFINITIONS 7

REFERENCES 7

REVISION HISTORY 8

Review and Approval for Clinical Data Publication

PURPOSE

The purpose of this document is to establish a review and approval process for the publication of clinical data. The procedure is intended to ensure a high level of scientific standards, to guarantee the accuracy of data, and to maintain the integrity of Medtronic study publications, as well as to reduce the impact of publications of clinical data on the worldwide regulatory approval process of the product under investigation.

SCOPE

The information in this document applies to all requests for clinical data and the development of publications that utilize data from the clinical studies sponsored, initiated, and conducted by the clinical /regulatory departments at Medtronic's Spinal and Biologics Business. These studies include, but are not limited to, those conducted under the FDA (IDE or IND) and other governmental regulations. Submissions of clinical trial data to governmental, regulatory, insurance, or other agencies inside or outside the United States to seek product approval, support continued clinical use, or support reimbursement/coverage decision are not covered under this procedure.

RESPONSIBILITIES

Indicator [1]	Function or Role	Summary of Responsibilities
[A]	Publication Coordinator	A Medtronic employee who is charged to coordinate a specific publication project.
[B]	Investigator/author	Site investigator/author who is requesting to publish clinical data responsible for adhering to the signed investigator agreement for the study and this policy.
[C]	Clinical Affairs staff	Medtronic clinical affair employees responsible for assisting with the request to publish clinical data.
[D]	Regulatory staff	Medtronic regulatory employees responsible for assisting with the request to publish clinical data.
[E]	Biostatistics and Strategic Research	Medtronic biostatistics and strategic research employees responsible for assisting with the request to publish clinical data.
[F]	Study Statistician/Analyst	Medtronic biostatistical and analytical employee who gathers data, documents the executed request, and saves all the datasets used, programs, and output.
[G]	Publication Committee	Medtronic employees who develop publication strategy and schedule, if necessary, make decisions on requests for publishing clinical data, and review all forms of publications for a specific device, clinical study, or project. The Publication Committee may include, but is not limited to, qualified individuals representing areas of clinical affairs, biostatistics, marketing/product development, health-economics/reimbursement, and regulatory. The head of Biostatistics and Strategic Research or his/her designee will work with various groups to set up the committee membership and notify each member via a memorandum.

[1] **Responsibility Indicators** are used throughout this document to highlight responsibilities for each affected function or role.

Review and Approval for Clinical Data Publication

INSTRUCTION

1 Publication of Data from Single Investigator Site [A] [B] [C] [D] [E] [F] [G]

An investigator can publish pilot and pivotal clinical study results specific to his/her clinical site when desired.

In advance, Medtronic must be notified of this in accordance with the signed investigator agreement for the study.

The final draft of the abstract, manuscript, or any other form of publication should be forwarded to Medtronic for review.

The publication coordinator will submit the manuscript to the publication committee for review, and send comments, if any, back to the investigator.

Medtronic reserves its right to delay such a publication until the full study results are published.

Through the publication coordinator, the investigator should supply a copy of the published abstract or article to Medtronic for documentation.

With the assistance and support of the publication coordinator, the Biostatistics and Strategic Research staff will use the CLF050-02, Clinical Data Publication Tracking Form to document the publication notification and review, along with a copy of the final publication.

If Medtronic is requested to provide summary and/or statistical analysis of clinical data, including summary data manually prepared, the Biostatistics and Strategic Research staff will work with the publication coordinator to prepare the CLF050-01, Clinical Data Publication Request Form and to seek the approvals from management responsible for the study from the Regulatory, Clinical Affairs, and Biostatistics and Strategic Research groups,.

According to the approved request, the Study Statistician/Analyst and/or other clinical staff complete the request and after appropriate internal reviews, send the results to the publication coordinator and/or directly to the investigator, as well as those who approved the request.

The Study Statistician/Analyst or other clinical staff should document the executed request and save all the datasets used, programs, and output. Other clinical staff will also make appropriate documentation if they have provided information for the publication.

For major data update of the publication, repeat Steps 1.2 to 1.10.

2 Publication of Data from Multiple Investigator Sites of Pivotal Trial or Data from Entire Cohort of Pilot Trial [A] [B] [C] [D] [E] [F] [G]

Investigators can publish results from a whole pilot study cohort and pooled pivotal clinical study results specific to their clinical sites when desired as long as the patient cohort size represents less than 50% of the total patient population for the pivotal study. Further, for pivotal studies with more than one treatment group, the patient cohort size for each treatment group being discussed cannot exceed 50% of the total number of patients per group.

In advance, Medtronic must be notified of this in accordance with the signed investigator agreement for the study.

For these types of publications, Medtronic is usually requested to provide summary and/or statistical analysis of clinical data. The Biostatistics and Strategic Research staff will work with the publication coordinator to prepare the CLF050-01, Clinical Data Publication Request Form and to seek the approvals from the publication committee.

According to the approved request, the Study Statistician/Analyst and/or other clinical staff complete the request and after appropriate internal reviews, send the results to the publication coordinator and/or directly to the investigator(s)/author(s), as well as those who approved the request.

The Study Statistician/Analyst should document the executed request and save all the datasets used, programs, and output. Other clinical staff will also make appropriate documentation if they have provided information for the publication.

Review and Approval for Clinical Data Publication

The final draft of the abstract, manuscript, or any other form of publication should be forwarded to Medtronic for review.

The publication coordinator will seek the publication committee for review, and send comments, if any, back to the leading investigator/author.

Medtronic reserves its right to delay such a publication until the full study results are published.

Through the publication coordinator, the investigator should supply a copy of the published abstract or article to Medtronic for documentation.

With the assistance and support of the publication coordinator, the Biostatistics and Strategic Research staff will use the CLF050-02, Clinical Data Publication Tracking Form to document the publication notification and review, along with a copy of the final publication.

For major data update of the publication, repeat Steps 2.2 to 2.10.

3 Publication of Data from Entire Pivotal Clinical Study or Combined Data from Multiple Studies [A] [B] [C] [D] [E] [F] [G]

For each such publication project, the Publication Committee will develop appropriate publication strategy and schedule in advance, if necessary and be responsible for reviewing and approving for such publications.

Investigators cannot publish any preliminary or final results for an entire pivotal clinical study without prior approval from Medtronic. The initial publication of the final results cannot precede:

3.1.1 a pre-approval public presentation of the results for regulatory purposes, such as at an FDA Advisory Panel meeting,

3.1.2 the receipt of an approvable letter from a regulatory agency if a prior pre-approval public presentation is not required, or

3.1.3 a decision not to pursue regulatory approval(s) of the product or technology.

Because of the usual time lapse from submitting to publishing, a manuscript can be submitted before the aforementioned events, but should be reasonably expected to be published after one of these events.

The amassing of final clinical results from more than one pivotal clinical study for a publication is not permissible without prior approval from Medtronic. The considerations from Step 3.2 above apply to this situation and every involved study must meet the criteria.

Any exception to the criteria outlined in Steps 3.2 and 3.3 should be approved by the Publication Committee, with the justification specified on the CLF050-01, Clinical Data Publication Request Form. An example for such an exemption is to publish results of auxiliary study data that are neither primary nor secondary study endpoints as defined in the study protocol. Company's strategic need may also justify such an exemption.

Even if one or more of these criteria are met, Medtronic may deny a publication request based on strategic regulatory considerations such as pending approval in more than one country.

A request to publish the final results for the entire pivotal clinical study or the combined final results must be reviewed and approved by the Publication Committee. The request is documented on the CLF050-01, Clinical Data Publication Request Form. The Biostatistics and Strategic Research staff will prepare the CLF050-01, Clinical Data Publication Request Form and seek the approvals from the Publication Committee.

The Study Statistician/Analyst should document the executed request and save all the datasets used, programs, and output. Other clinical staff will also make appropriate documentation if they have provided information for the publication.

If the need arises, Medtronic staff or external consultant can develop and provide the study results, along with the description of study methodologies, via a publication template, including tables and graphs suitable for the publication, to ensure the accuracy and improve the efficiency.

The publication coordinator will send the study results and/or a template to the investigator(s)/author(s) and coordinate activities and communications for completing the publication draft.

Review and Approval for Clinical Data Publication

The final draft of the abstract, manuscript, or any other form of publication should be forwarded to Medtronic for review.

The publication coordinator will seek the publication committee for review, and send comments, if any, back to the lead investigator/author.

Through the publication coordinator, the lead investigator/author should supply a copy of the published abstract or article to Medtronic for documentation.

With the assistance and support of the publication coordinator, the Biostatistics and Strategic Research staff should use the CLF050-02, Clinical Data Publication Tracking Form to document the publication notification and review, along with a copy of the final publication.

For major data update of the publication, repeat Steps 3.6 to 3.13.

4 Publication of Subgroup Analysis of Pivotal Trial [A] [B] [C] [D] [E] [F] [G]

Subgroup analyses that are not pre-specified in the study protocol are exploratory by nature. Publication of subgroup analysis results may also jeopardize the regulatory approval of the product under investigation, because of the issues associated with pooling data over various subgroups. If pooling data is not justified, the statistical power for assessing primary and secondary study hypotheses will be greatly decreased and thus the probability to meet the study objectives will be drastically decreased. It may also restrict the indications for the product use.

Therefore, publication of subgroup analysis results is not permissive before the criteria described in Steps 3.2 and 3.3 are met.

Any publication of subgroup analyses, regardless of patient cohort, should be subject to the same level of scrutiny described in Section 3 for review and approval.

Some examples of subgroup analyses that may impact the regulatory approval process are: comparing smoking patients with non-smoking patients, patients with worker's compensation with those without worker's compensation, radiculopathy patients with myelopathy patients, patients treated at one levels with those treated at two levels, and comparing patients treated at different spinal levels (e.g., L4-L5 versus L5-S1).

5 Dissemination of Regulatory Progress Reports of Clinical Trial [A] [B] [C] [D] [E] [F] [G]

Regulatory progress reports of a clinical trial, such as annual reports to FDA, are periodically distributed to individual investigators and their Institutional Review Boards (IRBs) according to the regulations. Such reports and other summaries of data may also be distributed inside or outside of Medtronic. Nevertheless, the use of such summary information and reports for any form of publications is subject to the procedures outlined above.

Use of US IDE trial data for international regulatory submissions or other purposes at any stages of the trial should have a separate review and approval process that at minimum involves the Regulatory, Clinical Affairs, Biostatistics and Strategic Research, and Global Healthcare Economics functions.

6 Data Mining of Regulatory Clinical Trial Data [A] [B] [C] [D] [E] [F]

Requests for analyses of IDE or other regulatory trial data for publications will in principle be limited to the trial investigator(s). Requests from other key opinion leaders (KOLs) or non-investigator surgeons for Medtronic may also be considered, if

6.1.1 The KOL/non-investigator surgeon has an effective confidentiality agreement with Medtronic;

6.1.2 There is no issue for complying all the relevant policies and codes of Medtronic business conduct; and

6.1.3 The request meets strategic research needs of the company.

In preparing for such a request, the publication coordinator should first seek the input from the marketing/product development group who sponsored the initial clinical study to align various publication interests and strategy.

The publication coordinator should work with the executive who is responsible for clinical affairs or his/her designee(s) to determine whether or not the request meets strategic research needs of the company.

Review and Approval for Clinical Data Publication

The publication coordinator is charged with the responsibilities to ensure that the conditions in Section 6.1 are met by approving the data request form.

All such requests will follow the procedure defined in this document and other relevant company procedures.

7 Access to Clinical Raw Data [A] [B] [C] [D] [E] [F] [G]

Because the sensitivity of health information and related regulations, Medtronic will not provide complete raw datasets of a clinical study to any non-Medtronic employee for non-regulatory purposes, unless the Executive Management responsible for Clinical Affairs approves the exemption. Any provision of raw data will be subject to legal review to ensure compliance with all applicable privacy laws. Specific queries of data such as description of adverse events of a particular type can be provided to the individuals who work on a particular publication project that is approved by Medtronic.

For publication purposes, Medtronic will assist in summarizing and analyzing the clinical data and provide the author(s) with necessary summary information.

In any case where the supply of raw datasets of a clinical study to any non-Medtronic employee for non-regulatory purposes is deemed necessary and approved by the Executive Management and reviewed by legal, the Medtronic employee who sends the datasets is responsible for ensuring that the recipient of the datasets is under a confidentiality contract with Medtronic. Any (hard copy or electronic) form of the raw data should either be returned to Medtronic or verified as destroyed after the completion of an intended project.

8 Approval Through E-mails [E] [F]

All the approvals aforementioned in this procedure can be communicated via e-mail and documented by the Biostatistics and Strategic Research staff.

9 Unapproved Uses [A] [C] [D] [G]

Sales personnel may not be involved in the funding or approval of any publication on unapproved uses or unapproved devices, except as permitted under Business Conduct Standard 6 as required by CQCR-048 Unapproved Uses of Approved Products.

Support of publication on unapproved uses or an unapproved device is subject to the requirement of Business Conduct Standards 3 and 6 as required by CQCR-048 Unapproved Uses of Approved Products.

When Medtronic has given support to a study of unapproved uses or an unapproved device, such support must be disclosed in the publication of the results.

Medtronic may not require a researcher to disseminate research findings prior to the approval of the unapproved uses or an unapproved device, other than providing a report of publishable quality or as permitted by the Notice of Availability. If the physician wishes to publish the article, he or she is free to do so.

The author of a publication may not be involved in promotional activities on behalf of Medtronic related to the subject of the research, before approval of the unapproved use/unapproved device or except as permitted by the Notice of Availability. Legal will determine whether activities are "promotional" as defined in Promotional Materials Policy QM-21.

RECORDS

The following records will be maintained according to the retention standards defined by regulatory agencies, applicable Medtronic Corporate Policies, and record retention procedures:

- CLF052-01
- CLF052-02
- E-mail approval documentation

Review and Approval for Clinical Data Publication

DEFINITIONS

Clinical raw data
By-subject data collected from clinical studies and stored/presented in either an electronic format or a hard-copy format. Any provision of raw data will be subject to legal review to ensure compliance with all applicable privacy laws.

Pilot clinical study
A small-scale clinical study typically having fewer than 50 patients. A pilot study is considered to be the same as a feasibility study.

Pivotal clinical study
A large-scale clinical study with hypothesis testing and a sample size based on statistical considerations. The results from the study are often intended to serve as primary support for regulatory approval(s).

Publish
This term encompasses all modes of public data conveyance including, but not limited to, journal articles, books, and abstracts.

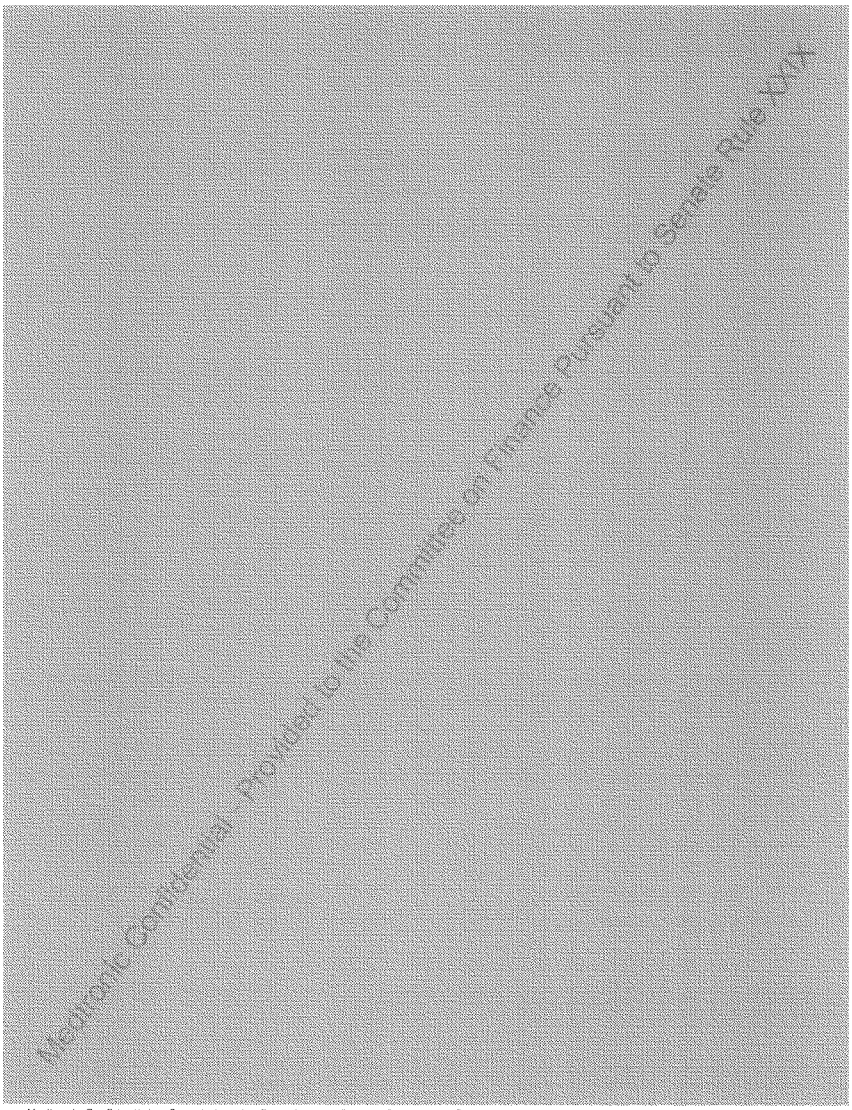
REFERENCES

CLF050-01, Clinical Data Publication Request Form 3, 4
CLF050-02, Clinical Data Publication Tracking Form 3, 4, 5
CQCR-048 Unapproved Uses of Approved Products 6
Promotional Materials Policy QM-21 6

Review and Approval for Clinical Data Publication

REVISION HISTORY

Version	Originator	Description of Change	Date
A	Guorong Ma	Initial release.	12/10/07
B	Vicky Powell	Added Section 9 and corrected grammar errors. Updated REFERENCES section.	07/07/08



Medtronic

Memphis Headquarters Local Instruction

Review and Approval for Clinical Data Publication

Document ID: **CL050** Version: **C**

Effective Date: **4/26/2010** Owner: **Lisa Griffin Vincent, Ph. D.**

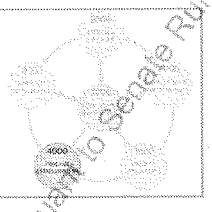


TABLE OF CONTENTS

PURPOSE 2

SCOPE 2

RESPONSIBILITIES 2

INSTRUCTION 3

1 Publication of Data from Single Investigator Site [A] [B] [C] [D] [E] [F] [G] 3

2 Publication of Data from Multiple Investigator Sites of Pivotal Trial or Data from Entire Cohort of Pilot Trial [A] [B] [C] [D] [E] [F] [G] 3

3 Publication of Data from Entire Pivotal Clinical Study or Combined Data from Multiple Studies [A] [B] [C] [D] [E] [F] [G] 4

4 Publication of Subgroup Analysis of Pivotal Trial [A] [B] [C] [D] [E] [F] [G] 5

5 Dissemination of Regulatory Progress Reports of Clinical Trial [A] [B] [C] [D] [E] [F] [G] 5

6 Data Mining of Regulatory Clinical Trial Data [A] [B] [C] [D] [E] [F] 5

7 Access to Clinical Raw Data [A] [B] [C] [D] [E] [F] [G] 6

8 Approval Through E-mails [E] [F] 6

9 Unapproved Uses [A] [C] [D] [G] 6

RECORDS 7

DEFINITIONS 7

REFERENCES 7

REVISION HISTORY 8

Review and Approval for Clinical Data Publication

PURPOSE

The purpose of this document is to establish a review and approval process for the publication of clinical data. The procedure is intended to ensure a high level of scientific standards, to guarantee the accuracy of data, and to maintain the integrity of Medtronic study publications, as well as to reduce the impact of publications of clinical data on the worldwide regulatory approval process of the product under investigation.

SCOPE

The information in this document applies to all requests for clinical data and the development of publications that utilize data from the clinical studies sponsored, initiated, and conducted by the clinical /regulatory departments at Medtronic's Spinal and Biologics Business. These studies include, but are not limited to, those conducted under the FDA (IDE or IND) and other governmental regulations. Submissions of clinical trial data to governmental, regulatory, insurance, or other agencies inside or outside the United States to seek product approval, support continued clinical use, or support reimbursement/coverage decision are not covered under this procedure.

RESPONSIBILITIES

Indicator [1]	Function or Role	Summary of Responsibilities
[A]	Publication Coordinator	A Medtronic employee who is charged to coordinate a specific publication project.
[B]	Investigator/author	Site investigator/author who is requesting to publish clinical data responsible for adhering to the signed investigator agreement for the study and this policy.
[C]	Clinical Affairs staff	Medtronic clinical affair employees responsible for assisting with the request to publish clinical data.
[D]	Regulatory staff	Medtronic regulatory employees responsible for assisting with the request to publish clinical data.
[E]	Biostatistics and Strategic Research	Medtronic biostatistics and strategic research employees responsible for assisting with the request to publish clinical data.
[F]	Study Statistician/Analyst	Medtronic biostatistical and analytical employee who gathers data, documents the executed request, and saves all the datasets used, programs, and output.
[G]	Publication Committee	Medtronic employees who develop publication strategy and schedule, if necessary, make decisions on requests for publishing clinical data, and review all forms of publications for a specific device, clinical study, or project. The Publication Committee may include, but is not limited to, qualified individuals representing areas of clinical affairs, biostatistics, marketing/product development, health-economics/reimbursement, and regulatory. The head of Biostatistics and Strategic Research or his/her designee will work with various groups to set up the committee membership and notify each member via a memorandum.

[1] **Responsibility Indicators** are used throughout this document to highlight responsibilities for each affected function or role.

Review and Approval for Clinical Data Publication

INSTRUCTION

1 Publication of Data from Single Investigator Site [A] [B] [C] [D] [E] [F] [G]

1.1 An investigator can publish, pilot and pivotal clinical study results specific to his/her clinical site when desired.

1.2 In advance, Medtronic must be notified of this in accordance with the signed investigator agreement for the study.

1.3 The final draft of the abstract, manuscript, or any other form of publication should be forwarded to Medtronic for review.

1.4 The publication coordinator will submit the manuscript to the publication committee for review, and send comments, if any, back to the investigator.

1.5 Medtronic reserves its right to delay such a publication until the full study results are published.

1.6 Through the publication coordinator, the investigator should supply a copy of the published abstract or article to Medtronic for documentation.

1.7 With the assistance and support of the publication coordinator, the Biostatistics and Strategic Research staff will use the **CLF050-02, Clinical Data Publication Tracking Form** to document the publication notification and review, along with a copy of the final publication.

1.8 If Medtronic is requested to provide summary and/or statistical analysis of clinical data, including summary data manually prepared, the Biostatistics and Strategic Research staff will work with the publication coordinator to prepare the **CLF050-01, Clinical Data Publication Request Form** and to seek the approvals from management responsible for the study from the Regulatory, Clinical Affairs, and Biostatistics and Strategic Research groups,.

1.9 According to the approved request, the Study Statistician/Analyst and/or other clinical staff complete the request and after appropriate internal reviews, send the results to the publication coordinator and/or directly to the investigator, as well as those who approved the request.

1.10 The Study Statistician/Analyst or other clinical staff should document the executed request and save all the datasets used, programs, and output. Other clinical staff will also make appropriate documentation if they have provided information for the publication.

1.11 For major data update of the publication, repeat Steps 1.2 to 1.10.

2 Publication of Data from Multiple Investigator Sites of Pivotal Trial or Data from Entire Cohort of Pilot Trial [A] [B] [C] [D] [E] [F] [G]

2.1 Investigators can publish results from a whole pilot study cohort and pooled pivotal clinical study results specific to their clinical sites when desired as long as the patient cohort size represents less than 50% of the total patient population for the pivotal study. Further, for pivotal studies with more than one treatment group, the patient cohort size for each treatment group being discussed cannot exceed 50% of the total number of patients per group.

2.2 In advance, Medtronic must be notified of this in accordance with the signed investigator agreement for the study.

2.3 For these types of publications, Medtronic is usually requested to provide summary and/or statistical analysis of clinical data. The Biostatistics and Strategic Research staff will work with the publication coordinator to prepare the **CLF050-01, Clinical Data Publication Request Form** and to seek the approvals from the publication committee.

2.4 According to the approved request, the Study Statistician/Analyst and/or other clinical staff complete the request and after appropriate internal reviews, send the results to the publication coordinator and/or directly to the investigator(s)/author(s), as well as those who approved the request.

2.5 The Study Statistician/Analyst should document the executed request and save all the datasets used, programs, and output. Other clinical staff will also make appropriate documentation if they have provided information for the publication.

2.6 The final draft of the abstract, manuscript, or any other form of publication should be forwarded to Medtronic for review.

2.7 The publication coordinator will seek the publication committee for review, and send comments, if any, back to the leading investigator/author.

2.8 Medtronic reserves its right to delay such a publication until the full study results are published.

2.9 Through the publication coordinator, the investigator should supply a copy of the published abstract or article to Medtronic for documentation.

2.10 With the assistance and support of the publication coordinator, the Biostatistics and Strategic Research staff will use the **CLF050-02, Clinical Data Publication Tracking Form** to document the publication notification and review, along with a copy of the final publication.

2.11 For major data update of the publication, repeat Steps 2.2 to 2.10.

3 Publication of Data from Entire Pivotal Clinical Study or Combined Data from Multiple Studies [A] [B] [C] [D] [E] [F] [G]

3.1 For each such publication project, the Publication Committee will develop appropriate publication strategy and schedule in advance, if necessary and be responsible for reviewing and approving for such publications.

3.2 Investigators cannot publish any preliminary or final results for an entire pivotal clinical study without prior approval from Medtronic. The initial publication of the final results cannot precede:

3.2.1 A pre-approval public presentation of the results for regulatory purposes, such as at an FDA Advisory Panel meeting,

3.2.2 The receipt of an approvable letter from a regulatory agency if a prior pre-approval public presentation is not required, or

3.2.3 A decision not to pursue regulatory approval(s) of the product or technology.

Because of the usual time lapse from submitting to publishing, a manuscript can be submitted before the aforementioned events, but should be reasonably expected to be published after one of these events.

3.3 The amassing of final clinical results from more than one pivotal clinical study for a publication is not permissible without prior approval from Medtronic. The considerations from Step 3.2 above apply to this situation and every involved study must meet the criteria.

3.4 Any exception to the criteria outlined in Steps 3.2 and 3.3 should be approved by the Publication Committee, with the justification specified on the **CLF050-01, Clinical Data Publication Request Form.** An example for such an exemption is to publish results of auxiliary study data that are neither primary nor secondary study endpoints as defined in the study protocol. Company's strategic need may also justify such an exemption.

3.5 Even if one or more of these criteria are met, Medtronic may deny a publication request based on strategic regulatory considerations such as pending approval in more than one country.

3.6 A request to publish the final results for the entire pivotal clinical study or the combined final results must be reviewed and approved by the Publication Committee. The request is documented on the **CLF050-01, Clinical Data Publication Request Form.** The Biostatistics and Strategic Research staff will prepare the **CLF050-01, Clinical Data Publication Request Form** and seek the approvals from the Publication Committee.

3.7 The Study Statistician/Analyst should document the executed request and save all the datasets used, programs, and output. Other clinical staff will also make appropriate documentation if they have provided information for the publication.

3.8 If the need arises, Medtronic staff or external consultant can develop and provide the study results, along with the description of study methodologies, via a publication template, including tables and graphs suitable for the publication, to ensure the accuracy and improve the efficiency.

3.9 The publication coordinator will send the study results and/or a template to the investigator(s)/author(s) and coordinate activities and communications for completing the publication draft.

3.10 The final draft of the abstract, manuscript, or any other form of publication should be forwarded to Medtronic for review.

3.11 The publication coordinator will seek the publication committee for review, and send comments, if any, back to the lead investigator/author.

3.12 Through the publication coordinator, the lead investigator/author should supply a copy of the published abstract or article to Medtronic for documentation.

3.13 With the assistance and support of the publication coordinator, the Biostatistics and Strategic Research staff should use the **CLF050-02, Clinical Data Publication Tracking Form** to document the publication notification and review, along with a copy of the final publication.

3.14 For major data update of the publication, repeat Steps 3.6 to 3.13.

4 Publication of Subgroup Analysis of Pivotal Trial [A] [B] [C] [D] [E] [F] [G]

4.1 Subgroup analyses that are not pre-specified in the study protocol are exploratory by nature. Publication of subgroup analysis results may also jeopardize the regulatory approval of the product under investigation, because of the issues associated with pooling data over various subgroups. If pooling data is not justified, the statistical power for assessing primary and secondary study hypotheses will be greatly decreased and thus the probability to meet the study objectives will be drastically decreased. It may also restrict the indications for the product use.

4.2 Therefore, publication of subgroup analysis results is not permissive before the criteria described in Steps 3.2 and 3.3 are met.

4.3 Any publication of subgroup analyses, regardless of patient cohort, should be subject to the same level of scrutiny described in Section 3 for review and approval.

4.4 Some examples of subgroup analyses that may impact the regulatory approval process are: comparing smoking patients with non-smoking patients, patients with worker's compensation with those without worker's compensation, radiculopathy patients with myelopathy patients, patients treated at one levels with those treated at two levels, and comparing patients treated at different spinal levels (e.g., L4-L5 versus L5-S1).

5 Dissemination of Regulatory Progress Reports of Clinical Trial [A] [B] [C] [D] [E] [F] [G]

5.1 Regulatory progress reports of a clinical trial, such as annual reports to FDA, are periodically distributed to individual investigators and their Institutional Review Boards (IRBs) according to the regulations. Such reports and other summaries of data may also be distributed inside or outside of Medtronic. Nevertheless, the use of such summary information and reports for any form of publications is subject to the procedures outlined above.

5.2 Use of CUS IDE trial data for international regulatory submissions or other purposes at any stages of the trial should have a separate review and approval process that at minimum involves the Regulatory, Clinical Affairs, Biostatistics and Strategic Research, and Global Healthcare Economics functions.

6 Data Mining of Regulatory Clinical Trial Data [A] [B] [C] [D] [E] [F]

6.1 Requests for analyses of IDE or other regulatory trial data for publications will in principle be limited to the trial investigator(s). Requests from other key opinion leaders (KOLs) or non-investigator surgeons for Medtronic may also be considered, if

6.1.1 The KOL/non-investigator surgeon has an effective confidentiality agreement with Medtronic;

6.1.2 There is no issue for complying all the relevant policies and codes of Medtronic business conduct; and

6.1.3 The request meets strategic research needs of the company.

6.2 In preparing for such a request, the publication coordinator should first seek the input from the marketing/product development group who sponsored the initial clinical study to align various publication interests and strategy.

6.3 The publication coordinator should work with the executive who is responsible for clinical affairs or his/her designee(s) to determine whether or not the request meets strategic research needs of the company.

6.4 The publication coordinator is charged with the responsibilities to ensure that the conditions in Section 6.1 are met by approving the data request form.

6.5 All such requests will follow the procedure defined in this document and other relevant company procedures.

7 Access to Clinical Raw Data [A] [B] [C] [D] [E] [F] [G]

7.1 Because the sensitivity of health information and related regulations, Medtronic will not provide complete raw datasets of a clinical study to any non-Medtronic employee for non-regulatory purposes, unless the Executive Management responsible for Clinical Affairs approves the exemption. Any provision of raw data will be subject to legal review to ensure compliance with all applicable privacy laws. Specific queries of data such as description of adverse events of a particular type can be provided to the individuals who work on a particular publication project that is approved by Medtronic.

7.2 For publication purposes, Medtronic will assist in summarizing and analyzing the clinical data and provide the author(s) with necessary summary information.

7.3 In any case where the supply of raw datasets of a clinical study to any non-Medtronic employee for non-regulatory purposes is deemed necessary and approved by the Executive Management and reviewed by legal, the Medtronic employee who sends the datasets is responsible for ensuring that the recipient of the datasets is under a confidentiality contract with Medtronic. Any (hard copy or electronic) form of the raw data should either be returned to Medtronic or verified as destroyed after the completion of an intended project.

8 Approval Through E-mails [E] [F]

8.1 All the approvals aforementioned in this procedure can be communicated via e-mail and documented by the Biostatistics and Strategic Research staff.

9 Unapproved Uses [A] [C] [D] [G]

9.1 Sales personnel may not be involved in the funding or approval of any publication on unapproved uses or unapproved devices as outlined by **CQRC-048 Unapproved Uses of Approved Products**, and consistent with Business Conduct Standards 3 and 6.

9.2 When Medtronic has given support to a study of unapproved uses or an unapproved device, such support must be disclosed in the publication of the results.

9.3 Employees are prohibited from requiring or compensating a researcher to speak about or broadly disseminate research findings prior to FDA approval of the unapproved uses, other than providing a report of publishable quality to Medtronic and/or a peer-reviewed journal for publication. If the researcher wishes to speak or otherwise disseminate research results without Medtronic's support, he/she may do so.

9.4 The author of a publication may not be involved in promotional activities on behalf of Medtronic related to the subject of the research, before approval of the unapproved use/unapproved device or except as permitted by the Notice of Availability.

9.5 Employees and Medtronic-contracted medical writers are explicitly prohibited from providing writing assistance on publications that are on unapproved uses of approved products. This prohibition does not apply to publications on studies conducted under 21 C.F.R. Parts 312 or 812.

Review and Approval for Clinical Data Publication

9.6 Appropriate disclosure of an employee's or medical writer's contribution (authorship or contributorship) according to the International Committee of Medical Journal Editors (ICMJE) requirements for disclosure in publications is required. This includes where Medtronic funds a third party-sponsored research program (e.g., physician sponsored) on unapproved uses to be conducted under 21 C.F.R. Parts 312 and 812, and the third party contracts with a medical writer to draft publications.

9.7 Legal will determine whether activities are "promotional" as defined in **QM21, Promotional Materials Policy**.

RECORDS

The following records will be maintained according to the retention standards defined by regulatory agencies, applicable Medtronic Corporate Policies, and record retention procedures:

- CLF052-01
- CLF052-02
- E-mail approval documentation

DEFINITIONS

Clinical raw data
By-subject data collected from clinical studies and stored/presented in either an electronic format or a hard-copy format. Any provision of raw data will be subject to legal review to ensure compliance with all applicable privacy laws.

Pilot clinical study
A small-scale clinical study typically having fewer than 50 patients. A pilot study is considered to be the same as a feasibility study.

Pivotal clinical study
A large-scale clinical study with hypothesis testing and a sample size based on statistical considerations. The results from the study are often intended to serve as primary support for regulatory approval(s).

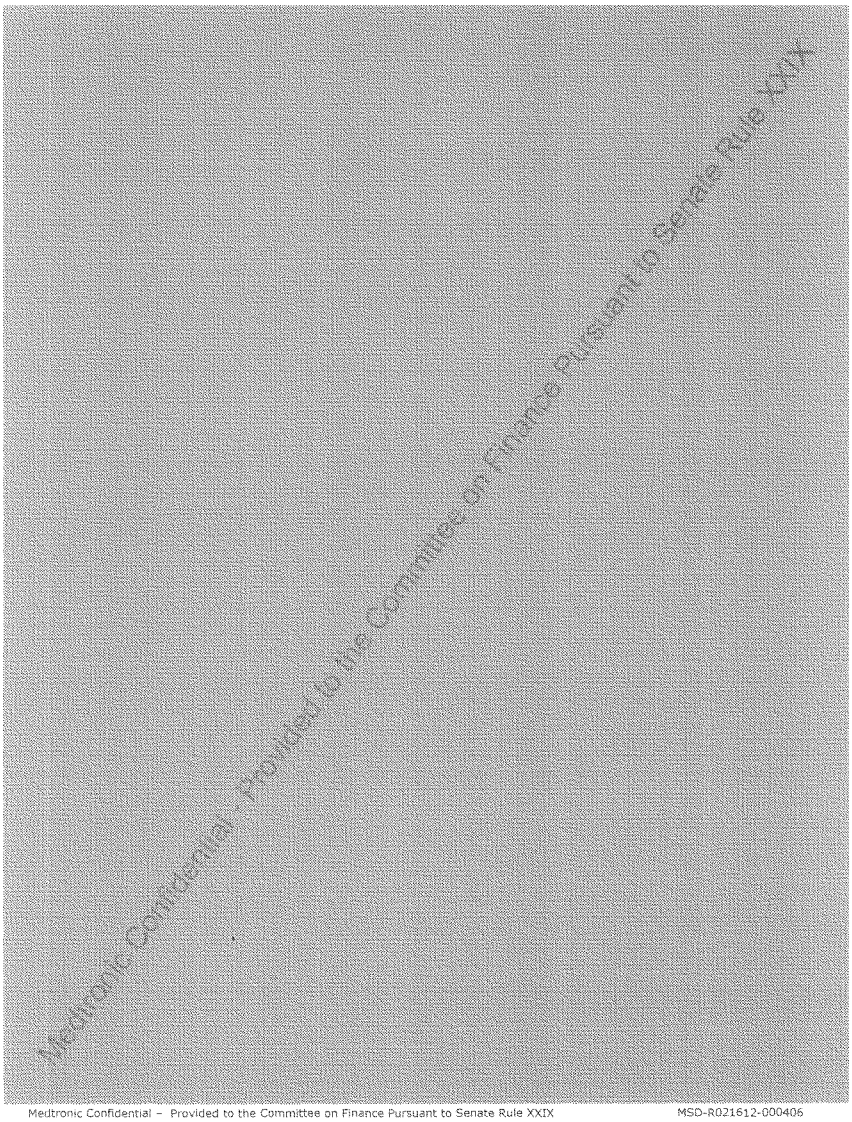
Publish
This term encompasses all modes of public data conveyance including, but not limited to, journal articles, books, and abstracts.

REFERENCES

CLF050-01, Clinical Data Publication Request Form 3, 4
CLF050-02, Clinical Data Publication Tracking Form 3, 4, 5
CQRC-048 Unapproved Uses of Approved Products 6
QM21, Promotional Materials Policy 6

REVISION HISTORY

Version	Originator	Description of Change	Date
A	Guorong Ma	Initial release.	12/10/07
B	Vicky Powell	Added Section 9 and corrected grammar errors. Updated REFERENCES section.	07/07/08
C	Alison Webster	Added additional elements from CQRC-048 Section 6, Research and Publication Strategies; Process Owner was changed to Lisa Griffin Vincent Ph. D.	04/26/10



Medtronic

Memphis Headquarters Local Instruction

Review and Approval for Clinical Data Publication

Document ID: **CL050** Version: **D**

Effective Date: **Feb. 18, 2011** Owner: **David Wootten, Ph.D.**

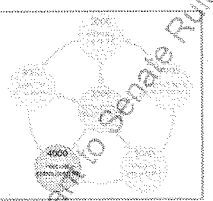


TABLE OF CONTENTS

PURPOSE 2

SCOPE 2

RESPONSIBILITIES 2

INSTRUCTION 3

1 Medtronic Employee Involvement and Non-Medtronic Employee Participation in Publication Projects 3
2 Organization of Medtronic Publication Committees 3
3 Organization of Investigator Publication Steering Committees 4
4 Timing on Release of Clinical Publications 4
5 Review of Publication Requests of Clinical Data 4
6 Review of Publications of Clinical Data 5
7 Dissemination of Regulatory Progress Reports of Clinical Trial [A] [B] [C] [D] [E] [F] [G] 5
8 Data Mining of Clinical Trial Data [A] [B] [C] [D] [E] [F] 6
9 Access to Clinical Raw Data [A] [B] [C] [D] [E] [F] [G] 6
10 Approval Through E-mails [E] [F] 6
11 Unapproved Uses [A] [C] [D] [G] 6

RECORDS 7

DEFINITIONS 7

REFERENCES 7

REVISION HISTORY 9

Medtronic

Review and Approval for Clinical Data Publication

PURPOSE

The purpose of this document is to establish a review and approval process for the publication of clinical data, including data used for health economics and reimbursement purposes. The procedure is developed to ensure a high level of scientific standards, to guarantee the accuracy of data, and to maintain the integrity of Medtronic study publications, as well as to align publications of clinical data with the worldwide regulatory approval process of the product under investigation. This procedure is updated in accordance with the **Scientific Publications Policy Related to MSB-Sponsored Research (P0004)**.

SCOPE

The information in this document applies to all requests for clinical data and the development of publications that utilize data from the clinical studies sponsored, initiated, or conducted by the clinical /regulatory departments or their agents at Medtronic's Spinal and Biologics Business. These studies include, but are not limited to, those conducted under the FDA (IDE or IND) and other governmental regulations, post-approval or post-marketing studies, and other types of clinical trials or clinical research studies. Submissions of clinical trial data to regulatory agencies inside or outside the United States to seek product approval or support continued clinical use should be governed by the established procedures for those purposes and thus are not covered under this procedure.

RESPONSIBILITIES

Indicator[1]	Function or Role	Summary of Responsibilities
[A]	Publication Coordinator	A Medtronic employee who is charged to coordinate specific publication projects and maintain proper documentation. Employee in Marketing and Sales functions cannot serve as a publication coordinator.
[B]	Investigator/author	Site investigator/author who is requesting to publish clinical data responsible for adhering to the signed investigator agreement for the study or other legal agreement.
[C]	Clinical Affairs staff	Medtronic clinical research employees responsible for assisting with the request to publish clinical data.
[D]	Regulatory staff	Medtronic regulatory employees responsible for assisting with the request to publish clinical data.
[E]	Biostatistics and Clinical Research	Medtronic biostatistics and clinical research employees responsible for assisting with the request to publish clinical data.
[F]	Study Statistician/Analyst	Medtronic biostatistical and analytical employee who gathers data, documents the executed request, and saves all the datasets used, programs, and output.

[1] **Responsibility Indicators** are used throughout this document to highlight responsibilities for each affected function or role.

Medtronic

Review and Approval for Clinical Data Publication

Indicator [1]	Function or Role	Summary of Responsibilities
[G]	Publication Committee	Medtronic employees who review and approve requests for publications and publications of clinical data. The Publication Committee includes at minimum qualified individuals representing areas of Clinical, Biostatistics, Marketing, Health-economics/Reimbursement, Legal, and Regulatory. Function leader in Clinical responsible for managing publication requests and publications will work with various groups to set up the committee membership for each specific publication request or publication project and notify each member.
[H]	Investigator Publication Steering Committee	A group of study investigators or other researchers, responsible for developing publication ideas and planning, determining authorship criteria, authorship responsibilities and expectations, and preparing for manuscripts or other forms of publications.

INSTRUCTION

1 Medtronic Employee Involvement and Non-Medtronic Employee Participation in Publication Projects

1.1 Medtronic employees must comply with the Scientific Publications Policy Related to MSB-Sponsored Research (P0004) when they are involved in any publication project.

1.2 Non-Medtronic employees who participate in a publication project should be properly informed of the Scientific Publications Policy Related to MSB-Sponsored Research (P0004) and this procedure (CL050), and comply with the policy and procedure.

1.3 A Medtronic publication coordinator is responsible for ensuring that the relevant agreements and documentations are in place before a publication project is initiated with non-Medtronic employees.

1.4 A publication steering committee that is comprised of investigators may be instituted to make decisions with regard to publication activities. A Medtronic publication coordinator can provide logistical and coordinating support for the steering committee.

2 Organization of Medtronic Publication Committees

2.1 A Medtronic publication committee will be project-specific for reviewing and approving requests for publications and publications of clinical data.

2.2 A Publication Committee includes at minimum; individuals representing areas of Clinical, Biostatistics, Marketing, Health-economics/Reimbursement, Legal, and Regulatory.

2.3 Function leader in Clinical Research responsible for managing publication requests and publications will work with various function groups to identify the committee membership for each specific publication request or publication project and notify each member.

2.4 Clinical Research (including Biostatistics) will manage the development, review and approval process for Requests for Publications and Publications related to clinical studies.

2.5 An employee in Clinical Research (including Biostatistics) serves as a publication coordinator for the clinical data publication process, while an employee in Health-economics/Reimbursement serves as a publication coordinator for Health-economics publications.

Medtronic

Review and Approval for Clinical Data Publication

3 Organization of Investigator Publication Steering Committees

3.1 All study investigators are invited to participate in publications planning.

3.2 A steering committee consisting of interested investigators may be formed for a clinical study to develop publication plans and to prepare for manuscripts or other forms of publications.

3.3 The investigators and not Medtronic, determine criteria for participation on the steering committee, authorship for the publications, and authorship responsibilities.. Medtronic may facilitate the process.

3.4 If there is a study principal investigator (PI), the PI serves as chair of the publications committee.

4 Timing on Release of Clinical Publications

4.1 As defined in the Scientific **Publications Policy Related to MSB-Sponsored Research (P0004)**, in general, no publications using data from a clinical study of a novel product or unapproved use of an approved product will be approved prior to the primary clinical study publication unless the publication is part of a study-specific publication plan (e.g., interim analysis, single-center data from a multi-center study, sub-study publication), driven by patient safety concerns, or other reviewed and approved data use situations.

4.2 A primary publication with protocol-defined endpoints cannot precede:

4.3 A pre-approval public presentation of the results for regulatory purposes, such as at an FDA Advisory Panel meeting,

4.4 The receipt of an approval letter from a regulatory agency if a prior pre-approval public presentation is not required, or

4.5 A decision not to pursue regulatory approval(s) of the product or technology.

Because of the usual time lapse from submitting to publishing, a manuscript can be submitted before the aforementioned events, but should be reasonably expected to be published after one of these events.

4.6 A primary publication should be developed based on the dataset that includes the finalized endpoint data with all possible patient follow-ups or a predefined interim analysis plan.

4.7 Publications with the data beyond the primary endpoints or after regulatory approvals for the product/indications under the investigation should be developed based on the dataset that includes the finalized data with all possible patient follow-ups or a predefined interim analysis plan for a given evaluation interval.

4.8 Release of publications with auxiliary data that are not necessarily defined in study protocols or those that are deemed to be necessary for patient safety or other public interests by the publication committee should be reviewed and approved by the publication committee.

4.9 The considerations from 4.2 above apply to the amassing of clinical results from more than one pivotal clinical study for a publication and every involved study must meet the criteria.

5 Review of Publication Requests of Clinical Data

5.1 Investigators shall not publish any preliminary or final results from a clinical study without prior approval from Medtronic.

5.2 Medtronic may deny a publication request.

5.3 Investigators or multiple Medtronic functions including Clinical, Medical Affairs, Research, Development, Reimbursement, Communications, and Marketing, but not Sales, may initiate a Request for Publication.

5.4 The following information is required, at a minimum, for a Request for Publication review.

- 5.4.1 Requestor (e.g., employee, investigator, physician) identification information
- 5.4.2 Description of the proposal for publication (i.e., specific publication plan)
- 5.4.3 Publication target or use of data (i.e., journal, meeting, data use)

5.4.4 Description of any data required and origin (e.g., specific studies) if applicable

5.4.5 Intended participation or contribution of any MSB employees or requested services (e.g., data analysis, writing)

5.5 A request to publish clinical data must be reviewed and approved by the Publication Committee. The request is documented on the **CLF050-01, Clinical Data Publication Request Form.** The publication coordinator, working with Biostatistics staff will prepare the **CLF050-01, Clinical Data Publication Request Form** and seek the approvals from the Publication Committee.

5.6 Medtronic Employee participation as authors or contributors must be approved as part of the review and approval process for the specific Request for Publication or Publication.

5.7 The Publication coordinator will document the outcome of review by the Publication committee.

5.8 If clinical data are requested, the responsible Study Statistician/Analyst should document the executed request and save all the datasets used, programs, and output. Other clinical staff will also make appropriate documentation if they have provided information for the publication.

5.9 Before clinical data are provided to non-Medtronic employee authors, a legal agreement must be in place to address the use of MSB research data and cover rights and obligations related to the publication effort. This may be incorporated in a clinical trials agreement, research agreement or consulting agreement for other related consulting or research services.

5.10 The publication coordinator will send the study results to the Investigator(s)/author(s) and coordinate activities and communications for completing the publication draft.

5.11 All authors must agree that the clinical data will be used only for the purposes specified on the approved **CLF050-01, Clinical Data Publication Request Form**. Any additional use of the data must be reviewed and approved by the Publication committee. Use of updated clinical data for the approved purposes should be also reviewed and approved by the Publication committee.

5.12 Publication coordinator is responsible for documenting analyses that are developed using clinical data, but performed by a non-Clinical group, such as for health-economic analysis.

5.13 Medtronic publication committee members will be provided with an executed data request to facilitate review of a draft publication. The data provided shall not be used for other purposes without prior approval by the Publication Committee.

6 Review of Publications of Clinical Data

6.1 The final draft of the abstract, poster, manuscript, presentation materials or any other form of publication shall be forwarded to Medtronic for review by the Publication committee.

6.2 The publication coordinator will coordinate the publication committee review. The publication coordinator will incorporate changes/comments, from the publication committee review and forward to the lead author.

6.3 The publication coordinator will track the status of a publication, and maintain a copy of the published form of a publication.

7 Dissemination of Regulatory Progress Reports of Clinical Trial [A] [B] [C] [D] [E] [F] [G]

7.1 Regulatory progress reports of a clinical trial, such as annual reports to FDA, are periodically distributed to individual investigators and their Institutional Review Boards (IRBs) according to the regulations. Such reports and other summaries of data may also be distributed internally to Medtronic employees, or to other external recipients. Nevertheless, such summary information and reports cannot be used for any form of publications without prior review and approval by the Medtronic Publication committee.

7.2 Use of US IDE/IND trial data for international regulatory submissions or other non-publication purposes at any stages of the trial should be subject to the review and approval process that at minimum involves the Regulatory, Clinical Research, Biostatistics, and Global Healthcare Economics functions.

8 Data Mining of Clinical Trial Data [A] [B] [C] [D] [E] [F]

8.1 Requests for analyses of clinical trial data for publications will in principle be limited to the trial investigator(s), through the Investigator Publication Steering Committee. Requests from other key opinion leaders (KOLs) or non-investigator surgeons/physicians may also be considered, if

8.1.1 The KOL/non-investigator surgeon has an effective confidentiality agreement with Medtronic;

8.1.2 All relevant policies and codes of Medtronic business conduct are followed;

8.1.3 The request is in accordance with the publication strategy of the company.

8.2 The publication coordinator and the Clinical Research executive or his/her designee(s) will determine whether the request is in accordance with the publication strategy of the company.

8.3 The publication coordinator is charged with the responsibilities to ensure that the conditions in Section 8.1 are met by approving the data request form.

8.4 All such requests will follow the procedure defined in this document and other relevant company procedures.

9 Access to Clinical Raw Data [A] [B] [C] [D] [E] [F] [G]

9.1 Due to the sensitivity of health information and related regulations, Medtronic will not provide complete raw datasets of a clinical study to any non-Medtronic employee for non-regulatory purposes, unless the Executive Management responsible for Clinical Research approves the exemption. Any provision of raw data will be subject to legal review to ensure compliance with all applicable privacy laws. Specific queries of data such as description of adverse events of a particular type can be provided to the individuals who work on a particular publication project that is approved by Medtronic.

9.2 For publication purposes, Medtronic or its agent will assist in summarizing and analyzing the clinical data and provide the author(s) with all necessary information.

9.3 In any case where the supply of raw datasets of a clinical study to any non-Medtronic employee for non-regulatory purposes is deemed necessary and approved by the Executive Management and reviewed by legal, the Medtronic employee who sends the datasets is responsible for ensuring that the recipient of the datasets is under a confidentiality contract with Medtronic. Any (hard copy or electronic) form of the raw data should either be returned to Medtronic or verified as destroyed after the completion of an intended project.

10 Approval Through E-mails [E] [F]

10.1 All the approvals aforementioned in this procedure can be communicated via e-mail and documented by the publication coordinator at a centralized location for specific publication projects.

11 Unapproved Uses [A] [C] [D] [G]

11.1 Sales personnel may not be involved in the funding or approval of any publication on unapproved uses or unapproved devices as outlined by **CQRC-048 Unapproved Uses of Approved Products**, and consistent with Business Conduct Standards 3 and 6.

11.2 When Medtronic supports a study of unapproved uses or an unapproved device, such support must be disclosed in the publication of the results.

11.3 Employees are prohibited from requiring or compensating a researcher to speak about or broadly disseminate research findings prior to FDA approval of the unapproved uses, other than providing a report of publishable quality to Medtronic and/or a peer-reviewed journal for publication. If the researcher wishes to speak or otherwise disseminate research results without Medtronic's support, he/she may do so.

Review and Approval for Clinical Data Publication

11.4 The author of a publication may not be involved in promotional activities on behalf of Medtronic related to the subject of the research, before approval of the unapproved use/unapproved device or except as permitted by the Notice of Availability.

11.5 Legal will determine whether activities are "promotional" as defined in **QM21, Promotional Materials Policy.**

11.6 The author of a publication may engage in activities as permitted by a Notice of Availability disseminated in accordance with **PL017, U.S Investigator/Patient Recruiting Materials for a MSB Clinical Study that Involve an Unapproved Use of an MSB Product.**

11.7 Employees and Medtronic-contracted medical writers are explicitly prohibited from providing writing assistance on publications that are on unapproved uses of approved products. This prohibition does not apply to publications on studies conducted under 21 C.F.R. Parts 312 or 812.

11.8 Appropriate disclosure of an employee's or medical writer's contribution (authorship or contributorship) according to the International Committee of Medical Journal Editors (ICMJE) requirements for disclosure in publications is required. This includes where Medtronic funds a third party-sponsored research program (e.g., physician-sponsored) on unapproved uses to be conducted under 21 C.F.R. Parts 312 and 812, and the third party contracts with a medical writer to draft publications.

RECORDS

The following records will be maintained according to the retention standards defined by regulatory agencies, applicable Medtronic Corporate Policies, and record retention procedures:

- CLF050-01, Clinical Data Publication Request Form
- E-mail approval documentation

DEFINITIONS

Clinical raw data
By-subject data collected from clinical studies and stored/presented in either an electronic format or a hard-copy format. Any provision of raw data will be subject to legal review to ensure compliance with all applicable privacy laws.

Pilot clinical study
A small-scale clinical study typically having fewer than 50 patients. A pilot study is considered to be the same as a feasibility study.

Pivotal clinical study
A large-scale clinical study with hypothesis testing and a sample size based on statistical considerations. The results from the study are often intended to serve as primary support for regulatory approval(s).

Publish
This term encompasses all modes of public data conveyance including, but not limited to, journal articles, books, presentation slides, and abstracts.

REFERENCES

CLF050-01, Clinical Data Publication Request Form 4, 5, 7

Review and Approval for Clinical Data Publication

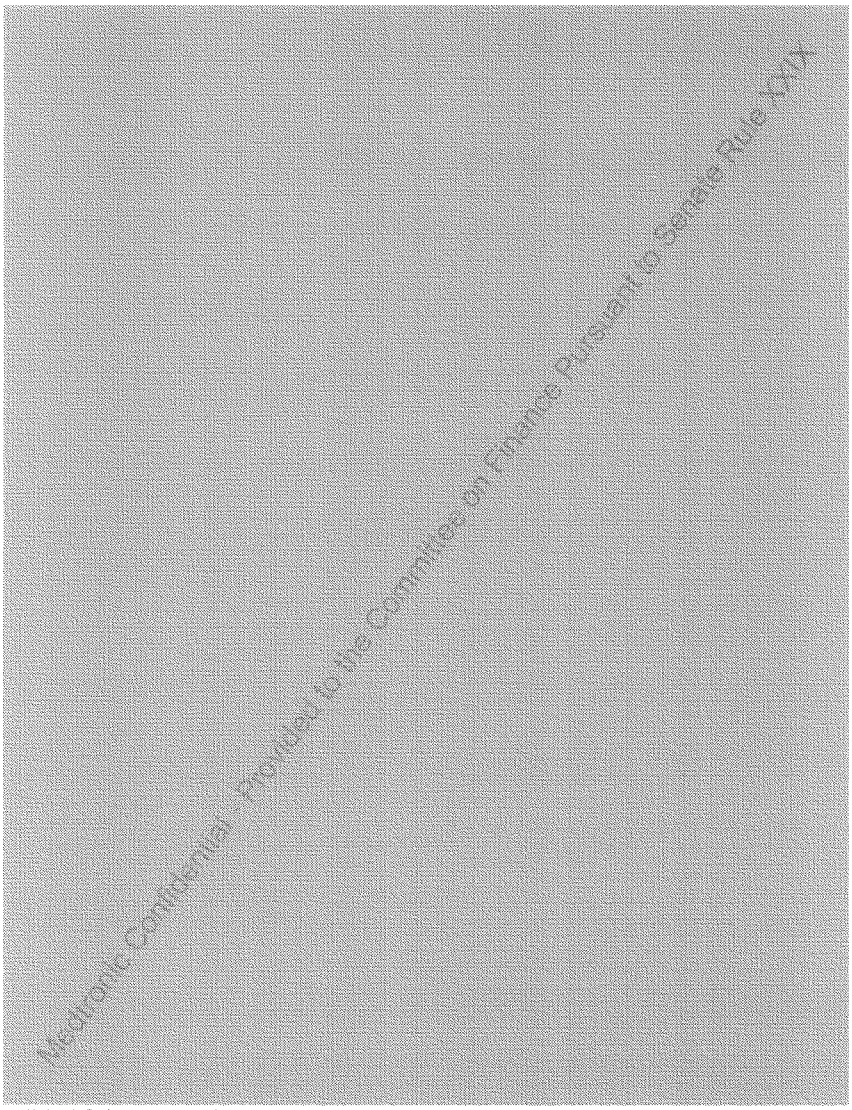
CQRC-048 Unapproved Uses of Approved Products 6
PL017, IDE Investigator and Patient Recruitment Material 6
QM21, Promotional Materials Policy 6

Medtronic

Review and Approval for Clinical Data Publication

REVISION HISTORY

Version	Originator	Description of Change	Date
A	Guorong Ma	Initial release.	12/10/07
B	Vicky Powell	Added Section 9 and corrected grammar errors. Updated REFERENCES section.	07/07/08
C	Alison Webster	Added additional elements from CQRC-048 Section 6, Research and Publication Strategies; Process Owner was changed to Lisa Griffin Vincent Ph. D.	04/26/10
D	David Wooten	Substantial changes dictated by the new Publications Policy (P0004). Process owner changed to David Wootten, PhD; Added post –approval or post marketing studies, and other types of clinical trials or clinical research studies in the Scope; Expanded responsibilities of Publication Committee Responsibilities section; Added Investigator Publication Steering Committee to Responsibilities section; Deleted Section 1, Publication of Data from Single Investigator Site and replaced Section 1 with, Medtronic Employee Involvement and Non-Medtronic Employee Participation in Publication Projects; Deleted Section 2, Publication of Data from Multiple Investigator Sites of Pivotal Trial or Data from Entire Cohort of Pilot Trial and replaced with Section 2, Organization of Medtronic Publication Committees; Deleted Section 3, Publication of Data from Entire Pivotal Clinical Study or Combined Data from Multiple Studies and replaced with Section 3, Organization of Investigator Publication Steering Committees; Deleted Section 4, Publication of Subgroup Analysis of Pivotal Trial and replaced with Section 4, Timing on Release of Clinical Publications; Moved Section 5, Dissemination of Regulatory Progress Reports of Clinical Trial, to Section 7, and replaced Section 5 with, Review of Publication Requests of Clinical Data; Moved Section 6, Data Mining of Regulatory Clinical Trial Data to section 8, and replaced with Section 6, Review of Publications of Clinical Data; Moved Section 7, Access to Clinical Raw Data to Section 9; Moved Section 8, Approval through emails to Section 10, Moved Section 9 Unapproved Uses to Section 11. Added PL017, U.S Investigator/Patient Recruiting Materials for a MSB Clinical Study that Involve an Unapproved Use of an MSB Product to References Section. Changed process owner from Lisa Griffin Vincent, Ph.D. to David Wooten, Ph.D.	Feb. 18, 2011



Medtronic

Memphis Headquarters Local Instruction

Review and Approval for Clinical Data Publication

Document ID: CL050 Version: E

Effective Date: Dec. 06, 2011 Owner: David Wootten, Ph.D.

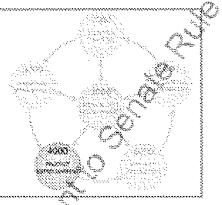


TABLE OF CONTENTS

PURPOSE 2

SCOPE 2

RESPONSIBILITIES 2

INSTRUCTION 3

1 Medtronic Employee Involvement and Non-Medtronic Employee Participation in Publication Projects 3
2 Organization of Medtronic Publication Committees 3
3 Organization of Investigator Publication Steering Committees 4
4 Timing on Release of Clinical Publications 4
5 Review of Publication Requests of Clinical Data 4
6 Review of Publications of Clinical Data 5
7 Dissemination of Regulatory Progress Reports of Clinical Trial [A] [B] [C] [D] [E] [F] [G] [H] 6
8 Data Mining of Clinical Trial Data [A] [B] [C] [D] [E] [F] 6
9 Access to Clinical Raw Data [A] [B] [C] [D] [E] [F] [G] [H] 6
10 Approval Through E-mails [A] [E] [F] 6
11 Unapproved Uses [A] [C] [E] [F] [H] 6

RECORDS 7

DEFINITIONS 7

REFERENCES 8

REVISION HISTORY 9

Medtronic

Review and Approval for Clinical Data Publication

PURPOSE

The purpose of this document is to establish a review and approval process for the publication of clinical data, including data used for health economics and reimbursement purposes. The procedure is developed to ensure a high level of scientific standards, and the accuracy of data, and to maintain the integrity of Medtronic study publications, as well as to align publications of clinical data with the worldwide regulatory approval process of the product under investigation. This procedure is updated in accordance with the **Scientific Publications Policy Related to Medtronic Spinal-Sponsored Research (P0004)**, and the needs for clinical evidence for Medtronic Spinal products and therapies.

SCOPE

The information in this document applies to all requests for clinical data and the development of publications that utilize data from the clinical studies sponsored, initiated, or conducted by the clinical/regulatory departments or their agents at Medtronic's Spinal Business. These studies include, but are not limited to, those conducted under the FDA (IDE or IND) and other governmental regulations, post-approval or post-marketing studies, and other types of clinical trials or clinical research studies. Submissions of clinical trial data to regulatory agencies inside or outside the United States to seek product approval or support continued clinical use should be governed by the established procedures for those purposes and thus are not covered under this procedure.

RESPONSIBILITIES

Indicator [1]	Function or Role	Summary of Responsibilities
[A]	Publication Coordinator	A Medtronic employee who is charged to coordinate specific publication projects and maintain proper documentation. Employee in Marketing and Sales functions cannot serve as a publication coordinator.
[B]	Investigator/author	Site investigator/author who is requesting to publish clinical data responsible for adhering to the signed investigator agreement for the study, authorship agreement or other legal agreement.
[C]	Clinical Affairs staff	Medtronic clinical research employees responsible for assisting with the request to publish clinical data.
[D]	Biostatistics and Clinical Research	Medtronic biostatistics and clinical research employees responsible for assisting with the request to publish clinical data.
[E]	Medical Affairs	Medtronic medical affairs employees responsible for assisting with the request to publish clinical data.
[F]	Regulatory staff	Medtronic regulatory employees responsible for assisting with the request to publish clinical data.
[G]	Study Statistician/Analyst	Medtronic biostatistical and analytical employee who gathers data, documents the executed request, and saves all the datasets used, programs, and output.

[1] **Responsibility Indicators** are used throughout this document to highlight responsibilities for each affected function or role.

Medtronic

Review and Approval for Clinical Data Publication

Indicator [1]	Function or Role	Summary of Responsibilities
[H]	Publication Committee	Medtronic employees who review and approve requests for publications and publications of clinical data. The Publication Committee includes at minimum qualified individuals representing areas of Clinical, Biostatistics, Health-economics/Reimbursement, Medical Affairs, Legal, and Regulatory. Function leader in Clinical Research and Biostatistics responsible for managing publication requests and publications will work with various groups to set up the committee membership for each specific publication request or publication project and notify each member.
[I]	Investigator Publication Steering Committee	A group of study investigators or other researchers, responsible for developing publication ideas and planning, determining authorship criteria, authorship responsibilities and expectations, and preparing for manuscripts or other forms of publications.

INSTRUCTION

1 Medtronic Employee Involvement and Non-Medtronic Employee Participation in Publication Projects

1.1 Medtronic employees must comply with the Scientific Publications Policy Related to Medtronic Spinal-Sponsored Research (P0004) when they are involved in any publication project.

1.2 Non-Medtronic employees who participate in a publication project should be properly informed of the Scientific Publications Policy Related to Medtronic Spinal-Sponsored Research (P0004) and this procedure (CL050), and comply with the policy and procedure.

1.3 A Medtronic publication coordinator is responsible for ensuring that the relevant agreements and documentations are in place before a publication project is initiated with non-Medtronic employees.

1.4 A publication steering committee that is comprised of investigators may be instituted to make decisions with regard to publication activities. A Medtronic publication coordinator can provide logistical and coordinating support for the steering committee.

2 Organization of Medtronic Publication Committees

2.1 A Medtronic publication committee will be project-specific for reviewing and approving Clinical Data Publication requests and publications incorporating clinical data from Medtronic Spinal sponsored research.

2.2 A Publication Committee includes at minimum; individuals representing areas of Clinical Research and Biostatistics, Clinical Trial Management, , Health-economics/Reimbursement, Legal, Medical Affairs, and Regulatory.

2.3 Function leader in Clinical Research and Biostatistics responsible for managing clinical data publication requests and publications will work with various function groups to identify the committee membership for each specific publication request or publication project and coordinate the activities of the publication committee.

2.4 Clinical Research and Biostatistics will manage the development, review and approval process for Clinical Data Publication Requests and related Publications.

2.5 An employee in Clinical Research and Biostatistics serves as a publication coordinator for the clinical data publication process, while an employee in Health-economics/Reimbursement serves as a publication coordinator for Health-economics publications.

Medtronic

Review and Approval for Clinical Data Publication

3 Organization of Investigator Publication Steering Committees

3.1 All study investigators may participate in publications planning.

3.2 A steering committee consisting of interested investigators may be formed for a clinical study to assist with development of publication plans and to prepare for manuscripts or other forms of publications.

3.3 The investigators and not Medtronic, determine criteria for participation on the steering committee, authorship for the publications, and authorship responsibilities.. Medtronic may facilitate the process.

3.4 If there is a study principal investigator (PI), the PI serves as chair of the publications committee.

4 Timing on Release of Clinical Publications

4.1 As defined in the Scientific **Publications Policy Related to Medtronic Spinal-Sponsored Research (P0004)**, in general, no publications using data from a clinical study of a novel product or unapproved use of an approved product will be approved prior to the primary clinical study publication unless the publication is part of a study-specific publication plan (e.g., interim analysis, single-center data from a multi-center study, sub-study publication), driven by patient safety concerns, or other reviewed and approved data use situations.

4.2 A primary publication with protocol-defined endpoints cannot precede:

4.2.1 A pre-approval public presentation of the results for regulatory purposes, such as at an FDA Advisory Panel meeting,

4.2.2 The receipt of an approval letter from a regulatory agency if a prior pre-approval public presentation is not required, or

4.2.3 A decision not to pursue regulatory approval(s) of the product or technology.

Due to the usual time lapse from submission to publication, a manuscript may be submitted before the aforementioned events, but should be reasonably expected to be published after one of these events.

4.3 A primary publication should be developed based on the dataset that includes the finalized endpoint data with all possible patient follow-ups or a predefined interim analysis plan.

4.4 Publications with the data beyond the primary endpoints or after regulatory approvals for the product/indications under the investigation should be developed based on the dataset that includes the finalized data with all possible patient follow-ups or a predefined interim analysis plan for a given evaluation interval.

4.5 Release of publications with auxiliary data that are not necessarily defined in study protocols or those that are deemed to be necessary for patient safety or other public interests by the publication committee must be reviewed and approved by the publication committee.

4.6 The considerations from 4.2 above apply to the amassing of clinical results from more than one pivotal clinical study for a publication and every involved study must meet the criteria.

5 Review of Publication Requests of Clinical Data

5.1 Investigators shall not publish any preliminary or final results from a clinical study without prior approval from Medtronic.

5.2 Medtronic may deny a publication request when/if;

5.2.1 The publication would precede any of the events outlined in 4.2

5.2.2 The publication would not include the complete dataset at a pre-defined follow-up interval

5.2.3 The publication would be in conflict with the pre-defined publication plan

5.2.4 The publication would contain confidential information

5.2.5 The publication could be perceived as promoting unapproved uses of an approved Medtronic Spinal product or therapy

5.3 A request to publish clinical data must be reviewed and approved by the Publication Committee. The request is documented on the **CLF050-01, Clinical Data Publication Request Form.** The publication coordinator, working

with Biostatistics staff will prepare the **CLF050-01, Clinical Data Publication Request Form** and seek the approvals from the Publication Committee.

5.4 Investigators or multiple Medtronic functions including Clinical, Medical Affairs, Research, Development, Reimbursement, and Communications but not Marketing and Sales may initiate a Clinical Data Publication Request.

5.5 The following information is required, at a minimum, for a Request for Publication review.

5.5.1 Requestor (e.g., employee, investigator, physician) identification information

5.5.2 Description of the proposal for publication (i.e., specific publication plan)

5.5.3 Publication target or use of data (i.e., journal, meeting, data use)

5.5.4 Description of any data required and origin (e.g., specific studies) if applicable

5.5.5 Intended participation or contribution of any MSB employees or requested services (e.g., data analysis, writing)

5.6 Medtronic Employee participation as authors or contributors must be approved as part of the review and approval process for the specific Request for Publication or Publication.

5.7 The Publication coordinator will document the outcome of review by the Publication committee.

5.8 If clinical data are requested, the responsible Study Statistician/Analyst should document the executed request and save all the datasets used, programs, and output. Other clinical staff will also make appropriate documentation if they have provided information for the publication.

5.9 Before clinical data are provided to non-Medtronic employee authors, an authorship agreement (separate agreement or included in the clinical trial agreement) must be executed with each author that is to receive the data. The authorship agreement will include;

5.9.1 Authors agreement that the clinical data will be used only for the purposes specified on the approved **CLF050-01, Clinical Data Publication Request Form** The obligation of the author to provide Medtronic Spinal the opportunity to review the publication prior to submission

5.9.2 The authors responsibility to fully disclose relationship's with Medtronic in any related publication

5.9.3 The authors responsibility to ensure authorship and contributorship is attributed appropriately

5.9.4 The authors obligation to not share data with anyone outside of the publication project.

5.9.5 Medtronic Spinal will not compensate for writing or editing activities

5.10 The publication coordinator will send the study results to the investigator(s)/author(s) and coordinate activities and communications for completing the publication draft.

5.11 Publication coordinator is responsible for documenting analyses that are developed using clinical data, but performed by a non-Clinical group, such as for health-economic analysis.

5.12 Medtronic publication committee members will be provided with an executed data request to facilitate review of a draft publication. The data provided shall not be used for other purposes without prior approval by the Publication Committee.

6 Review of Publications of Clinical Data

6.1 The final draft of the abstract, poster, manuscript, presentation materials or any other form of publication shall be forwarded to Medtronic for review by the Publication committee.

6.2 The publication coordinator will coordinate the publication committee review. The publication coordinator will incorporate changes/comments, from the publication committee review and forward to the lead author.

6.3 The publication coordinator will track the status of a publication, and maintain a copy of the published form of a publication.

Medtronic

Review and Approval for Clinical Data Publication

7 Dissemination of Regulatory Progress Reports of Clinical Trial [A] [B] [C] [D] [E] [F] [G] [H].

7.1 Regulatory progress reports of a clinical trial, such as annual reports to FDA, are periodically distributed to individual investigators and their Institutional Review Boards (IRBs) according to the regulations. Such reports and other summaries of data may also be distributed internally to Medtronic employees, or to other external recipients. Nevertheless, such summary information and reports cannot be used for any form of publications without prior review and approval by the Medtronic Publication committee.

7.2 Use of US IDE/IND trial data for international regulatory submissions or other non-publication purposes at any stages of the trial should be subject to the review and approval process that at minimum involves the Regulatory, Clinical Research, Biostatistics, and Global Healthcare Economics functions.

8 Data Mining of Clinical Trial Data [A] [B] [C] [D] [E] [F]

8.1 Requests for analyses of clinical trial data for publications will in principle be limited to the trial investigator(s), through the Investigator Publication Steering Committee. Requests from other key opinion leaders (KOLs) or non-investigator surgeons/physicians may also be considered, if

8.1.1 The KOL/non-investigator surgeon has an effective confidentiality agreement with Medtronic;

8.1.2 All relevant policies and codes of Medtronic business conduct are followed;

8.1.3 The request is in accordance with the publication strategy of the company.

8.2 The publication coordinator and the Clinical Research executive or his/her designee(s) will determine whether the request is in accordance with the publication strategy of the company.

8.3 The publication coordinator is charged with the responsibilities to ensure that the conditions in Section 8.1 are met by approving the data request form.

8.4 All such requests will follow the procedure defined in this document and other relevant company procedures.

9 Access to Clinical Raw Data [A] [B] [C] [D] [E] [F] [G] [H]

9.1 Medtronic will provide complete raw datasets of a clinical study to non-Medtronic employees with approval by Executive Management responsible for Clinical Research. Dissemination of raw data will be subject to legal review to ensure compliance with all applicable privacy laws. For publication purposes, Medtronic or its agent will assist in summarizing and analyzing the clinical data and provide the author(s) with all necessary information.

9.2 In any case where the supply of raw datasets of a clinical study to any non-Medtronic employee for non-regulatory purposes is deemed necessary and approved by the Executive Management and reviewed by legal, the Medtronic employee who sends the datasets is responsible for ensuring that the recipient of the datasets is under a confidentiality contract with Medtronic. Any (hard copy or electronic) form of the raw data should either be returned to Medtronic or verified by the recipient (e-mail confirmation) as destroyed after the completion of an intended project.

10 Approval Through E-mails [A] [E] [F]

10.1 All the approvals aforementioned in this procedure can be communicated via e-mail and documented by the publication coordinator at a centralized location for specific publication projects.

11 Unapproved Uses [A] [C] [E] [F] [H]

11.1 Sales personnel may not be involved in the funding or approval of any publication on unapproved uses or unapproved devices as outlined by **CQRC-048 Unapproved Uses of Approved Products**, and consistent with Business Conduct Standards 3 and 6.

11.2 When Medtronic supports a study of unapproved uses or an unapproved device, such support must be disclosed in the publication of the results.

Medtronic

Review and Approval for Clinical Data Publication

11.3 Employees are prohibited from requiring or compensating a researcher to speak about or broadly disseminate research findings prior to FDA approval of the unapproved uses, other than providing a report of publishable quality to Medtronic and/or a peer-reviewed journal for publication. If the researcher wishes to speak or otherwise disseminate research results without Medtronic's support, he/she may do so.

11.4 The author of a publication may not be involved in promotional activities on behalf of Medtronic related to the subject of the research, before approval of the unapproved use/unapproved device or except as permitted by the Notice of Availability.

11.5 Legal will determine whether activities are "promotional" as defined in **QM21, Promotional Materials Policy**.

11.6 The author of a publication may engage in activities as permitted by a Notice of Availability disseminated in accordance with **PL017, U.S Investigator/Patient Recruiting Materials for a MSB Clinical Study that Involve an Unapproved Use of an MSB Product**.

11.7 Employees and Medtronic-contracted medical writers are explicitly prohibited from providing writing assistance on publications that are on unapproved uses of approved products. This prohibition does not apply to publications on studies conducted under 21 C.F.R. Parts 312 or 812.

11.8 Appropriate disclosure of an employee's or medical writer's contribution (authorship or contributorship) according to the International Committee of Medical Journal Editors (ICMJE) requirements for disclosure in publications is required. This includes where Medtronic funds a third party-sponsored research program (e.g., physician-sponsored) on unapproved uses to be conducted under 21 C.F.R. Parts 312 and 812, and the third party contracts with a medical writer to draft publications.

RECORDS

The following records will be maintained according to the retention standards defined by regulatory agencies, applicable Medtronic Corporate Policies, and record retention procedures:

- CLF050-01, Clinical Data Publication Request Form
- E-mail approval documentation

DEFINITIONS

Clinical raw data
By-subject data collected from clinical studies and stored/presented in either an electronic format or a hard-copy format. Any provision of raw data will be subject to legal review to ensure compliance with all applicable privacy laws.

Pilot clinical study
A small-scale clinical study typically having fewer than 50 patients. A pilot study is considered to be the same as a feasibility study.

Pivotal clinical study
A large-scale clinical study with hypothesis testing and a sample size based on statistical considerations. The results from the study are often intended to serve as primary support for regulatory approval(s).

Publish
This term encompasses all modes of public data conveyance including, but not limited to, journal articles, books, presentation slides, and abstracts.

REFERENCES

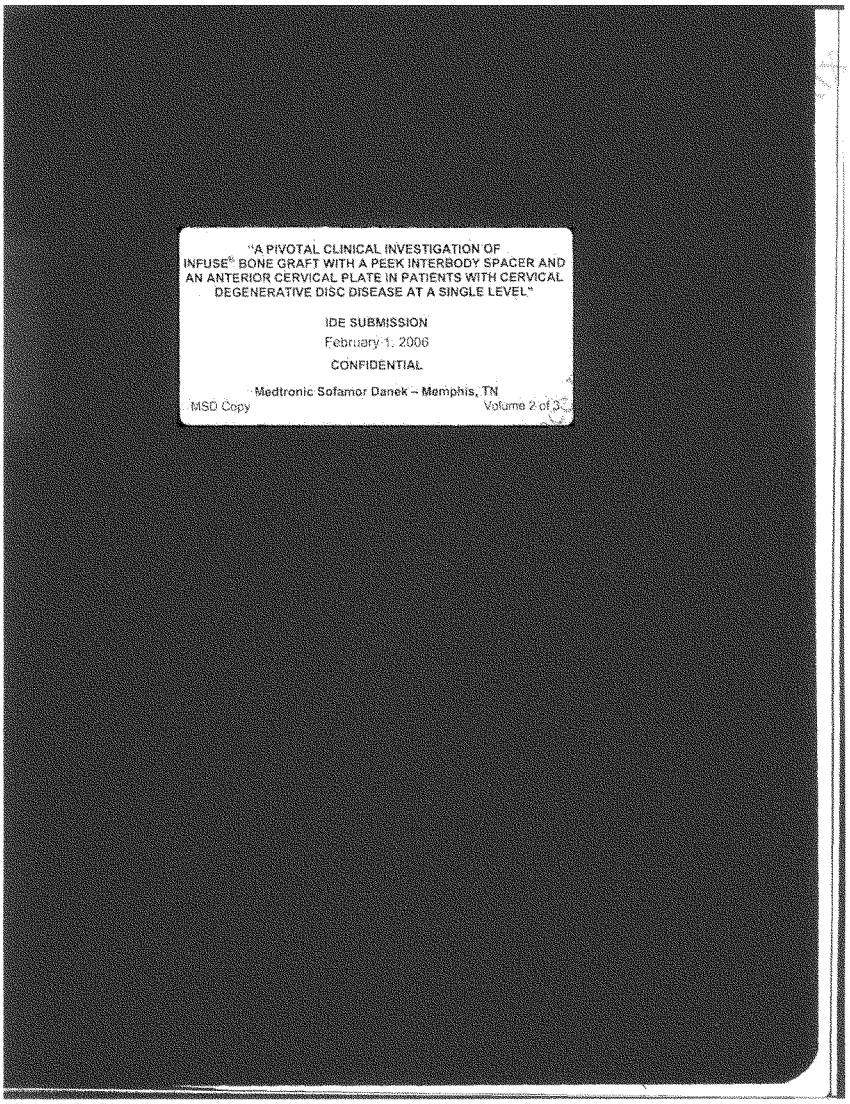
CLF050-01, Clinical Data Publication Request Form 4, 5, 7
CQRC-048 Unapproved Uses of Approved Products 6
PL017, IDE Investigator and Patient Recruitment Material 7
QM21, Promotional Materials Policy 7

Medtronic

Review and Approval for Clinical Data Publication

REVISION HISTORY

Version	Originator	Description of Change	Date
A	Guorong Ma	Initial release.	12/10/07
B	Vicky Powell	Added Section 9 and corrected grammar errors. Updated REFERENCES section.	07/07/08
C	Alison Webster	Added additional elements from CQRC-048 Section 6, Research and Publication Strategies; Process Owner was changed to Lisa Griffin Vincent Ph. D.	04/26/10
D	David Wooten	Substantial changes dictated by the new Publications Policy (P0004). Process owner changed to David Wootten, PhD; Added post –approval or post marketing studies, and other types of clinical trials or clinical research studies in the Scope; Expanded responsibilities of Publication Committee Responsibilities section; Added Investigator Publication Steering Committee to Responsibilities section; Deleted Section 1, Publication of Data from Single Investigator Site and replaced Section 1 with, Medtronic Employee Involvement and Non-Medtronic Employee Participation in Publication Projects; Deleted Section 2, Publication of Data from Multiple Investigator Sites of Pivotal Trial or Data from Entire Cohort of Pilot Trial and replaced with Section 2, Organization of Medtronic Publication Committees; Deleted Section 3, Publication of Data from Entire Pivotal Clinical Study or Combined Data from Multiple Studies and replaced with Section 3, Organization of Investigator Publication Steering Committees; Deleted Section 4, Publication of Subgroup Analysis of Pivotal Trial and replaced with Section 4, Timing on Release of Clinical Publications; Moved Section 5, Dissemination of Regulatory Progress Reports of Clinical Trial, to Section 7, and replaced Section 5 with, Review of Publication Requests of Clinical Data; Moved Section 6, Data Mining of Regulatory Clinical Trial Data to section 8, and replaced with Section 6, Review of Publications of Clinical Data; Moved Section 7, Access to Clinical Raw Data to Section 9; Moved Section 8, Approval through emails to Section 10, Moved Section 9 Unapproved Uses to Section 11. Added PL017, U.S Investigator/Patient Recruiting Materials for a MSB Clinical Study that Involve an Unapproved Use of an MSB Product to References Section. Changed process owner from Lisa Griffin Vincent, Ph.D. to David Wooten, Ph.D.	Feb. 18, 2011
E	David Wootten	Added Medical Affairs as a responsible function or role. Changed Medtronic Spinal and Biologics to Medtronic Spinal throughout the document. Added section 5.2.1 – 5.2.5. Added sections 5.9.1 – 5.9.5. Revised section 9 to clarify access to raw datasets. Changed process owner from Suzanne Baker to David Wootten.	Dec. 06, 2011



INVESTIGATIONAL PLAN
PROTOCOL

1.0 GENERAL INFORMATION

1.1 Introduction

This pivotal clinical study is being conducted to evaluate the use of INFUSE® Bone Graft, the PEEK Interbody Spacer, and a titanium Medtronic Sofamor Danek (MSD) anterior cervical plate as a method of facilitating single-level spinal fusion in patients with symptomatic cervical degenerative disc disease (DDD). In this study, all of the patients will receive the investigational treatment described above. Control data for this study will be taken from the control arms of the following ongoing MSD studies: (1) the Artificial Cervical Disc (also known as PRESTIGE® Cervical Disc System) pivotal IDE trial (IDE# G010188) and (2) the BRYAN® Cervical Disc System pivotal IDE trial (IDE# G000123). Control patients in both of these studies received an anterior cervical discectomy, followed by fusion using the ATLANTIS® Anterior Cervical Plate System and allograft bone.

All sites will follow a common Clinical Investigational Plan (CIP) that consists of the protocol and accompanying case report forms, risk analysis, investigator's agreement, patient informed consent, IRB certification, labeling, and monitoring information.

1.2 Device Description

The investigational implant to be used in this clinical trial consists of three separate components: INFUSE Bone Graft, the PEEK Interbody Spacer, and an anterior cervical plate.

following surgery. If a woman becomes pregnant after enrollment in the study, she will be followed for the duration of the study; however, she will be considered a protocol deviation.

6.21 Device Explant and Return Procedure

Any PEEK Interbody Spacer that is explanted during a second surgery for any reason should be returned for analysis according to the procedures outlined in the Plan for the Retrieval and Analysis of Explanted Devices provided in the CIP. Any anterior cervical plate component that is removed will not be returned to the sponsor for evaluation.

6.22 Quality Control Procedures

This section describes the procedures to assure the study is conducted, recorded, and reported in accordance with the CIP, Medtronic Sofamor Danek Work Instructions, and 21 CFR 812.

6.22.1 Internal Monitoring

Monitoring will be performed by Medtronic Sofamor Danek clinical staff and/or representatives through frequent communication with the study site and on-site monitoring.

Protocol data is to be collected at the site on sponsor-provided case report forms or in an Electronic Data Capture (EDC) system. In the case of the CRF, the completed form is faxed into Medtronic Sofamor Danek who, upon receipt, will double data entry the CRF into a Clinical Database Management System (CDMS). Whether by CRF or by EDC, once data is in the CDMS, data quality scripts will execute, generating discrepancy queries, which are then communicated to and addressed by the site. Database users are required to

authenticate themselves at login with a password that expires on a regular basis. Only properly trained and authorized users are provided access to the study within the CDMS. All data activity is tracked within a reproducible audit trail.

Sites will be required to provide copies of source documents to Medtronic Sofamor Danek, as noted in Section 6.14 of this protocol. Source documents must be available for regulatory review by Medtronic Sofamor Danek and/or the FDA. Each site will maintain records of communications with Medtronic Sofamor Danek clinical staff on study progress, discrepancy resolutions, or any other issues needing resolution.

6.22.2 Clinical Trial Monitoring

The conduct of the clinical trial will be in compliance with applicable sections of 21 CFR 812.

The clinical monitoring for this trial will be conducted by Medtronic Sofamor Danek or a qualified designee (may be a contract research organization). The names and addresses of designated monitor representatives are provided in the Monitoring Information section of the CIP.

Monitors may change periodically; however, Medtronic Sofamor Danek does not consider this a significant change to the CIP. Medtronic Sofamor Danek will notify FDA and all participating investigators and IRBs of any changes to this information yearly in the annual report.

6.22.3 Pre-Study Visit

Prior to the enrollment of the first patient at each clinical site, a pre-study visit with the investigator and the study staff will be conducted. The purpose of the visit is to train the investigator and the clinical staff on the CIP and the following study elements: IRB/EC requirements, regulatory requirements, device accountability, product preparation, storage information, case report forms, procedure for obtaining informed consent, procedure for reporting adverse events, financial disclosure, radiograph requirements, and data collection procedures. In addition, Medtronic Sofamor Danek representative(s) may also meet with the radiology department, laboratory, operating room, and IRB coordinator, as well as with other departments relevant to the study.

6.22.4 Periodic Visit(s)

The purpose of periodic visits is to monitor the study. During periodic site visits, compliance with the protocol will be reviewed, as well as adequacy of facilities, records maintenance, change in personnel, training of new personnel, informed consent, adherence to data collection schedules, unresolved data discrepancy issues, device accountability, IRB, and regulatory requirements. Study files, patient CRF folders, patient clinic and hospital records will need to be reviewed.

An interim site-monitoring visit will be conducted during the enrollment period (within the first five patients) so that potential issues can be addressed. Additional periodic site visits will be based on site performance and will occur at least annually.

6.22.5 Annual Site Visit

Annual site visits will not be required in addition to the periodic visits due the frequency of the periodic visits as stated in the Section 6.22.4 of this protocol.

6.22.6 Investigation Closeout Visit

An investigation closeout visit to the center may be made as necessary at the study conclusion of site participation. Any ongoing responsibilities will be discussed with the investigator and the study site coordinator.

6.23 Data Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board (DSMB) will be formed to oversee the progress and the accumulation of the clinical investigation data. A description of the DSMB for this investigation and of the DSMB's operational procedures is provided in the following sections.

6.23.1 Composition of DSMB

The multidisciplinary membership of the DSMB for this clinical investigation will include two physicians (who are not study investigators) and a biostatistician or epidemiologist. The members should be ethically and scientifically supportive of the study objectives and design. In order to assure freedom from apparent significant conflicts of interest, these three board members will not be Medtronic Sofamor Danek employees, will not have a royalty arrangement with Medtronic Sofamor Danek, and do not own or control, directly or indirectly, more than $50,000 worth of Medtronic, Inc. stock. The members will be

compensated for their activities associated with the DSMB. Compensation will be based upon an agreed hourly consultation rate plus any incurred expenses.

A confidentiality agreement will be executed with each DSMB member. This agreement will also summarize the expected activities of the DSMB, compensation, and financial disclosures related to Medtronic Sofamor Danek. Copies of executed agreements and curriculum vitae will be maintained in the IDE files for this study at Medtronic Sofamor Danek.

6.20.2 DSMB Procedures

- DSMB members will receive a copy of the final investigational plan for their files.
- DSMB will evaluate the results of the study on a periodic basis. They may be asked to make recommendations. Any DSMB recommendation to the sponsor will represent a consensus. The DSMB also will provide a justification for its recommendation.
- Based on the confidentiality of the investigation and the resulting data, DSMB members cannot disseminate any information regarding the investigation, the results, or its findings and recommendations to any person other than Medtronic Sofamor Danek.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

SEP 2 2 2006

OCT 3 2006

Medtronic Sofamor Danek
c/o Ms. Deborah Desrochers
Director, Clinical & Regulatory Affairs
1800 Pyramid Place
Memphis, Tennessee 38132

Re: G060021
INFUSE® Bone Graft/PEEK Interbody Spacer/Anterior Cervical Plate
Indications for Use: Anterior cervical discectomy and fusion (ACDF) to treat patients with single-level (C3-C7) symptomatic cervical degenerative disc disease (CDDD).
Dated: August 24, 2006
Received: August 25, 2006
CMS Reimbursement Category: B3
Annual Report Due: One year from the date of this letter.

Dear Ms. Desrochers:

The Food and Drug Administration (FDA) has reviewed the amendment to your investigational device exemptions (IDE) application. Your application is conditionally approved because you have only addressed some deficiencies cited in our March 3, 2006, disapproval letter. You may begin your investigation at an institution in accordance with the investigational site waiver granted below. Your investigation is limited to 20 institutions and 230 subjects.

This approval is being granted on the condition that, within 45 days from the date of this letter, you submit information correcting the following deficiencies:

1. In response to Deficiency #5 of the March 3, 2006, letter, you state that you will continually monitor adverse events to determine if these require immediate attention of the study monitoring committee. In addition, all such information will be discussed with the FDA, as necessary. While we agree that these are appropriate measures when evaluating safety data during the course of a clinical trial, you did not provide specific stopping rules related to the serious adverse events that were identified in the March 3, 2006, letter and in your response. No specific rules were established to determine if and when a trial will be stopped to prevent further risks to subjects. As previously requested, please provide specific stopping rules for the serious adverse events identified (i.e., death, tumor formation, severe cervical edema, and serious unanticipated adverse events). These rules should include specific values (i.e., numbers of reports or subjects) and detailed plans of action in the event that these values are reached or exceeded during the IDE study.

2. You propose a propensity score analysis. However, the analysis datasets on which the propensity score analysis will be performed are not specified. We believe propensity score analyses should be conducted on both the primary analysis dataset and the per-protocol dataset. This kind of sensitivity analysis will check if additional bias is introduced due to different loss to follow-up patterns or protocol deviations. Please conduct propensity score analyses on both of these datasets and evaluate the robustness of the results.

3. In the simulation study to assess the probability of Type I-like and Type II-like errors for the proposed analysis plan, a 7.65% posterior probability of claiming non-inferiority is reported when the true overall success rate in the control group is 0.75 and is 0.65 in the investigational group (the borderline case). We believe a 7.65% posterior probability of a Type I-like error is too high. Please decrease this probability of Type I-like error by either: 1) increasing the number of subjects before the first interim analysis, or 2) increasing the probability of claiming statistical non-inferiority at the interim analysis to 97.5% (for example), instead of 95%. If the study design and the statistical analysis plan are modified, please conduct and present a new set of simulations to evaluate the new study design.

4. In determining the sample size, the same 0.75 overall success rate for both the investigational group and the control group is assumed, as well as a fixed non-inferiority margin of 10%, a power of 80%, and a significance level of 5%. A fixed sample size of 400 is used for the control group. To adjust for the efficiency loss due to the proposed propensity score covariate adjustment, an additional 25 patients are added to the investigational group. After an adjustment of 15% for loss to follow-up, the required sample size for the investigational group is 225 ± 5 patients. We believe the current adjustment on sample size for propensity score analysis (the 25 additional investigational patients) is somewhat arbitrary. The amount of overlap in propensity scores between the investigational and the control groups will determine to what extent control subjects will be used in the analysis, and hence the probability of Type I-like error and the power of the study. Please perform a simulation study to assess the required sample size and the probabilities of Type I-like and Type II-like errors under different results of the propensity score analysis. Please contact FDA's statisticians directly to discuss the details such simulation studies.

5. In response to Deficiency #10.a., you state that the PEEK Interbody Spacer is the same as the endcaps for the 510(k) cleared VERTE-STACK. However, in other parts of your IDE amendment, you state that the PEEK Interbody Spacer is the same as the CORNERSTONE PSR. It is also noted that the expulsion and subsidence tests were conducted on samples of the CORNERSTONE PSR. It is unclear which 510(k) device represents the PEEK Interbody Spacer. Please clarify.

6. In response to Deficiency #10.c., you state that there are no surgical instruments unique to the proposed investigational device. However, the surgical technique manual references trial sizers. It is assumed that the trial sizers could not be considered "general surgical instruments" because they should be specific to the sizes and geometries of the offered PEEK Interbody Spacer. Please provide a full description of the trial spacers, including material(s) of manufacture.

7. In response to Deficiency #10.d., you state that a list of surgical instruments is provided in the surgical technique manual. While this is appropriate and adequate for the sake of the surgical technique, Deficiency #10.d. requested a complete table of system components. The requested table is meant to be a comprehensive listing of all components related to the investigational device, including the anterior cervical plate components, the PEEK Interbody Spacer components, all INFUSE Bone Graft components, and all surgical instruments, including trial sizers. Please provide such a table to FDA for the sake of completeness.

The conditions of approval identified above represent the issues that we believe need to be resolved before your IDE application can be fully approved. In developing the conditions of approval, we carefully considered the relevant statutory criteria for Agency decision-making as well as the burden that may be incurred in your attempt to respond to the conditions of approval. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at:
http://www.fda.gov/cdrh/modact/leastburdensome.html

This information should be identified as an IDE supplement referencing the IDE number above, and must be submitted in triplicate to:

IDE Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

FDA will waive those requirements regarding submission and prior FDA approval of a supplemental application and receipt of certification of institutional review board (IRB) approval for the addition of investigational sites (21 CFR 812.35(b)) provided:

1. The total number of investigational sites does not exceed 20.

2. You maintain current records on:

   a. the names and addresses of all investigational sites,
   b. the names and addresses of all investigators, identifying those that are currently participating,
   c. the names, addresses and chairpersons of all IRBs,
   d. the dates of IRB approvals, and
   e. the dates of first shipments or first use of investigational devices for all participating institutions.

3. Within 5 days of reaching the investigational site limit, you submit to FDA a current list containing the information specified in 2(a-e) above.

4. The current investigator list to be submitted to FDA at 6-month intervals (21 CFR 812.150(b)(4)) will contain the information specified in 2(a-e) above.

5. You submit to FDA, within 2 days of receipt of a request by FDA, a current list containing the information specified in 2(a-e) above.

6. The reviewing IRB does not require any significant changes in the investigational plan or in the informed consent, that is, require any change which may increase the risks to subjects or affect the scientific soundness of the study. (Please note: If a significant change is requested, this change must be submitted to FDA for review and approval prior to initiating the study at that investigational site.) Minor changes requested by the IRB may be made without prior FDA approval.

If you agree to these conditions, you may begin an investigation at a new investigational site after the IRB has approved the investigation. No documentation should be submitted for any institution within the approved limit until the investigational site limit is reached or the 6-month current investigator list is due. FDA assumes that you have agreed to the conditions of this waiver unless you specifically notify us in writing of your disagreement. Please note, however, that you must submit a supplemental IDE application, and receive FDA approval, prior to expanding the investigation beyond the limit specified above. Additionally, if you do not agree to these conditions, you must comply with the full requirements for the submission to FDA of a supplemental IDE application for new investigational sites not already specifically approved for participation in your study (21 CFR 812.35(b)).

We would like to point out that FDA approval of your IDE application does not imply that this investigation will develop sufficient safety and effectiveness data to assure FDA approval of a premarket approval (PMA) application for this device. You may obtain guidance for the preparation of a PMA application from our Device Advice website (http://www.fda.gov/cdrh/devadvice/pma) or from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597.

You should also give serious consideration to the following item which is considered important for the analysis of your data for the purposes of determining safety and effectiveness for a future PMA application:

8. We recommend you carefully check the overlap in propensity scores between the investigational group and the control group, especially for each subclass defined by the quartiles of the propensity scores. Small overlap in propensity scores between the two treatment groups within one or more of the subclasses will result in imbalance in the number of subjects in each treatment group, and hence may cause problems for the proposed Bayesian hierarchical models based on the propensity score subclasses.

Page 5 – Ms. Deborah Desrochers

We recognize that the proposed pivotal clinical trial may be used to support a Premarket Approval Application (PMA) and if approved, it is likely that a post-approval study (PAS) may be requested as a Condition of Approval (CoA). As the original IDE cohort can sometimes be used to gather long-term safety and effectiveness data after market approval, we suggest you consider obtaining patient informed consent and IRB approval at the initiation of the study so that enrolled subjects will be followed for a period of at least 5 years. FDA believes this may reduce patient loss to follow-up during the marketing application review process and keep many subjects available to participate in such a PAS if ordered. Your decision whether to incorporate this recommendation into your protocol will not impact any FDA decision regarding the approvability of an IDE or PMA application. In addition, please note that other clinical studies besides continued follow-up of IDE subjects, including prospective studies which enroll new patients, may also be required as CoA should a PMA be approved.

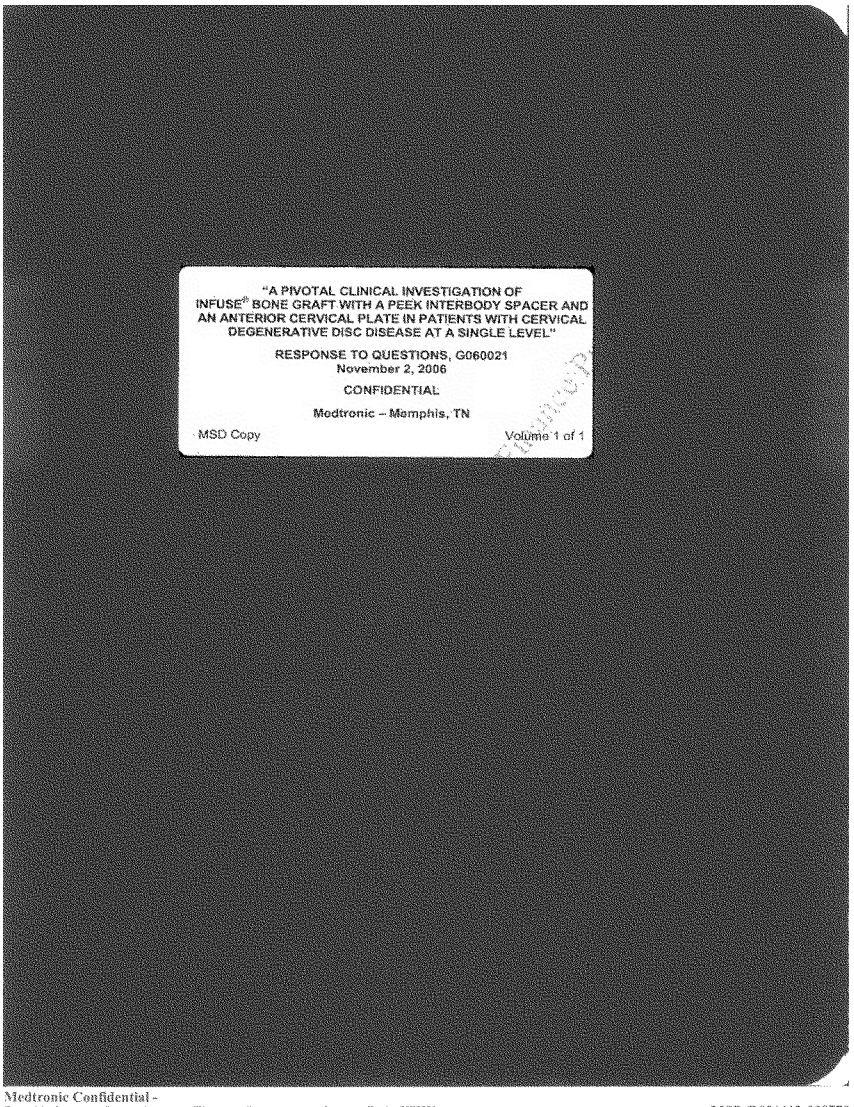
We have enclosed the guidance document entitled "Sponsor's Responsibilities for a Significant Risk Device Investigation" to help you understand the functions and duties of a sponsor. Also enclosed is the guidance document "Investigators' Responsibilities for a Significant Risk Device Investigation" which you should provide to participating investigators.

Please note that the above conditions of approval should be satisfied within 45 days from the date of this letter or we may take steps to propose withdrawal of approval of your IDE application. If you have any questions, please contact Mr. Sergio M. de del Castillo at (301) 594-2036.

Sincerely yours,

Mark N. Melkerson
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures
(1) Sponsor's Responsibilities for a Significant Risk Device Investigation
(2) Investigators' Responsibilities for a Significant Risk Device Investigation


"A PIVOTAL CLINICAL INVESTIGATION OF INFUSE® BONE GRAFT WITH A PEEK INTERBODY SPACER AND AN ANTERIOR CERVICAL PLATE IN PATIENTS WITH CERVICAL DEGENERATIVE DISC DISEASE AT A SINGLE LEVEL"
RESPONSE TO QUESTIONS, G060021
November 2, 2006
CONFIDENTIAL
Medtronic – Memphis, TN
MSD Copy
Volume 1 of 1

Medtronic
SOFAMOR DANEK

Regulatory Affairs Department

Medtronic Sofamor Danek
1800 Pyramid Place
Memphis, TN 38132
www.medtronic.com

tel 901.396.3133
fax 901.346.9738
tel 800.876.3133

CONFIDENTIAL

November 2, 2006

IDE Document Mail Center (HFZ-401)
Food and Drug Administration
Center for Devices and Radiological Health
9200 Corporate Blvd.
Rockville, MD 20850

RE: INFUSE® Bone Graft/PEEK Interbody Spacer/Anterior Cervical Plate
G060021

Dear Sir/Madam:

Attached are responses to the deficiencies that were included in a letter from FDA dated September 22, 2006, concerning the pivotal IDE submission for the INFUSE® Bone Graft/PEEK Interbody Spacer/Anterior Cervical Plate, G060021. This non-randomized IDE, which proposed a clinical study with 225 patients who have cervical degenerative disc disease at one treatment level, was conditionally approved by FDA and limited to 20 institutions. Please note that we only requested 15 sites for this IDE and would like to limit the amount to that number.

In addition to the responses to the deficiencies and revised versions of the documents that were affected by these responses, we are submitting updated versions of several documents. The documents in question were revised to correct typographical and formatting errors and to update contact information. The overall content of these documents was not changed from the original versions submitted. The affected documents are provided in Attachments E-G. We are providing six paper copies for your review.

We believe that this submission addresses FDA's remaining concerns and are seeking full approval. We appreciate your timely review of this submission and request that a copy of FDA's response be faxed to me at (901) 346-9738 when available. If you have any questions, please call me, Martin Yahiro, M.D., or Julie Blair at (901) 396-3133. Thank you for your continued assistance.

Sincerely,

Deborah Desrochers
Director, Clinical & Regulatory Affairs

RESPONSE TO QUESTIONS

1. **In response to Deficiency #5 of the March 3, 2006, letter, you state that you will continually monitor adverse events to determine if these require immediate attention of the study monitoring committee. In addition, all such information will be discussed with the FDA, as necessary. While we agree that these are appropriate measures when evaluating safety data during the course of a clinical trial, you did not provide specific stopping rules related to the serious adverse events that were identified in the March 3, 2006, letter and in your response. No specific rules were established to determine if and when a trial will be stopped to prevent further risks to subjects. As previously requested, please provide specific stopping rules for the serious adverse events identified (i.e., death, tumor formation, severe cervical edema, and serious unanticipated adverse events). These rules should include specific values (i.e., numbers of reports or subjects) and detailed plans of action in the event that these values are reached or exceeded during the IDE study.**

MEDTRONIC RESPONSE:
Based on the nature of the clinical study (implantation of the device), we believe that stopping rules are only applicable during the enrollment period of the clinical trial and should be referred to as "suspension of enrollment" rules. Patients who are already implanted with the device must continue to be followed, so the study will not be stopped (*i.e.*, patients no longer evaluated) based on the occurrence of these adverse events.

Because some adverse events can result from general surgical procedures and may not relate to the device, the rules for suspension of enrollment will only apply to adverse events that are determined to be related to INFUSE® Bone Graft.

The following rules will be added to the protocol for serious adverse events, which may result in suspension of enrollment after the cause and severity of the event have been determined.

- Implant-associated patient death

  If any patient dies from an adverse event that is determined to be implant-associated, then the enrollment will be suspended in the clinical trial.

- Serious unanticipated implant-associated adverse event

  If any patient has an adverse event that is determined to be a serious (WHO Grade 3 or 4 classification), unanticipated implant-associated event, then the enrollment will be suspended in the clinical trial.

- Serious life-threatening cervical edema

  If any patient has a cervical edema (not caused by a hematoma) that is determined to be life-threatening (WHO Grade 4 classification) and is determined to be related to the implant, then the enrollment will be suspended in the clinical trial.

In addition, any malignancies reported in the clinical trial will be forwarded to the FDA. Because a causal association between a malignancy and the device is difficult to demonstrate, a specific number of malignancies will not be defined for the stopping rules. We will, however, report each malignancy to FDA as soon as it is reported to us and continually monitor the rates of malignancies in both the investigational and historical control groups for comparison. The company will discuss with FDA any concerns relating to malignancies and the device to determine whether or not enrollment should continue at any point in the clinical trial.

For any of these categories of adverse events that may result in a suspension of enrollment, the Investigator and Safety Monitoring Committee will research the details of the adverse event and recommend to the company whether or not enrollment should be suspended. A consideration for suspending enrollment will be whether or not the adverse event was an isolated event specifically caused by factors unique to the individual patient (*e.g.*, unknown allergy to the device).

Prior to suspension of enrollment, discussions will be held between FDA and the company to discuss the adverse event, its relationship to the implant, the severity of the event, and justification of suspension of enrollment.

If an adverse event occurs that results in a suspension of enrollment, further discussions will be held with FDA on whether or not enrollment should resume and what is needed to resume the enrollment.

These suspension of enrollment rules have been included in the protocol, which is provided in Attachment A.

2. **You propose a propensity score analysis. However, the analysis datasets on which the propensity score analysis will be performed are not specified. We believe propensity score analyses should be conducted on both the primary analysis dataset and the per-protocol dataset. This kind of sensitivity analysis will check if additional bias is introduced due to different loss to follow-up patterns or protocol deviations. Please conduct propensity score analyses on both of these datasets and evaluate the robustness of the results.**

MEDTRONIC RESPONSE:
It has certainly been our intention to apply the propensity score adjustment for both the primary dataset and per-protocol dataset analyses. We have explicitly added the statement to indicate this in Section III.1 of the updated Statistical Considerations, provided in Attachment B.

3. **In the simulation study to assess the probability of Type I-like and Type II-like errors for the proposed analysis plan, a 7.65% posterior probability of claiming non-inferiority is reported when the true overall success rate in the control group is 0.75 and is 0.65 in the investigational group (the borderline case). We believe a 7.65% posterior probability of a Type I-like error is too high. Please decrease this probability of Type I-like error by either: 1) increasing the number of subjects before the first interim analysis; or 2) increasing the probability of claiming statistical non-inferiority at the interim analysis to 97.5% (for example), instead of 95%. If the study design and the statistical analysis plan are modified, please conduct and present a new set of simulations to evaluate the new study design.**

MEDTRONIC RESPONSE:
For this particular study, we decided to eliminate the formal interim analysis as previously proposed, mainly from the operational considerations. The updated Statistical Considerations reflects this change.

4. **In determining the sample size, the same 0.75 overall success rate for both the investigational group and the control group is assumed, as well as a fixed non-inferiority margin of 10%, a power of 80%, and a significance level of 5%. A fixed sample size of 400 is used for the control group. To adjust for the efficiency loss due to the proposed propensity score covariate adjustment, an additional 25 patients are added to the investigational group. After an adjustment of 15% for loss to follow-up, the required sample size for the investigational group is 225 ± 5 patients. We believe the current adjustment on sample size for propensity score analysis (the 25 additional investigational patients) is somewhat arbitrary. The amount of overlap in propensity scores between the investigational and the control groups will determine to what extent control subjects will be used in the analysis, and hence the probability of Type I-like error and the power of the study. Please perform a simulation study to assess the required sample size and the probabilities of Type I-like and Type II-like errors under different results of the propensity score analysis. Please contact FDA's statisticians directly to discuss the details of such simulation studies.**

MEDTRONIC RESPONSE:
We acknowledge that the addition of 25 investigational patients for loss of efficiency because of propensity score adjustment is arbitrary. We believe,

however, that the addition should be sufficient, since the inclusion/exclusion criteria used for the investigational patients are very similar to those used for the control patients and thus we fully expect that the propensity scores will be well overlapped between the investigational group and control group.

As in any other clinical trials, assumptions used for calculating sample sizes are based on educated guesses, prior knowledge, and expectations about the products under investigation. The assumptions we used for calculating the sample size were based on the expected outcomes after adjusting propensity score. The simulation suggested by FDA using different results of the propensity score analysis would be purely based on something arbitrary and only satisfy some theoretical curiosity. It would not help the sponsor to determine a sample size in a practical way. Some arbitrary decision still needs to be made. Thus, we do not believe that the suggested simulation is necessary and practically meaningful. In addition, we also make the following reasoning in support of our argument against such an unnecessary simulation.

For a given sample size, the type-I error rate is only dependent on 1) the significance level to be used and 2) the number and timing of interim analyses. Even if some of the control patients in theory could be dropped because of not matched propensity scores, it should not affect type-I error rate as long as no multiple analyses are to be performed. Again, we fully expect that the propensity scores will be well overlapped in this study. Failure to appropriately take account of effects of covariates and thus causing biases in assessing treatment effect is an issue completely different from determining sample size.

As we may all agree, the type-I error rate is a concern for FDA, but the power is more a concern for the sponsor, except that the exposure of the investigational device/treatment to an unnecessarily large number of patients should be avoided. As Dr. Telba Irony presented many times at statistical/clinical trial meetings and the draft Bayesian guidance document stated:

> At any point before or during a Bayesian clinical trial, you can obtain the posterior distribution for the sample size. Therefore, at any point in the trial, you can compute the expected additional number of observations needed to meet the stopping criterion. In other words, the sample size distribution is continuously updated as the trial goes on. Because the sample size is not explicitly part of the stopping criterion, the trial can be ended at the precise point where enough information has been gathered to answer the important questions. ... When sizing a Bayesian trial, FDA recommends you decide in advance on the minimum sample size according to safety and effectiveness endpoints because safety endpoints may lead to a larger sample size. FDA also recommends you include a minimum level of information from the current trial to enable verification of model assumptions and appropriateness of prior information used. This practice also enables the clinical community to gain experience with the

device. We recommend the maximum sample size be defined according to economical, ethical, and regulatory considerations.

The proposed sample size of 225 investigational patients was calculated based on the overall success rates estimated from the results of our previous IDE trials with cervical interbody fusion devices. Those estimates reflect what are expected after adjusting propensity score effects. We believe that such a sample size should be adequate to characterize safety and effectiveness profiles of the investigational device. Furthermore, based on the cost and benefit consideration in this particular case, the sponsor is not likely to be willing to run a study much larger than the proposed sample size.

Therefore, we think the proposed sample size is both reasonable and practical.

5. **In response to Deficiency #10a, you state that the PEEK Interbody Spacer is the same as the endcaps for the 510(k) cleared VERTE-STACK. However, in other parts of your IDE amendment, you state that the PEEK Interbody Spacer is the same as the CORNERSTONE PSR. It is also noted that the explusion and subsidence tests were conducted on samples of the CORNERSTONE PSR. It is unclear which 510(k) device represents the PEEK Interbody Spacer. Please clarify.**

MEDTRONIC RESPONSE:
The name "PEEK Interbody Spacer" was a generic name chosen to represent the investigational PEEK device used in this study. The PEEK Interbody Spacer and CORNERSTONE PSR device (with lateral ports) are equivalent devices. The CORNERSTONE PSR device is in the 510(k)-cleared VERTE STACK family of devices, cleared for corpectomy for tumor or trauma.

6. **In response to Deficiency #10c, you state that there are no surgical instruments unique to the proposed investigational device. However, the surgical technique manual references trial sizers. It is assumed that the trial sizers could not be considered "general surgical instruments" because they should be specific to the sizes and geometries of the offered PEEK Interbody Spacer. Please provide a full description of the trial spacers, including material(s) of manufacture.**

MEDTRONIC RESPONSE:
The trial sizers that will be utilized in the IDE are considered "general surgical instruments" because they can be used with other implants, such as various bone configurations or other products that are approved for use outside of the United States. Listed below is information on the material of the trials. Please note that set type 576, which was listed in the submission dated August 24, 2006, has now been changed to set type M24. This has been changed in the study surgical technique, provided in Attachment C. However, no changes have been made to the instruments themselves or the set configuration that was previously submitted.

Set Type 100
Trial Heads: 17-4 PH stainless steel
Handle: 6061-T6 aluminum
Trial Shaft: 17-4 PH stainless steel

Set Types 200 and 398
Trial Heads: 17-4 PH stainless steel
Handle Insert: Ti 6Al-4V
Trial Shaft: 17-4 PH stainless steel
Handle Tip: 17-4 PH stainless steel
Handle Cap: 17-4 PH stainless steel

Set Types 566 and M24
Handle Core: 17-4 PH stainless steel
Trial Heads: 17-4 PH stainless steel
Rasp Heads: 465 stainless steel
Handle: silicone

A variety of trial sets are available so that the investigators may utilize any one of the trial sets, which are specific to the size of the device and may already be at their hospitals.

7. **In response to Deficiency #10d, you state that a list of surgical instruments is provided in the surgical technique manual. While this is appropriate and adequate for the sake of the surgical technique, Deficiency #10d requested a complete table of system components. The requested table is meant to be a comprehensive listing of all components related to the investigational device, including the anterior cervical plate components, the PEEK Interbody Spacer components, all INFUSE Bone Graft components, and all surgical instruments, including trial sizers. Please provide such a table to FDA for the sake of completeness.**

MEDTRONIC RESPONSE:
As requested, a complete table of the system components is provided in Attachment D.

Attachment A
Revised Protocol

INVESTIGATIONAL PLAN
PROTOCOL

1.0 GENERAL INFORMATION

1.1 Introduction

This pivotal clinical study is being conducted to evaluate the use of INFUSE® Bone Graft, the PEEK Interbody Spacer, and a titanium Medtronic anterior cervical plate as a method of facilitating single-level spinal fusion in patients with symptomatic cervical degenerative disc disease (DDD). In this study, all of the patients will receive the investigational treatment described above. Control data for this study will be taken from the control arms of the following ongoing Medtronic studies: (1) the Artificial Cervical Disc (also known as PRESTIGE® Cervical Disc System) pivotal IDE trial (IDE# G010188) and (2) the BRYAN® Cervical Disc System pivotal IDE trial (IDE# G000123). Control patients in both of these studies received an anterior cervical discectomy, followed by fusion using an ATLANTIS® or ATLANTIS VISION® Anterior Cervical Plate and allograft bone.

All sites will follow a common Clinical Investigational Plan (CIP) that consists of the protocol and accompanying case report forms, risk analysis, investigator's agreement, patient informed consent, institutional review board (IRB) certification, labeling, and monitoring information.

1.2 Device Description

The investigational implant to be used in this clinical trial is composed of three separate components: INFUSE Bone Graft, the PEEK

IRB and regulatory requirements. Study files, patient CRF folders, and patient clinic and hospital records (both paper and electronic) will need to be reviewed.

An interim site-monitoring visit will be conducted during the enrollment period (within the first five patients) so that potential issues can be addressed. Additional periodic site visits will be based on site performance and will occur at least annually.

6.23.5 Annual Site Visit

Annual site visits will not be required in addition to the periodic visits due the frequency of the periodic visits as stated in the Section 6.23.4 of this protocol.

6.23.6 Investigation Closeout Visit

An investigation closeout visit to the center may be made as necessary at the study conclusion of site participation. Any ongoing responsibilities will be discussed with the investigator and the study site coordinator.

6.24 Study Monitoring Procedures and Stopping Rules

6.24.1 Study Monitoring Committee

A formal Data Safety Monitoring Board (DSMB) will not be utilized in this study of this device. However, an independent study monitoring committee will oversee the progress and the accumulation of the clinical investigation data, in addition to the study sponsor.

6.24.2 Suspension of Enrollment

Enrollment may be suspended in the clinical trial if certain serious adverse events occur, which may warrant examination

of the cause prior to continuation of enrollment into the study. However, patients who are already implanted with the device must continue to be followed, so the study will not be stopped (*i.e.*, patients no longer evaluated) based on the occurrence of these adverse events.

The following "suspension of enrollment" rules apply to serious adverse events, which may result in suspension of enrollment after the cause and severity of the event have been determined:

- Implant-associated patient death
- Serious unanticipated implant-associated adverse event;
- Serious, life-threatening cervical edema classified as implant-associated with Grade 4 severity (WHO classification system) and not caused by a hematoma.

In addition, any malignancies reported in the clinical trial will be forwarded to the FDA. The rates of malignancies will be monitored to determine whether or not enrollment should be suspended, based on malignancies.

For any of these categories of adverse events that may result in a suspension of enrollment, the Investigator and Study Monitoring Committee will research the details of the adverse event and recommend to the company whether or not enrollment should be suspended. A consideration for suspending enrollment will be whether or not the adverse event was an isolated event specifically caused by factors unique to the individual patient (*e.g.*, unknown allergy to the device).

Each investigator will be notified by the clinical staff if enrollment is to be suspended. The initial contact will be made by telephone and followed by an official letter from the Sponsor.

INVESTIGATIONAL PLAN
PROTOCOL

1.0 GENERAL INFORMATION

1.1 Introduction

This pivotal clinical study is being conducted to evaluate the use of INFUSE® Bone Graft, the PEEK Interbody Spacer, and a titanium Medtronic anterior cervical plate as a method of facilitating single-level spinal fusion in patients with symptomatic cervical degenerative disc disease (DDD). In this study, all of the patients will receive the investigational treatment described above. Control data for this study will be taken from the control arms of the following ongoing Medtronic studies: (1) the Artificial Cervical Disc (also known as PRESTIGE® Cervical Disc System) pivotal IDE trial (IDE# G010188) and (2) the BRYAN® Cervical Disc System pivotal IDE trial (IDE# G000123). Control patients in both of these studies received an anterior cervical discectomy, followed by fusion using an ATLANTIS® or ATLANTIS VISION® Anterior Cervical Plate and allograft bone.

All sites will follow a common Clinical Investigational Plan (CIP) that consists of the protocol and accompanying case report forms, risk analysis, investigator's agreement, patient informed consent, institutional review board (IRB) certification, labeling, and monitoring information.

1.2 Device Description

The investigational implant to be used in this clinical trial is composed of three separate components: INFUSE Bone Graft, the PEEK Interbody Spacer, and an anterior cervical plate (either the ATLANTIS or ATLANTIS VISION Anterior Cervical Plate).

folders, and patient clinic and hospital records (both paper and electronic) will need to be reviewed.

An interim site-monitoring visit will be conducted during the enrollment period (within the first five patients) so that potential issues can be addressed. Additional periodic site visits will be based on site performance and will occur at least annually.

6.23.5 Annual Site Visit

Annual site visits will not be required in addition to the periodic visits due the frequency of the periodic visits as stated in the Section 6.23.4 of this protocol.

6.23.6 Investigation Closeout Visit

An investigation closeout visit to the center may be made as necessary at the study conclusion of site participation. Any ongoing responsibilities will be discussed with the investigator and the study site coordinator.

6.24 Study Monitoring Procedures and Suspension of Enrollment Rules

6.24.1 Study Monitoring Committee

An independent Study Monitoring Committee will oversee the progress and the accumulation of the clinical investigation data, in addition to the Sponsor. The Committee will meet a minimum of three times per year throughout the duration of this study.

6.24.2 Suspension of Enrollment Rules

Enrollment may be suspended in this clinical trial if certain serious adverse events occur more often than the expected

rate. Further examination of the event may be needed or discussions with FDA held prior to re-starting enrollment into the study. However, patients who are already implanted with the device must continue to be followed, so the study will not be stopped (*i.e.,* patients no longer evaluated) based on the rate of occurrence of these adverse events.

"Suspension of enrollment" rules will apply only to certain serious adverse events, as defined below:

- Serious, life-threatening cervical edema, defined as:
  - swelling of the neck (not caused by a hematoma), excluding those that definitely or potentially occurred as a result of an external event (e.g., bee sting allergy) or co-morbidity (e.g., history of severe asthma), of such a degree that obstructs or threatens to obstruct the airway and necessitates endotracheal intubation or tracheostomy for airway management.
  - swelling of the neck (not caused by a hematoma), excluding those that definitely or potentially occurred as a result of an external event (e.g., bee sting allergy) or co-morbidity (e.g., history of severe asthma), of such a degree that obstructs or threatens to obstruct the airway and necessitates readmission to the hospital for airway management.
- Tumor formation, not including non-malignant (benign) tumors and basal cell and squamous cell skin cancers;
- Serious unanticipated adverse event classified as implant-associated, implant/surgical procedure-associated, or undetermined; or

- Patient death that is determined to be an unreasonable risk to other patients, excluding deaths that definitely or potentially occurred as a result of an external event (e.g., motor vehicle accident) or comorbidity (e.g., history of cardiovascular disease).

NOTE: The following are **NOT** considered trigger events for suspension of study enrollment:

- Evaluation and/or treatment of serious, life-threatening airway compromise caused by hematoma;
- Evaluation and/or treatment in the office or Emergency Room of cervical edema that is not considered life-threatening;
- Re-admission to the hospital for observation and/or treatment of cervical edema that is not causing life-threatening airway compromise;
- Treatment with corticosteroids of cervical edema that is not considered life-threatening;
- Non-malignant (benign) tumors;
- Basal cell carcinoma (skin);
- Squamous cell carcinoma (skin);
- Death that definitely or potentially occurred as a result of an external (unrelated) event (e.g., motor vehicle accident) or co-morbidity (e.g., history of cardiovascular disease);
- Serious, life-threatening edema that definitely or potentially occurred as a result of an external (unrelated) event (e.g., bee sting allergy) or co-morbidity (e.g., history of severe asthma).

Table 4 lists the rates of occurrence that will result in a suspension of enrollment for the given adverse event., *i.e.,* numbers are above the expected rate.

Table 4. Example Numbers of Events That Would Trigger the Suspension of Enrollment

Event	Expected Rate	Suspension of Enrollment Criterion: P(pINFUSE > pExpected | data) > 95%				
		Number of Patients Enrolled				
		20	50	100	150	200
Cervical edema	0%	1	1	1	1	1
Tumors	0.41%	1	1	2	2	3
Serious UAE	0%	1	1	1	1	1
Deaths	0%	1	1	1	1	1

For any of the categories of adverse events described above that may result in a suspension of enrollment, the Study Monitoring Committee will examine the details of the adverse event, as researched and reported by the investigational site, and recommend to the Sponsor whether or not enrollment should be suspended based on the rules listed above.

6.24.3 Procedure for Suspending Enrollment

6.24.3.1 Sponsor Notification

If any adverse event that could potentially suspend enrollment occurs during this study, the Clinical Staff should be contacted by telephone or email within one business day of being notified of the event. In addition, each investigational site will be provided with a specific study management form to be used to notify the sponsor of a potential enrollment-suspending event. This form and the Adverse Event Case Report Form must be completed by the Investigator and faxed to the Sponsor, also within one business day of being notified of the event. Prior to study enrollment,

each investigational site will be trained on the suspension of enrollment rules for the study and the reporting criteria for any violations of these rules.

6.24.3.2 Sponsor Evaluation

Upon receipt of initial information from the site regarding the adverse event, the Sponsor will evaluate the reported adverse event according to the suspension of enrollment rules listed in Section 6.24.2. As necessary, Medtronic will contact the investigational site to request any additional information regarding the adverse event and the site's preliminary assessment of the cause. Once collected, all of the preliminary clinical information will be immediately forwarded to the Study Monitoring Committee to evaluate the adverse event. The Study Monitoring Committee must immediately make a determination as to whether or not the serious adverse event meets the study's suspension of enrollment criteria. If the Study Monitoring Committee determines that there is a possibility that the serious adverse event presents an unreasonable risk to other subjects, the Study Monitoring Committee will notify Medtronic of its findings. Medtronic will then immediately suspend study enrollment and notify the FDA, investigators, and IRBs within 5 days of notification.

If in its preliminary determination the Study Monitoring Committee does not find the adverse event presents an unreasonable risk to other subjects, the Sponsor

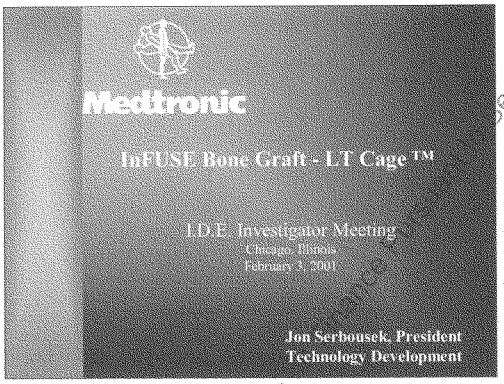
will continue to provide any updates on the cause or circumstances of the event to the Study Monitoring Committee that may cause it to reconsider its decision. If the Study Monitoring Committee later determines after additional information that the adverse event presents an unreasonable risk to other subjects, the Study Monitoring Committee will notify Medtronic of its findings, and Medtronic will then immediately suspend study enrollment and notify the FDA, investigators, and IRBs.

6.24.4 Suspension Notification Procedure

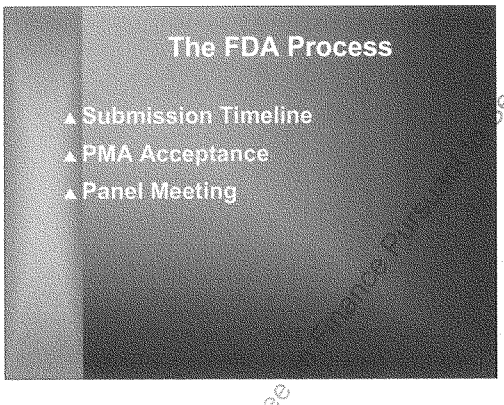
Each investigator will be notified by the clinical staff if enrollment is to be suspended. **Investigators will also be instructed not to implant any study devices, even in consented patients, until further notification by Medtronic.** The initial contact will be made by telephone and followed by an official letter from the Sponsor.

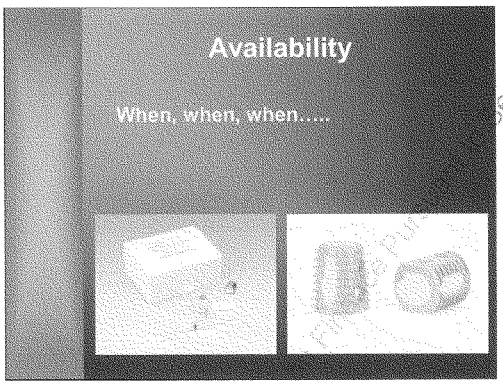
From: Tara Hood
Sent: Friday, February 2, 2001 04:25:35 PM
To: Neil Beals
CC: Tara Hood
Subject: Investigator Meeting Presentations 2-3-01

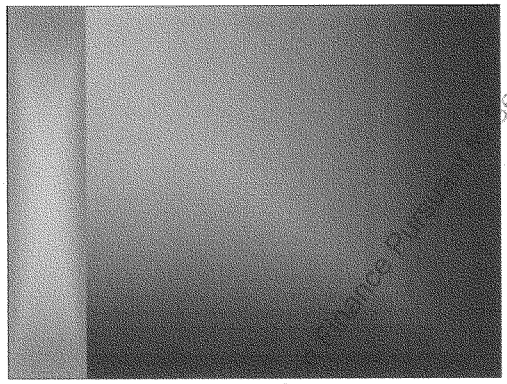
Attachments: Jon & Rick Presentation 2-3-01.ppt; Rod Riedel Presentation 2-3-01.ppt; Zdeblick Presentation 2-3-01.ppt; Bailey Presentation 2-3-01.ppt; Neil Beals Presentation 2-3-01.ppt; Bill Martin Presentation 2-3-01.ppt

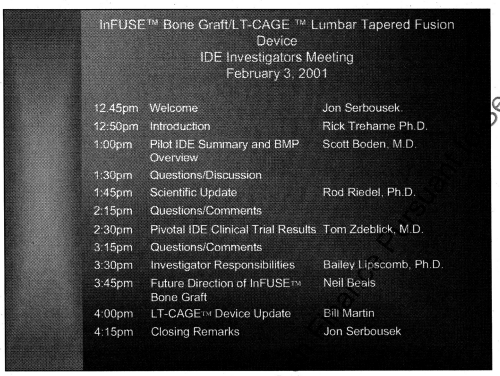


2









rhBMP-2 preclinical safety studies

Gerard Riedel, PhD
Project Director, rhBMP-2
Genetics Institute, Inc.
Cambridge, Massachusetts USA

GENETICS INSTITUTE

rhBMP-2/ACS is an osteoinductive implantable product indicated for the treatment of long bone fractures that require open surgical management.

rhBMP-2/ACS improves current fracture management by:

- Inducing bone at implantation site
- Preventing delayed union
- Reducing the need for secondary interventions
- Accelerating fracture union

Recombinant human bone morphogenetic protein - 2 (rhBMP-2)

- Discovered / developed at Genetics Institute
  - member of a large (>24) protein family of growth and differentiation factors (GDFs)
- Osteoinductive in patients:
  - Boden, Zdeblick, Sandhu, and Heim. 2000. Spine 25: 376-381.
  - Boyne et al. 1997. Int J Period Rest Dent 17: 11-25

rhBMP-2 mechanism of action

- Differentiation factor (vs growth factor)
- Receptors and signaling pathway identified
- Local administration (surgical implantation) is required for bone induction

Implantation of rhBMP-2 requires a matrix

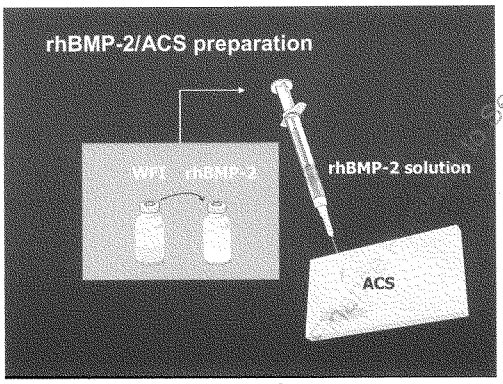
- Delivers rhBMP-2 dose to surgical site
- Retains rhBMP-2 at site
- Provides an environment for bone induction
- Resorbed during bone induction

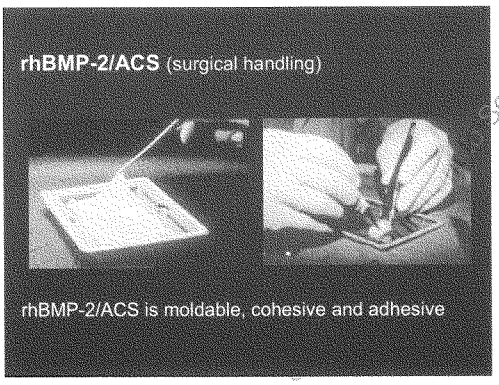
ACS = absorbable collagen sponge

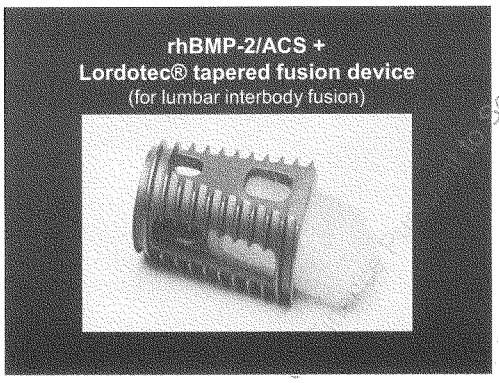
- Manufactured by Integra LifeSciences
- Sold in US/CAN/EUR/JP as a hemostatic agent:
  - since 1981, with excellent safety record
  - CE mark issued January, 1999
- Bovine tendon Type I collagen
  - Manufacture process meets/exceeds US/EU guidance re transmissable spongiform encephalopathy agents (TSEs)

ACS Manufacture
(TSE Safety Assurance)

- ACS safety assurance score = 25
  (Guideline: ≥ 20)
- ACS is US-sourced and tendon-derived
- ACS manufacturing process
  - Exceeds European standards (prEN 12442, Part 1)
  - Viral inactivation demonstrated



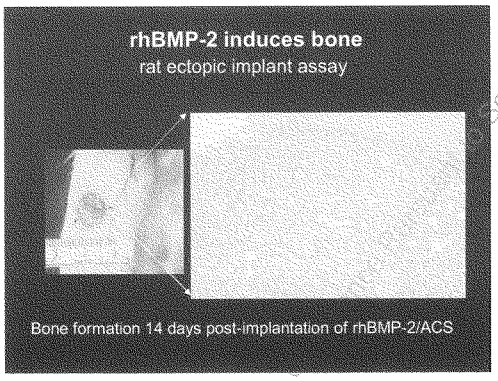




rhBMP-2/ACS is an osteoinductive implantable product indicated for the treatment of long bone fractures that require open surgical management.

rhBMP-2/ACS improves current fracture management by:

- Inducing bone at implantation site
- Preventing delayed union
- Reducing the need for secondary interventions
- Accelerating fracture union



BMP-2 biology affects the selection and design of safety studies

- BMP-2 protein is highly conserved across species
  - rhBMP-2 can be used in all animal studies
- rhBMP-2 is osteoinductive
  - Is osteoinduction limited to local implantation site?
  - Does rhBMP-2 cause any local or systemic adverse effects?
  - Is rhBMP-2 released from an implant into the systemic circulation?
  - How long is rhBMP-2 retained at an implant site?

BMP-2 biology affects the selection and design of safety studies

- BMP proteins have been isolated from osteosarcomas
  - Does rhBMP-2 have any effect on tumor cells?
- BMP-2 protein functions during embryogenesis
  - Does rhBMP-2 affect reproduction / fetal development?

rhBMP-2/ACS is an osteoinductive implantable product indicated for the treatment of long bone fractures that require open surgical management.

rhBMP-2/ACS improves current fracture management by:

- Inducing bone at implantation site
- Preventing delayed union
- Reducing the need for secondary interventions
- Accelerating fracture union

rhBMP-2 studies in tumors

- Extramural academic studies
  - Screening studies
    - presence of BMPs/BMP receptors in tumors
    - some tumors/ tumor cell lines produce BMPs / BMP receptors
    - possible diagnostic/prognostic tool
  - Pharmacology studies
    - Effect of BMPs on tumor growth in vitro
    - All studies (except two) report either no effect or tumor growth inhibition
    - Two studies report growth promotion of tumor cell lines in vitro: pancreatic (2), prostate (1)

rhBMP-2 studies in tumors

- Human tumor cell studies
  - Assess tumor cell line growth promotion
    - osteosarcoma (4), carcinomas of prostate (2), breast (3), lung (2), tongue (2) bladder (1)
  - Assess primary tumor cell growth promotion
    - rhBMP-2 administered to 65 primary tumor samples
    - Soda et al. 1998 Anticancer Drugs 9: 327-331.
- **Results: either no effect, or growth inhibition** (in 25% of samples)

rhBMP-2/ACS preclinical safety studies

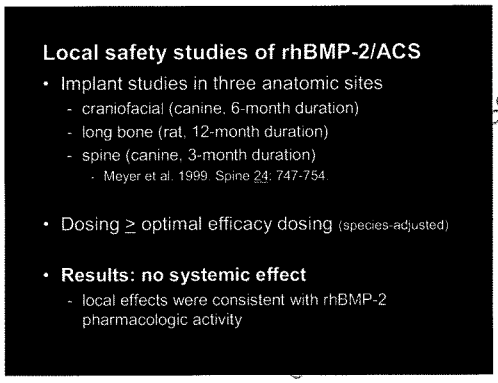
- Systemic toxicity of rhBMP-2
  - acute or sub-acute dosing
- Reproductive toxicity of rhBMP-2
  - segment I, II
- Local toxicity of rhBMP-2/ACS
  - implant studies with short/long-term follow-up
- ADME studies
  - systemic/local administration

Systemic toxicity studies of rhBMP-2

- Design
  - IV administration
    - systemic exposure >1000X expected in patients
  - two species (rat and canine)
  - two dosing schedules
    - single (acute)
    - sub-chronic (daily for 28-days)
- **Results: no systemic effect**
  - nodules at injection site (in 28-day experiments)
  - no bone formation at remote sites

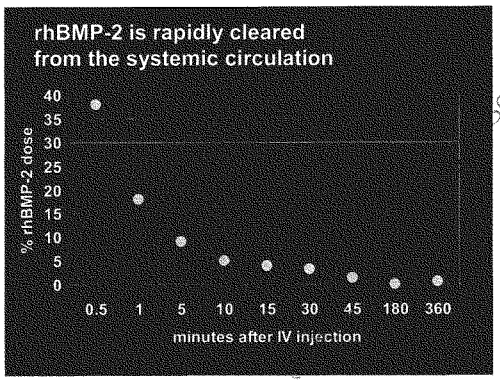
Reproductive toxicity studies of rhBMP-2

- General fertility
  - one species (rat) , IV administration
- Teratology
  - two species (rat and rabbit), IV administration
- Cumulative systemic exposure >1000X expected in patients
- **Results: No reproductive effect**



ADME studies of rhBMP-2

- Pharmacokinetics
  - rats (adults and juveniles) and NHP
  - IV administration
- Biodistribution
  - rats
- **Results:** rhBMP-2 is cleared rapidly from the circulation, primarily through the liver, and rapidly degraded/excreted into urine

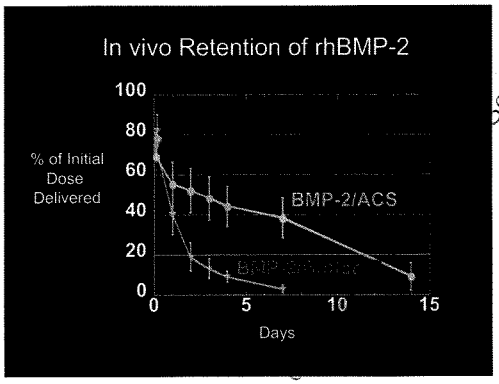


ADME studies of rhBMP-2/ACS

- Biodistribution
  - two species (rats, rabbits)
  - two implant sites (ectopic, long-bone osteotomy)
- **Results:**
  - **rhBMP-2 is released slowly from implant site**
  - **low systemic availability**
    - maximum rhBMP-2 detected = 0.1% of dose

rhBMP-2 retention at implantation site

- Radiolabelled rhBMP-2 applied to ACS
- Rabbit ulnar osteotomy model
- Gamma camera data collection
- Methods validated by direct measurement



rhBMP-2/ACS is an osteoinductive implantable product indicated for the treatment of long bone fractures that require open surgical management.

rhBMP-2/ACS improves current fracture management by:

- Inducing bone at implantation site
- Preventing delayed union
- Reducing the need for secondary interventions
- Accelerating fracture union

Additional rhBMP-2 studies

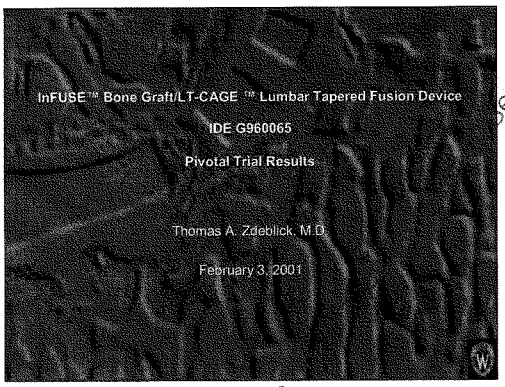
- Tripartite guideline safety studies
  - cytotoxicity, mutagenicity, others
  - no effect
- General pharmacology studies
  - behavior, locomotion, other body functions
  - no effect

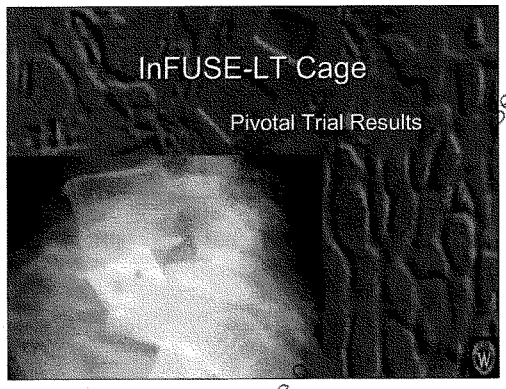
rhBMP-2 preclinical safety profile

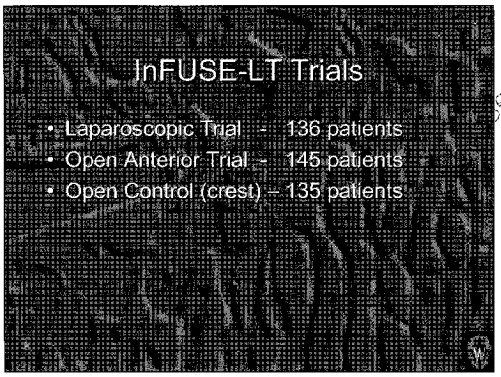
- **No systemic effects**
  - implantation or IV administration
- **Probable cause = low systemic exposure**
  - slow release from implantation site ($T_{½}$ = days)
  - rapid systemic clearance ($T_{½}$ = minutes)
- **Preclinical results suggest that clinical therapeutic window will be "wide"**

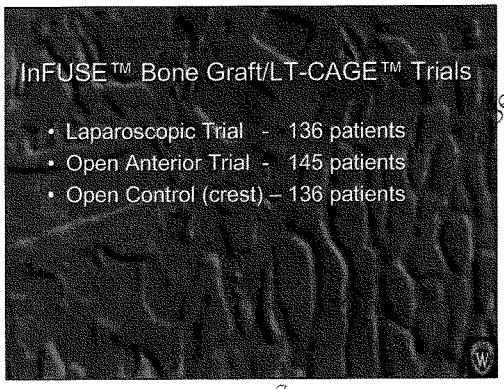
Findings/Recommendations

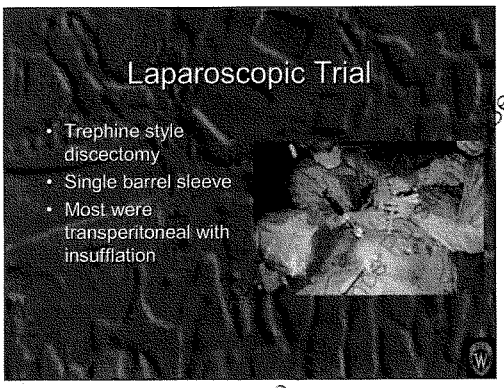
- Preclinical safety assessment supports use of of rhBMP-2 and rhBMP-2/ACS in spine fusion surgery
- No dose-limiting toxicity detected (at rhBMP-2 doses ≤ 5 mg/kg)
- Consider the literature and risk/benefit before implanting rhBMP-2/ACS at the site of a known tumor

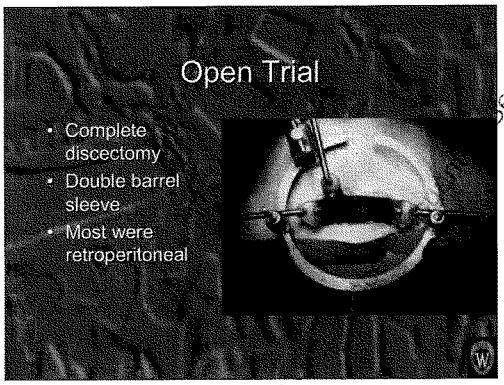


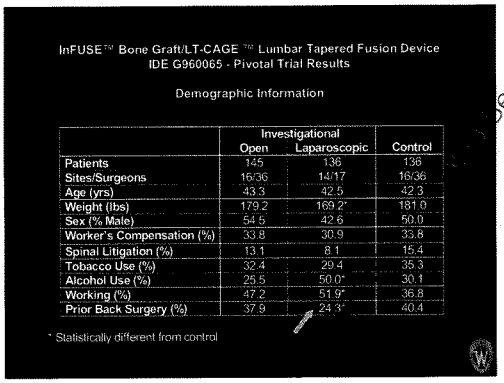










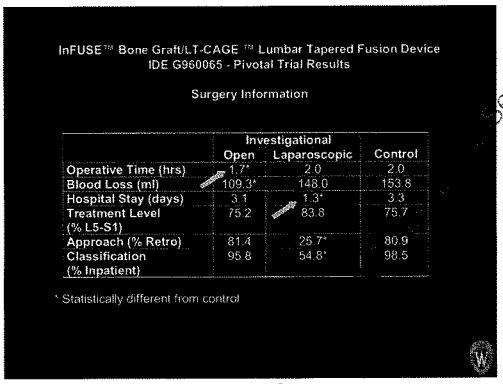


InFUSE™ Bone Graft/LT-CAGE ™ Lumbar Tapered Fusion Device
IDE G960065 - Pivotal Trial Results

Demographic Information

	Investigational		Control
	Open	Laparoscopic	
Patients	145	136	136
Sites/Surgeons	16/36	14/17	16/36
Age (yrs)	43.3	42.5	42.3
Weight (lbs)	179.2	169.2*	181.0
Sex (% Male)	54.5	42.6	50.0
Worker's Compensation (%)	33.8	30.9	33.8
Spinal Litigation (%)	13.1	8.1	15.4
Tobacco Use (%)	32.4	29.4	35.3
Alcohol Use (%)	25.5	50.0*	30.1
Working (%)	47.2	51.9*	36.8
Prior Back Surgery (%)	37.9	24.3*	40.4

* Statistically different from control

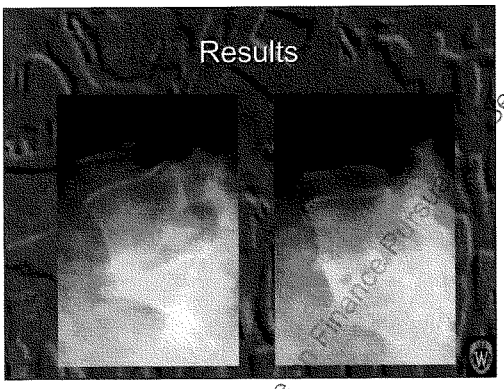


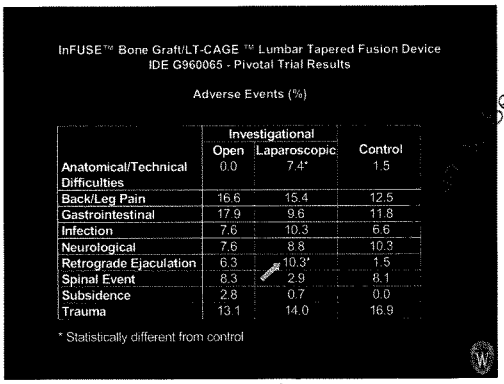
InFUSE™ Bone Graft/LT-CAGE ™ Lumbar Tapered Fusion Device
IDE G960065 - Pivotal Trial Results

Surgery Information

	Investigational		Control
	Open	Laparoscopic	
Operative Time (hrs)	1.7*	2.0	2.0
Blood Loss (ml)	109.3*	148.0	153.8
Hospital Stay (days)	3.1	1.3*	3.3
Treatment Level (% L5-S1)	75.2	83.8	75.7
Approach (% Retro)	81.4	25.7*	80.9
Classification (% Inpatient)	95.8	54.8*	98.5

* Statistically different from control



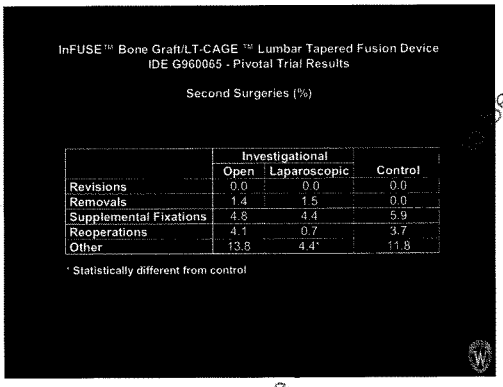


InFUSE™ Bone Graft/LT-CAGE ™ Lumbar Tapered Fusion Device
IDE G960065 - Pivotal Trial Results

Adverse Events (%)

	Investigational		
	Open	Laparoscopic	Control
Anatomical/Technical Difficulties	0.0	7.4*	1.5
Back/Leg Pain	16.6	15.4	12.5
Gastrointestinal	17.9	9.6	11.8
Infection	7.6	10.3	6.6
Neurological	7.6	8.8	10.3
Retrograde Ejaculation	6.3	10.3*	1.5
Spinal Event	8.3	2.9	8.1
Subsidence	2.8	0.7	0.0
Trauma	13.1	14.0	16.9

* Statistically different from control

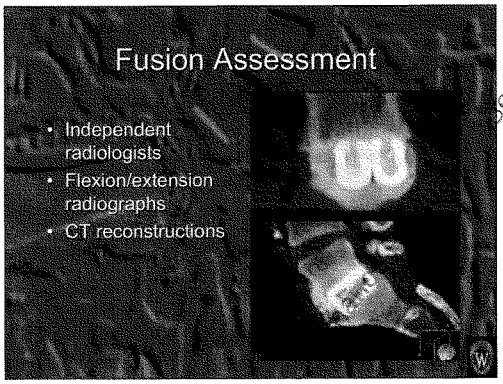


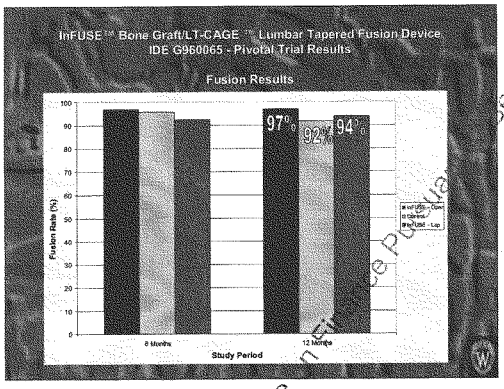
InFUSE™ Bone Graft/LT-CAGE ™ Lumbar Tapered Fusion Device
IDE G960065 - Pivotal Trial Results

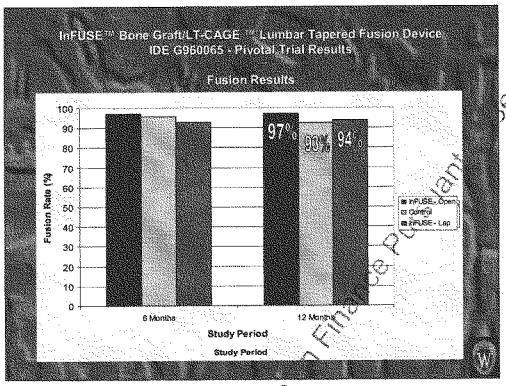
Second Surgeries (%)

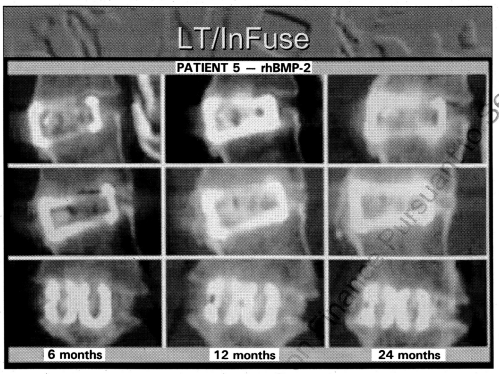
	Investigational		
	Open	Laparoscopic	Control
Revisions	0.0	0.0	0.0
Removals	1.4	1.5	0.0
Supplemental Fixations	4.8	4.4	5.9
Reoperations	4.1	0.7	3.7
Other	13.8	4.4*	11.8

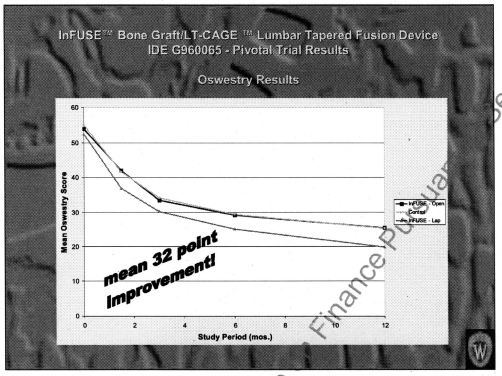
* Statistically different from control

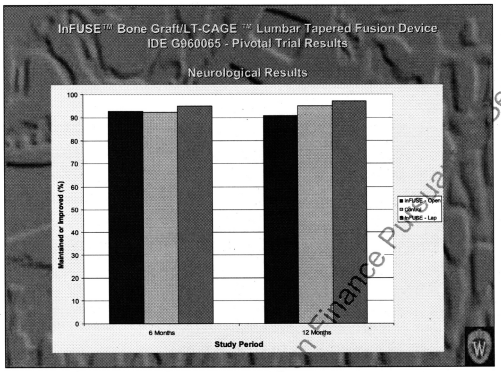


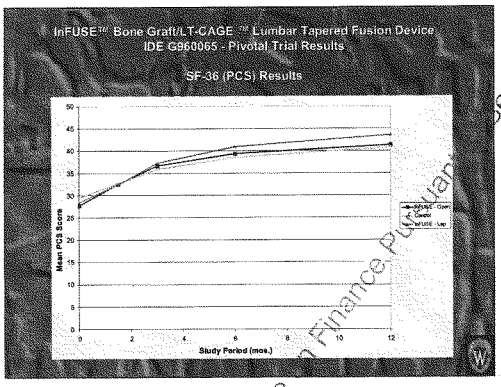


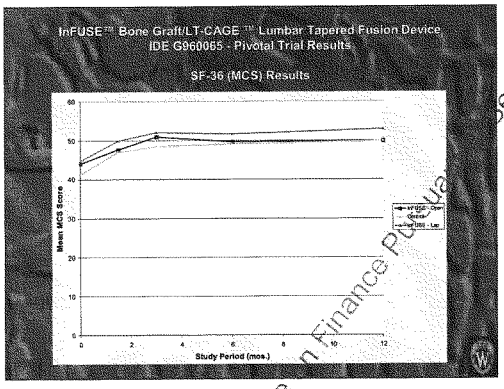


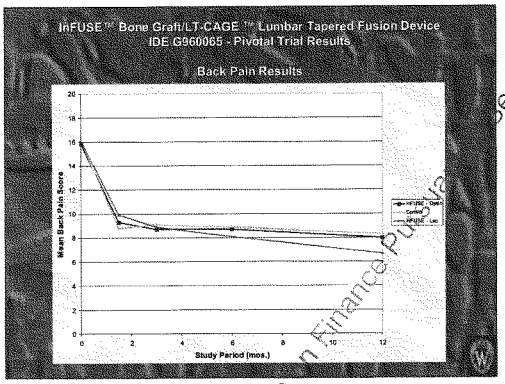


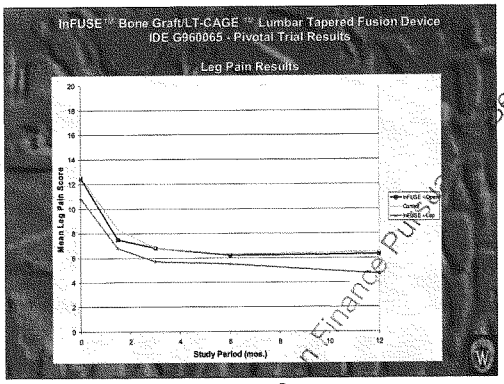


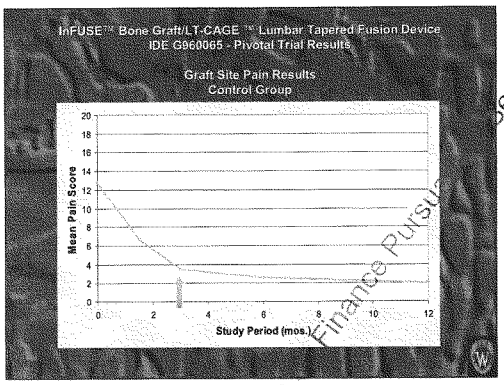


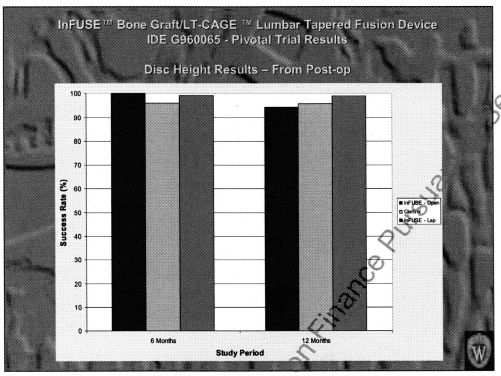


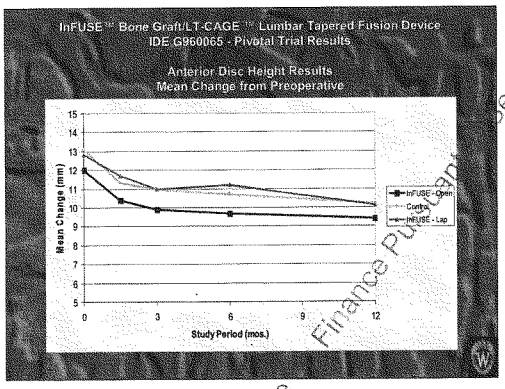


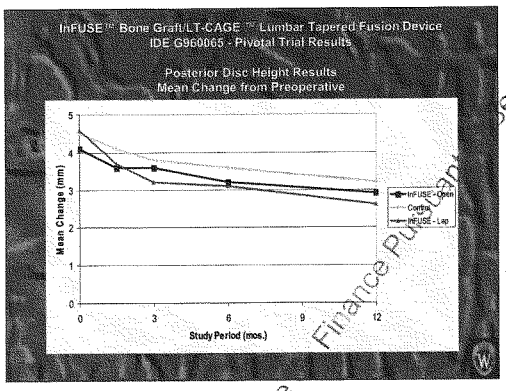


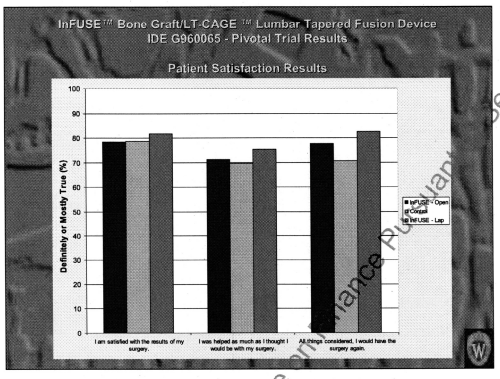


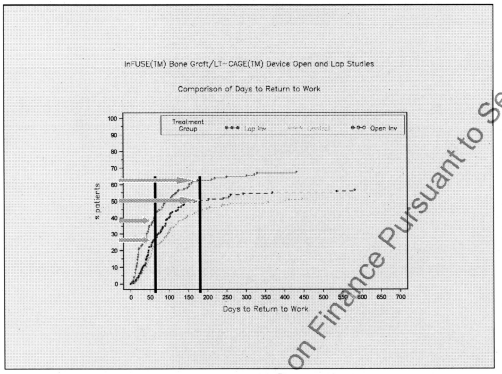


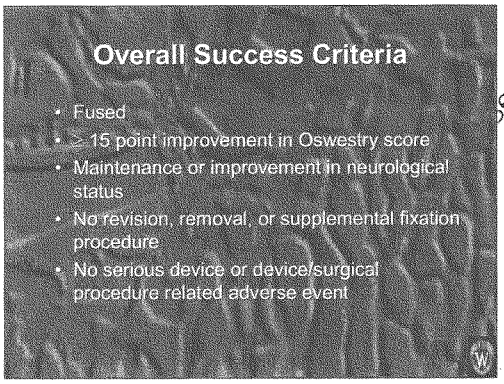


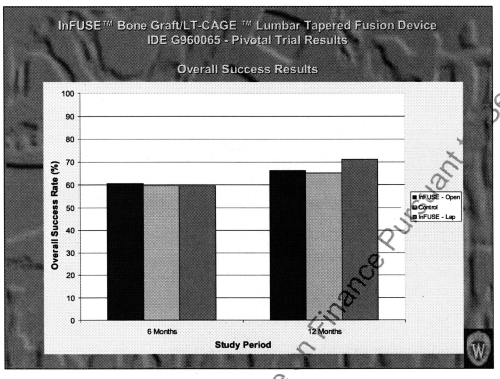


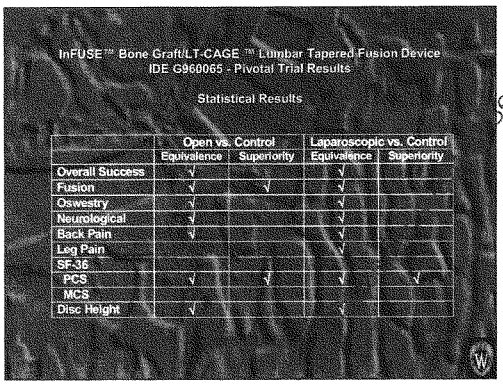




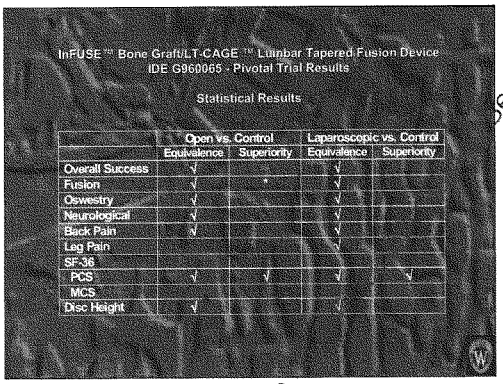


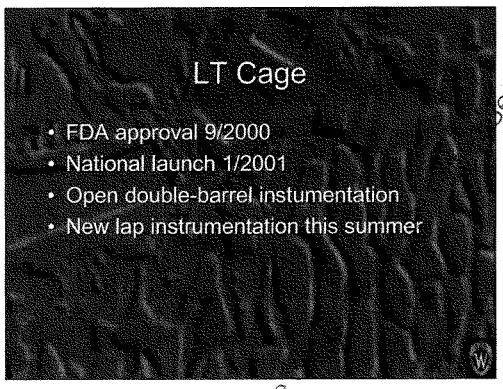


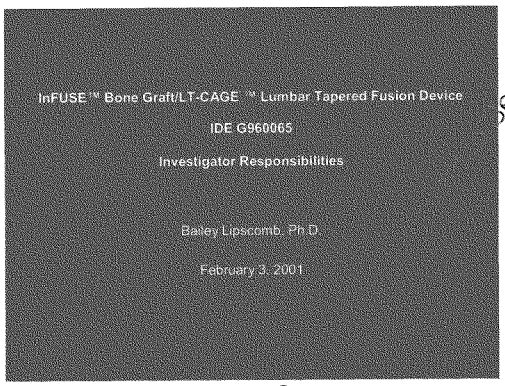


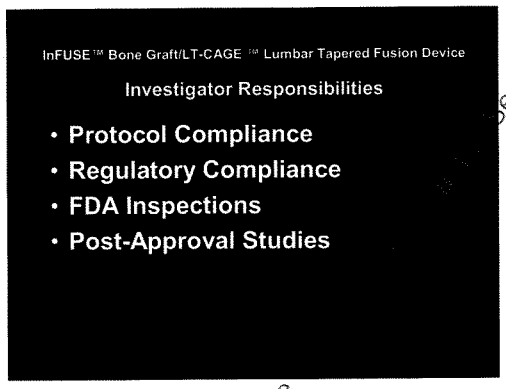


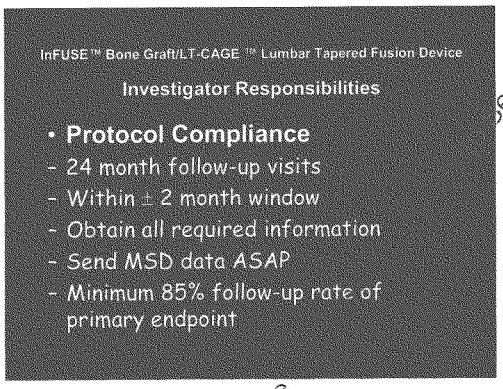
	Open vs. Control		Laparoscopic vs. Control	
	Equivalence	Superiority	Equivalence	Superiority
Overall Success	√		√	
Fusion	√	√	√	
Oswestry	√		√	
Neurological	√		√	
Back Pain	√		√	
Leg Pain			√	
SF-36				
PCS	√	√	√	√
MCS				
Disc Height	√		√	

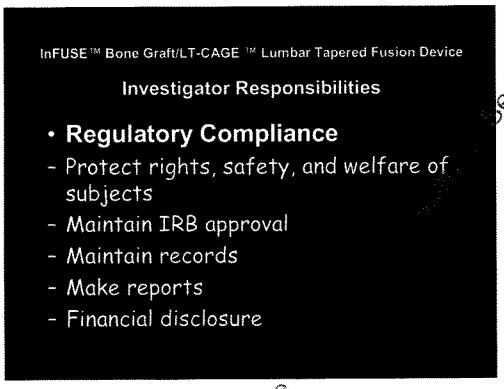


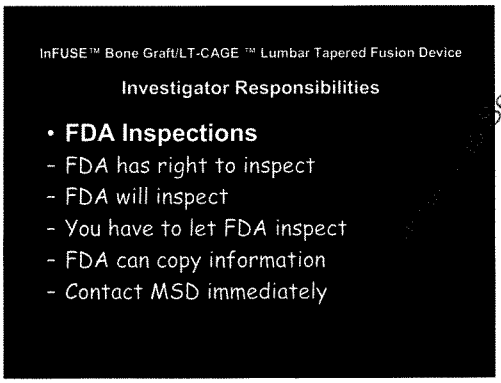












Market Introduction

- InFUSE™ Bone Graft/LT CAGE™ (open ALIF & laparoscopic)
- (Expected) first BMP to the market

InFUSE™ Bone Graft Market Introduction Initiatives

- Publications
- Medical Education/Training
  - Surgeon
  - MSD sales force
- Reimbursement (cost/benefit models)
  - Hospital
  - Payer

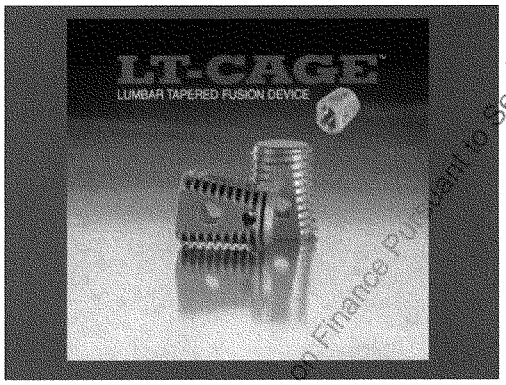
MSD Corporate Objective

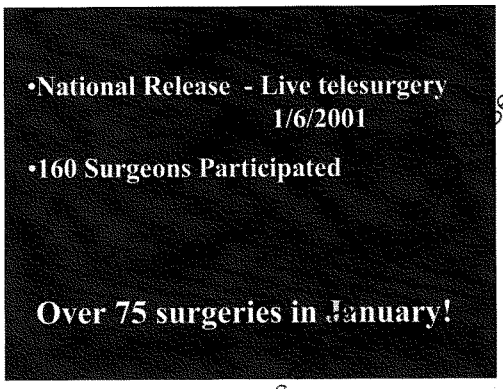
To establish InFUSE™ Bone Graft as the new "gold standard" for spinal fusion procedures in the U.S., replacing iliac crest autologous bone graft.

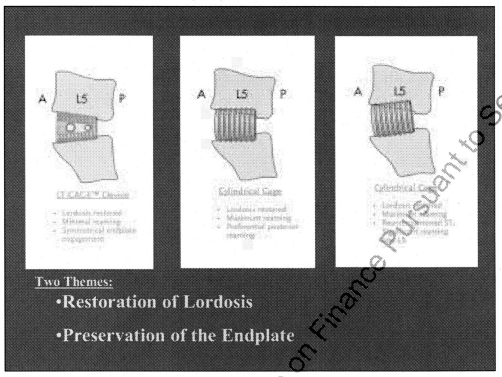
Future/Ongoing Studies

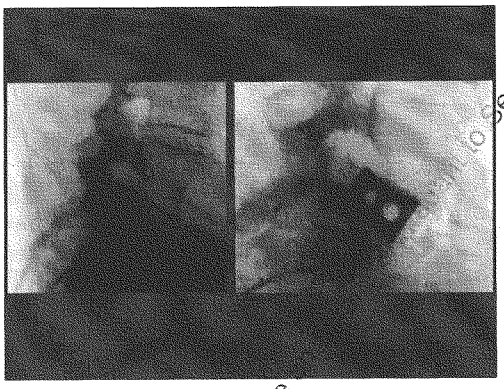
Potential Clinical Indications for InFUSE
- ACDF
- PLIF/TLIF
- P/L Degen (extender)
- Deformity (extender)

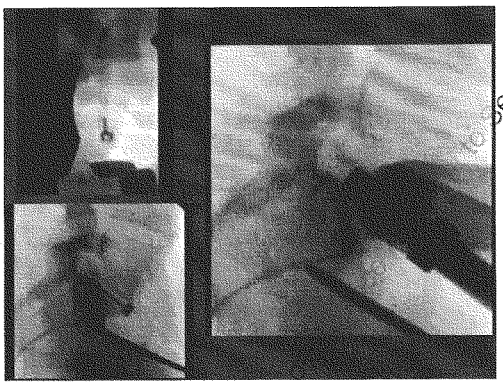
Alternative Carriers
- Compression resistant matrix
- Injectable, compression resistant matrix

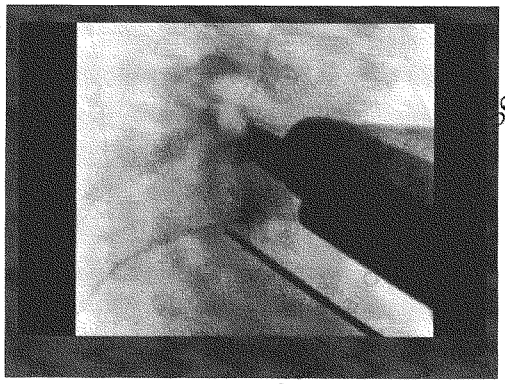


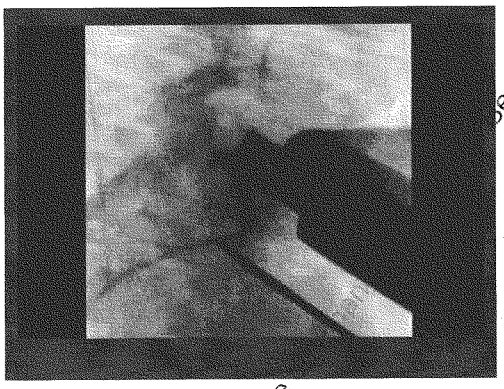


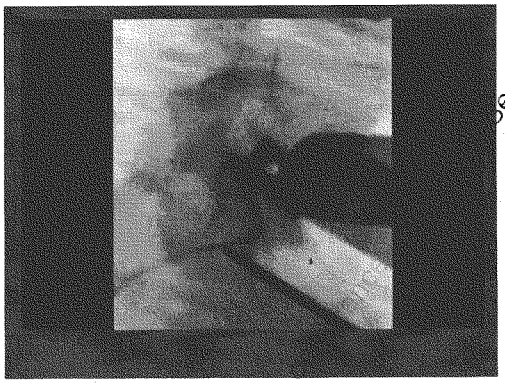


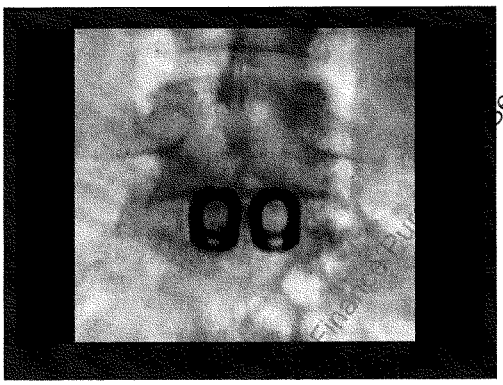


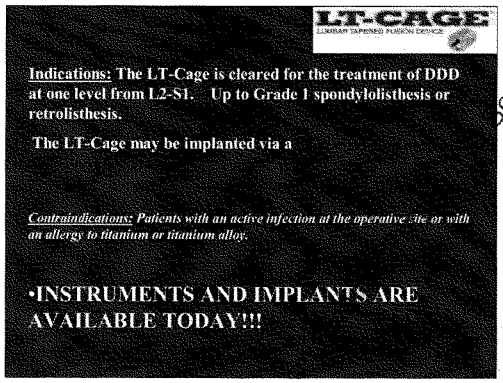












From: JKB[redacted]
Sent: Saturday, June 9, 2001 05:26:35 PM
To: Pete Wehrly; Neil Beals; Tara Hood; Bailey Lipscomb
Subject: Bone Dowel BMP manuscript

Attachments: Bone Dowel BMP Paper-rev.doc; FIGURES.doc

Pete, Neil, Tara, Bailey:

I have attached two WORD 2000 documents. I had an editor at the Hughston Foundation do a quick review of the paper. This review did not include any of Brad Estes contributions.

The editor raised some issues regarding the number of figures and the need to document financial support for the project. I have not yet incorporated any of these changes. We need to decide which charts and tables and how many x-rays to include in the manuscript.

I just finished up 16 surgical cases this past week. Don't worry, I also have several more excuses up my sleeve.

I am leaving for the SSAF meeting in the morning. Yes, I know the meeting does not start until Thursday BUT I wanted to be sure I was there on time and well prepared. I will be happy to review any updates in Hawaii.

Thanks for all of your help and support.

Ken Burkus

QQ AU: Please decide what terminology you want to use when referring to the groups so we can be consistent throughout the text, tables, and figures (i.e., investigational, rhBMP-2, or InFUSE).XQQ

Clinical and Radiographic Outcomes Following Anterior Lumbar Interbody Fusion Using Recombinant Human Bone Morphogenetic Protein-2

QQ AU: Please supply all author's affiliations. XQQ

J. Kenneth Burkus, MD
Columbus, Georgia

Ensor Transfeldt, MD
Minneapolis, Minnesota

Scott H. Kitchel, MD
Eugene, Oregon

Robert Watkins, MD
Los Angeles, California

Richard Balderston, MD
Philadelphia, Pennsylvania

QQ AU: Please acknowledge source of support, if any. Medtronic Sofamor Danek?

Address correspondence and reprint requests to: J.K. Burkus, MD, The Hughston Clinic, PC, [redacted]

ABSTRACT

QQ AU: Please shorten abstract to 250 words. It is now 311 words. XQQ

Study Design. At 24 months, we evaluated the clinical and radiographic outcomes in 46 patients who underwent a single-level anterior lumbar discectomy and interbody fusion (ALIF) and received either recombinant human bone morphogenetic protein-2 (rhBMP-2) or autogenous iliac crest bone graft.

QQ AU: Shouldn't this be changed to 45 patients? In the text you say 1 pt died at 6 months. XQQ

Objectives. To determine the safety and efficacy of INFUSE™, a recombinant human bone morphogenetic protein-2 and an absorbable collagen sponge in ALIF in the lumbar spine with threaded cortical allografts.

Summary of Background Data. In primates, rhBMP-2 used with allograft dowels increases rates of interbody fusion by promoting osteoinduction and enhancing incorporation of the allograft. In a small series of human patients undergoing ALIF with a tapered cylindrical fusion cage, rhBMP2 has been shown to promote osteoinduction and fusion.

Methods. In this prospective, non-blinded, multicenter trial, 46 patients underwent a single-level ALIF procedure. The investigational patients underwent fusion using two threaded cortical allograft dowels with rhBMP-2 soaked collagen sponges and those in the control group received two threaded allograft dowels with autogenous iliac crest bone graft. Clinical outcomes were assessed using the Oswestry Low Back Pain Disability Questionnaire, Short Form SF-36, neurologic status, work status, and back and leg pain questionnaires.

Radiographic aassessment was used to evaluate the progression of fusion at 6, 12, and 24 months after surgery.

Results. All patients in the investigational group (rhBMP-2) showed radiographic evidence of bony induction and early incorporation of the cortical allografts, and they demonstrated fusion at 1 year that remained at 2 years. The investigational group showed faster clinical improvement and higher rates of success than the control group. There were no adverse events related to the use of rhBMP-2 and the collagen sponge carrier.

Conclusions. The use of rhBMP-2 is a promising method of facilitating anterior intervertebral spinal fusion and of decreasing pain in patients who have undergone anterior lumbar fusion surgery with structural allograft bone dowels.

KEY WORDS: **QQ AU: Please supply 3–8 key words. XQQ**

PRECIS

In 46 patients who had anterior lumbar interbody fusion and were followed for 2 years, the group that received rhBMP-2 on a collagen sponge carrier showed faster clinical improvement ($P = .067$) and higher rates of success ($P = .032$) when compared with the group that received autogenous iliac crest bone graft.

QQ AU: Correct? XQQ

INTRODUCTION

Cylindrical threaded allograft dowels are designed as stand-alone intervertebral implants that function as an instrumented anterior lumbar interbody fusion. They are not intradiscal spacers that require additional segmental stabilization. The threaded dowels are designed to withstand lumbar compressive loads while maximizing device porosity and to promote load sharing between the allograft and the host bone. These devices are seated within the central portion of the disc space through a controlled insertion technique. Impacted allografts, when used alone for interbody fusion in the lumbar spine, have a high rate of pseudarthrosis and subsidence. Contemporary reports of large clinical series of anterior interbody fusions using impacted grafts have shown varying rates of fusion and differing clinical outcomes.[1,6-9,11,14-16,18,20,21] The threaded dowels resist expulsion and stabilize the bone–implant interface. Threaded bone dowels offer increased strength to support cancellous graft material.[4,17] A clinical series of 43 patients followed for more than one year showed a high fusion rate and improved clinical outcomes (5). **QQ AU: SPINE does not allow unpublished data in the references. Has this abstract been published in Orthopaedic Transactions or elsewhere? XQQ**

Recombinant human bone morphogenetic protein-2 (rhBMP-2) is an osteoinductive growth factor. In both animal and human studies, it has been proven to be capable of consistently inducing new bone formation.[2,3] In a study involving anterior lumbar interbody fusion in nonhuman primates, rhBMP-2 and an absorbable collagen sponge carrier was shown to promote fusion through

osteoinduction.[12] New bone formation appeared to be superior to autogenous iliac crest graft with cortical dowel allograft. Similarly, in a preliminary clinical study involving the use of rhBMP-2 and a tapered cylindrical titanium cage in humans, arthrodesis was found to occur more reliably in patients treated with rhBMP-2 than in control patients treated with autogenous bone graft.[3]

We report the two-year clinical and radiographic results of the use of rhBMP-2 with a collagen sponge carried inside a cylindrical threaded cortical allograft dowel in patients undergoing anterior lumbar interbody fusion.

MATERIALS AND METHODS

Study Design

QQ AU: Do the data given include the patient who died at 6 months? I suggest excluding that patient's data from the results and adding a statement to that effect after the description of the initial patient enrollment. Was informed consent obtained? How were the patients randomly assigned? Did appropriate IRBs have to approve the study? XQQ

This prospective, randomized, non-blinded study was conducted under an approved investigational device exemption (IDE). Forty-six patients were enrolled at five investigational sites between April and September 1998. The patients were randomly assigned into two study groups. The control group received autogenous iliac crest bone graft; the investigational group received InFUSE™ (Medtronic Sofamor Danek, Memphis, TN), the recombinant human bone morphogenetic protein-2. Data were collected preoperatively, intraoperatively,

and at 6 weeks, 3 months, 6 months, 12 months and 24 months postoperatively. Operative procedure details and adverse events were also recorded.

Patients

All patients were between the ages of 18 and 65 years and had symptomatic degenerative lumbar spondylosis at the L4-L5 or L5-S1 levels. All patients had had pain for at least 6 months before their surgery. Their painful low back condition was recalcitrant to nonoperative treatment modalities, such as physical therapy, aerobic conditioning, and anti-inflammatory medications. All patients were considered candidates for a single-level stand-alone anterior lumbar interbody fusion.

Patients were excluded from the study if they had spinal conditions other than degenerative disc disease, multi-level spondylosis, or grade II or higher spondylolisthesis. Other exclusion criteria were symptomatic spondylosis outside of the L4-L5 or L5-S1 disc space levels and if they were 40% above ideal body weight, had a history of chronic use of steroidal or nonsteroidal anti-inflammatory medications, and had a history of disc space infection. **QQ AU: Do you mean "or" in previous sentence? Did pts have to have all or just one of the criteria for exclusion? XQQ**

Twenty-four patients were randomly assigned to the InFUSE™ (rhBMP-2) group (Table 1). Twenty-two patients were randomly assigned to the control group receiving autograft.

One patient was lost to follow-up in the control group and was excluded from the study. This patient died in a house fire at 6 months postoperatively. All

other patients were followed for a minimum of 2 years after surgery. No adverse events occurred which were related to the use of InFUSE™.

Surgical Technique

All patients underwent an open anterior lumbar discectomy and interbody fusion. Both transperitoneal and retroperitoneal approaches to the lumbosacral spine were undertaken. In each case, a complete discectomy was carried out. The nucleus pulposis and the cartilaginous endplates are circumferentially removed; however, the bony endplates were preserved. Following reaming and tapping of the disc space, two allograft dowels were inserted into each disc space.

InFUSE™ (recombinant human bone morphogenetic protein-2) used was reconstituted using sterile water. The solution was applied to a bovine collagen sponge. The BMP-soaked sponge was placed in the hollow central portion of the bone dowel before its insertion into the prepared disc space. Additional sponges were placed between the bone dowels. No autogenous grafts were used in the investigational group. The control group received morcellized autogenous iliac crest graft placed within the bone dowels.

In the investigational, or InFUSE™ (rhBMP-2) group, 11 patients (45.8%) had surgery at the L4-L5 level and 13 (54%) had surgery at the L5-S1 level (Table 2). In the control group, surgery was performed at the L4-L5 level in eight patients (36%) and at the L5-S1 level in 14 patients (64%).The mean operative time in the InFUSE™ (rhBMP-2) group was 103 minutes compared with the control group 114 minutes. The investigational group had surgery more

commonly at the L4-L5 level. This exposure of the L4-L5 disc space often involves a tedious mobilization of the iliac vessels and requires more time when compared with the exposure at the L5-S1 level. Blood loss averaged less in this group than in the control group ($P = 0.026$). The average hospital stay was similar in both groups.

Clinical Outcome Measurements

Clinical outcomes were measured using several well-established instruments: the Oswestry Low Back Pain Disability Questionnaire, the Short Form SF-36 Questionnaire, back and leg pain questionnaires, and assessment of the patient's neurologic status. **QQ AU: My ignorance but...is it necessary to give a description of how neurologic status was assessed? XQQ**

Radiographic Outcome Measurements

Fusion was assessed by plain radiographs, dynamic motion radiographs, and by CT scans. Anteroposterior, lateral, and flexion-extension lateral radiographs were obtained at each clinic visit at 6 weeks, 3, 6, 12, and 24 months. On plain radiographs, fusion was defined as less than 5° of angular motion, less than 3 mm of translation, and an absence of radiolucent lines covering at least 50% of the implant surfaces. CT scans with sagittal reconstructions were evaluated at 3, 6, 12 and 24 months. On the CT scans, fusion was defined by the presence of continuous trabecular bone formation through both of the dowels. Two independent, blinded radiologists interpreted all radiographs. In cases where the fusion outcome differed, a third independent, blinded radiologist was used.

RESULTS

Clinical Outcomes

At 24 months, the investigational InFUSE™ patients had consistently higher rates of success than the control patients in their overall neurologic scores (Fig. 1). More than 87% of patients in the InFUSE™ group showed neurologic improvement at 3 months after surgery. These results were maintained at the final 2-year follow-up assessment. More than 95% of patients in the autograft control group showed initial neurologic improvement at 3 months postoperatively. These clinical results deteriorated at 2 years. Only 73% of patients showed neurologic improvement at their last follow-up examination.

Patients in the investigational InFUSE™ group showed an improvement in back pain analog scores of more than 7 points at their initial postoperative visit at 6 weeks (Fig. 2). In this group, back pain continued to improve and pain scores averaged nearly a 9-point improvement at 2 years after surgery. The control group's improvement in back pain followed a similar pattern. However, there was only a 5-point improvement in average back pain scores in this group.

The investigational InFUSE™ group also showed higher rates of success in relief of leg pain (Fig. 3). In the InFUSE™ group, leg pain improved by more than 5 points within six weeks of surgery. These results remained unchanged at last follow-up examination.

The investigational InFUSE™ group had higher rates of success in both the Physical (PCS) and Mental Component (MCS) scores on the SF-36 Questionnaires (Figs. 4 and 5). The Oswestry Disability Questionnaire assessed pain associated with activities. Seventy-one percent of the patients in the InFUSE™ group showed an improvement of at least 15 points in their disability scores at three months postoperatively (Fig. 6). This compared favorably with the 43% of patients in the control group ($P = 0.032$). At 12 months, 83% of the InFUSE™ patients improved more than 15 points compared with 58% of the control group. This finding was unchanged at the 2-year follow-up. The control group's success rate at 2 years is comparable to that of other interbody fusion constructs (Fig. 7). **QQ AU: Need references to other published studies. XQQ**

Patients in the investigational InFUSE™ group were able to return to work sooner than in the control group. Higher percentages of patients in the investigational group were also able to return to work (Fig. 8).

No patients in the investigational InFUSE™ group complained of iliac crest graft site pain. The control group reported persistence of graft site pain at 2 years after surgery (Fig. 9). **QQ AU: Delete this figure? XQQ**

No patients in the InFUSE™ group required an addition surgical procedure in the immediate perioperative period; one patient in the control group required an early return to surgery to reposition a misplaced dowel (Table 3). **QQ AU: Correct placement of Table 3? XQQ** Four patients underwent supplemental posterior fixation 1 year after their primary surgery. In the InFUSE™ group, one patient continued to have persistent low backache at 1

year. The radiographs met the criterion for fusion; however, the attending physician elected to reoperate and insert posterior pedicle fixation. Three patients in the control group had supplemental posterior fixation inserted 1 year after their initial surgery. In each of these cases, the patients complained of persistent low back and referred leg pain and their radiographs showed evidence of an incomplete fusion.

Radiographic Outcomes

At 6 months after surgery, 19 patients (91%) in the rhBMP-2 group had evidence of interbody fusion compared with 13 patients (65%) in the control group ($P = 0.067$) (Fig. 10). At 12 months, all patients in the investigational group had evidence of fusion while 17 patients in the control group (90%) showed evidence of fusion at 1 year. At the final 2-year follow-up, all patients in the rhBMP-2 group continued to have radiographic evidence of fusion. Bony integration of the allografts to the vertebral endplates and trabeculated new bone formation across the fused interspace was seen in all patients. At 2 years, only 15 patients (68%) in the control group were considered to have evidence of fusion. In the control group, there were no failures of the allograft dowels. Radiographic lucencies developed at the interface of the allograft to the vertebral endplate. There was no migration of the implants.

DISCUSSION

This study is the first clinical report of the efficacy of the rhBMP-2 used with cortical allograft to promote anterior lumbar intervertebral fusion in humans. All patients who received InFUSE™ (rhBMP-2) showed radiographic evidence of bone induction and early incorporation of the cortical allografts. All patients in this group had evidence of fusion at 1 year. Overall, the InFUSE™ group showed faster clinical improvements and higher rates of success when compared with the control group. There were no adverse events related to the use of InFUSE™ and the collagen sponge carrier.

We found recombinant human bone morphogenetic protein-2 to be a promising method of facilitating anterior intervertebral spinal fusion and of decreasing pain and improving clinical outcomes of anterior lumbar fusion surgery with allograft bone devices.

QQ AU: Should any financial support be acknowledged? XQQ

REFERENCES

1. Blumenthal SL, Baker J, Dossett A, et al. The role of anterior lumbar fusion for internal disc disruption. Spine 1988;13: 566-569.

2. Boden SD, Schimandle JH, Hutton WC. Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 1995;20: 2633-2644.

3. Boden SD, Zdeblick TA Sandhu HS, et al. The use of rhBMP-2 in interbody fusion cages. Spine 2000;25: 376-381.

4. Boyd LM, Estes BT, Liu M. Biomechanics of Lumbar Interbody Constructs: Effect of Design and Materials. In: Husson JL, LeHuec JC, eds. Chirurgie Endoscopique et Mini-invasive du Rachis. Montpelier: Sauramps Médical, 1999: 181-192.

QQ AU: The following abstract cannot be used unless it has been published somewhere. XQQ

5. Burkus JK, Dorchak JD, Sanders DL, et al. Single-level anterior lumbar interbody fusion using threaded cortical bone allografts. (1999) North American Spine Society Meeting of the Americas, Miami, Florida

6. Crock HV. Anterior lumbar interbody fusion: indications for its use and notes on surgical technique. Clin Orthop 1982;165:157-163.

7. Dennis S, Watkins R, Landaker S, et al. Comparison of disc space heights after anterior lumbar interbody fusion. Spine 1989;14:876-878.

8. Flynn JC, Houque MA. Anterior fusion of the lumbar spine. J Bone Joint Surg 1979;61A:1143-1150.

9. Freebody D, Bendall R, Taylor RD. Anterior transperitoneal lumbar fusion. J Bone Joint Surg 1971;53B: 617.

10. Hacker RJ. Comparison of interbody fusion approaches for disabling low back pain. Spine 1997;22:660-665.

11. Harmon PH. Anterior excision and vertebral body fusion operation for intervertebral disc syndromes of the lower lumbar spine. Clin Orthop 1963;26: 107-127.

12. Hecht BP, Fischgrund JS, Herkowitz HN, et al. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999;7: 629-636.

13. Kumar A, Kozak JA, Doherty BJ, et al. Interspace distraction and graft subsidence after anterior lumbar fusion with femoral strut allograft. Spine 1993;18: 2393-2400.

14. Lane JD, Moore ES: Transperitoneal approach to the intervertebral disc in the lumbar area. Annals of Surgery 1948;127:537. **QQ AU Please supply inclusive page nos. XQQ**

15. Leong JC, Chun SY, Grange WJ, et al. Long-term results of lumbar intervertebral disc prolapse. Spine 1983;8:793-799.

16. Loguidice VA, Johnson RG, Guyer RD, et al. Anterior lumbar interbody fusion. Spine 1988;13:366-369.

QQ AU: The following abstract cannot be used unless it has been published somewhere. XQQ

17. Morales RW, Pettine KA, Salib RM. A biomechanical study of bone allografts used in lumbar interbody fusions. North American Spine Society – 6th Annual Meeting, Keystone, Colorado 1991

18. Sacks S. Anterior interbody fusion of the lumbar spine. J Bone Joint Surg 1965;47B: 211. **QQ AU: Inclusive page nos.?XQQ**

19. Sandhu HS, Kanim LEA, Toth JM, et al. Experimental spinal fusion with recombinant human bone morphogenetic protein 2 without decortication of osseous elements. Spine 1997;22: 1171-80.

20. Stauffer RN, Coventry MB. Anterior interbody lumbar spine fusion. J Bone Joint Surg 1972;54A: 756-768.

21. Taylor TKF. Anterior interbody fusion in the management of disorders of the lumbar spine. J Bone Joint Surg 1970;52B: 784.

22. Tencer AF, Hampton D, Eddy S. Biomechanical properties of threaded inserts for lumbar interbody spinal fusion. Spine 1995;20:2408-2414.

23. Wittenberg RH, Moeller J, Shea M, et al. Compressive strength of autologous and allogenous bone grafts for thoracolumbar and cervical spine fusion. Spine 1990;15:1073-1078.

TABLE 1. Patient demographic data in 46 patients. **QQ AU: Correct? XQQ**

QQ AU: What is "MDII"? Why not label groups Investigational (rhBMP-2) and Control as they are labelled in the text?XQQ

Demographic Data	InFUSE MD II	Autograft MD II
No. of patients	24	22*
Age (years)	41.5	45.6
Weight (lbs)	172.7	176.0
Sex (male/female)	8/16	10/12
Workers' compensation (%)	5 (21)	7(32)
Spinal litigation (%)	4 (17)	4(18)
Tobacco use (%)	8 (33)	6(27)
Previous surgeries (%)	11 (46)	7 (32)

*One patient died an accidental death at 6 months after surgery.

QQ AU: I suggest deleting this patient from the study results. XQQ

Table 2.Intraoperative Data

Surgical Data	InFUSE MD II	Autograft MD II
Operative time (min)	103	114
Blood loss (mL)	124.1	245.0
Levels (%)		
L4-L5	11 (46)	8 (36)
L5-S1	13 (54)	14 (64)
Hospital stay (days)	3.4	3.7

Table 3. Additional Surgeries

AA QQ: Correct to add (%) to "supplemental fixation," "reoperation," and "other" cell entries? XQQ

Procedure	InFUSE MD II	Autograft MD II
Removals	0	0
Revisions	0	0
Supplemental fixation (%)	1 (4.2)	3 (13.6)
Reoperation (%)	0	1 (4.5)
Other	7 (29.2)	2 (9.1)

LEGEND OF FIGURES **QQ AU: The journal states "No more than 8 figures." They consider a figure with A and B parts as 2 figures. XQQ**

Figure 1. Neurologic outcomes of of investigational and control groups.

Figure 2. Back pain outcome scores of investigational and control groups.

Figure 3. Leg pain outcome scores of investigational and control groups.

Figure 4. SF-36 Physical Component Scores of investigational and control groups.

Figure 5. SF-36 Mental Component Scores of investigational and control groups.

Figure 6. Oswestry Disability Questionnaire scores of investigational and control groups.

Figure 7. Comparison of control group's Oswestry scores with those of other interbody devices. **QQ AU: Which is wrong—the text and legend, which says control group, or figure label (BMP/BD)?**

Figure 8. Return-to-work status of investigational and control groups.

Figure 9. Iliac crest bone graft harvest site pain of investigational and control groups. **QQ AU: Suggest deleting this one. XQQ**

Figure 10. Fusion rates of investigational and control groups.

QQ AU: Cite the following figures in the text. Please use letters (A, B, C, etc.) I will renumber later. XQQ

Figure 1: A. Anteroposterior radiograph shows disc space collapse at LS15. B. Lateral radiograph shows a normal appearing L4-5 and L3-4 disc spaces. At L5S1, there is disc space collapse with minimal retrolithesis.

Figure 2: MRI scan shows isolated disc space collapse and disc desiccation at the L5S1 level. The adjacent discs at L3-4 and L4-5 show no evidence of degenerative changes.

Figure 3: A. Anteroposterior radiograph following anterior interbody fusion at L5S1 shows positioning of cylindrical bone dowels within the disc space. B. Lateral radiograph shows restoration of normal disc space height and improvement in segmental lordosis. The implants engaged the peripheral margins of the disc space.

Figure 4: Dynamic flexion and extension lateral radiographs taken at three month postoperatively show no motion at the L5S1 disc space. There are no lucencies at the allograft-vertebral endplate interface.

Figure 5: CAT scan at three months postoperatively shows incorporation of the allograft to the vertebral endplate.

Figure 6: Lateral radiographs at one-year (A) and two-years (B) postoperatively shows incorporation of the allografts to the vertebral endplate with no radiographic lucencies. Lordosis and disc space height have been maintained without change from the initial postoperative radiographs.

Fig. 1. Neurologic outcomes after surgery.

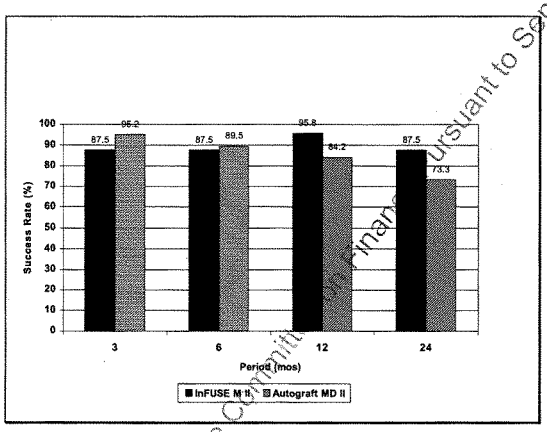


Fig. 2. Back pain outcomes after surgery.

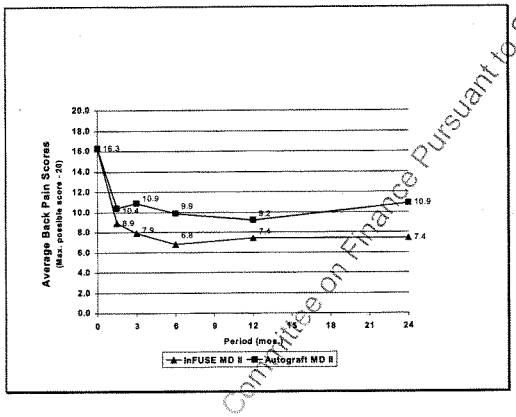


Fig. 3. Leg pain outcomes following surgery.

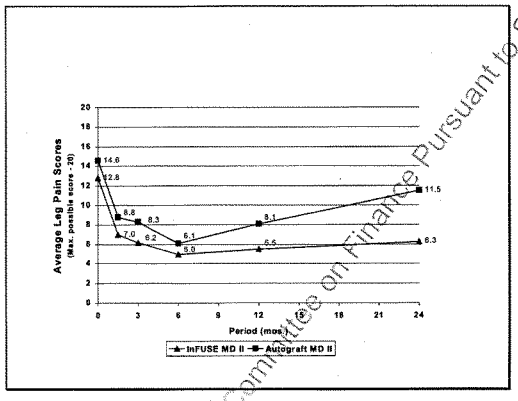


Fig. 4. SF36 Physical Component Score following surgery.

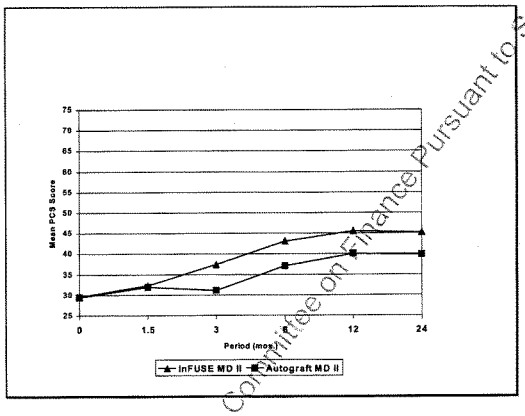


Fig. 5. SF36 Mental Component Score after surgery.

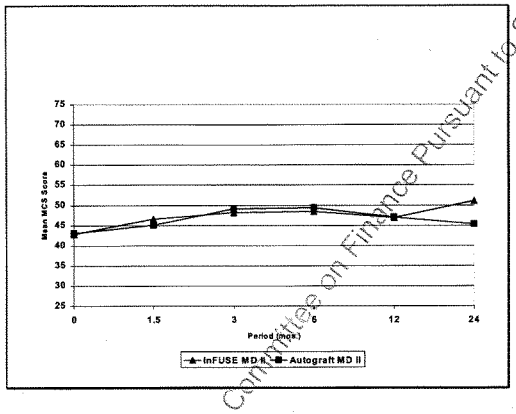


Fig. 6. Oswestry Disability Questionnaire outcome after surgery.

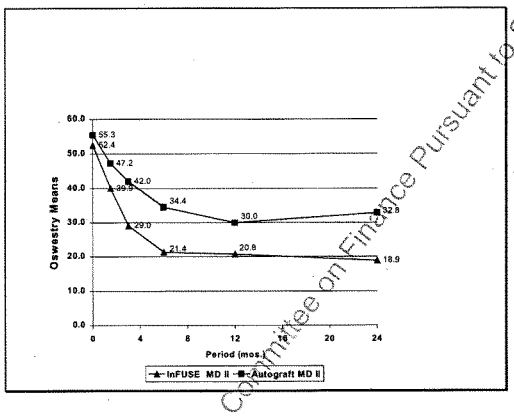


Fig. 7. Comparison of control group outcome to other interbody devices.

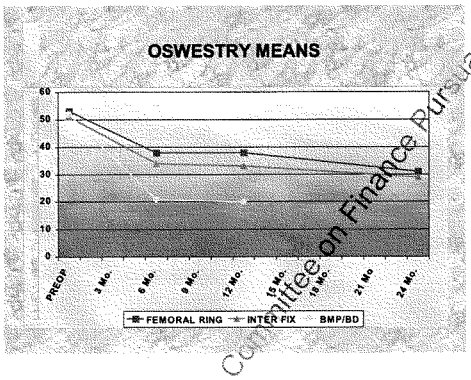


Fig. 8. Return to work status after surgery.

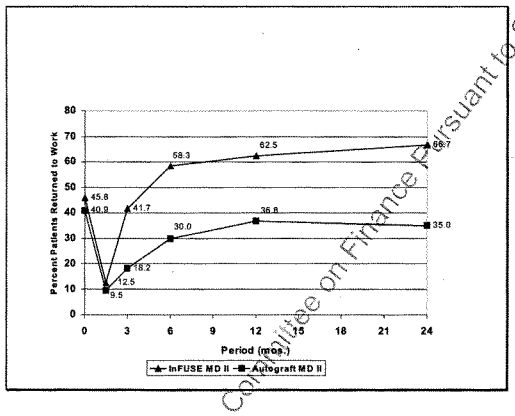


Fig. 9. Iliac crest bone graft harvesting site pain

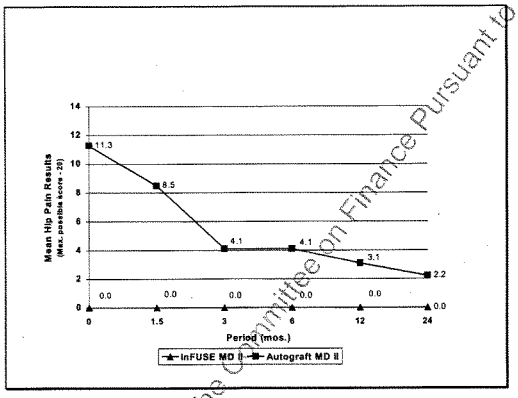
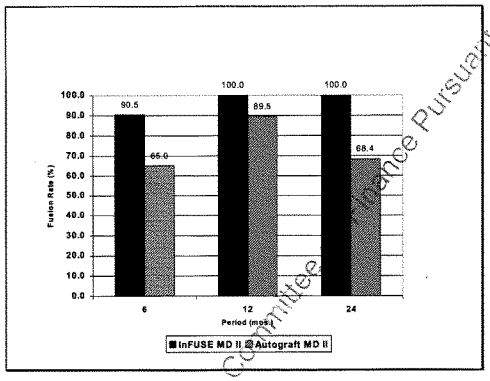


Fig. 10. Fusion outcomes after surgery



From: Pete Wehrly
Sent: Friday, July 20, 2001 03:22:36 PM
To: Neil Beals
Subject: FW: SRS Paper

Attachments: CAT Scan BMP LT Cage.doc

Let's discuss.

Pete

-----Original Message-----
From: John Kenneth Burkus [SMTP:jkb[redacted]
Sent: Friday, July 20, 2001 3:11 PM
To: Pete Wehrly; Bill Martin
Subject: SRS Paper

Pete and Bill,

The SRS has nominated the paper on CT Fusion Assessment of LT CAGE and BMP for expedited review in SPINE.

I have enclosed a copy of the paper. This is my first draft.

I need some help with this paper. I have NOT completed any type of statistical review of the data. I have no idea how to establish "significance" and/or "p" values.

Would you be able to review the data with an eye toward how best to present the data and any type of statistical review?

I also have a great deal of trouble doing graphs. Could I get some help with the graphic display of the data?

Thanks,

Ken Burkus

PROSPECTIVE RANDOMIZED STUDY OF RADIOGRAPHIC ASSESSMENT OF INTERBODY FUSION USING rhBMP-2

J. Kenneth Burkus, MD

John D. Dorchak, MD

D. Lynn Sanders, CCRC

The Hughston Clinic
Columbus, Georgia

Address correspondence and reprint requests to: J.K. Burkus, MD, The Hughston Clinic, [redacted]

ABSTRACT

Study Design. This paper evaluates the prospective radiographic outcomes at six, twelve, and twenty-four months postoperatively of 42 patients who underwent a single level anterior lumbar discectomy and interbody fusion. It compares the investigational patients (two tapered cylindrical fusion devices with rhBMP-2 soaked collagen sponges) with the control patients (two tapered cylindrical fusion devices with autogenous iliac crest bone graft).

Objectives. To determine the patterns and rates of osteoinduction associated with the use of recombinant human bone morphogenetic protein 2 (rhBMP-2) and an absorbable collagen sponge (ACS) in anterior interbody fusion in the lumbar spine with a tapered cylindrical fusion device (LT-CAGE™).

Summary of Background Data. rhBMP-2 used with allograft dowels has been demonstrated to increase rates of interbody fusion by promoting osteoinduction and enhancing incorporation of the allograft. In a small series of human patients undergoing ALIF with a tapered cylindrical fusion cage, rhBMP-2 with an ACS carrier has been shown to promote osteoinduction and fusion.

Methods. In this prospective, non-blinded, single center study, 42 patients underwent a single level anterior lumbar discectomy and interbody fusion. Patients were randomly divided into two study groups: a control group underwent interbody fusion using the LT-CAGE™ device with autogenous iliac crest bone graft, and the investigational group underwent interbody fusion using the LT-CAGE™ device with rhBMP-2 and an absorbable collagen sponge (ACS). Anteroposterior, lateral, flexion/extension lateral and CAT scans were used to

evaluate the pattern of osteoinduction within the interbody space and the progression of fusion at 6, 12 and 24 months postoperatively.

Results. All patients receiving rhBMP-2 showed radiographic evidence of bone induction within the interbody cages at six months postoperatively. New bone formation occurred within the disc space outside of the cages by six months in eighteen patients (18/20; 82%). By two years, all patients showed new formation outside of the cages. Once new bone formation was identified, no patients developed a pseudarthrosis. Bone maturation and remodeling was identified as an increase in radiographic density within the disc space as well as within the cages.

Conclusions. The use of rhBMP-2 is a promising method of facilitating anterior intervertebral spinal fusion in patients who have undergone anterior lumbar fusion surgery.

INTRODUCTION:

Clinical studies of anterior lumbar interbody fusion have identified differing rates of fusion (5,8,10,15). The variation in fusion outcome are in part determined by the surgical technique, bone graft material and method of intervertebral fixation (4). Recombinant human bone morphogenetic protein-2 (rhBMP-2, Genetics Institute, Cambridge, MA) is an osteoinductive growth factor (1). In both animal and human studies, it has been proven to be capable of consistently inducing new bone formation (2,13,14). In a study involving anterior lumbar interbody fusion in nonhuman primates, rhBMP-2 and an absorbable collagen sponge carrier was shown to promote fusion through osteoinduction (11). New bone formation appeared to be superior to autogenous iliac crest graft with cortical dowel allograft.

In a preliminary human clinical study involving the use of rhBMP-2 and threaded cortical bone dowels, high rates of fusion were seen (7). Similarly, in a small clinical study, rhBMP-2 and a tapered cylindrical titanium cage in humans, arthrodesis was found to occur more reliably in patients treated with rhBMP-2 than in controls treated with autogenous bone graft (3).

Radiographic imaging of a developing fusion mass after anterior lumbar surgery is challenging in patients who have metallic interbody implants (9,12). Thin-cut CT imaging is the most efficacious method of identifying bone formation within second-generation cages (6). Recombinant human bone morphogenetic protein-2 (rhBMP-2) has been shown to promote osteoinduction and fusion. To determine its osteoinductive capability with a threaded, cylindrical, tapered

interbody device (LT-CAGE™, Medtronic Sofamor Danek, Memphis, TN) and an absorbable collagen sponge (ACS), we evaluated the radiographic outcomes of forty-two patients who underwent a single-level anterior interbody fusion with the LT-CAGE device. We compared the radiographic outcomes in the investigational patients (LT-CAGE with rhBMP-2) with the outcomes in the control patients (LT-CAGE with autogenous bone graft).

MATERIALS AND METHODS

Patients:

Between August 1998 and March 1999, 45 patients with symptomatic single-level degenerative disc disease were enrolled in this prospective randomized nonblinded study. All patients were between the ages of 18 and 65 years and had symptomatic degenerative lumbar spondylosis at the L4-5 or L5-S1 levels. All patients had disabling low back or leg pain, or both, that had lasted for at least 6 months and had not resolved with nonoperative treatment. All patients were considered candidates for a single level stand-alone anterior lumbar interbody fusion. No patients had osteoporosis. Patients were excluded from the study if they had spinal conditions other than degenerative disc disease, multi-level spondylosis, or Grade II or higher spondylolisthesis. Other exclusion criteria were symptomatic spondylosis outside of the L4-5 or L5-S1 disc space levels and if they were 40% above ideal body weight, had a history of chronic use of steroidal or non-steroidal anti-inflammatory medications, and had a history of disc space infection. Patients were randomized to receive autogenous iliac crest bone graft with the LT-CAGE device or rhBMP-2 on a collagen sponge carrier with the LT-CAGE device.

Forty-two patients were followed for two years after surgery. Three patients were eliminated from this study for failure to complete the two-year follow-up. In the investigational rhBMP-2 group, two patients did not complete their two-year follow-up. One patient died of an unrelated coronary event at nine months postoperatively. One patient was lost to follow-up after his twelve-month

radiographic assessment. In the control autograft group, one patient was lost to follow-up after the six-month assessment.

The control autogenous bone graft group consisted of twenty patients (11 men, 9 women) whose average age at surgery was 44.2 years, and the investigational rhBMP-2 group consisted of twenty-two patients (11 men, 11 women) whose average age was 41.7 years. In the autograft group, two patients (10%) had used tobacco within six months before surgery compared with four patients (18%) in the rhBMP-2 group.

Surgical Procedure

The patients underwent an anterior lumbar interbody fusion procedure through an open retroperitoneal approach at a single study site by the two senior surgeons. In each case, a complete discectomy was carried out. The nucleus pulposis and the cartilaginous endplates were circumferentially removed; however, the bony endplates were preserved. Following precise reaming of the endplates, two LT-CAGE devices were inserted into the disc space.

The rhBMP-2 used was reconstituted using sterile water. The solution was applied to a bovine collagen sponge and allowed to bind to the sponge for fifteen minutes. The BMP-soaked sponge was then placed in the hollow central portion of the LT-CAGE before its insertion into the prepared disc space. No additional sponges were placed outside of the devices. No autogenous grafts were utilized in the investigational group. The control group received morcellized autogenous iliac crest graft placed within the cages and within the disc space surrounding the cages.

Radiographic Outcome Measurements:

Plain radiographs and thin-cut CT scans were used to evaluate patterns of osteoinduction at 2 days and at 6, 12, and 24 months after surgery. Fusion was defined as an absence of radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation of less than 5° on flexion-extension lateral radiographs, and continuous trabecular bone growth connecting the vertebral bodies. Two independent, blinded radiologists interpreted all radiographs and CT scans. In cases where the fusion outcome differed, a third independent radiologist was used.

Thin-cut CT scans were used to assess new bone formation and bone remodeling within and around the fusion cages. On the CAT scans, fusion was defined by the presence of continuous trabecular bone formation through both of the dowels. The changes in density within the cages were determined by precisely measuring the Hounsfield units (HU) within each cage on the serial CT scans. To reduce imaging artifact (9), Hounsfield units were recoded within the central portion of the cages (at least 3 mm from the metallic side wall of the cages) and were calibrated against known densities on each scan.

RESULTS

Plain Radiographs

At twelve months postoperatively, one patient in the control group was identified as having a pseudarthrosis. Radiographs showed radiolucencies surrounding the majority of the implants and motion of greater than five degrees on dynamic radiographs. This patient underwent a posterior instrumented fusion to stabilize the lumbar motion segment. No other patients in the investigational group or the control group were identified as having a pseudarthrosis on plain radiographic studies.

Bone Density Changes within Cages:

In the rhBMP-2 group, immediate postoperative CT scans showed an average density of 156 HU (range, 94-226 HU) within the central portion of the LT-CAGE; the control group showed an average 533 HU (range, 403-712 HU). At six months, the investigational group showed an average increase to 325 HU (range, 178-488 HU), at one year an increase to an average of 447 HU (range, 303-703 HU), and at two years an increase to 522 HU (range, 434-789 HU). In the autograft control group, the average density within the cage at six months was 575 HU (range, 379-714 HU), at 1 year an average of 643 HU (range, 462-903 HU), and at two years an average of 750 HU (range, 474-933 HU).

Progression of densities within the cages correlated with evidence of fusion on standard plain radiographic measurements. One patient in the control group developed a pseudarthrosis at one year. This patient showed increased density of the autogenous grafts within the cages.

Bone Formation Outside of Cages:

In the rhBMP-2 group, at six months, new bone formation was identified outside of the cages in eighteen patients (82%); at one year, in twenty-one patients (95%); and at two years, in twenty-two patients (100%). In the autograft group, at six months, new bone formation was identified outside of the cages in ten patients (50%); at one year, in sixteen patients (80%); and at two years, in nineteen patients (95%).

DISCUSSION

Osteoinduction has been shown to occur within the LT CAGE. In the rhBMP-2 group bone formation, as evidenced by progressive density on thin-cut CT scans, more than doubled within six months of surgery and increased more than threefold by two years. New bone formation outside of the cages had occurred by six months and in all patients by two years. Rates of new bone formation and fusion exceeded those of the autograft control group.

High fusion rates associated with new bone formation inside and outside of the cages can be achieved without harvesting bone from the iliac crest and without device-related adverse events. The use of rhBMP-2 with the LT-CAGE device is a promising method of facilitating anterior intervertebral spinal fusion in patients who have degenerative lumbar disc disease.

REFERENCES

1. Boden SD, Schimandle JH, Huttton WC: Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion: Part II: Study of dose, carrier, and species. Spine 20: 2633-2644, 1995

2. Boden SD, Horton WC, Martin G, Truss T, Sandhu H: Laproscopic anterior arthrodesis with rhBMP-2 in a titanium interbody threaded cage. J Spinal Disord 11: 95-101, 1998.

3. Boden SD, Zdeblick TA Sandhu HS, Heim SE: The use of rhBMP-2 in interbody fusion cages. Spine 25: 376-381, 2000

4. Boyd, L.M.; Estes, B.T. and Liu M. "Biomechanics of Lumbar Interbody Constructs, *Effect of Design and Materials*." Chirurgie Endoscopique et Mini-invasive du Rachis. Ed. Husson JL, LeHuec JC. Sauramps Médical. Montpelier, France. pp 181-192, 1999.

5. Burkus JK, Dorchak JD, Sanders DL, Foor BD: Single-level anterior lumbar interbody fusion using threaded cortical bone allografts. North American Spine Society Meeting of the Americas, Miami, Florida, May 1999.

6. Burkus JK, Foley K, Haid R, LeHuec JC: Surgical interbody research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior lumbar interbody surgery. Neurosurg Focus 10: 1-9, 2001.

7. Burkus JK, Transfeldt EE, Kitchel SH, Watkins R, Balderston RA: A prospective and randomized study assessing the clinical and radiographic outcomes of patients treated with rhBMP-2 and threaded cortical bone dowels in

the lumbar spine. North American Spine Society Annual meeting, New Orleans, LA, October 25-28, 114, 2000.

8. Camissa FP, Dhawlikar SH, Parvateneni HK, Sandhu HS: Radioluncies surrounding allograft bone dowels in the early post-operative period. North American Spine Society Annual meeting, San Francisco, CA October 28-31, 273, 1998.

9. Cizek GR, Boyd LM: Imaging Pitfalls of interbody spinal implants. Spine 25: 2633-2636, 2000.

10. Flynn JC, Houque MA: Anterior fusion of the lumbar spine. J Bone Joint Surg 61A: 1143-1150, 1979

11. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A: The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 7: 629-636, 1999

12. Heithoff KB, Mullin WJ, Holte D, Renfrew DL, Gilbert TJ: Failure of radiographic detection of pseudarthrosis in patients with titanium lumbar interbody fusion cages. North American Spine Society Annual meeting, Chicago, IL October 20-23, 14, 1999.

13. Sandhu HS, Kanim LEA, Toth JM, Kabo JM, Liu D, Delamarter RB, Dawson EG: Experimental spinal fusion with recombinant human bone morphogenetic protein 2 without decortication of osseous elements. Spine 22: 1171-80, 1997

14. Schimandle JH, Boden SD, Huttton WC: Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 20: 1326-1337, 1995

15. Stauffer RN, Coventry MB: Anterior interbody lumbar spine fusion. J Bone Joint Surg 54A: 756-768, 1972

From: Neil Beals
Sent: Monday, July 30, 2001 07:33:36 AM
To: Bill Martin
CC: Pete Wehrly
Subject: FW: Bone Dowel BMP manuscript

Attachments: Final Bone Dowel BMP Paper.doc

Bill: let's discuss open LT INFUSE paper; we need to coordinate Burkus/Gornet/Zdeblick efforts and make sure everyone is in agreement. Neil

-----Original Message-----
From: JKB[redacted]
Sent: Sunday, July 29, 2001 4:02 PM
To: Michael DeMane
Cc: Pete Wehrly; Bill Martin; Bailey Lipscomb; Neil Beals; Tara Hood
Subject: Bone Dowel BMP manuscript

Dear Mike,

Thank you for your kind words of encouragement in regards to the LT CAGE InFUSE FDA audit.

As you know, the BMP studies continue to be a team effort. The studies could not proceed without Pete Wehrly's leadership in the Interbody Division; Bill Martin's steadfast determination, Bailey's brains; Neil's administrative skills and Tara's attention to detail.

I have attached the final (I hope) collaborative manuscript for the Bone Dowel BMP paper. The last few radiographic figures are being processed and the paper will be sent off to SPINE.

I greatly appreciate and I am indebted to you for the clinical research opportunities that you have provided me.

I hope to begin work on the Open LT CAGE InFUSE manuscript when I return from out west.

Respectfully yours,

Ken Burkus

Clinical and Radiographic Outcomes Following Anterior Lumbar Interbody Fusion Using Recombinant Human Bone Morphogenetic Protein-2

J. Kenneth Burkus, MD
Columbus, Georgia

Ensor Transfeldt, MD
Minneapolis, Minnesota

Scott H. Kitchel, MD
Eugene, Oregon

Robert Watkins, MD
Los Angeles, California

Richard Balderston, MD
Philadelphia, Pennsylvania

Address correspondence and reprint requests to: J.K. Burkus, MD, The Hughston Clinic, [redacted]

ABSTRACT

Study Design. This paper evaluates the prospective clinical and radiographic outcomes at twenty-four months of 45 patients who underwent a single level anterior lumbar discectomy and interbody fusion. It compares the investigational patients (two threaded cortical allograft dowels with rhBMP-2 soaked collagen sponges) with the control patients (two threaded allograft dowels with autogenous iliac crest bone graft).

Objective. To determine the safety and effectiveness of the use of InFUSE™ Bone Graft, a recombinant human bone morphogenetic protein-2 (rhBMP-2) applied to an absorbable collagen sponge in anterior lumbar interbody fusion with threaded cortical allografts.

Summary of Background Data. In nonhuman primates, rhBMP-2 used with allograft dowels has been demonstrated to increase rates of interbody fusion by promoting osteoinduction and enhancing incorporation of the allograft. Also, in a small series of human patients undergoing ALIF with a tapered cylindrical metal fusion cage, InFUSE™ Bone Graft has been shown to promote osteoinduction and fusion.

Methods. In this prospective, non-blinded, multicenter trial, 46 patients underwent a single level anterior lumbar discectomy and interbody fusion. This clinical trial compared two study groups: a control group receiving threaded cortical allograft dowels with autogenous iliac crest bone graft, and an investigational group receiving threaded cortical allograft dowels with InFUSE™ Bone Graft. Patients were randomized and equally divided in the two study groups. Clinical outcomes

were assessed using several methods including Oswestry Low Back Pain Disability Questionnaire, Short Form SF-36, neurologic status, work status and back and leg pain questionnaires. Anteroposterior, lateral, flexion/extension radiographs and CT scans were used to evaluate the progression of fusion at 6, 12 and 24 months postoperatively.

Results. All patients receiving InFUSE™ Bone Graft showed radiographic evidence of bone induction and early incorporation of the cortical allografts. All patients in the investigational group were determined to be fused at one year and remained so at two years. The investigational InFUSE™ Bone Graft group showed higher rates of success at 12 and 24 months for fusion, neurological, and back and leg pain when compared to the control autograft group. There were no unanticipated adverse events related to the use of InFUSE™ Bone Graft.

Conclusions. The use of InFUSE™ Bone Graft is a promising method of facilitating anterior intervertebral spinal fusion, decreasing pain, and improving clinical outcomes in patients who have undergone anterior lumbar fusion surgery with structural threaded cortical allograft bone dowels.

INTRODUCTION

Cylindrical threaded allograft dowels can be used as stand-alone intervertebral implants that function as an instrumented anterior lumbar interbody fusion. They are not intradiscal spacers that require additional segmental stabilization. The threaded cortical bone dowels can withstand lumbar compressive loads and promote load sharing between the allograft and the host bone while maximizing device porosity (4,15). These interbody constructs are implanted within the central portion of the disc space through a controlled insertion technique. Impacted allografts, when used alone for interbody fusion in the lumbar spine, have a high rate of pseudarthrosis and subsidence (8,11,19). Contemporary reports of large clinical series of anterior interbody fusions using impacted grafts have shown varying rates of fusion and differing clinical outcomes (1,7,9,12,13,14,16). The threaded dowels resist expulsion and stabilize the bone-implant interface (4). In addition, threaded cortical bone dowels offer increased strength to support cancellous graft material (17). In one clinical series, 43 patients were followed for more than one year showing a high fusion rate and improved clinical outcomes (5).

This report presents the two-year clinical and radiographic results of the use of rhBMP-2 with a collagen sponge inside cylindrical threaded cortical allograft dowels in patients undergoing anterior lumbar interbody fusion.

MATERIALS AND METHODS

Study Design

This prospective, randomized, non-blinded study was conducted under an approved investigational device exemption (IDE). Forty-six patients at five investigational sites completed surgery between April and August 1998. The patients were randomized into two study groups. The control group received autogenous iliac crest bone graft; the investigational group receive InFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, TN), recombinant human bone morphogenetic protein-2 applied to applied to absorbable collagen sponge and used in conjunction with the MD II threaded cortical bone dowel (Regeneration Technologies, Inc., Alachua, FL). Data were collected preoperatively, intraoperatively, and at 6 weeks, 3, 6, 12 and 24 months postoperatively. Operative procedure details and adverse events were also recorded.

Patient Population

All patients were between the ages of 19 and 68 years and had symptomatic degenerative disc disease at the L4-5 or L5-S1 levels (Figure 1). All patients had pain for at least six months before their surgery. The painful low back condition was recalcitrant to nonoperative treatment modalities, such as physical therapy, bedrest, and anti-inflammatory medications. All patients were considered candidates for a single level stand-alone anterior lumbar interbody fusion.

Patients were excluded from the study if they had spinal conditions other than single level symptomatic degenerative disc disease or Grade 0 or 1

spondylolisthesis. Other exclusion criteria were symptomatic degenerative disc disease outside of the L4-5 or L5-S1 disc space levels, patients 40% above ideal body weight or condition requiring medications that might interfere with fusion, such as steroids or nonsteroidal anti-inflammatory medications.

Surgical Technique

All patients underwent an open anterior lumbar discectomy and interbody fusion. Either a transperitoneal or a retroperitoneal approach to the lumbosacral spine was undertaken. In each case, a complete discectomy was carried out. The nucleus pulposis and the cartilaginous endplates were circumferentially removed; however, the bony endplates were preserved prior to reaming and tapping of the endplate for receipt of the dowel. Two allograft bone dowels were then inserted into each disc space.

RhBMP-2 was reconstituted using sterile water and then applied to the ACS. The collagen sponge prepared with rhBMP-2 was then placed into the central portion of the bone dowel prior to its insertion into the prepared disc space. Additional InFUSE™ Bone Graft (rhBMP-2 prepared sponges) were placed between the bone dowels. No autogenous grafts were utilized in the investigational group. The control group received morcellized autogenous iliac crest graft in conjunction with the threaded cortical bone dowels.

Clinical Outcome Measurements

Clinical outcomes were measured using several well-established instruments: the Oswestry Low Back Pain Disability Questionnaire, the Short

Form SF-36 Questionnaire. In addition, back and leg pain questionnaires were employed along with assessment of the patient's neurological status.

Radiographic Outcome Measurements

Fusion was assessed by plain radiographs, including anteroposterior, lateral, and flexion-extension lateral radiographs, and by CT scans (6). Fusion was defined as bridging bone connecting the adjacent vertebral bodies either through the implants or around the implants, less than 5 degrees of angular motion, less than or equal to 3 mm of translation, and an absence of radiolucent lines around more than 50% of either of the implant surfaces. Thin slice (1mm) CT scans with sagittal reconstructions were evaluated at 6, 12 and 24 months On the CT scans, fusion was defined by the presence of continuous trabecular bone formation between the vertebral bodies. Two independent, blinded radiologists interpreted all radiographs. In cases where the fusion outcome differed, a third independent, blinded radiologist was utilized.

RESULTS

Patient Demographics

Twenty-two patients received the control treatment with autograft. In this group, there were 10 men and 12 women (Table 1). The average age was 45.6 years and the average weight was 176 pounds. Seven patients (31.8%) had prior lumbar surgery, six (27.3%) used tobacco within the past 6 months, four (18.2%) had pending litigation, and seven (31.8%) were seeking worker's compensation. Twenty-four patients received the investigational treatment with InFUSE™ Bone Graft. The average age was 41.5 years and the average weight was 172.7 pounds. Eleven patients (45.8%) had prior lumbar surgery, eight (33.3%) used tobacco within the past 6 months, four (16.7%) had pending litigation, and five (20.8%) were seeking worker's compensation.

Surgery

In the control group, surgery was performed at the L4-5 level in eight patients (36.4%) and at the L5-S1 level in 14 patients (63.6%) (Table 2). In the investigational rhBMP-2 group, 11 patients (45.8%) had surgery at the L4-5 level and 13 (54.2%) had surgery at the L5-S1 level. The mean operative time in the InFUSE™ Bone Graft group was 108 minutes compared to the control group 114 minutes. The investigational group had surgery more commonly at the L4-5 level. This exposure of the L4-5 disc space often involves a tedious mobilization of the iliac vessels and requires more time when compared to the exposure at the L5-S1 level. The average blood loss was 124cc for the InFUSE™ Bone Graft group as compared to 245cc in the control group (p=0.026). The average hospital stay

was similar in both groups (3.4 days in the InFUSE™ Bone Graft group versus 3.7 days in the control group).

Clinical Outcomes

One patient was lost to follow-up in the control group and was excluded from the study; this patient died in a house fire at six months postoperatively. All other patients were followed for a minimum of two years following surgery. No unanticipated adverse events occurred which were related to the use of InFUSE™ Bone Graft (rhBMP-2 and the collagen sponge carrier).

At 24 months the investigational patients (rhBMP-2) showed a higher rate of success than the control patients in their overall neurological scores (Figure 2). More than 87% of patients in the rhBMP-2 group were considered to be a neurological success (defined as equivalence or improvement from the preoperative condition) at three months following surgery. These results were maintained at the final two-year follow-up. More than 95% of patients in the autograft control group were considered to be a neurological success at three months postoperatively. These clinical results deteriorated at two years with 73% of patients considered being a neurological success at the last follow-up.

Patients in the investigational group (rhBMP-2) showed an improvement in back pain analog scores (maximum pain score = 20) of more than seven points at their initial postoperative visit at six weeks (Figure 3). In this group, back pain continued to improve and averaged close to a nine-point improvement in pain scores at two years postoperatively. The control group's improvement in back

pain followed a similar pattern. However, improvements in back pain were only approximately five points in this group at 24 months postoperative.

The investigational InFUSE™ Bone Graft group also showed greater of relief of leg pain (Figure 4). In this group, leg pain improved by more than five points within six weeks of surgery. These results remained virtually unchanged for the investigational group at last follow-up of 24 months. However, while the autogenous graft group showed initial improvement of greater than 5 points, the improvement at 24 months decreased to 3.1 points.

The investigational group showed higher mean scores at 24 months in both the Physical (PCS) and Mental (MCS) Components on the SF-36 (Figures 5 and 6). The Oswestry Disability Questionnaire assessed pain associated with activities; the mean Oswestry scores are displayed in Figure 7. Seventy-one percent (71%) of the patients in the InFUSE™ Bone Graft group showed an improvement of at least 15 points in their disability scores at three months postoperatively. This compared favorably to the 43% of patients in the control autograft group (p=0.075). At 12 months, 83% of the InFUSE™ Bone Graft patients improved more than 15 points compared to 58% of the controls. This finding was similar at the two-year follow-up.

Higher percentages of patients in the investigational group were also able to return to work (Figure 8). These patients were also able to return to work earlier than those in the control group.

Autograft bone was not harvested from the iliac crest in the investigational InFUSE™ Bone Graft; in this group, bone graft site pain was not measured and

was assumed to be zero. In the control group, bone graft site pain was as high as 11.3 on a 20-point scale and declined to 2.2 at the 24 month time point. Graft site pain, to some degree, persisted at two years following surgery (Figure 9).

No patients in the InFUSE™ Bone Graft group required an additional surgical procedure in the immediate perioperative period; one patient in the control group required an early return to surgery to remove residual disc material (Table 3). Four patients underwent supplemental posterior fixation procedure after their primary surgery. In the InFUSE™ Bone Graft group, one patient continued to have persistent low back pain at two years postoperatively. The radiographs met the criterion for fusion; however, the attending physician elected to reoperate and supplement the interbody grafts with insertion of posterior pedicle fixation due to slight motion in the facet joints. Three patients in the control group had supplemental posterior fixation inserted from 7 months to 20 months following their initial surgeries. In each of these cases, the patients complained of persistent low back pain and in some instances referred leg pain.

Radiographic Outcomes

At six months following surgery, 19 patients (90.5%) in the InFUSE™ Bone Graft group had evidence of interbody fusion as compared to 13 patients (65%) in the control group (p=0.067) (Figures 10 and 11). At 12 months, all patients (100%) in the investigational group were fused while the control group showed evidence of fusion in 17 patients (89.5%) at one year. One patient in the investigational group did meet the criteria for an anterior interbody fusion; however, the attending physician identified motion within the facet joints and

elected to add supplemental posterior fixation to the spinal motion segment. In this study, this patients was recorded as having a successful interbody fusion at the one-year and two-year follow-up. At the final two-year radiographic follow-up, all patients (100%) in the rhBMP-2 group remained fused (Figure 12). All patients demonstrated bony integration of the allografts to the vertebral endplates and trabeculated new bone formation across the fused interspace. At two years in the control autograft group, 13 patients (68.4%) were considered fused. In the control group, there were no failures of the allograft dowels. Radiographic lucencies developed at the interface of the allograft to the vertebral endplate. There was no migration of the implants.

DISCUSSION

Recombinant human bone morphogenetic protein-2 (rhBMP-2) is an osteoinductive growth factor (2,18). Marshall Urist discovered demineralized bone matrix's capabilities of inducing ectopic bone formation in a rat muscle pouch and introduced the concept that bone growth factors can induce new bone formation independent of the bone tissue environment (20). Bone morphogenetic protein-2 is one of several proteins identified from bone tissue that acts as an osteoinductive cytokine and induces the differentiation of pluripotential precursor cell along an osteogenic line. A pure form of this protein can be produced through standard recombinant technology. The human cDNA sequence is created through the use of oligonucleotide probes, and these clones are then spliced into a viral vector and transfected into a carrier cell in a process called recombination. These carrier cells (Chinese hamster ovary cells) have the ability to produce large quantities of rhBMP-2. Creating recombinant human proteins in this manner avoids potential complications associated with disease transmission from allograft or xenograft sources. The availability of rhBMP-2 in pure "unlimited" sources has the ability to greatly enhance spinal fusion results while lowering pain scores associated with a bone graft harvesting procedure. This assessed the effectiveness of this recombinant protein impregnated on a collagen sponge in a threaded cortical allograft dowel for the treatment of degenerative disc disease through an anterior interbody fusion.

To date, in both animal and human studies, rhBMP-2 has been shown to be capable of inducing new bone formation (2,17). In a study involving anterior

lumbar interbody fusion in nonhuman primates, rhBMP-2 and an absorbable collagen sponge carrier was shown to promote fusion through osteoinduction (10). New bone formation appeared to be superior to autogenous iliac crest graft with cortical dowel allograft. Similarly, in a preliminary clinical study involving the use of InFUSE™ Bone Graft and a tapered cylindrical titanium cage in humans, arthrodesis was found to occur more reliably in patients treated with rhBMP-2 than in controls treated with autogenous bone graft (3).

This study is the first clinical report of the effectiveness of rhBMP-2 used with cortical allograft to promote anterior lumbar intervertebral fusion in humans. All patients receiving rhBMP-2 showed radiographic evidence of bone induction and early incorporation of the cortical allografts. All patients in this group fused at one year and remained so at 2 years. One patient in this group had additional posterior fixation. Overall, the InFUSE™ Bone Graft group showed faster clinical improvements and higher rates of success when compared to the control group. There were no unanticipated adverse events related to the use of rhBMP-2 and the collagen sponge carrier.

CONCLUSION

In forty-five patients who had anterior lumbar interbody fusion and were followed for two years, the group that received the recombinant human bone morphogenetic protein 2 on a collagen sponge carrier (INFUSE™ Bone Graft) showed faster clinical improvement (P= 0.067) and higher rates of success (P= 0.032) when compared with the group that received autogenous iliac crest bone graft. rhBMP-2 has been shown to be a promising method of facilitating anterior intervertebral spinal fusion and of decreasing pain and improving clinical outcomes after anterior lumbar fusion surgery with allograft bone dowels.

REFERENCES

1. Blumenthal SL, Baker J, Dossett A, Selby DK. The role of anterior lumbar fusion for internal disc disruption. Spine 1988;13:566-569.

2. Boden SD, Schimandle JH, Hutton WC. Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 1995;20:2633-2644.

3. Boden SD, Zdeblick TA Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Spine 2000;25:376-381.

4. Boyd, L.M.; Estes, B.T. and Liu M. "Biomechanics of Lumbar Interbody Constructs, *Effect of Design and Materials*." Chirurgie Endoscopique et Mini-invasive du Rachis. Ed. Husson JL, LeHuec JC. Sauramps Médical. Montpelier, France. pp 181-192, 1999.

5. Burkus JK, Dorchak JD, Sanders DL, Foor BD: Single-level anterior lumbar interbody fusion using threaded cortical bone allografts. North American Spine Society Meeting of the Americas, Miami, Florida, 1999.

6. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. Neurosurg Focus 2001;10:1-9.

7. Crock HV. Anterior lumbar interbody fusion: indications for its use and notes on surgical technique. Clin Orthop 1982;165:157-163.

8. Flynn JC, Houque MA. Anterior fusion of the lumbar spine. J Bone Joint Surg 1979;61A:1143-1150.

9. Harmon PH. Anterior excision and vertebral fusion operation for intervertebral disc syndromes of the lower lumbar spine: three to five year results in 244 cases. Clin Orthop 1963;26:107-127.

10. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A. The use of recombinant human bone morphogenetic protein-2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999;24:629-636.

11. Kumar A, Kozak JA, Doherty BJ, Dickson JH. Interspace distraction and graft subsidence after anterior lumbar fusion with femoral strut allograft. Spine 1993;18:2393-2400.

12. Lane JD, Moore ES. Transperitoneal approach to the intervertebral disc in the lumbar area. Annals of Surgery 1948;127:537-551.

13. Loguidice VA, Johnson RG, Guyer RD, Stith WJ, Ohnmeiss DD, Hochschuler SH, Rashbaum RF. Anterior lumbar interbody fusion. Spine 1988;13:366-369.

14. Leong JC, Chun SY, Grange WJ, Fang D: Long-term results of lumbar intervertebral disc prolapse. Spine 1983;8:793-799.

15. Morales RW, Pettine KA, Salib RM. A biomechanical study of bone allografts used in lumbar interbody fusions. North American Spine Society – 6th Annual Meeting, Keystone, Colorado 1991

16. Sacks S. Anterior interbody fusion of the lumbar spine. J Bone Joint Surg 1965;47B:211-223.

17. Sandhu HS, Kanim LEA, Toth JM, Kabo JM, Liu D, Delamarter RB, Dawson EG. Experimental spinal fusion with recombinant human bone morphogenetic protein-2 without decortication of osseous elements. Spine 1997;22:1171-80.

18. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995; 20:1326-1337.

19. Stauffer RN, Coventry MB. Anterior interbody lumbar spine fusion. J Bone Joint Surg 1972;54A:756-768.

20. Urist MR. Bone: Formation by autoinduction. Science 1965;150:893-899.

TABLES

TABLE 1. Patient demographic data

Demographic Data	InFUSE™ Bone Graft	Autograft
No. of patients	24	22*
Age (years)	41.5	45.6
Weight (lbs)	172.7	176.0
Sex (male/female)	8/16	10/12
Workers' compensation (%)	5 (21)	7(32)
Spinal litigation (%)	4 (17)	4(18)
Tobacco use (%)	8 (33)	6(27)
Previous surgeries (%)	11 (46)	7 (32)

*One patient died an accidental death at 6 months after surgery.

Table 2. Intraoperative Data

Surgical Data	InFUSE™ Bone Graft	Autograft
Operative time (min)	108	114
Blood loss (mL)	124.1	245.0
Levels (%)		
L4-L5	11 (46)	8 (36)
L5-S1	13 (54)	14 (64)
Hospital stay (days)	3.4	3.7

Table 3. Additional Surgeries

Procedure	InFUSE™ Bone Graft	Autograft
Removals	0	0
Revisions	0	0
Supplemental fixation (%)	1 (4.2)	3 (13.6)
Reoperation (%)	0	1 (4.5)

LEGENDS TO FIGURES

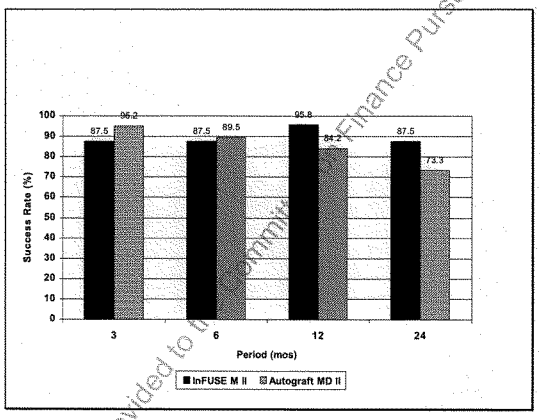
Figure 1: Standing lateral lumbar radiograph shows at the L5S1 level there is significant disc space narrowing with sclerosis of the bony endplates and minimal retrolithesis. The adjacent L4-5 and L3-4 disc spaces have normal heights and no evidence of instability.

Figure 11: A. At six months postoperatively, a neutral lateral radiograph shows restoration of normal disc space height and improvement in segmental lordosis. Dynamic flexion (B) and extension (C) lateral radiographs show no motion at the L5S1 disc space. There are no lucencies at the allograft-vertebral endplate interface. D. CT scan shows incorporation of the allograft to the vertebral endplate.

Figure 12: Lateral radiographs at one-year (A) and two-years (B) postoperatively shows incorporation of the allografts to the vertebral endplate with no radiographic lucencies. Lordosis and disc space height have been maintained without change from the initial postoperative radiographs.

Figure 2: Neurologic outcomes*

Anterior Lumbar Interbody Fusion using MDII bone dowels comparing rhBMP-2 and a collagen sponge carrier (InFUSE Bone Graft) to iliac crest autograft



* Success based upon the postoperative neurologic condition being improved or no worse than the preoperative condition

Figure 3: Back pain outcomes

Anterior Lumbar Interbody Fusion using MDII bone dowels comparing rhBMP-2 and a collagen sponge carrier (InFUSE Bone Graft) to iliac crest autograft

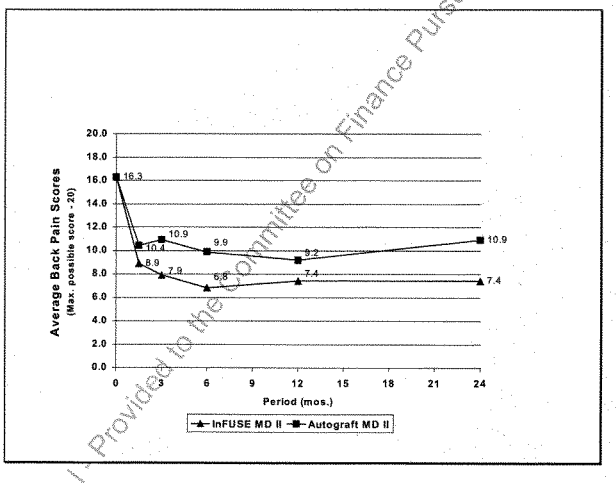


Figure 4: Leg pain outcomes

Anterior Lumbar Interbody Fusion using MDII bone dowels comparing rhBMP-2 and a collagen sponge carrier (InFUSE Bone Graft) to iliac crest autograft

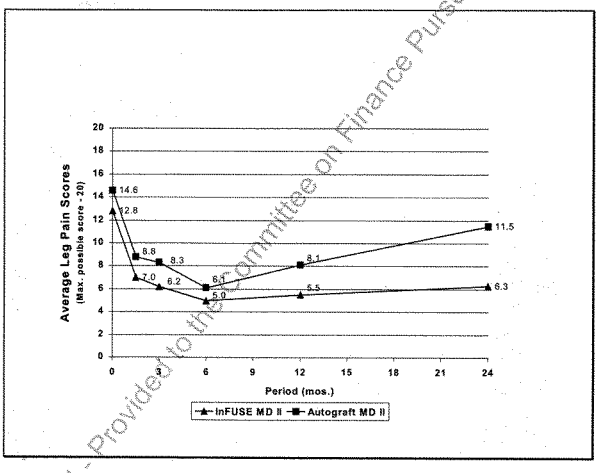


Figure 5: SF36 Physical Component Score outcomes.

Anterior Lumbar Interbody Fusion using MDII bone dowels comparing rhBMP-2 and a collagen sponge carrier (InFUSE Bone Graft) to iliac crest autograft

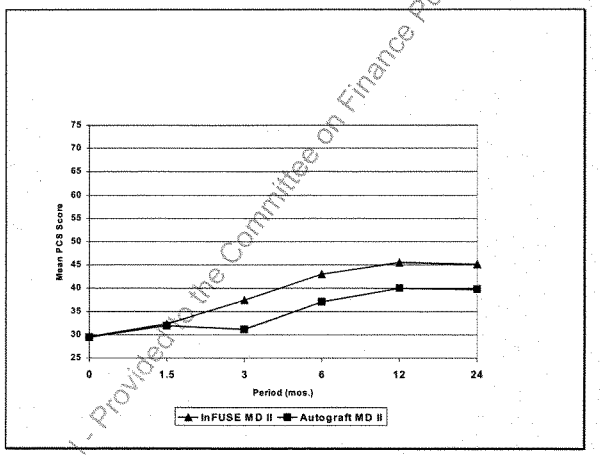


Figure 6: SF36 Mental Component Score outcomes

Anterior Lumbar Interbody Fusion using MDII bone dowels comparing rhBMP-2 and a collagen sponge carrier (InFUSE Bone Graft) to iliac crest autograft

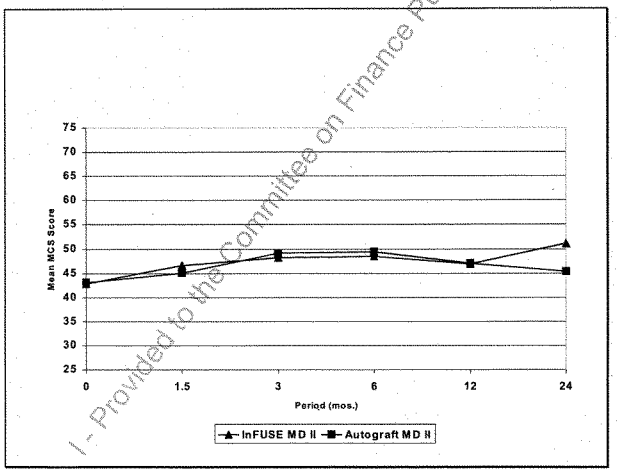


Figure 7: Oswestry Disability Questionnaire outcomes

Anterior Lumbar Interbody Fusion using MDII bone dowels comparing rhBMP-2 and a collagen sponge carrier (InFUSE Bone Graft) to iliac crest autograft

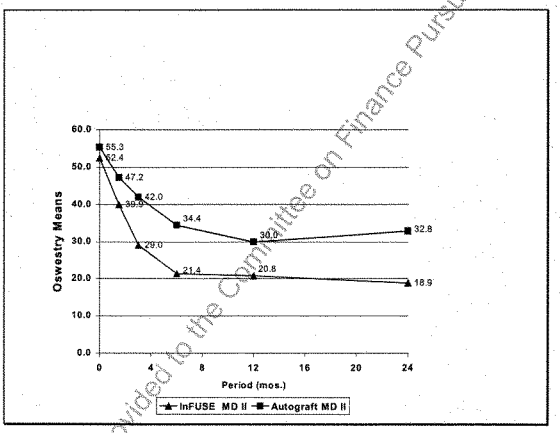


Figure 8: Return to work status (%)

Anterior Lumbar Interbody Fusion using MDII bone dowels comparing rhBMP-2 and a collagen sponge carrier (InFUSE Bone Graft) to iliac crest autograft

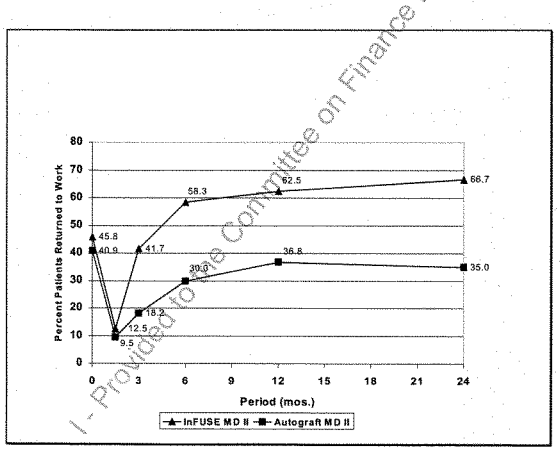


Figure 9: Iliac Crest bone graft harvesting site pain

Anterior Lumbar Interbody Fusion using MDII bone dowels comparing rhBMP-2 and a collagen sponge carrier (InFUSE Bone Graft) to iliac crest autograft

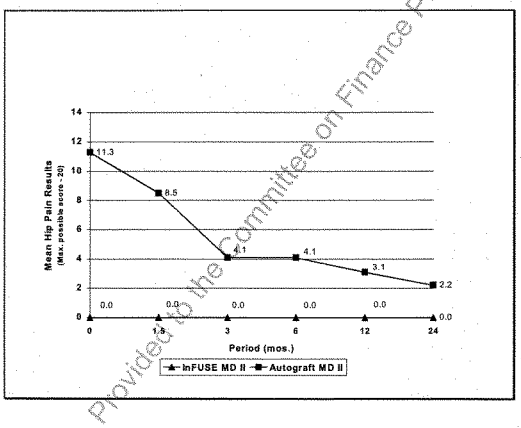
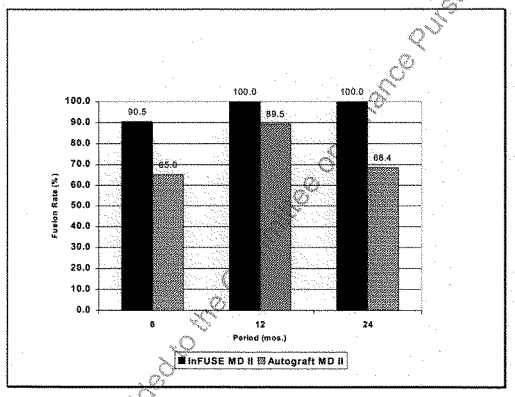


Figure 10: Fusion outcomes following surgery

Anterior Lumbar Interbody Fusion using MDII bone dowels comparing rhBMP-2 and a collagen sponge carrier (InFUSE Bone Graft) to iliac crest autograft



TM

From: Bill Martin
Sent: Monday, September 24, 2001 03:30:18 PM
To: Neil Beals
CC: Pete Wehrly
Subject: RE: SRS Paper

Attachments: FW .msg

I'll save you the pain of the first 30 e-mails and just send you the latest communication.
Note:
1) This paper was written by Dr. Burkus using only his data.
2) This is the same paper that I mentioned to you as an FYI about 3 weeks ago, if you remember I described it as a radiographic study that involved getting P values and additional information from Gurong and crew.

-----Original Message-----
From: Neil Beals
Sent: Monday, September 24, 2001 3:04 PM
To: Bill Martin
Cc: Pete Wehrly
Subject: RE: SRS Paper

thanks - can you send draft of info to me?

-----Original Message-----
From: Bill Martin
Sent: Monday, September 24, 2001 8:38 AM
To: Neil Beals; Pete Wehrly
Subject: RE: SRS Paper

Already done. Long, painstaking process of getting "p" values, edits, tables made and illustrations.
Complete - no further action needed.
-Bill

-----Original Message-----
From: Neil Beals
Sent: Friday, September 21, 2001 5:31 PM
To: Pete Wehrly; Bill Martin
Subject: FW: SRS Paper

do either of you know whatever happened here? do we/I need to do anything at this point?

-----Original Message-----
From: Pete Wehrly
Sent: Friday, July 20, 2001 3:23 PM
To: Neil Beals
Subject: FW: SRS Paper

Let's discuss.

Pete

-----Original Message-----
From: John Kenneth Burkus [redacted]
Sent: Friday, July 20, 2001 3:11 PM
To: Pete Wehrly; Bill Martin
Subject: SRS Paper

Pete and Bill,

The SRS has nominated the paper on CT Fusion Assessment of LT CAGE and BMP for expedited review in SPINE.

I have enclosed a copy of the paper. This is my first draft.

I need some help with this paper. I have NOT completed any type of statistical review of the data. I have no idea how to establish "significance" and/or "p" values.

Would you be able to review the data with an eye toward how best to present the data and any type of statistical review?

I also have a great deal of trouble doing graphs. Could I get some help with the graphic display of the data?

Thanks.

Ken Burkus << File: CAT Scan BMP LT Cage.doc >>

From: Bill Martin
Sent: Monday, August 27, 2001 05:36:57 PM
To: 'Lynn Sanders (E-mail)[redacted]
Subject: FW:

Attachments: CAT Scan BMP LT Cage_.doc

Lynn,
Here are edits to the verbage. Consider these as edits from Bailey, Tara, and Guorong. A couple of items to note:

- Please be sure to add the charts, etc. that I sent seperately to Dr. Burkus.
- Note that the beginning of the paper sounds choppy (due to my edits), you may need to decide how to better handle the 42 vs. 26 patients.
- Note that the investigational patient that was lost at 12 months to (patient #66) was determined to have radiolucency leading to fusion failure at 12 months. My understanding is that Dr. Burkus and Dorchak interpreted his films as fused - I don't know how to settle that one except to say that Dr. Burkus should report it as he sees best.

Lynn,
Hope this helps -let me know if you have any questions or if you need more info - thanks!
Bill

PROSPECTIVE RANDOMIZED STUDY OF RADIOGRAPHIC ASSESSMENT OF INTERBODY FUSION USING rhBMP-2

J. Kenneth Burkus, MD

John D. Dorchak, MD

D. Lynn Sanders, CCRC

The Hughston Clinic
Columbus, Georgia

Address correspondence and reprint requests to: J.K. Burkus, MD, The Hughston Clinic, [redacted]

ABSTRACT

Study Design. This paper evaluates the prospective radiographic outcomes of 42 patients who underwent a single level anterior lumbar discectomy and interbody fusion. A total of 116 CAT Scans were gathered at six, twelve, and twenty-four month follow-up. Of the 42 patients, 26 had hounsfield unit measurements recorded at 4 intervals (immediate post-op, six, twelve, and twenty-four months. Forty-one of forty-two patients had radiographic fusion assessment at 24 months to assess bone formation outside of the cages.. It compares the investigational patients (two tapered cylindrical fusion devices with rhBMP-2 soaked collagen sponges) with the control patients (two tapered cylindrical fusion devices with autogenous iliac crest bone graft).

Objectives. To determine the patterns and rates of osteoinduction associated with the use of recombinant human bone morphogenetic protein 2 (rhBMP-2) and an absorbable collagen sponge (ACS) in anterior interbody fusion in the lumbar spine with a tapered cylindrical fusion device (LT-CAGE™).

Summary of Background Data. rhBMP-2 used with allograft dowels has been demonstrated to increase rates of interbody fusion by promoting osteoinduction and enhancing incorporation of the allograft. In a small series of human patients undergoing ALIF with a tapered cylindrical fusion cage, rhBMP-2 with an ACS carrier has been shown to promote osteoinduction and fusion.

Methods. In this prospective, non-blinded, single center study, 42 patients underwent a single level anterior lumbar discectomy and interbody fusion. Patients were randomly divided into two study groups: a control group underwent

Deleted: s

Deleted: postoperatively of 42 patients who underwent a single level anterior lumbar discectomy and interbody fusion

interbody fusion using the LT-CAGE™ device with autogenous iliac crest bone graft, and the investigational group underwent interbody fusion using the LT-CAGE™ device with rhBMP-2 and an absorbable collagen sponge (ACS). Anteroposterior, lateral, flexion/extension lateral and CAT scans were used to evaluate the pattern of osteoinduction within the interbody space and the progression of fusion at 6, 12 and 24 months postoperatively.

Results. All patients receiving rhBMP-2 showed radiographic evidence of bone induction within the interbody cages at six months postoperatively. New bone formation occurred within the disc space outside of the cages by six months in eighteen patients (18/20; 82%). By two years, all patients showed new formation outside of the cages. Once new bone formation was identified, no patients developed a pseudarthrosis. Bone maturation and remodeling was identified as an increase in radiographic density within the disc space as well as within the cages.

Conclusions. The use of rhBMP-2 is a promising method of facilitating anterior intervertebral spinal fusion in patients who have undergone anterior lumbar fusion surgery.

INTRODUCTION:

Clinical studies of anterior lumbar interbody fusion have identified differing rates of fusion (5,8,10,15). The variation in fusion outcome are in part determined by the surgical technique, bone graft material and method of intervertebral fixation (4). Recombinant human bone morphogenetic protein-2 (rhBMP-2, Genetics Institute, Cambridge, MA) is an osteoinductive growth factor (1). In both animal and human studies, it has been proven to be capable of consistently inducing new bone formation (2,13,14). In a study involving anterior lumbar interbody fusion in nonhuman primates, rhBMP-2 and an absorbable collagen sponge carrier was shown to promote fusion through osteoinduction (11). New bone formation appeared to be superior to autogenous iliac crest graft with cortical dowel allograft.

In a preliminary human clinical study involving the use of rhBMP-2 and threaded cortical bone dowels, high rates of fusion were seen (7). Similarly, in a small clinical study, rhBMP-2 and a tapered cylindrical titanium cage in humans, arthrodesis was found to occur more reliably in patients treated with rhBMP-2 than in controls treated with autogenous bone graft (3).

Radiographic imaging of a developing fusion mass after anterior lumbar surgery is challenging in patients who have metallic interbody implants (9,12). Thin-cut CT imaging is the most efficacious method of identifying bone formation within second-generation cages (6). Recombinant human bone morphogenetic protein-2 (rhBMP-2) has been shown to promote osteoinduction and fusion. To determine its osteoinductive capability with a threaded, cylindrical, tapered

interbody device (LT-CAGE™, Medtronic Sofamor Danek, Memphis, TN) and an absorbable collagen sponge (ACS), we evaluated the radiographic outcomes of forty-two patients who underwent a single-level anterior interbody fusion with the LT-CAGE device. We compared the radiographic outcomes in the investigational patients (LT-CAGE with rhBMP-2) with the outcomes in the control patients (LT-CAGE with autogenous bone graft).

MATERIALS AND METHODS

Patients:

Between August 1998 and March 1999, 45 patients with symptomatic single-level degenerative disc disease were enrolled in this prospective randomized nonblinded study. All patients were between the ages of 18 and 65 years and had symptomatic degenerative lumbar spondylosis at the L4-5 or L5-S1 levels. All patients had disabling low back or leg pain, or both, that had lasted for at least 6 months and had not resolved with nonoperative treatment. All patients were considered candidates for a single level stand-alone anterior lumbar interbody fusion. No patients had osteoporosis. Patients were excluded from the study if they had spinal conditions other than degenerative disc disease, multi-level spondylosis, or Grade II or higher spondylolisthesis. Other exclusion criteria were symptomatic spondylosis outside of the L4-5 or L5-S1 disc space levels and if they were 40% above ideal body weight, had a history of chronic use of steroidal or non-steroidal anti-inflammatory medications, and had a history of disc space infection. Patients were randomized to receive autogenous iliac crest bone graft with the LT-CAGE device or rhBMP-2 on a collagen sponge carrier with the LT-CAGE device.

Forty-two patients were followed for two years after surgery. Three patients were eliminated from this study for failure to complete the two-year follow-up. In the investigational rhBMP-2 group, one patientdid not complete their two-year follow-up and was lost to follow-up after his twelve-month radiographic assessment. In the control autograft group, one patient was lost to follow-up after

Deleted: Three

Deleted: two

Deleted: s

Deleted: . One patient died of an unrelated coronary event at nine months postoperatively. One patient

the six-month assessment, and one patient died of an unrelated coronary event at nine months postoperatively.

The control autogenous bone graft group consisted of twenty patients (11 men, 9 women) whose average age at surgery was 44.2 years, and the investigational rhBMP-2 group consisted of twenty-two patients (11 men, 11 women) whose average age was 41.7 years. In the autograft group, two patients (10%) had used tobacco within six months before surgery compared with four patients (18%) in the rhBMP-2 group.

Surgical Procedure

The patients underwent an anterior lumbar interbody fusion procedure through an open retroperitoneal approach at a single study site by the two senior surgeons. In each case, a complete discectomy was carried out. The nucleus pulposis and the cartilaginous endplates were circumferentially removed; however, the bony endplates were preserved. Following precise reaming of the endplates, two LT-CAGE devices were inserted into the disc space.

The rhBMP-2 used was reconstituted using sterile water. The solution was applied to a bovine collagen sponge and allowed to bind to the sponge for fifteen minutes. The BMP-soaked sponge was then placed in the hollow central portion of the LT-CAGE before its insertion into the prepared disc space. No additional sponges were placed outside of the devices. No autogenous grafts were utilized in the investigational group. The control group received morcellized autogenous iliac crest graft placed within the cages and within the disc space surrounding the cages.

Radiographic Outcome Measurements:

Plain radiographs and thin-cut CT scans were used to evaluate patterns of osteoinduction at 2 days and at 6, 12, and 24 months after surgery. Fusion was defined as an absence of radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation of less than 5° on flexion-extension lateral radiographs, and continuous trabecular bone growth connecting the vertebral bodies. Two independent, blinded radiologists interpreted all radiographs and CT scans. In cases where the fusion outcome differed, a third independent radiologist was used.

Thin-cut CT scans were used to assess new bone formation and bone remodeling within and around the fusion cages. On the CAT scans, fusion was defined by the presence of continuous trabecular bone formation through both of the dowels. The changes in density within the cages were determined by precisely measuring the Hounsfield units (HU) within each cage on the serial CT scans. To reduce imaging artifact (9), Hounsfield units were recoded within the central portion of the cages (at least 3 mm from the metallic side wall of the cages) and were calibrated against known densities on each scan.

RESULTS

Plain Radiographs

At twelve months postoperatively, one patient in the control group was identified as having a pseudarthrosis. Radiographs showed radiolucencies surrounding the majority of the implants and motion of greater than five degrees on dynamic radiographs. This patient underwent a posterior instrumented fusion to stabilize the lumbar motion segment. No other patients in the investigational group or the control group were identified as having a pseudarthrosis on plain radiographic studies.

Bone Density Changes within Cages:

In the rhBMP-2 group, immediate postoperative CT scans showed an average density of 156 HU (range, 94-226 HU) within the central portion of the LT-CAGE; the control group showed an average 533 HU (range, 403-712 HU). At six months, the investigational group showed an average increase to 325 HU (range, 178-488 HU), at one year an increase to an average of 447 HU (range, 303-703 HU), and at two years an increase to 522 HU (range, 434-789 HU). In the autograft control group, the average density within the cage at six months was 575 HU (range, 379-714 HU), at 1 year an average of 643 HU (range, 462-903 HU), and at two years an average of 750 HU (range, 474-933 HU).

Progression of densities within the cages correlated with evidence of fusion on standard plain radiographic measurements. One patient in the control group developed a pseudarthrosis at one year. This patient showed increased density of the autogenous grafts within the cages.

Bone Formation Outside of Cages:

In the rhBMP-2 group, at six months, new bone formation was identified outside of the cages in eighteen patients (82%); at one year, in twenty-one patients (95%); and at two years, in twenty-two patients (100%). In the autograft group, at six months, new bone formation was identified outside of the cages in ten patients (50%); at one year, in sixteen patients (80%); and at two years, in nineteen patients (95%). Importantly, all bone growth was contained within the interbody space. No ectopic bone formation was noted.

DISCUSSION

Osteoinduction has been shown to occur within the LT CAGE. In the rhBMP-2 group bone formation, as evidenced by progressive density on thin-cut CT scans, more than doubled within six months of surgery and increased more than threefold by two years. New bone formation outside of the cages had occurred by six months and in all patients by two years. Rates of new bone formation and fusion exceeded those of the autograft control group.

High fusion rates associated with new bone formation inside and outside of the cages can be achieved without harvesting bone from the iliac crest and without device-related adverse events. The use of rhBMP-2 with the LT-CAGE device is a promising method of facilitating anterior intervertebral spinal fusion in patients who have degenerative lumbar disc disease.

REFERENCES

1. Boden SD, Schimandle JH, Huttton WC: Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 20: 2633-2644, 1995

2. Boden SD, Horton WC, Martin G, Truss T, Sandhu H: Laproscopic anterior arthrodesis with rhBMP-2 in a titanium interbody threaded cage. J Spinal Disord 11: 95-101, 1998.

3. Boden SD, Zdeblick TA Sandhu HS, Heim SE: The use of rhBMP-2 in interbody fusion cages. Spine 25: 376-381, 2000

4. Boyd, L.M.; Estes, B.T. and Liu M. "Biomechanics of Lumbar Interbody Constructs, *Effect of Design and Materials.*" Chirurgie Endoscopique et Mini-invasive du Rachis. Ed. Husson JL, LeHuec JC. Sauramps Medical. Montpelier, France. pp 181-192, 1999.

5. Burkus JK, Dorchak JD, Sanders DL, Foor BD: Single-level anterior lumbar interbody fusion using threaded cortical bone allografts. North American Spine Society Meeting of the Americas, Miami, Florida, May 1999.

6. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical interbody research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior lumbar interbody surgery. Neurosurg Focus 10: 1-9, 2001.

7. Burkus JK, Transfeldt EE, Kitchel SH, Watkins R, Balderston RA: A prospective and randomized study assessing the clinical and radiographic outcomes of patients treated with rhBMP-2 and threaded cortical bone dowels in

the lumbar spine. North American Spine Society Annual meeting, New Orleans, LA, October 25-28, 114, 2000.

8. Camissa FP, Dhawlikar SH, Parvateneni HK, Sandhu HS: Radiolucnies surrounding allograft bone dowels in the early post-operative period. North American Spine Society Annual meeting, San Francisco, CA October 28-31, 273, 1998.

9. Cizek GR, Boyd LM: Imaging Pitfalls of interbody spinal implants. Spine 25: 2633-2636, 2000.

10. Flynn JC, Houque MA: Anterior fusion of the lumbar spine. J Bone Joint Surg 61A: 1143-1150, 1979

11. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A: The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 7: 629-636, 1999

12. Heithoff KB, Mullin WJ, Holte D, Renfrew DL, Gilbert TJ: Failure of radiographic detection of pseudarthrosis in patients with titanium lumbar interbody fusion cages. North American Spine Society Annual meeting, Chicago, IL October 20-23, 14, 1999.

13. Sandhu HS, Kanim LEA, Toth JM, Kabo JM, Liu D, Delamarter RB, Dawson EG: Experimental spinal fusion with recombinant human bone morphogenetic protein 2 without decortication of osseous elements. Spine 22: 1171-80, 1997

14. Schimandle JH, Boden SD, Huttton WC: Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 20: 1326-1337, 1995

15. Stauffer RN, Coventry MB: Anterior interbody lumbar spine fusion. J Bone Joint Surg 54A: 756-768, 1972

From: JKB[redacted]
Sent: Monday, October 29, 2001 09:32:47 PM
To: Mat Gornet[redacted]; Tom Zdeblick[redacted] Neil Beals[redacted]; Peter Wehrly[redacted]; Clark Charlton[redacted]; Tara Hood[redacted]
CC: Mike DeMane[redacted]
Subject: Open LT BMP manuscript

Attachments: LT BMP Paper.1.doc

Dear Sirs and Ma'am:

I have attached the first draft of the Open LT CAGE BMP manuscript that reports on the two year data. I have written this draft for submission to SPINE.

There are several obvious faults:
1. There are too many tables - I will need help from MSD to covert some of the tables into figures (I.e. grafts). Help me with this.
2. The bibliography is incomplete and the text is not adequately referenced. I am working on this and would appreciate suggestions, additions and deletions.
3. There are no clinical figures (x-rays of clinical cases) - they are coming - no problem there.
4. The discussion sucks. I would like to emphasize Tom's concept of "Fusion Disease" and emphasize the concept of overall clinical success. I will be working on integrating these ideas into the discussion. Again, any ideas or help would be appreciated.

I hope to put forward a time table and method for getting this paper completed by December first with input from all concerned parties at the SIRG meeting in Seattle.

Good luck with your travels. God bless you all and I look forward to seeing you on Wednesday afternoon. I am leaving tomorrow afternoon.

Best regards,
Ken Burkus

rhBMP-2 and the LT-CAGE™ Device in the Lumbar Spine.

Matthew F. Gornet MD*

J. Kenneth Burkus MD†

Curtis Dickman, MD‡

Thomas A. Zdeblick MD§

*Staff Physician, Missouri Bone and Joint Institute, St. Louis, Missouri

†Staff Physician, Spine Service, The Hughston Clinic, P.C., Columbus, Georgia

‡Barrows Institute, Phoenix, Arizona

§Chairman, Department of Orthopaedic Surgery, University of Wisconsin, Madison, Wisconsin

Address correspondence and reprint requests to J.K. Burkus, MD, The Hughston Clinic, [redacted]

ABSTRACT

Study Design. A prospective, randomized, nonblinded, multicenter study of 279 patients who underwent a single-level anterior lumbar interbody fusion. Patients were randomized into two groups: one received autogenous iliac crest bone graft with the LT-CAGE™ device, the other, recombinant human bone morphogenetic protein-2 (rhBMP-2) on a collagen sponge carrier with the LT-CAGE™ device.

Objectives. To determine clinical and radiographic outcomes in patients treated for single-level degenerative lumbar disc disease with a stand-alone anterior interbody fusion using a tapered cylindrical fusion device with autogenous bone graft or rhBMP-2 and an absorbable collagen sponge carrier.

Summary of Background Data. In a small series of human patients undergoing anterior lumbar interbody fusion with a tapered cylindrical fusion cage, rhBMP-2 has been shown to promote osteoinduction and fusion.

Methods. In this prospective nonblinded study, 279 patients were randomly divided into 2 groups: the investigational group (143 patients) underwent interbody fusion using two tapered cylindrical fusion cages (LT-CAGE™) and rhBMP-2 on an absorbable collagen sponge, and a control group (136 patients) underwent the procedure and received the devices and autogenous iliac crest bone graft. Clinical outcomes were assessed using neurologic status, work status, and Oswestry Low Back Pain Disability and back and leg pain questionnaires. Plain radiographs and computed tomographic scans were used to evaluate fusion.

Results. The mean operative time and blood loss was less in the investigational rhBMP-2 group (1.6 hours and 109.8 ml.) than in the control group (2.0 hours and 153.1

ml.). At 12 months after surgery, the fusion rate for the investigational group was 96.9% compared with 92.6% for the control group; at 24 months, the investigational group fusion rate of 94.5% remained higher than the control at 88.7%. At all postoperative intervals, the mean Oswestry, back pain, and leg pain scores and neurologic status improved in both treatment groups compared with preoperative scores and were similar in both groups.

Conclusions. The investigational patient group had shorter operative times and less blood loss. At 24 months, this group had a fusion rate that was nearly 6 percentage points greater than the control autograft group. Overall success rates, based upon Oswestry outcome, neurologic status, and fusion were similar in the two groups.

Key words: anterior lumbar interbody fusion, bone morphogenetic protein, osteoinduction, radiography, interbody fusion cages

Key points:

- Fusion rates for patients treated with rhBMP-2 were higher at 12 and 24 months compared with those patients treated with autograft.
- Operative times and blood loss were less for those patients treated with rhBMP-2 compared with those patients who underwent iliac crest bone graft harvesting.
- At all postoperative time periods, patients in both treatment group showed improvement in Oswestry disability scores, in neurologic status and in back and leg pain outcomes.

Précis

In a 2-year prospective randomized study of 279 patients, the investigational group that received rhBMP-2 with the LT-CAGE device had an overall success rate (fusion, neurological and Oswestry success, no second surgery failures, and no adverse device-related events) that was equivalent to the control group that received autogenous bone graft with the LT-CAGE device.

INTRODUCTION

Degenerative changes within a lumbar spinal motion segment are, in part, evidenced by the presence of radial tears or fissures in the annulus fibrosus, disc space desiccation and collapse, and the formation of radial osteophytes. These morphologic changes within the spinal motion segment can lead to loss of the intervertebral disc's ability to accommodate normal biomechanical stresses and can cause pain. Fusion of the degenerative and unstable spinal motion segment can give significant relief from this disabling and often progressive condition.

Anterior lumbar interbody fusion (ALIF) is an effective treatment for patients with symptomatic degenerative disc disease. Lumbar spine stabilization procedures that do not interfere with the posterior spinal muscles have some significant advantages (9,10,14-16,19). The anterior approach to the lumbosacral spine enables the surgeon to expand the disc space and re-establish the normal anatomic alignment and relationships of the spinal motion segment while avoiding injury to the posterior paravertebral muscles. The anterior approach also retains all posterior-stabilizing structures and avoids epidural scarring and perineural fibrosis. Adjacent segment degeneration in the lumbar spine after anterior interbody fusion may also be reduced (17).

Stand-alone ALIF has been associated with high rates of pseudarthrosis, graft subsidence, and graft extrusion. Supplemental posterior segmental spinal instrumentation has been advocated to stabilize interbody grafts and increase rates of fusion. Recently, cylindrical, threaded intervertebral devices with autogenous bone

grafts have been shown to stabilize a lumbar motion segment after anterior discectomy. Their use has lead to high rates of fusion and to improved clinical outcomes.

In primate animal models, recombinant human bone morphogenetic protein 2 (rhBMP-2) and an absorbable collagen sponge carrier has been shown to promote osteoinduction and fusion after ALIF. In a small series of human patients who underwent stand-alone ALIF with tapered fusion cages (LT-CAGE™ devices; Medtronic Sofamor Danek, Memphis, TN), the use of rhBMP-2 was also shown to promote osteoinduction and fusion (4). To further evaluate this method, we evaluated the clinical and radiographic outcomes at 24 months of 279 patients who underwent a single level ALIF. We compared the outcomes in the investigational patients (LT-CAGE™ devices with rhBMP-2) with those in the control patients (LT-CAGE™ devices with autogenous bone).

MATERIALS AND METHODS

Study Design. Between August 1998 and July 1999, 279 patients were enrolled in this prospective, randomized, nonblinded study at 16 investigational sites. Patients were randomized in a 1:1 manner into two groups: the investigational group received rhBMP-2 on an absorbable collagen sponge carrier with the LT-CAGE™ device (LT-CAGE™ device; Medtronic Sofamor Danek, Memphis, TN) and the control group received autogenous iliac crest bone graft with the LT-CAGE™ device.

Patient Data. Preoperatively, all patients had symptomatic, single-level degenerative lumbar disc disease and symptoms of disabling low back or leg pain, or both of at least

6 months' duration that had not responded to nonoperative treatments. The two treatment groups were very similar demographically, and there were no statistically significant differences ($P < 0.05$) for any of the variables (Table 1). The rhBMP-2 group consisted of 143 patients and the control group consisted of 136 patients. The average age at surgery was 43.3 years for the rhBMP-2 group and 42.3 years for the control group. In the the rhBMP-2 group, 47 patients (32.9%) had used tobacco within 6 months before surgery compared with 49 patients (36%) in the control group. The percentage of patients with pending litigation was 12.6% and 16.2% in the rhBMP-2 and control groups, respectively. The percentage of patients seeking worker's compensation was 32.9% in the rhBMP-2 group and 34.6% in the control group.

Clinical and Radiographic Outcome Measurements. Patient assessments were completed preoperatively, during hospitalization, and postoperatively at 6 weeks and at 3, 6, 12, and 24 months. Clinical outcomes were assessed using neurologic status, work status, patient satisfaction, and Oswestry Low Back Pain Disability, back, leg, and graft site pain questionnaires.

Radiographs and computed tomography (CT) scans were used to evaluate fusion at 6, 12, and 24 months postoperatively. Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent radiologist was used to adjudicate conflicting fusion findings. Fusion was defined as: an absence of radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation less than 5° on flexion-extension radiographs, and continuous trabecular bone growth connecting the vertebral bodies. There was good agreement between the radiologists reviewing the studies. At 6, 12, and 24 months after surgery, agreement

between the independent reviewers was over 98%. Patients having secondary surgeries due to nonunions were considered as having failed fusions and were included as failures in all fusion calculations.

Clinical and Radiographic Follow-up. The rate of patient return for follow-up was high at all postoperative periods (Table 2). At 12 months, the rate of patient return for both treatment groups exceeded 96%. At 24 months, the follow-up rate for the investigational group was 92.5% and the control group rate was 90.8%.

Surgical Technique. All patients underwent the ALIF procedure through an open approach. Patients were placed in the supine position on the operating room table. Fluoroscopy was used throughout the surgical procedure. A vertical or transverse incision was made over the lumbosacral spine. A retroperitoneal exposure was carried out in 81% (226/279) of patients, and a transperitoneal exposure was used in 19% (53/279) of patients. The parasympathetic nerve complex was bluntly mobilized and retracted from the surgical field: electrocautery was not used during this portion of the surgical procedure. Segmental vessels were sequentially identified, ligated, and divided. The great vessels were mobilized exposing the anterior surface and lateral borders of the disc space. The mid-point of the disc space was identified with radiographic markers and fluoroscopy.

An incision was made in the anterior portion of the annulus, removing the anterior longitudinal ligament and the anteriolateral borders of the annulus fibrosus. Under direct visualization the entire contents of the disc space were removed including the nucleus pulposis and the cartilaginous endplates. Great care was taken to protect and preserve the bony vertebral endplates. The disc space was sequentially distracted to the height

of normal adjacent disc space height. A double barrel guide was inserted into the disc space and the bony endplates were precisely prepared with a reamer.

In the investigational group, each cage was filled with an rh-BMP-2 soaked collagen sponge. No autogenous bone grafts or local reamings were used in this group. The cages were sequentially inserted through the guide tube into the prepared intervertebral disc space. Cage placement was evaluated with fluoroscopy in both the anteroposterior and lateral dimensions. In the control group, two cage devices were packed with morcellized autogenous bone graft harvested from the iliac crest.

RESULTS

Surgery

The mean operative time in the investigational, or rhBMP-2, group (1.6 hours) was less than in the control group (2.0 hours) (Table 3). The average blood loss in the rhBMP-2 group was 109.3 ml as compared with 153.8 ml in the control group. The operative time and blood loss was less in the investigational group despite the fact that the more technically demanding and time consuming approach to the L4-L5 level was performed more frequently in the investigational group (25.9%, 37/143) than in the control group (23.5%, 32/136). The average hospital stay was similar in both groups (3.1 days for the investigational group vs. 3.3 days for the control group). There were no unanticipated device-related adverse events in either treatment group.

Complications

Vascular events. Eleven intraoperative vascular events occurred: 6 were in the investigational group (4.2%) and 5, in the control group (3.7%). The most common injury (6/11) was a laceration of the iliac vein. Two control group patients developed deep venous thrombosis and were treated with anticoagulation medications.

Retrograde ejaculation. Six male patients (4%, 6/146) complained of retrograde ejaculation after surgery. In these patients, the L5-S1 disc space was approached 5 times (83.3%, 5/6). A transperitoneal approach was used in 4 of the 6 patients (66.6%). This complication occurred in 13.3% (4/30) of the men who underwent a transperitoneal approach and occurred in only 1.8% (2/116) of men who underwent a retroperitoneal approach. In two patients, the retrograde ejaculation resolved by 12 months after surgery; one patient underwent a retroperitoneal approach, the other a transperitoneal approach.

Iliac crest graft site. In the control group, 8 adverse events related to harvesting of the iliac crest graft were identified in 8 patients (5.9%). These events included 3 injuries to the lateral femoral cutaneous nerve, 2 avulsion fractures of the anterior superior iliac spine, 1 infection and 1 hematoma. None required an additional surgery. There were no graft site adverse events in the investigational group since the use of rhBMP-2 precluded the need to harvest bone graft.

The level of postoperative pain and morbity associated with the iliac crest graft harvesting was measured using numeral rating scales for pain intensity and duration (Table 4). The highest levels of pain were noted immediately after surgery at 12.7 points

out of 20 points. By 24 months after surgery, the pain scores were reduced to an average of 1.8 points; however, **??** % patients still reported graft site discomfort and 16% were bothered by the appearance of graft site.

Clinical Outcomes

Oswestry Disability Questionnaire scores. The Oswestry Low Back Pain Disability Questionnaire measured pain associated with activities. The Oswestry Questionnaire was administered preoperatively as well as at each postoperative visit. At all postoperative time periods for both the investigational and the control treatment groups, the mean overall Oswestry scores were similar at the time periods for both treatment groups and consistently demonstrated improvements as compared with the preoperative scores (Table 5). At 24 months, the mean improvements in the Oswestry scores were 29.0 points in the investigational group and 29.5 points in the controls. In the rhBMP-2 group, 76.9% of patients showed an improvement of at least 15 points in their disability scores at 12 months postoperatively and compared favorably to 75.8% of patients in the control group. These success rates were maintained at 24 months with each group showing a 73% success rate.

Neurologic Status. Neurologic status of the patients was determined by evaluating four neurologic measurements: motor function, sensory function, deep tendon reflexes and sciatic tension signs. Values for each of the 4 subsets of objective findings were totaled and expressed as a percentage of the maximum possible score. Each measurement was compared with the patient's preoperative score. Neurologic success was based on demonstrating maintenance or improvement in all four neurologic measurements. At 12 and 24 months after surgery, the overall neurologic

success rates for the investigational group were 81.8% and 82.8% respectively as compared with 84.7% and 83.3% rates for the control group (Table 6).

Back Pain. Back pain intensity and duration were assessed using a 20-point numeric rating scale. Adding the numeric rating scores for back pain intensity and pain duration allowed examiners to derive a composite back pain score (Table 7). The mean back pain scores at all postoperative periods were improved from the preoperative mean values for both treatment groups. The mean improvements in back pain scores at both 12 and 24 months were greater for the investigational group than for the control autograft group.

Back pain success on an individual patient basis was determined by comparing the postoperative score with the preoperative score. Success was based on the patient having at least a 3-point improvement in back pain score after surgery (Table 8). At 12 and 24 months after surgery, the investigational group had back pain success rates of 79.1% and 74.6%, respectively. These rates were similar to the respective rates in the control group of 72.8% and 78.7%.

Leg Pain. Leg pain was assessed in a similar manner using a numeric rating scale for both the intensity and duration of painful symptoms. Mean leg pain scores improved significantly after surgery (Table 9). Outcomes were similar in both treatment groups. Leg pain success was defined as a function of the patient's preoperative complaints. If a patient had a preoperative pain score of 10 points or more, success was defined as a 3-point improvement on his or her postoperative scores. In those patients who had preoperative leg pain scores of less than 10 points, success was defined as maintenance or improvement in scores when compared with their preoperative

condition. At 12 months after surgery, the leg pain success rates were similar in both treatment groups. The investigational group had a success rate of 72.1% and the control group had success rate of 72.8%. At 24 months, the success rate in the investigational group improved to 80.3% and was higher than the 74.1% result in the control group.

Work Status. Many factors affect a patient's work status,such as the nature of the work performed and ability of the work place to accommodate work restrictions. The work status of the investigational patients was better than that of the control patients at most postoperative follow-up intervals (Table 10). For patients who were working prior to surgery, the median return to work time was 63.5 days in the investigational group and 64.5 days in the control group.

Patient Satisfaction. At 12 and 24 months after surgery, the results were similar in each treatment group. At 24 months, 81.2% of the investigational patients and 80.4% of the controls were satisfied with their surgical outcomes. In the investigational group, 82% said they would undergo surgery again compared with 76.7% of the control patients who would undergo surgery again. In the investigational group, 74.6% believed that they were helped as much as they had expected to be from the surgery; 76.6% of the control group felt they had been.

Radiographic Outcomes

Fusion status of the study patients was evaluated on plain radiographs and CT scans. At six months after surgery, 128 patients (97.0%) in the investigational group had evidence of interbody fusion compared with 115 patients (95.8 %) in the control group (Table 11). At 12 months, 125 patients (96.9 %) in the investigational group were fused.

The control group showed evidence of fusion in 111 patients (92.5%) at one year. At 24 months postoperatively, the investigational group had a 94.5% fusion rate almost a six-percentage point higher fusion rate that the control group (88.7%).

Secondary Surgical Procedures

In the investigational group, 11 patients (7.0%) had a second surgery and 14 patients (10.3%) in the control group had second surgeries. In the investigational group, two patients had implant removals: One removal occurred at 5 days after surgery, and the other at four months. In both patients, implant removal was necessitated by poor placement of the cage during the initial surgery. Eight investigational patients underwent supplemental fixation for pseudarthrosis, and one underwent supplemental fixation after posterior decompression for persistent radicular symptoms after the initial surgery. In the control group, 12 patients underwent supplemental posterior fixation for a pseudarthrosis and two underwent supplemental posterior fixation for persistent discogenic pain.

DISCUSSION

Spinal fusions can be performed anteriorly, posteriorly, or posterolaterally. Instrumentation can also be used to stabilize the spinal motion segment and promote fusion. Traditionally, fusions in the lumbar spine have been performed through a posterior approach. After a successful posterolateral lumbar spinal fusion, patients often have significant relief of their painful symptoms. However, the posterolateral approach

and the lateral exposure of the transverse processes of the lumbar spine can compromise the patient's functional outcome (13). The paraspinal muscles must be detached from the posterior spinal elements and transverse processes during the surgical exposure for the lateral fusion. This injury to the spinal muscles of the lumbar spine limits the patient's ultimate rehabilitation potential (1). Several studies have demonstrated significant loss of paraspinal muscle strength and muscle atrophy in patients with persistent back pain after posterolateral lumbar spinal fusion (12,18,22). The surgeon strips the paraspinal muscles from their anatomic attachments to the spine and then reattaches them to the lateral fusion mass and retained spinal elements. However, postoperative healing and scar tissue formation interferes with the normal independent function of the paravertebral muscle groups. The loss of their normal anatomic attachment sites, formation of scar tissue, and loss of independent muscle function compromise the paravertebral muscles.

At 12 months, the overall success rate (defined as fusion, neurological and Oswestry success, no second surgery failures, and no serious device related adverse events) was statistically equivalent between the two treatment groups. The investigational, or rhBMP-2, group had a 96.9% fusion rate at one year compared with 92.6% in the control group. This finding is important because the use of rhBMP-2 is associated with high fusion rates without the need for harvesting bone from the iliac crest, thereby eliminating the adverse effects and long-term symptoms associated with that procedure. RhBMP-2 is a promising method of facilitating anterior intervertebral spinal fusion and of decreasing pain and improving clinical outcomes after anterior lumbar fusion when used with the LT-CAGE™ device.

REFERENCES

1. Beimborn DS, Morrissey MC: A review of the literature related to trunk muscle performance. *Spine* 13:655-660, 1988.

2. Blumenthal SL, Baker J, Dossett A, Selby DK. The role of anterior lumbar fusion for internal disc disruption. Spine 1988;13:566-9.

3. Boden SD, Schimandle JH, Hutton WC. 1995 Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 1995;20:2633-44.

4. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25:376-81.

5. Boyd, L.M.; Estes, B.T. and Liu M. "Biomechanics of Lumbar Interbody Constructs, *Effect of Design and Materials*." Chirurgie Endoscopique et Mini-invasive du Rachis. Ed. Husson JL, LeHuec JC. Sauramps Médical. Montpelier, France. pp 181-92, 1999.

6. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. Neurosurg Focus 2001;10:1-9.

7. Crock HV. Anterior lumbar interbody fusion: indications for its use and notes on surgical technique. Clin Orthop 1982;165:157-63.

8. Flynn JC, Hoque MA. Anterior fusion of the lumbar spine. End result study with long-term follow-up. J Bone Joint Surg 1979;61A:1143-50.

9. Goldner JL, Urbaniak JR, McCollom DE: Anterior excision and interbody spinal fusion for chronic low back pain. *Orthop Clin North Am* 2:543-568, 1971

10. Harmon PH. Anterior excision and vertebral fusion operation for intervertebral disc syndromes of the lower lumbar spine: three to five year results in 244 cases. Clin Orthop 1963;26:107-27.

11. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999;24:629-36.

12. Jonsson B: The functions of individual muscles in the lumbar part of the spinae muscle. *Electromyography* 10:5-21, 1970.

13. Kahanovitz N, Viola K, Gallagher M: Long term strength assessment of postoperative diskectomy patients. *Spine* 14:402-403,1989.

14. Lane JD, Moore ES. Transperitoneal approach to the intervertebral disc in the lumbar area. Annals of Surgery 1948;127:537-51.

15. Loguidice VA, Johnson RG, Guyer RD, Stith WJ, Ohnmeiss DD, Hochschuler SH, Rashbaum RF. Anterior lumbar interbody fusion. Spine 1988;13:366-9.

16. Leong JC, Chun SY, Grange WJ, Fang D: Long-term results of lumbar intervertebral disc prolapse. Spine 1983;8:793-9.

17. Penta M, Sandhu A, Fraser RD: Magnetic resonance imaging assessment of disc degeneration 10 years after anterior lumbar interbody fusion. *Spine* 20: 743-747, 1995.

18. Rantanen J, Hurme M, Falck B, Alaranta H, Nykvist F, Lehto M, Einola S, Kalimo H: The lumbar multifidus muscle five years after surgery for a lumbar intervertebral disc herniation. *Spine* 18:568-574, 1993.

19. Sacks S. Anterior interbody fusion of the lumbar spine. J Bone Joint Surg [Br] 1965;47:211-23.

20. Sandhu HS, Kanim LEA, Toth JM, et al. Experimental spinal fusion with recombinant human bone morphogenetic protein-2 without decortication of osseous elements. Spine 1997;22:1171-80.

21. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995; 20:1326-37.

22. Sihvonen T, Herno A, Paljarvi L, Airaksinen O, Partanen J, Tapaninaho A: Local denervation atrophy of paraspinal muscles in postoperative failed back syndrome. *Spine* 18:575-581, 1993.

23. Stauffer RN, Coventry MB. Anterior interbody lumbar spine fusion. J Bone Joint Surg [Am]1972;54:756-68.

24. Urist MR. Bone: Formation by autoinduction. Science 1965;150:893-9.

Table 1. Patient Data

Variable	Investigational (n=143)	Control (n=136)	P value *
Age (yrs.)			
n	143	136	0.369
Mean	43.3	42.3	
Weight (lbs.)			
n	143	134	0.639
Mean	179.1	181.1	
Sex [n (%)]			
Male	78 (54.5)	68 (50.0)	0.473
Female	65 (45.5)	68 (50.0)	
Workers' Compensation [n (%)]	47 (32.9)	47 (34.6)	0.801
Spinal Litigation [n (%)]	18 (12.6)	22 (16.2)	0.400
Tobacco Used [n (%)]	47 (32.9)	49 (36.0)	0.615
Preop Work Status [n (%)]	68 (47.6)	50 (36.8)	0.071
Working			

*For continuous variables, P values are from ANOVA. For categorical variables, P values are from Fisher's exact test or chi-square test.

Table 2. Patient Accountability

Investigational Group

	Preop	Surgery	6 Weeks	3 Months	6 Months	12 Months	24 Months
Theoretical							
Follow-up[1]	143	143	143	143	143	143	143
Deaths	0	0	0	0	0	0	0
(Cumulative)							
Failures[2]	0	0	1 (1)	0 (1)	3 (4)	1 (5)	4 (9)
(Cumulative)							
Expected[3]	143	143	142	142	139	138	133
Number Evaluated	143	143	141	141	137	133	123
Percent Follow-up	100.0%	100.0%	99.3%	99.3%	98.6%	96.4%	92.5%

Control Group

	Preop	Surgery	6 Weeks	3 Months	6 Months	12 Months	24 Months
Theoretical							
Follow-up[1]	136	136	136	136	136	136	136
Deaths	0	0	0	0	0	1	1
(Cumulative)							
Failures[2]	0	0	0	0	1 (1)	4 (5)	7 (12)
(Cumulative)							
Expected[3]	136	136	136	136	135	130	120
Number Evaluated	136	136	134	134	133	126	109
Percent Follow-up	100.0%	100.0%	98.5%	98.5%	98.5%	96.9%	90.8%

[1] Theoretical = Patients who have entered the follow-up window.
[2] Failures include device removals, revisions and supplemental fixations.
[3] Expected = Theoretical – Cumulative Deaths – Cumulative Failures

Table 3. Surgery Information

Variable	Investigational (n=143)	Control (n=136)
Operative Time (hrs)		
n	143	136
Mean	1.6	2.0
Blood Loss (ml)		
n	142	136
Mean	109.8	153.1
Hospital Stay (days)		
n	143	136
Mean	3.1	3.3
Treatment Levels [n (%)]		
L4-L5	37 (25.9)	32 (23.5)
L5-S1	106 (74.1)	103 (75.7)
L5-L6	0 (0.0)	1 (0.7)
Operative Approach [n (%)]		
Retroperitoneal	116 (81.1)	110 (80.1)
Transperitoneal	27 (18.9)	26 (19.1)

TABLE 4. Iliac Crest Graft Site Pain and Appearance Scores

Period	Variable	Control
Discharge	Pain Score	
	n	134
	Mean	12.7
	P value[1]	<0.001
	Appearance of Graft Site	
	Poor[2]	13 (9.8)
6 Weeks	Pain Score	
	n	132
	Mean	6.7
	P value	<0.001
	Appearance of Graft Site	
	Poor	5 (3.8)
3 Months	Pain Score	
	n	134
	Mean	3.5
	P value	<0.001
	Appearance of Graft Site	
	Poor	3 (2.3)
6 Months	Pain Score	
	n	132
	Mean	2.6
	P value	<0.001
	Appearance of Graft Site	
	Poor	5 (3.8)
12 Months	Pain Score	
	n	130
	Mean	2.1
	P value	<0.001
	Appearance of Graft Site	
	Poor	5 (3.8)
24 Months	Pain Score	
	n	117
	Mean	1.8
	P value	<0.001
	Appearance of Graft Site	
	Poor	3 (2.6)

[1] P values are from Student's *t* test comparing mean with zero.
[2] Poor= "It bothers me very much."

TABLE 5 – Oswestry Low Back Pain Disability Scores

Period	Variable	Investigational	Control
Preoperative			
	n	143	136
	Mean	53.7	55.1
6 Weeks			
	n	140	131
	Mean	42.1	41.4
Improvement from Preoperative			
	Mean	11.4	13.6
	P value[1]	<0.001	<0.001
3 Months			
	n	141	134
	Mean	33.5	34.2
Improvement from Preoperative			
	Mean	19.9	20.8
	P value	<0.001	<0.001
6 Months			
	n	136	131
	Mean	29.3	29.4
Improvement from Preoperative			
	Mean	24.4	25.4
	P value	<0.001	<0.001
12 Months			
	n	130	125
	Mean	25.5	25.6
Improvement from Preoperative			
	Mean	27.7	28.9
	P value	<0.001	<0.001
24 Months			
	n	122	108
	Mean	23.9	23.8
Improvement from Preoperative			
	Mean	29.0	29.5
	P value	<0.001	<0.001

[1]

TABLE 6. Neurologic Outcomes

Period	Variable	Investigational (n=143) n (%)	Control (n=136) n (%)
6 Weeks	Overall		
	Success	110 (80.3)	108 (83.7)
	Failure	27 (19.7)	21 (16.3)
3 Months	Overall		
	Success	119 (84.4)	103 (77.4)
	Failure	22 (15.6)	30 (22.6)
6 Months	Overall		
	Success	106 (77.9)	106 (80.9)
	Failure	30 (22.1)	25 (19.1)
12 Months	Overall		
	Success	108 (81.8)	105 (84.7)
	Failure	24 (18.2)	19 (15.3)
24 Months	Overall		
	Success	101 (82.8)	90 (83.3)
	Failure	21 (17.2)	18 (16.7)

TABLE 7. Back Pain Outcomes

Period	Variable	Investigational	Control
Preoperative			
	n	143	136
	Mean	15.8	16.1
7 Weeks			
	n	139	132
	Mean	9.3	8.8
Improvement from Preoperative			
	Mean	6.5	7.4
	P value[1]	<0.001	<0.001
4 Months			
	n	140	134
	Mean	8.7	9.0
Improvement from Preoperative			
	Mean	7.1	7.1
	P value	<0.001	<0.001
7 Months			
	n	136	131
	Mean	8.6	8.9
Improvement from Preoperative			
	Mean	7.3	7.1
		<0.001	<0.001

13 Months			
	n	129	125
	Mean	8.0	8.4
Improvement from Preoperative			
	Mean	7.8	7.6
	P value	<0.001	<0.001
25 Months			
	n	122	108
	Mean	7.3	7.9
Improvement from Preoperative			
	Mean	8.4	8.1
	P value	<0.001	<0.001

TABLE 8. Back Pain Success Rates

Variable	Investigational n (%)	Control n (%)
6 Weeks		
Success	107/139 (77.0)	101/132 (76.5)
Failure	32/139 (23.0)	31/132 (23.5)
3 Months		
Success	103/140 (73.6)	105/134 (78.4)
Failure	37/140 (26.4)	29/134 (21.6)
6 Months		
Success	106/136 (77.9)	94/131 (71.8)
Failure	30/136 (22.1)	37/131 (28.2)
12 Months		
Success	102/129 (79.1)	91/125 (72.8)
Failure	27/129 (20.9)	34/125 (27.2)
24 Months		
Success	91/122 (74.6)	85/108 (78.7)
Failure	31/122 (25.4)	23/108 (21.3)

TABLE 9. Leg Pain Scores

Period	Variable	Investigational	Control
		n = 143	n = 136
Preoperative			
	n	143	136
	Mean	12.5	12.5
6 Weeks			
	n	139	132
	Mean	7.5	8.4
Improvement from Preoperative	n	139	132
	Mean	5.1	4.1
	P value[1]	<0.001	<0.001
3 Months			
	n	140	134
	Mean	6.8	6.8
Improvement from Preoperative	n	140	134
	Mean	5.6	5.6
	P value	<0.001	<0.001
6 Months			
	n	136	131
	Mean	6.3	6.3
Improvement from Preoperative	n	136	131
	Mean	6.4	6.3

	P value	<0.001	<0.001
12 Months			
	n	129	125
	Mean	6.3	6.6
Improvement from Preoperative	n	129	125
	Mean	6.4	5.6
	P value	<0.001	<0.001
24 Months			
	n	122	108
	Mean	6.3	6.3
Improvement from Preoperative	n	122	108
	Mean	6.5	5.9
	P value	<0.001	<0.001

[1] P values for change from preoperative in each group are from paired test.

TABLE 10. Return To Work Status

Period	Variable	Investigational n (%)	Control n (%)
3 Months	Working	54 (38.3)	38 (28.4)
	Not Working	42 (29.8)	43 (32.1)
	Was Not Working Before Surgery	45 (31.9)	53 (39.6)
6 Months	Working	69 (50.7)	60 (45.5)
	Not Working	25 (18.4)	29 (22.0)
	Was Not Working Before Surgery	42 (30.9)	43 (32.6)
12 Months	Working	72 (55.0)	63 (50.4)
	Not Working	20 (15.3)	19 (15.2)
	Was Not Working Before Surgery	39 (29.8)	43 (34.4)
24 Months	Working	80 (66.1)	60 (56.1)
	Not Working	11 (9.1)	13 (12.1)
	Was Not Working Before Surgery	30 (24.8)	34 (31.8)

Table 11. Rates of Radiographic Fusion [Number (%) of Patients]

Variable	Investigational (n=143) n (%)	Control (n=136) n (%)
6 Months		
Success	128/132 (97.0)	115/120 (95.8)
Failure	4/132 (3.0)	5/120 (4.2)
12 Months		
Success	127/131 (96.9)	112/121 (92.6)
Failure	4/131 (3.1)	9/121 (7.4)
24 Months		
Success	120/127 (94.5)	102/115 (88.7)
Failure	7/127 (5.5)	13/115 (11.3)

From: Neil Beals
Sent: Wednesday, October 31, 2001 01:49:27 PM
To: 'JKB[redacted]
CC: 'Peter Wehrly'[redacted]; 'Clark Charlton[redacted]; McKay, Bill
BCC: Hood, Tara
Subject: RE: Open LT Cage BMP paper

Ken:

I sincerely appreciate your initiative to develop this draft and keep us going in the right direction. I have reviewed the draft and made a number of comments. As with anything, it will be best for us to discuss these points but I thought it would be worthwhile to pass along my initial comments. Again, these are strictly from me and many of them are intended to prompt discussion. I'm sure others who review this will have separate (and often better) ideas. Our hope is that the final outcome is a landmark paper. Hopefully we will find time at NASS to go over these.

Thanks again.

[We may have already discussed these points by the time you are able to pick up this email but I thought I would go ahead and convey some initial thoughts.]

Some GENERAL COMMENTS
1) I think we'll need to devise some means of tracking edits made by various individuals; given the scope of this paper, we will want to review with a number of people for accuracy and to solicit different perspectives and sometimes it is confusing to those involved as to which draft is being reviewed - any thoughts how we can best manage this process?

2) current draft refers to InFUSE as rhBMP-2 while usually referencing only LT Cage (instead of a more generic descriptor); I recommend some consistency, either using generic terms like rhBMP-2/ACS and tapered metal cage or tradenames; arguments can be made either way but I think we should establish agreed upon approach

3) I think bigger deal should be made of elimination of donor site pain with InFUSE; this is not referenced in summary and not really emphasized in paper (so far); I would put that front and center in results, discussion, and conclusion so that "equivalent" results aren't received as a let down

4) I'm not sure about the use of FDA-defined success rates in this paper; do most surgeons relate to these? can we establish other means of defining success in this study?

5) we should probably discuss key points to be made in this paper and the order of their importance or sequence they are presented in paper; my initial thoughts are:

- quality of study

- surgery data findings
- elimination of donor site pain
- clinical outcomes
- work status
- fusion/radiographic findings
- safety/ antibody results

6) could use more references

Comments for DISCUSSION Section
Points which I think would be of interest to expand on in discussion include:
1) study protocol and design
2) ALIF procedure and use of stand alone cages
3) quality of study - note demographics and closeness of each group to one another
4) quality of study - % f/u
5) surgery data and findings including stat sig differences (or time, blood loss) and trends (hospital stay) with explanations and implications

6) operative approach and incidence of retrograde ejac with explanation and implications
7) donor site pain - significance of this finding (first prospective study?) and its implications
8) clinical outcomes (Oswestry, SF-36, BP, LP) - note trends with graphs and discuss implications
9) success factors - discuss how success is measured and relevance of these data
10) work status findings and implications
11) fusion results showing trends with InFUSE - explanation and implications
12) value of CTs in assessing fusion supported with examples from study; significance of their use and serial review showing bone formation and remodeling

13) immune response - review antibody data and explain findings and implications

Additional DISCUSSION points
1) Address safety of rhBMP-2 and InFUSE specifically systemic effects, toxicity, and BSE concerns with ACS
2) address bone formation and issue or concern of extra bone formation supported by this study
3) cite various unknowns and future research direction based upon findings from this study

thanks Ken. Neil

-----Original Message-----
From: JKE[redacted] [SMTP[redacted]
Sent: Friday, October 26, 2001 7:02 PM
To: Neil Beals; Peter Wehrly; Clark Charlton
Subject: Fw: Open LT Cage BMP paper

Here is an update on the two papers already submitted to SPINE.

I gave my first draft of the open LT BMP paper to a Hughston medical writer to review. I hope to work on the manuscript some more this weekend. In any event, I will have an early edited first draft version of the Open BMP LT study at the SIRG meeting at NASS. I hope to discus with you what should be done with the 20 grand.

Best,
Ken
----- Original Message -----
From: Carol Binns <mailto:[redacted]
To: Burkus, MD, J Kenneth <[redacted]
Sent: Friday, October 26, 2001 6:05 PM
Subject: Open LT Cage BMP paper

Dr. Burkus,
I am still working on the paper and will have it to you before the weekend is over.

I called SPINE today regarding your other 2 submissions. "Clinical and Radiographic Outcomes of ALIF using rhBMP-2" has been through the review process but Dr. Weinstein wanted to send it to additional reviewers. Sounds like there may have been some disagreement among them. The second set of reviews are due next week. With regard to the status of "Radiographic Assessment of Interbody Fusion Using rhBMP-2", those reviews are due in the editorial office 11/12.

Carol Binns
Medical Writer
Hughston Sports Medicine Foundation

From: JKE[redacted]
Sent: Tuesday, November 27, 2001 05:52:39 AM
To: Peter Wehrly[redacted]; Bailey Lipscomb[redacted]; Neil Beals[redacted]; Tara Hood[redacted]; Clark Charlton[redacted]
Subject: LT BMP manuscript

Attachments: LT BMP Paper.3.doc

Sirs and Ma'am

I want to make it perfectly clear that there is NO WAY that Tennessee is a top ten Team let alone should be ranked in the top five. Now, I do not like Florida all that much BUT I do not think that Tennessee will be ranked in the top 25 after this weekend. Look at it this way at least Tennessee with NOT have to get beat by Auburn in the SEC Title Game with the loss this weekend.

War Eagle

I have attached the last LT BMP Draft. I would like to finish all the major work on the paper this weekend. Hell there ain't no good games to watch on TV.

A Prospective, Randomized Lumbar Fusion Study using rhBMP-2 with Tapered Interbody Cages

Matthew F. Gornet MD*

J. Kenneth Burkus MD†

Curtis Dickman, MD‡

Thomas A. Zdeblick MD§

*Staff Physician, Missouri Bone and Joint Institute, St. Louis, Missouri

†Staff Physician, Spine Service, The Hughston Clinic, P.C., Columbus, Georgia

‡Barrows Institute, Phoenix, Arizona

§Chairman, Department of Orthopaedic Surgery, University of Wisconsin, Madison, Wisconsin

Address correspondence and reprint requests to J.K. Burkus, MD, The Hughston Clinic, [redacted]

ABSTRACT

Study Design. In a multi-center, prospective, randomized, nonblinded, 2-year study, 279 patients who a single-level anterior lumbar interbody fusion with a cylindrical tapered fusion cages were randomized into two groups: one received autogenous iliac crest bone graft, the other, recombinant human bone morphogenetic protein-2 (rhBMP-2) on a collagen sponge carrier.

Objectives. The objective of the study was to determine the clinical and radiographic outcomes in patients treated for single-level degenerative lumbar disc disease with a stand-alone anterior interbody fusion using tapered threaded titanium fusion cages with autogenous bone graft or rhBMP-2 and an absorbable collagen sponge carrier.

Summary of Background Data. In a small series of human patients undergoing anterior lumbar interbody fusion with a tapered titanium fusion cage, rhBMP-2 has been shown to promote osteoinduction and fusion.

Methods. In this prospective nonblinded study, 279 patients were randomly divided into 2 groups which underwent interbody fusion using two tapered threaded cages: the investigational group (143 patients) included the use of rhBMP-2 on an absorbable collagen sponge, and a control group (136 patients) autogenous iliac crest bone graft. Clinical outcomes were assessed using neurologic status, work status, and Oswestry Low Back Pain Disability scores and back and leg pain questionnaires. Plain radiographs and computed tomographic scans were used to evaluate fusion at 6,12 and 24 months postoperatively.

Results. The mean operative time and blood loss was less in the investigational rhBMP-2 group (1.6 hours and 109.8 ml.) than in the autograft control group (2.0 hours

and 153.1 ml.). At 24 months, the investigational group fusion rate of 94.5% remained higher than the control at 88.7%. At all postoperative intervals, the mean Oswestry, back pain, and leg pain scores and neurologic status improved in both treatment groups compared with preoperative scores and were similar in both groups. In the control group, 8 adverse events related to harvesting of the iliac crest graft were identified in 8 patients (5.9%) and at 24 months following surgery, 32% patients still reported graft site discomfort and 16% were bothered by the appearance of graft site.

Conclusions. The investigational patient group had shorter operative times and less blood loss. At 24 months, this group had a fusion rate that was nearly 6 percentage points greater than the control autograft group with a probability of superiority of 90.2 percent. Overall results show that the use of rhBMP-2 can eliminate the need for harvesting iliac crest graft for successful lumbar fusions.

Key words: anterior lumbar interbody fusion, bone morphogenetic protein, osteoinduction, radiography, interbody fusion cages

Key points:

- Fusion rates for both treatment groups were high at all studied intervals. At 24 months, the rate of fusion for patients treated with rhBMP-2 was nearly 6 percentage points higher on average (94.5% vs. 88.7%) than with those patients treated with autograft with a probability of superiority of 90.2 percent.
- The average operative time was1.6 hours for those patients treated with rhBMP-2 as compared to 2.0 hours in the autograft group. This result was statistically different.
- Operative times and blood loss were less for those patients treated with rhBMP-2 compared with those patients who underwent iliac crest bone graft harvesting.
- At all postoperative time periods, patients in both treatment group showed improvement in Oswestry disability scores, in neurologic status and in back and leg pain outcomes.
- The use of rhBMP-2 in anterior lumbar interbody fusion procedures eliminates the complications of iliac crest bone harvesting including postoperative pain and scaring.

Précis

In a 2-year prospective randomized study of 279 patients, the investigational group that received rhBMP-2 with the tapered cage device had a higher rate of fusion, reduced operative times, and decreased blood loss when compared to the control group that received autogenous bone graft with the LT-CAGE device. The rhBMP-2 group had no complications or complaints arising from an iliac crest bone harvesting procedure.

INTRODUCTION

Degenerative changes within a lumbar spinal motion segment are, in part, evidenced by the presence of radial tears or fissures in the annulus fibrosus, disc space desiccation and collapse, and the formation of radial osteophytes. These morphologic changes within the spinal motion segment can lead to loss of the intervertebral disc's ability to accommodate normal biomechanical stresses and can cause pain. Fusion of the degenerative and unstable spinal motion segment can give significant relief from this disabling and often progressive condition (2,7,9).

Anterior lumbar interbody fusion (ALIF) is an effective treatment for patients with symptomatic degenerative disc disease. Lumbar spine stabilization procedures that do not interfere with the posterior spinal muscles have some significant advantages (9,10,14-16,19). The anterior approach to the lumbosacral spine enables the surgeon to expand the disc space and re-establish the normal anatomic alignment and relationships of the spinal motion segment while avoiding injury to the posterior paravertebral muscles. The anterior approach also retains all posterior-stabilizing structures and avoids epidural scarring and perineural fibrosis. Adjacent segment degeneration in the lumbar spine after anterior interbody fusion may also be reduced (17).

Stand-alone ALIF procedures using autogenous bone grafts alone has been associated with high rates of pseudarthrosis, graft subsidence, and graft extrusion (8,23). Supplemental posterior segmental spinal instrumentation has been advocated to stabilize interbody grafts and increase rates of fusion. Recently, cylindrical, threaded

intervertebral devices with autogenous bone grafts have been shown to stabilize a lumbar motion segment after anterior discectomy. Their use has lead to high rates of fusion and to improved clinical outcomes (4).

In non-human primate animal models, recombinant human bone morphogenetic protein 2 (rhBMP-2) applied to an absorbable collagen sponge carrier has been shown to promote osteoinduction and fusion after ALIF (11). In a small series of human patients who underwent stand-alone ALIF with tapered fusion cages the use of rhBMP-2 applied a collagen sponge was also shown to promote osteoinduction and fusion (4). To further evaluate this method, we evaluated the clinical and radiographic outcomes at 24 months of 279 patients who underwent a single level ALIF. We compared the outcomes in the investigational patients (rhBMP-2) with those in the control patients (autogenous bone).

MATERIALS AND METHODS

Study *Design.* Between August 1998 and July 1999, 279 patients were enrolled in this prospective, randomized, nonblinded, FDA approved study at 16 investigational sites. All patients underwent a single level anterior lumbar fusion with the LT-CAGE™ device (LT-CAGE™ devices; Medtronic Sofamor Danek, Memphis, TN). Patients were randomized in a 1:1 manner into two groups: the investigational group received rhBMP-2 on an absorbable collagen sponge carrier and the control group received autogenous iliac crest bone graft. InFUSE Bone Graft™ (Medtronic Sofamor Danek, Memphis, TN)

is the trademarked name for recombinant human bone morphogenetic protein 2 applied to an absorbable collagen sponge.

Patient Data. Preoperatively, all patients had symptomatic, single-level degenerative lumbar disc disease and symptoms of disabling low back or leg pain, or both of at least 6 months' duration that had not responded to nonoperative treatments. The two treatment groups were very similar demographically, and there were no statistically significant differences ($P < 0.05$) for any of the variables (Table 1). The rhBMP-2 group consisted of 143 patients and the control group consisted of 136 patients. The average age at surgery was 43.3 years for the rhBMP-2 group and 42.3 years for the control group. In the rhBMP-2 group, 47 patients (32.9%) had used tobacco within 6 months before surgery compared with 49 patients (36%) in the control group. The percentage of patients with pending litigation was 12.6% and 16.2% in the rhBMP-2 and control groups, respectively. The percentage of patients seeking worker's compensation was 32.9% in the rhBMP-2 group and 34.6% in the control group.

Clinical and Radiographic Outcome Measurements. Patient assessments were completed preoperatively, during hospitalization, and postoperatively at 6 weeks and at 3, 6, 12, and 24 months. Clinical outcomes were assessed using neurologic status, work status, patient satisfaction, and Oswestry Low Back Pain Disability, back, leg, and graft site pain questionnaires.

Radiographs and computed tomography (CT) scans were used to evaluate fusion at 6, 12, and 24 months postoperatively . Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent, blinded radiologist was used to adjudicate conflicting fusion findings. Fusion was defined as: an absence of

radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation less than 5° on flexion-extension radiographs, and continuous trabecular bone growth connecting the vertebral bodies (6). There was good agreement between the radiologists reviewing the studies. At 6, 12, and 24 months after surgery, agreement between the independent reviewers was over 98%. Patients having secondary surgeries due to persistent low back symptoms and clinically suspected nonunions were considered as having failed fusions and were included as failures in all fusion calculations, regardless of their independent radiologic assessment.

Clinical and Radiographic Follow-up. The rate of patient return for follow-up was high at all postoperative periods (Table 2). At 12 months, the rate of patient return for both treatment groups exceeded 96%. At 24 months, the follow-up rate for the investigational group was 92.5% and the control group rate was 90.8%.

Surgical Technique. All patients underwent the ALIF procedure through an open approach. Patients were placed in the supine position on the operating room table. Fluoroscopy was used throughout the surgical procedure. A vertical or transverse incision was made over the lumbosacral spine. A retroperitoneal exposure was carried out in 81% (226/279) of patients, and a transperitoneal exposure was used in 19% (53/279) of patients. The parasympathetic nerve complex was bluntly mobilized and retracted from the surgical field: electrocautery was not used during this portion of the surgical procedure. Segmental vessels were sequentially identified, ligated, and divided. The great vessels were mobilized exposing the anterior surface and lateral borders of the disc space. The mid-point of the disc space was identified with radiographic markers and fluoroscopy.

An incision was made in the anterior portion of the annulus, removing the anterior longitudinal ligament and the anteriolateral borders of the annulus fibrosus. Under direct visualization the entire contents of the disc space were removed including the nucleus pulposis and the cartilaginous endplates. Great care was taken to protect and preserve the bony vertebral endplates. The disc space was sequentially distracted to the height of normal adjacent disc space height. A double barrel guide was inserted into the disc space and the bony endplates were precisely prepared with a reamer.

In the investigational group, each cage was filled with a rhBMP soaked collagen sponge. No autogenous bone grafts or local reamings were used in this group. The cages were sequentially inserted through the guide tube into the prepared intervertebral disc space. Cage placement was evaluated with fluoroscopy in both the anteroposterior

and lateral dimensions. In the control group, two cage devices were packed with morcellized autogenous bone graft harvested from the iliac crest.

Postoperatively, patients were placed in a soft lumbar corset. Activities were advanced by the treating physician. Isometric strengthening and exercise program were started at six weeks postoperatively.

RESULTS

Surgery

The mean operative time in the investigational rhBMP-2 group (1.6 hours) was less than in the control group (2.0 hours) (Table 3). The average blood loss in the rhBMP-2 group was 109.3 ml as compared with 153.8 ml in the control group. The operative time and blood loss was less in the investigational group despite the fact that the more technically demanding and time consuming approach to the L4-L5 level was performed more frequently in the investigational group (25.9%, 37/143) than in the control group (23.5%, 32/136). The average hospital stay was similar in both groups (3.1 days for the investigational group vs. 3.3 days for the control group). There were no unanticipated device-related adverse events in either treatment group.

Complications

Vascular events. Eleven intraoperative vascular events occurred: 6 were in the rhBMP group (4.2%) and 5, in the autograft group (3.7%). The most common injury (6/11) was a laceration of the iliac vein. Two control group patients developed deep venous thrombosis and were treated with anticoagulation medications.

Retrograde ejaculation. Six male patients (4.1%, 6/146) complained of retrograde ejaculation after surgery. In these patients, the L5-S1 disc space was approached 5 times (83.3%, 5/6). A transperitoneal approach was used in 4 of the 6 patients (66.6%). This complication occurred in 13.3% (4/30) of the men who underwent a transperitoneal approach and occurred in only 1.8% (2/116) of men who underwent a retroperitoneal approach. In two patients, the retrograde ejaculation resolved by 12 months after surgery; one patient underwent a retroperitoneal approach, the other a transperitoneal approach.

Iliac crest graft site. In the control group, 8 adverse events related to harvesting of the iliac crest graft were identified in 8 patients (5.9%). These events included 3 injuries to the lateral femoral cutaneous nerve, 2 avulsion fractures of the anterior superior iliac spine, 1 infection and 1 hematoma. None required an additional surgery. There were no graft site adverse events in the investigational group since the use of rhBMP-2 precluded the need to harvest bone graft.

The level of postoperative pain and morbidity associated with the iliac crest graft harvesting was measured using numeric rating scales for pain intensity and duration (Table 4). After surgery, all of the control patients experienced hip donor site pain. The highest levels of pain were noted immediately after surgery at 12.7 points out of 20

points. The percentage of patients experiencing pain decreased over time; however, at 24 months after surgery, nearly one-third of the control patients (32%) still experienced pain. At two years, the graft site pain scores averaged 1.8 points and, in addition, 16% of the control patients were bothered by the appearance of graft site.

Clinical Outcomes

Oswestry Disability Questionnaire scores. The Oswestry Low Back Pain Disability Questionnaire measured pain associated with activities. The Oswestry Questionnaire was administered preoperatively as well as at each postoperative visit. At all postoperative time periods for both the investigational and the control treatment groups, the mean overall Oswestry scores were similar at the time periods for both treatment groups. At all postoperative visits, both treatment groups demonstrated statistical improvements as compared with the preoperative scores that were maintained through two years (Table 5). At 24 months, the mean improvements in the Oswestry scores were 29.0 points in the investigational group and 29.5 points in the controls. In the rhBMP-2 group, 76.9% of patients showed an improvement of at least 15 points in their disability scores at 12 months postoperatively and compared favorably to 75.8% of patients in the control group.

Neurologic Status. Neurologic status of the patients was determined by evaluating four neurologic measurements: motor function, sensory function, deep tendon reflexes and sciatic tension signs. Values for each of the 4 subsets of objective findings were totaled and expressed as a percentage of the maximum possible score. Each measurement was compared with the patient's preoperative score. Neurologic success was based on demonstrating maintenance or improvement in all four

neurologic measurements. At 12 and 24 months after surgery, the overall neurologic success rates for the investigational group were 81.8% and 82.8% respectively as compared with 84.7% and 83.3% rates for the control group (Table 6).

Back Pain. Back pain intensity and duration were assessed using a 20-point numeric rating scale. Adding the numeric rating scores for back pain intensity and pain duration allowed examiners to derive a composite back pain score (Table 7). The mean back pain scores at all postoperative periods were improved from the preoperative mean values for both treatment groups. The mean improvements in back pain scores at both 12 and 24 months were greater for the investigational group than for the control autograft group.

Back pain success on an individual patient basis was determined by comparing the postoperative score with the preoperative score. Success was based on the patient having at least a 3-point improvement in back pain score after surgery (Table 8). At 12 and 24 months after surgery, the investigational group had back pain success rates of 79.1% and 74.6%, respectively. These rates were similar to the respective rates in the control group of 72.8% and 78.7%.

Leg Pain. Leg pain was assessed in a similar manner using a numeric rating scale for both the intensity and duration of painful symptoms. Mean leg pain scores improved significantly after surgery (Table 9). Outcomes were similar in both treatment groups. Leg pain success was defined as a function of the patient's preoperative complaints. If a patient had a preoperative pain score of 10 points or more, success was defined as a 3-point improvement on his or her postoperative scores. In those patients who had preoperative leg pain scores of less than 10 points, success was

defined as maintenance or improvement in scores when compared with their preoperative condition. At 12 months after surgery, the leg pain success rates were similar in both treatment groups. The investigational group had a success rate of 72.1% and the control group had success rate of 72.8%. At 24 months, the success rate in the investigational group improved to 80.3% and was higher than the 74.1% result in the control group.

Work Status. Many factors affect a patient's work status, such as the nature of the work performed and ability of the work place to accommodate work restrictions. The work status of the investigational patients was better than that of the control patients at most postoperative follow-up intervals (Table 10). For patients who were working prior to surgery, the median return to work time was 63.5 days in the investigational group and 64.5 days in the control group. More people in both treatment groups were working at the two-year follow-up than were working prior to their surgery. At last follow-up, in the investigational group, 80 patients were employed while only 54 were employed prior to surgery. Similarly, in the control group, 38 were working prior to surgery and 60 were working at two years following surgery.

Patient Satisfaction. At 12 and 24 months after surgery, the results were similar in each treatment group. At 24 months, 81.2% of the investigational patients and 80.4% of the controls were satisfied with their surgical outcomes. In the investigational group, 82% said they would undergo surgery again compared with 76.7% of the control patients who would undergo surgery again. In the investigational group, 74.6% believed that they were helped as much as they had expected to be from the surgery; 76.6% of the control group felt they had been.

Radiographic Outcomes

Fusion status of the study patients was evaluated on plain radiographs and CT scans (Figs. 1-3). At six months after surgery, 97.0% of patients in the investigational group had evidence of interbody fusion compared with 115 patients (95.8 %) in the control group (Table 11). At 12 months, 125 patients (96.9 %) in the investigational group were fused. The control group showed evidence of fusion in 111 patients (92.5%) at one year. At 24 months postoperatively, the investigational group had a 94.5% fusion rate almost a six-percentage point higher fusion rate that the control group (88.7%).

Secondary Surgical Procedures

In the investigational group, 11 patients (7.0%) had a second surgery and 14 patients (10.3%) in the control group had second surgeries. In the investigational group, two patients had implant removals: One removal occurred at 5 days after surgery, and the other at four months. In both patients, implant removal was necessitated by poor placement of the cage during the initial surgery. Eight investigational patients underwent supplemental fixation for presumed pseudarthrosis, and one underwent supplemental fixation after posterior decompression for persistent radicular symptoms after the initial surgery. In the control group, 12 patients underwent supplemental posterior fixation for a presumed pseudarthrosis and two underwent supplemental posterior fixation for persistent discogenic pain. In **??? percent** (??/22) of these cases (**??**/9 in the investigational group and **??**/13 in the control group) the fusion was radiographically solid but posterior instrumentation was inserted by the treating physician based upon clinical symptoms of persistent pain. In **??** percent of these cases, pain improved following the secondary posterior surgical procedure.

DISCUSSION

Spinal fusions can be performed anteriorly, posteriorly, or posterolaterally. Instrumentation can also be used to stabilize the spinal motion segment and promote fusion. Traditionally, fusions in the lumbar spine have been performed through a posterior approach. After a successful posterolateral lumbar spinal fusion, patients often have significant relief of their painful symptoms. However, the posterolateral approach and the lateral exposure of the transverse processes of the lumbar spine can compromise the patient's functional outcome (13). The paraspinal muscles must be detached from the posterior spinal elements and transverse processes during the surgical exposure for the lateral fusion. This injury to the spinal muscles of the lumbar spine limits the patient's ultimate rehabilitation potential (1). Several studies have demonstrated significant loss of paraspinal muscle strength and muscle atrophy in patients with persistent back pain after posterolateral lumbar spinal fusion (12,18,22). The surgeon strips the paraspinal muscles from their anatomic attachments to the spine and then reattaches them to the midline fascia and retained spinal elements. However, postoperative healing and scar tissue formation interferes with the normal independent function of the paravertebral muscle groups. The loss of their normal anatomic attachment sites, formation of scar tissue, and loss of independent muscle function compromise the paravertebral muscles.

Stand-alone anterior lumbar interbody fusion avoids these complications of posterior "fusion disease". The anterior approach retains all posterior-stabilizing structures and avoids epidural scarring and perineural fibrosis. There is no need for

paraspinal muscle stripping, retraction, or denervation of the adjacent facet joint. The approach is a muscle splitting one that does not compromise existing posterior spinal elements and has the capability to reestablishes normal disc space height and restores the normal sagittal contours of the lumbar spine. This allows a faster and often more complete functional recovery of the patient. Long-term follow-up studies have not shown significant rates of adjacent segment degeneration after anterior interbody fusion (17).

Numerous clinical studies have documented the efficacy and improved outcomes with this procedure. Femoral ring allografts have been widely used; however, these intradiscal spacers alone do not provide enough stability to consistently promote fusion, and they have been associated with high rates of postoperative subsidence (2). Anterior femoral ring allografts often require an additional instrumented posterior spinal fusion to stabilize the spinal motion segment. Recent advances in metallic interbody fusion devices have been introduced to stabilize intervertebral grafts and have been used to encourage fusion and prevent disc space collapse during the healing process (5).

This study represents one of the largest prospective clinical evaluations of stand alone ALIF procedures. The randomized patient groups had no statically significant differences in all parameters assessed. Clinical and radiographic follow-up exceeded 90% at all intervals.

The investigational BMP group did not undergo an autogenous bone graft harvesting procedure. This lead to statistical significant reduction in operative time and in decreased blood loss during the procedure. Retrograde ejaculation was associated

with transabdominal approached to the lumbosacral spine. The incidence of retrograde ejaculation following a retroperitoneal approach was 1.8%.

The difficulty in obtaining anterior interbody fusion through fusion cages lies in the appropriate preparation of the endplate. The endplate must be partially removed in order to allow healing potential to the vertebral bodies. However, if excessive endplate resection is performed subsides may occur and ultimately, pseudarthrosis. The procedure described in this paper helps enhance this fusion in two different ways. The LT CAGE performs minimal endplate resection thus preserving the weight bearing portions of the endplate to allow greater restoration of lordosis and to prevent subsidence. The use of recombinant human bone morphogenetic protein has accelerated fusion in animal models (3,20,21). This should also allow the fusion procedure to occur in humans more rapidly and more thoroughly. Indeed, from a radiographic standpoint this was true: 97% of patients with LT cages and rhBMP-2 had radiographic evidence of a solid fusion at one year.

This study's fusion assessment protocol was one of the first to use thin-cut 1mm CT scans to evaluate new bone formation (6). The thin walled second generation LT CAGE reduced imaging artifact in the instrumented disc space. New bone formation inside and outside of the intervertebral cages was reliably identified on these CT scans. New bone formation was identified within all cages filled with BMP that remained implanted for more than 6 months. Fusion failure was documented in the BMP treated group because of a secondary surgical procedure not because of failure of new bone formation. All new bone formation was found within the instrumented disc space. There was no ectopic bone formation outside of the annular confines of the disc space: there

was no bone formation extending posteriorly into the spinal canal or laterally into the neuroforamina.

Recombinant human bone morphogenetic protein is an osteoinductive growth factor that stimulates pleuripotential cells to form bone (24). It is presumed in this study that exposure of a bleeding cancellous bone allowed influx of pleuripotential cells that were affected by the BMP bound to the collagen carrier sponge. The investigational, or rhBMP-2, group had a 96.9% fusion rate at one year compared with 92.6% in the control group. At 24 months postoperatively, the investigational group had a 94.5% fusion rate almost a six-percentage point higher fusion rate that the control group (88.7%) with a probability of superiority of 90.2 percent. This range of affect was limited to essentially the disc space. Areas between the cages, lateral to the cages, and anterior and posterior cages did ossify; but in no case did this ossification extend outside of the confines of the vertebral column. No heterotopic ossification in the epidural space or within the peritoneal cavity or retroperitoneal space occurred. No metastatic calcifications were seen in this study.

The final assessment of a successful interbody fusion is difficult. Independent radiologists were utilized to carefully scrutinize the plain x-rays, flexion/extension films, and CT scans in each case. The reconstructed CT scans proved to be the most useful method of determining the success of the arthrodesis. Bridging trabecular bone seen on the coronal and sagittal reconstructed images was the final arbiter at determining whether a successful fusion occurred. Only gross motion from a pseudarthrosis could be seen on the flexion/extension films and can most reproducibly be seen as a change in lucency between vertebral body and cage during the flexion/extension sequence.

Finally, the question of how a patient with a radiographic solid arthrodesis but persistent pain is handled remains indeterminate. In several instances in this study, the treating surgeon elected to proceed with a posterior instrumented fusion in the face of persistent pain and a successful arthrodesis. By the treating clinician's statement, these patients were noted to have pseudarthrosis. However, there is no accurate way to determine whether these were true radiographic pseudarthrosies or not. In fact, fewer than half of the patients that went on to have posterior instrumentation for a presumed pseudarthrosis achieved significant pain relief. Despite these rigorous criteria for determining successful fusion, we were able to obtain a very high rate of radiographic success.

The mean improvements and Oswestry score (29.0 and 29.5 points) are amongst the highest improvements in the literature. We feel this is due in part to the successful combination of anterior approach, threaded tapered titanium fusion cages, and a high degree of successful arthrodesis.

rhBMP-2 is a promising method of facilitating anterior intervertebral spinal fusion and of decreasing pain and improving clinical outcomes after anterior lumbar fusion when used with the LT-CAGE™ device. The use of rhBMP-2 is associated with high fusion rates without the need for harvesting bone from the iliac crest, thereby eliminating the adverse effects and long-term symptoms associated with that procedure. The combination of this threaded tapered fusion cage and rhBMP-2 may be efficacious in the treatment of challenging with patients such as smokers and patients with associated medical disabilities.

REFERENCES

1. Beimborn DS, Morrissey MC: A review of the literature related to trunk muscle performance. *Spine* 13:655-660, 1988.

2. Blumenthal SL, Baker J, Dossett A, Selby DK. The role of anterior lumbar fusion for internal disc disruption. Spine 1988;13:566-9.

3. Boden SD, Schimandle JH, Hutton WC. 1995 Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 1995;20:2633-44.

4. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25:376-81.

5. Boyd, L.M.; Estes, B.T. and Liu M. "Biomechanics of Lumbar Interbody Constructs, *Effect of Design and Materials*." Chirurgie Endoscopique et Mini-invasive du Rachis. Ed. Husson JL, LeHuec JC. Sauramps Médical. Montpelier, France. pp 181-92, 1999.

6. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. Neurosurg Focus 2001;10:1-9.

7. Crock HV. Anterior lumbar interbody fusion: indications for its use and notes on surgical technique. Clin Orthop 1982;165:157-63.

8. Flynn JC, Hoque MA. Anterior fusion of the lumbar spine. End result study with long-term follow-up. J Bone Joint Surg 1979;61A:1143-50.

9. Goldner JL, Urbaniak JR, McCollom DE: Anterior excision and interbody spinal fusion for chronic low back pain. *Orthop Clin North Am* 2:543-568, 1971

10. Harmon PH. Anterior excision and vertebral fusion operation for intervertebral disc syndromes of the lower lumbar spine: three to five year results in 244 cases. Clin Orthop 1963;26:107-27.

11. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999;24:629-36.

12. Jonsson B: The functions of individual muscles in the lumbar part of the spinae muscle. *Electromyography* 10:5-21, 1970.

13. Kahanovitz N, Viola K, Gallagher M: Long term strength assessment of postoperative diskectomy patients. *Spine* 14:402-403,1989.

14. Lane JD, Moore ES. Transperitoneal approach to the intervertebral disc in the lumbar area. Annals of Surgery 1948;127:537-51.

15. Loguidice VA, Johnson RG, Guyer RD, Stith WJ, Ohnmeiss DD, Hochschuler SH, Rashbaum RF. Anterior lumbar interbody fusion. Spine 1988;13:366-9.

16. Leong JC, Chun SY, Grange WJ, Fang D: Long-term results of lumbar intervertebral disc prolapse. Spine 1983;8:793-9.

17. Penta M, Sandhu A, Fraser RD: Magnetic resonance imaging assessment of disc degeneration 10 years after anterior lumbar interbody fusion. *Spine* 20: 743-747, 1995.

18. Rantanen J, Hurme M, Falck B, Alaranta H, Nykvist F, Lehto M, Einola S, Kalimo H: The lumbar multifidus muscle five years after surgery for a lumbar intervertebral disc herniation. *Spine* 18:568-574, 1993.

19. Sacks S. Anterior interbody fusion of the lumbar spine. J Bone Joint Surg [Br] 1965;47:211-23.

20. Sandhu HS, Kanim LEA, Toth JM, et al. Experimental spinal fusion with recombinant human bone morphogenetic protein-2 without decortication of osseous elements. Spine 1997;22:1171-80.

21. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995; 20:1326-37.

22. Sihvonen T, Herno A, Paljarvi L, Airaksinen O, Partanen J, Tapaninaho A: Local denervation atrophy of paraspinal muscles in postoperative failed back syndrome. *Spine* 18:575-581, 1993.

23. Stauffer RN, Coventry MB. Anterior interbody lumbar spine fusion. J Bone Joint Surg [Am]1972;54:756-68.

24. Urist MR. Bone: Formation by autoinduction. Science 1965;150:893-9.

LEDGENDS TO FIGURES

Figure 1: Lateral standing radiograph of the lumbosacral spine shows disc space collapse at L5-S1 and early radial osteophyte formation. There is loss of segmental lordosis at the disc space to 15 degrees.

Figure 2: Standing lateral radiograph at 24 months postoperatively shows restoration of anatomic disc space height at the L5-S1 interspace and improvement of segmental lordosis to 27 degrees. New bone formation can be seen anterior to the cages.

Figure 3: Thin-cut one-millimeter CT scan sagittal reconstruction at 24 months postoperatively shows new bone formation within the LT CAGE and new bone formation anterior to the cage but within the confines of the disc space.

Table 1. Patient Data

Variable	Investigational (n=143)	Control (n=136)	P value *
Age (yrs.)			
n	143	136	0.369
Mean	43.3	42.3	
Weight (lbs.)			
n	143	134	0.639
Mean	179.1	181.1	
Sex [n (%)]			
Male	78 (54.5)	68 (50.0)	0.473
Female	65 (45.5)	68 (50.0)	
Workers' Compensation [n (%)]	47 (32.9)	47 (34.6)	0.801
Spinal Litigation [n (%)]	18 (12.6)	22 (16.2)	0.400
Tobacco Used [n (%)]	47 (32.9)	49 (36.0)	0.615
Preop Work Status [n (%)]	68 (47.6)	50 (36.8)	0.071
Working			

*For continuous variables, P values are from ANOVA. For categorical variables, P values are from Fisher's exact test or chi-square test.

Table 2. Patient Accountability

Investigational Group	Preop	Surgery	6 Weeks	3 Months	6 Months	12 Months	24 Months
Theoretical							
Follow-up[1]	143	143	143	143	143	143	143
Deaths	0	0	0	0	0	0	0
(Cumulative)							
Failures[2]	0	0	1 (1)	0 (1)	3 (4)	1 (5)	4 (9)
(Cumulative)							
Expected[3]	143	143	142	142	139	138	133
Number Evaluated	143	143	141	141	137	133	123
Percent Follow-up	100.0%	100.0%	99.3%	99.3%	98.6%	96.4%	92.5%

Control Group	Preop	Surgery	6 Weeks	3 Months	6 Months	12 Months	24 Months
Theoretical							
Follow-up[1]	136	136	136	136	136	136	136
Deaths	0	0	0	0	0	1	1
(Cumulative)							
Failures[2]	0	0	0	0	1 (1)	4 (5)	7 (12)
(Cumulative)							
Expected[3]	136	136	136	136	135	130	120
Number Evaluated	136	136	134	134	133	126	109
Percent Follow-up	100.0%	100.0%	98.5%	98.5%	98.5%	96.9%	90.8%

[1] Theoretical = Patients who have entered the follow-up window.
[2] Failures include device removals, revisions and supplemental fixations.
[3] Expected = Theoretical – Cumulative Deaths – Cumulative Failures

Table 3. Surgery Information

Variable	Investigational (n=143)	Control (n=136)
Operative Time (hrs)		
n	143	136
Mean	1.6	2.0
Blood Loss (ml)		
n	142	136
Mean	109.8	153.1
Hospital Stay (days)		
n	143	136
Mean	3.1	3.3
Treatment Levels [n (%)]		
L4-L5	37 (25.9)	32 (23.5)
L5-S1	106 (74.1)	103 (75.7)
L5-L6	0 (0.0)	1 (0.7)
Operative Approach [n (%)]		
Retroperitoneal	116 (81.1)	110 (80.1)
Transperitoneal	27 (18.9)	26 (19.1)

TABLE 4. Iliac Crest Graft Site Pain and Appearance Scores

Period	Variable	Control
Discharge	Pain Score	
	n	134
	Mean	12.7
	P value[1]	<0.001
	Appearance of Graft Site	
	Poor[2]	13 (9.8)
6 Weeks	Pain Score	
	n	132
	Mean	6.7
	P value	<0.001
	Appearance of Graft Site	
	Poor	5 (3.8)
3 Months	Pain Score	
	n	134
	Mean	3.5
	P value	<0.001
	Appearance of Graft Site	
	Poor	3 (2.3)
6 Months	Pain Score	
	n	132
	Mean	2.6
	P value	<0.001
	Appearance of Graft Site	
	Poor	5 (3.8)
12 Months	Pain Score	
	n	130
	Mean	2.1
	P value	<0.001
	Appearance of Graft Site	
	Poor	5 (3.8)
24 Months	Pain Score	
	n	117
	Mean	1.8
	P value	<0.001
	Appearance of Graft Site	
	Poor	3 (2.6)

[1] P values are from Student's *t* test comparing mean with zero.
[2] Poor= "It bothers me very much."

TABLE 5 – Oswestry Low Back Pain Disability Scores

Period	Variable	Investigational	Control
Preoperative			
	n	143	136
	Mean	53.7	55.1
6 Weeks			
	n	140	131
	Mean	42.1	41.4
Improvement from Preoperative			
	Mean	11.4	13.6
	P value[1]	<0.001	<0.001
3 Months			
	n	141	134
	Mean	33.5	34.2
Improvement from Preoperative			
	Mean	19.9	20.8
	P value	<0.001	<0.001
6 Months			
	n	136	131
	Mean	29.3	29.4
Improvement from Preoperative			
	Mean	24.4	25.4
	P value	<0.001	<0.001
12 Months			
	n	130	125
	Mean	25.5	25.6
Improvement from Preoperative			
	Mean	27.7	28.9
	P value	<0.001	<0.001
24 Months			
	n	122	108
	Mean	23.9	23.8
Improvement from Preoperative			
	Mean	29.0	29.5
	P value	<0.001	<0.001

[1]

TABLE 6. Neurologic Outcomes

Period	Variable	Investigational (n=143) n (%)	Control (n=136) n (%)
6 Weeks	Overall		
	Success	110 (80.3)	108 (83.7)
	Failure	27 (19.7)	21 (16.3)
3 Months	Overall		
	Success	119 (84.4)	103 (77.4)
	Failure	22 (15.6)	30 (22.6)
6 Months	Overall		
	Success	106 (77.9)	106 (80.9)
	Failure	30 (22.1)	25 (19.1)
12 Months	Overall		
	Success	108 (81.8)	105 (84.7)
	Failure	24 (18.2)	19 (15.3)
24 Months	Overall		
	Success	101 (82.8)	90 (83.3)
	Failure	21 (17.2)	18 (16.7)

TABLE 7. Back Pain Outcomes

Period	Variable	Investigational	Control
Preoperative	n	143	136
	Mean	15.8	16.1
6 Weeks	n	139	132
	Mean	9.3	8.8
Improvement from Preoperative	Mean	6.5	7.4
	P value[1]	<0.001	<0.001
3 Months	n	140	134
	Mean	8.7	9.0
Improvement from Preoperative	Mean	7.1	7.1
	P value	<0.001	<0.001
6 Months	n	136	131
	Mean	8.6	8.9
Improvement from Preoperative	Mean	7.3	7.1
	P value	<0.001	<0.001
12 Months	n	129	125
	Mean	8.0	8.4
Improvement from Preoperative	Mean	7.8	7.6
	P value	<0.001	<0.001
24 Months	n	122	108
	Mean	7.3	7.9
Improvement from Preoperative	Mean	8.4	8.1
	P value	<0.001	<0.001

TABLE 8. Back Pain Success Rates

Variable	Investigational n (%)	Control n (%)
6 Weeks		
Success	107/139 (77.0)	101/132 (76.5)
Failure	32/139 (23.0)	31/132 (23.5)
3 Months		
Success	103/140 (73.6)	105/134 (78.4)
Failure	37/140 (26.4)	29/134 (21.6)
6 Months		
Success	106/136 (77.9)	94/131 (71.8)
Failure	30/136 (22.1)	37/131 (28.2)
12 Months		
Success	102/129 (79.1)	91/125 (72.8)
Failure	27/129 (20.9)	34/125 (27.2)
24 Months		
Success	91/122 (74.6)	85/108 (78.7)
Failure	31/122 (25.4)	23/108 (21.3)

TABLE 9. Leg Pain Scores

Period	Variable	Investigational n = 143	Control n = 136
Preoperative			
	n	143	136
	Mean	12.5	12.5
6 Weeks			
	n	139	132
	Mean	7.5	8.4
Improvement from Preoperative	n	139	132
	Mean	5.1	4.1
	P value[1]	<0.001	<0.001
3 Months			
	n	140	134
	Mean	6.8	6.8
Improvement from Preoperative	n	140	134
	Mean	5.6	5.6
	P value	<0.001	<0.001
6 Months			
	n	136	131
	Mean	6.3	6.3
Improvement from Preoperative	n	136	131
	Mean	6.4	6.3

	P value	<0.001	<0.001
12 Months			
	n	129	125
	Mean	6.3	6.6
Improvement from Preoperative	n	129	125
	Mean	6.4	5.6
	P value	<0.001	<0.001
24 Months			
	n	122	108
	Mean	6.3	6.3
Improvement from Preoperative	n	122	108
	Mean	6.5	5.9
	P value	<0.001	<0.001

† P values for change from preoperative in each group are from paired test.

TABLE 10. Return To Work Status

Period	Variable	Investigational n (%)	Control n (%)
3 Months	Working	54 (38.3)	38 (28.4)
	Not Working	42 (29.8)	43 (32.1)
	Was Not Working Before Surgery	45 (31.9)	53 (39.6)
6 Months	Working	69 (50.7)	60 (45.5)
	Not Working	25 (18.4)	29 (22.0)
	Was Not Working Before Surgery	42 (30.9)	43 (32.6)
12 Months	Working	72 (55.0)	63 (50.4)
	Not Working	20 (15.3)	19 (15.2)
	Was Not Working Before Surgery	39 (29.8)	43 (34.4)
24 Months	Working	80 (66.1)	60 (56.1)
	Not Working	11 (9.1)	13 (12.1)
	Was Not Working Before Surgery	30 (24.8)	34 (31.8)

Table 11. Rates of Radiographic Fusion [Number (%) of Patients]

Variable	Investigational (n=143) n (%)	Control (n=136) n (%)
6 Months		
Success	128/132 (97.0)	115/120 (95.8)
Failure	4/132 (3.0)	5/120 (4.2)
12 Months		
Success	127/131 (96.9)	112/121 (92.6)
Failure	4/131 (3.1)	9/121 (7.4)
24 Months		
Success	120/127 (94.5)	102/115 (88.7)
Failure	7/127 (5.5)	13/115 (11.3)

From: Neil Beals
Sent: Saturday, December 1, 2001 12:24:40 PM
To: Bill McKay
CC: Clark Charlton
Subject: RE: Open LT Cage BMP paper

I agree completely with Boden's comments but we must deal with info (reported fusion rate) that is out there for InFUSE. I think that we will have to report both for a while. Neil

-----Original Message-----
From: Bill McKay
Sent: Tuesday, November 27, 2001 4:56 PM
To: Neil Beals
Cc: Clark Charlton
Subject: RE: Open LT Cage BMP paper

Neil,

When we had that FDA Panel preparation meeting in Atlanta a couple of weeks ago on the preclinical/safety presentations, Boden was all over Bailey about reporting the true "radiographic" fusion rate. He said no one is using the FDA definition of including secondary surgeries even though they were determined fused radiographically, and it makes us look bad compared to other publications (i.e. BAK data-they didn't include secondary surgeries as fusion failures). He said no one will understand the FDA definition and it only hurts us.

He said we should report the true radiographic fusion rate first, and then as a minor side note give the FDA fusion rate only after it has been clearly defined so it doesn't cause confusion.

Dr. Burkus needs to make this change in his Spine manuscript. The Publication "summary" for example at the beginning of the paper, should only include the true radiographic fusion rate of 100% for BMP-2.

Bill

-----Original Message-----
From: Neil Beals
Sent: Monday, November 26, 2001 8:33 AM
To: Bill McKay
Subject: RE: Open LT Cage BMP paper

I am not aware of anyone reporting data from our studies in any way except by FDA criteria. I have no problem and in fact prefer alternative report but we will need to reconcile with what is out there - any thoughts?

-----Original Message-----
From: Bill McKay
Sent: Sunday, November 25, 2001 10:55 PM
To: Neil Beals
Subject: RE: Open LT Cage BMP paper

Neil,

It is very important that Ken report the radiographic fusion rate and not the fusion rate per the FDA criteria of including revision surgeries as fusion failures even though the independent radiologist determined them as fused. Did he? If not, he needs to change it. Dr. Boden said nobody uses the FDA criteria and the data will be mis-interpreted.

Bill

> -----Original Message-----
> **From:** Neil Beals
> **Sent:** Wednesday, October 31, 2001 2:58 PM
> **To:** JKE[redacted]
> **Cc:** Peter Wehrly; Clark Charlton; Bill McKay
> **Subject:** RE: Open LT Cage BMP paper
>
> Ken:
>
> I sincerely appreciate your initiative to develop this draft and keep us going in the right direction. I have reviewed the draft and made a number of comments. As with anything, it will be best for us to discuss these points but I thought it would be worthwhile to pass along my initial comments. Again, these are strictly from me and many of them are intended to prompt discussion. I'm sure others who review this will have separate (and often better) ideas. Our hope is that the final outcome is a landmark paper. Hopefully we will find time at NASS to go over these.
>
> Thanks again.
>
> [We may have already discussed these points by the time you are able to pick up this email but I thought I would go ahead and convey some initial thoughts.]
>
> Some GENERAL COMMENTS
> 1) I think we'll need to devise some means of tracking edits made by various individuals; given the scope of this paper, we will want to review with a number of people for accuracy and to solicit different perspectives and sometimes it is confusing to those involved as to which draft is being reviewed - any thoughts how we can best manage this process?
>
> 2) current draft refers to InFUSE as rhBMP-2 while usually referencing only LT Cage (instead of a more generic descriptor); I recommend some consistency,

either using generic terms like rhBMP-2/ACS and tapered metal cage or tradenames; arguments can be made either way but I think we should establish agreed upon approach

3) I think bigger deal should be made of elimination of donor site pain with InFUSE; this is not referenced in summary and not really emphasized in paper (so far); I would put that front and center in results, discussion, and conclusion so that "equivalent" results aren't received as a let down

4) I'm not sure about the use of FDA-defined success rates in this paper; do most surgeons relate to these? can we establish other means of defining success in this study?

5) we should probably discuss key points to be made in this paper and the order of their importance or sequence they are presented in paper; my initial thoughts are:

- quality of study
- surgery data findings
- elimination of donor site pain
- clinical outcomes
- work status
- fusion/radiographic findings
- safety/ antibody results

6) could use more references

Comments for DISCUSSION Section
Points which I think would be of interest to expand on in discussion include:
1) study protocol and design
2) ALIF procedure and use of stand alone cages
3) quality of study - note demographics and closeness of each group to one another
4) quality of study - % f/u
5) surgery data and findings including stat sig differences (or time, blood loss) and trends (hospital stay) with explanations and implications

6) operative approach and incidence of retrograde ejac with explanation and implications
7) donor site pain - significance of this finding (first prospective study?) and its implications
8) clinical outcomes (Oswestry, SF-36, BP, LP) - note trends with graphs and discuss implications
9) success factors - discuss how success is measured and relevance of these data
10) work status findings and implications
11) fusion results showing trends with InFUSE - explanation and implications

12) value of CTs in assessing fusion supported with examples from study; significance of their use and serial review showing bone formation and remodeling

13) immune response - review antibody data and explain findings and implications

Additional DISCUSSION points
1) Address safety of rhBMP-2 and InFUSE specifically systemic effects, toxicity, and BSE concerns with ACS
2) address bone formation and issue or concern of extra bone formation supported by this study
3) cite various unknowns and future research direction based upon findings from this study

thanks Ken. Neil

-----Original Message-----
From: [redacted]
Sent: Friday, October 26, 2001 7:02 PM
To: Neil Beals; Peter Wehrly; Clark Charlton
Subject: Fw: Open LT Cage BMP paper

Here is an update on the two papers already submitted to SPINE.

I gave my first draft of the open LT BMP paper to a Hughston medical writer to review. I hope to work on the manuscript some more this weekend. In any event, I will have an early edited first draft version of the Open BMP LT study at the SIRG meeting at NASS. I hope to discus with you what should be done with the 20 grand.

Best,
Ken
----- Original Message -----
From: Carol Binns [redacted]
To: Burkus, MD, J Kenneth [redacted]
Sent: Friday, October 26, 2001 6:05 PM
Subject: Open LT Cage BMP paper

Dr. Burkus,
I am still working on the paper and will have it to you before the weekend is over.

I called SPINE today regarding your other 2 submissions. "Clinical and Radiographic Outcomes of ALIF using rhBMP-2" has been through the review process but Dr. Weinstein wanted to send it to additional reviewers. Sounds like there may have been some disagreement among them. The second set of reviews are due next week. With regard to the status of "Radiographic Assessment of Interbody Fusion Using rhBMP-2", those reviews are due in the editorial office 11/12.

Carol Binns
Medical Writer
Hughston Sports Medicine Foundation

From: Neil Beals
Sent: Saturday, December 8, 2001 08:36:03 PM
To: Bailey Lipscomb
CC: Clark Charlton; Bill McKay; Pete Wehrly
Subject: Open LT InFUSE Manuscript

A quick update on manuscript....

I sat down with Ken Burkus and Tom Zdeblick during SIRG meeting at discussed paper being prepared to submit to Spine. Tom had several very good comments and suggestions and agreed to spend some more time on draft and provide his comments to Ken to incorporate. I am not sure if he has done this yet or not but he was working on it during the meeting. Tom emphasized that the paper should not be a rehash of what is presented to the FDA and instead should focus on the message that is of interest to surgeons. Towards this he believes that we should be careful to define criteria for success and then report results of study. This will require new statistical analysis and changes in the write-up. Bailey, I am not sure if Ken or Tom will request this directly from you or as me to f/u. Tom also emphasized that we need to explain fusion results and offer explanations about failures in the study. He was surprised at the high number of Neuro failures and felt we should explain this better. Back and leg pain scores (20 pt scales) need to be explained and possibly reassessed with 2 0-10 point scales for each. Finally, Tom emphasized that this will be regarded as landmark paper and stressed that we need to get it right even if it pushes back submission date a little; Ken really wants to get this in ASAP but I think he agreed. Neil

P.S. I think it will also be advisable to address questions/comments raised in reviews of 2 papers submitted by Ken.

From: JKB[redacted]
Sent: Tuesday, January 1, 2002 03:57:04 PM
To: Peter Wehrly[redacted]
CC: Mike DeMane[redacted]; Neil Beals[redacted]; Elizabeth Kimball[redacted]
Subject: Revised Bone Dowel BMP manuscript

Attachments: Revised & Reprint Bone Dowel BMP Paper.2.doc

Pete,

Here is, I hope, your first of many BMP presents for the New Year.

I have attached my revisions of the Bone Dowel BMP paper responding to the SPINE journal's editorial comments and criticisms. I have redone many of the tables and some of the illustrations. I think it is a much stronger paper now.

I will have the staff at the Hughston Foundation review the work before I resubmit the manuscript.

I am looking forward to seeing you on Sunday in Atlanta.

I greatly appreciate all of the support and personal kindness that you have shown me.

Best wishes for the New Year.

Ken Burkus

Clinical and Radiographic Outcomes of Anterior Lumbar Interbody Fusion Using Recombinant Human Bone Morphogenetic Protein-2

J. Kenneth Burkus, MD*

Ensor Transfeldt, MD†

Scott H. Kitchel, MD‡

Robert Watkins, MD§

and

Richard Balderston, MD‖

* Hughston Spine Service, The Hughston Clinic, Columbus, Georgia

† Twin Cities Spine Service, Minneapolis, Minnesota

‡ Orthopedic Healthcare NW, Eugene, Oregon

§ The Center for Spinal Surgery, Los Angeles, California

‖ 3B Orthopedics, Philadelphia, Pennsylvania

This study was sponsored by Medtronic Sofamor Danek.

Address correspondence and reprint requests to: J.K. Burkus, MD, The Hughston Clinic, PC, [redacted]

Deleted: 01/01/02

ABSTRACT

Study Design. A prospective nonblinded multicenter study of outcomes in patients undergoing single-level anterior lumbar discectomy and interbody fusion.

Objective. To determine the safety and effectiveness of InFUSE Bone Graft™ applied to an absorbable collagen sponge in anterior lumbar interbody fusion with threaded cortical allografts.

Summary of Background Data. In primates, rhBMP-2 used with allograft dowels was shown to increase rates of interbody fusion by promoting osteoinduction and enhancing incorporation of the allograft. And recently, in a small series of human patients undergoing ALIF with a tapered cylindrical metal fusion cage, InFUSE Bone Graft™ has been shown to promote osteoinduction and fusion.

Methods. Forty-six patients underwent a single level anterior lumbar discectomy and interbody fusion. They were randomly assigned to one of two groups, and the results in the investigational patients who received threaded cortical allograft dowels with InFUSE Bone Graft™ were compared with those in the control patients who received threaded allograft dowels with autogenous iliac crest bone graft. Clinical outcomes were assessed using neurologic status, work status, and Oswestry Low Back Pain Disability, Short Form-36, and back and leg pain questionnaires. Anteroposterior, lateral, flexion-extension radiographs, and computed tomography scans were used to evaluate the progression of fusion at 6, 12, and 24 months after surgery.

Results. All patients who received InFUSE Bone Graft™ showed radiographic evidence of bony induction and early incorporation of the cortical allografts. All patients in this group had fusions at 12 months that remained fused at 24 months. At 12 and 24 months,

Deleted: 01/01/02

the investigational group showed higher rates of fusion and improved neurologic status and back and leg pain when compared with the control group. There were no unanticipated adverse events related to the use InFUSE Bone Graft™.

Conclusion. The use of InFUSE Bone Graft™ is a promising method of facilitating anterior intervertebral spinal fusion, decreasing pain, and improving clinical outcomes in patients who have undergone anterior lumbar fusion surgery with structural threaded cortical allograft bone dowels.

Key words: bone morphogenetic protein, degenerative disc disease, lumbar spine, spinal fusion

Deleted: 01/01/02

INTRODUCTION

Cylindrical threaded allograft dowels can be used as stand-alone intervertebral implants that function as an instrumented anterior lumbar interbody fusion. They are not intradiscal spacers that require additional segmental stabilization. The threaded cortical bone dowels can withstand lumbar compressive loads and can promote load sharing between the allograft and the host bone while maximizing device porosity.[4,15] These interbody constructs are implanted within the central portion of the disc space through a controlled insertion technique. Impacted allografts, when used alone for interbody fusion in the lumbar spine, have a high rate of pseudarthrosis and subsidence.[8,11,19] Contemporary reports of large clinical series of anterior interbody fusions using impacted grafts have shown varying rates of fusion and differing clinical outcomes.[1,7,12-14,16] The threaded dowels resist expulsion and stabilize the bone-implant interface.[4] Threaded bone dowels, in addition, offer increased strength to support cancellous graft material.[17] In one clinical series, 43 patients were followed for more than 1 year and had a high fusion rate and improved clinical outcomes.[5]

InFUSE Bone Graft™ (Medtronic Sofamor Danek, Memphis, TN) is recombinant human bone morphogenetic protein applied to an absorbable collagen sponge. It replaces autogenous bone grafts and eliminates the complications associated with iliac crest graft harvesting. In a clinical series of patients undergoing an ALIF procedure with a tapered cylindrical metal fusion cage, InFUSE Bone Graft™ has been shown to promote osteoinduction and increase rates of fusion (3). This report presents the 2-year clinical and radiographic results of the use of rhBMP-2 with a collagen sponge carrier inside a

Deleted: 01/01/02

cylindrical threaded cortical allograft dowel in patients undergoing anterior lumbar interbody fusion.

MATERIALS AND METHODS

Study Design

This prospective, randomized, non-blinded study was conducted under an approved investigational device exemption (IDE). Forty-six patients at five investigational sites had surgery between April and August 1998. The patients were randomly assigned to 1 of 2 study groups. The investigational group received InFUSE Bone Graft™, recombinant human bone morphogenetic protein-2 (rhBMP-2) applied to an absorbable collagen sponge carrier and used in conjunction with the MD-II™ threaded cortical bone dowel (Regeneration Technologies, Inc., Alachua, FL). The control group received autogenous iliac crest bone graft. Data were collected preoperatively, intraoperatively, and at 6 weeks, 3, 6, 12 and 24 months postoperatively. Operative procedure details and adverse events were also recorded.

Degenerative Lumbar Disc Disease

Degenerative lumbar disc disease refers to a specific pain syndrome that originates from degenerative changes and instability patterns within the intervertebral disc. It is diagnosed by a history of clinical complaints, physical findings and neuroradiographic studies. This syndrome is characterized by chronic and, at times, incapacitating low back pain, which is often referred to the buttock and posterior thigh. The referred leg-pain pattern rarely extends below the knees and radiates in a nondermatomal distribution into the lower extremities. Painful symptoms are usually exacerbated by vigorous activities and relieved by rest. Prolonged sitting may be painful,

Deleted: 01/01/02

and patients often complain of difficulty finding a comfortable position. Patients with this degenerative condition do not usually exhibit objective neurologic deficits. Positive sciatic tension signs are also uncommon. Patients will commonly have restricted range of motion of the lumbar spine, tenderness to palpation over the affected lumbar motion segment and paravertebral muscle spasm.

The diagnosis is confirmed with neuroradiographic studies, including plain radiographs, magnetic resonance imaging (MRI), and discography. Plain radiographs often show signs of instability such as disc space collapse, radial osteophytes, retrolithesis, or spondylolisthesis, or a combination of this. Dynamic flexion-extension lateral radiographs are sometimes necessary to demonstrate patterns of sagittal plane translation. In these degenerative conditions, MR imaging demonstrates desiccation of the disc, sclerosis of the adjacent vertebral endplates, and radial protrusion of the annulus. Discography can identify radial tears in the annulus fibrosis and early degenerative changes in the disc. However, the diagnosis of painful degenerative lumbar disc disease is confirmed with a positive provocative pain response with discography. In order to accurately identify the pain generator, discography must elicit a concordant reproduction of the patient's painful symptoms at the time of the injection. The radiographic findings and the provocative pain response seen with discography must be correlated with other neuroradiographic studies and clinical findings. Discography cannot be used alone to select patients for surgery.

Patient Population

All patients were between the ages of 19 and 68 years and had symptomatic degenerative disc disease at the L4-L5 or L5-S1 levels. All patients had had low back

Deleted: 01/01/02

pain for at least 6 months before their surgery that was recalcitrant to nonoperative treatment modalities, such as physical therapy, bed rest, and anti-inflammatory medications. All patients had plain radiographic findings documenting single-level degenerative disc disease. All patients underwent at least one other additional confirmatory neuroradiographic study including MR imaging, CT-enhanced myleography and/or discography. All patients were considered candidates for a single-level stand-alone anterior lumbar interbody fusion.

Patients were excluded from the study if they had spinal conditions other than single-level symptomatic degenerative disc disease or Grade 0 or 1 spondylolisthesis. Other exclusion criteria were symptomatic disc disease at a level other than the L4-L5 or L5-S1 disc space levels, obesity (more than 40% above ideal body weight), a history of discitis, or a medical condition that required medication, such as steroids or nonsteroidal anti-inflammatory medications, that could interfere with fusion.

The investigational group comprised 24 patients who were treated with InFUSE Bone Graft™ (Table 1). There were 22 patients in the control treatment group who were treated with autograft. One patient in the control group was lost to follow-up and was excluded from the study; and 1 patient died in a house fire at 6 months after surgery. All other patients were followed for a minimum of 24 months after surgery.

Surgical Technique

All patients underwent an open anterior lumbar discectomy and interbody fusion. Either a transperitoneal or a retroperitoneal approach to the lumbosacral spine was undertaken. In each patient, a complete discectomy was carried out. An incision was made in the annulus fibrosis; the nucleus pulposus and the cartilaginous endplates were

Deleted: 01/01/02

circumferentially removed. The bony endplates were preserved prior to reaming and tapping of the endplate for receipt of the dowel. Two allograft bone dowels were then inserted into each disc space.

The rhBMP-2 was reconstituted using sterile water and was used as a "single dose" at 1.5mg/ml. This dosage was the same in all patients studied. The solution (1.5 mg rhBMP-2/ml) was then applied to an absorbable collagen sponge. Next, the collagen sponge was placed into the central portion of the bone dowel before being inserted into the prepared disc space. Additional InFUSE Bone Graft™ (or rhBMP-2 prepared sponges) was placed between the bone dowels. No autogenous grafts were utilized in the investigational group.

The control group received morcellized autogenous iliac crest graft in conjunction with the threaded cortical bone dowels. The iliac grafts were harvested through a separate incision directly over the iliac wing. The ilium inner or outer table of the ilium was subperiostealily exposed and corticocancellous grafts were harvested. A single cortex was persevered in all cases; no bicortical iliac grafts were obtained. The central opening of the dowels were packed with the bone graft prior to insertion into the disc space. Additional bone graft was packed between and anterior to the dowels.

All patients were treated with a lumbosacral corset following surgery. Patients wore the orthosis for 6 to 12 weeks following surgery. Patients were encouraged to ambulate for activities immediately following surgery. Physical activities were advanced at the discretion of the attending surgeon. Clinical Outcome Measurements

Patient assessments were completed preoperatively, during their hospitalization and postoperatively at 6 weeks and 3, 6, 12 and 24 months. Clinical outcomes were

Deleted: 01/01/02

measured using well-established instruments including: Oswestry Low Back Pain Disability Questionnaire, Short Form SF 36, neurologic status, work status, patient satisfaction, and back, leg and graft site pain questionnaires. The Oswestry Low Back pain Disability Questionnaire was self-administered and used to measure the level of pain and disability associated with various activities. Neurological status assessment was based on four objective clinical measurements including motor, sensory, reflexes and sciatic tension signs. Success in neurologic outcome was based upon maintenance of or improvement in condition for each parameter tested. The Short Form SF 36 was a self-administered questionnaire that measures specific health concepts related to physical functioning, social functioning and health perceptions. It is comprised of both a Physical Component Summary (PCS) and a Mental Component Summary (MCS). Three patient satisfaction questions were administered at each postoperative time period. Success of each question was defined as either a "definitely true" or "mostly true" response. Low back, leg and iliac graft site pain were evaluated using numerical rating scales that identified both pain intensity and duration. Standard visual analog scales were used for pain intensity and duration of the painful symptoms. The two scores were added together to derive a composite score.

Radiographic Outcome Measurements

Radiographs and CT scans were used to evaluate fusion at 6, 12 and 24 months postoperatively. Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent radiologist was used to adjudicate conflicting fusion findings. Fusion was assessed by plain radiographs—using anteroposterior, lateral, and flexion-extension lateral views.[6] Fusion was defined as bridging bone connecting the

Deleted: 01/01/02

adjacent vertebral bodies either through the implants or around the implants, less than 5 degrees of angular motion, less than or equal to 3 mm of translation, and an absence of radiolucent lines around more than 50% of either of the implant surfaces. Thin slice (1 mm) computed tomography scans with sagittal reconstructions were evaluated at 6, 12, and 24 months. On the CT scans, fusion was defined by the presence of continuous trabecular bone formation between the vertebral bodies. Bridging trabecular bone between adjacent vertebra and radiolucencies around the implants were assessed on both plain radiographs and CT scans. Angular motion and translation was assessed on the dynamic plain radiographs alone. A fusion was considered successful only if all four criteria were achieved: 1) bridging trabecular bone connecting the two vertebral bodies either through the dowels or around the dowels on thin-cut CT scans; 2) no angular motion of 5 degree or more on dynamic plain radiographs; 3) no sagittal translation of more than 3 millimeter on dynamic plain radiographs and 4) no radiolucencies that involved more than half of the interfaces between the dowels and the host vertebral endplates.

RESULTS

Surgery

In the investigational group, 11 patients (45.8%) had surgery at the L4-L5 level and 13 (54.2%) had surgery at the L5-S1 level (Table 2). In the control group, surgery was performed at the L4-L5 level in 8 patients (36.4%) and at the L5-S1 level in 14 patients (63.6%). The mean operative time was slightly longer in the control group. The investigational group had surgery more commonly at the L4-L5 level. This exposure of the L4-L5 disc space often involves a tedious mobilization of the iliac vessels and

Deleted: 01/01/02

requires more time when compared with the exposure at the L5-S1 level. The average blood loss was less in the investigational group than in the control group ($P = 0.026$). The average hospital stay was similar in both groups.

Clinical Outcomes

No unanticipated adverse events that were related to the use of InFUSE™ Bone Graft (rhBMP-2 and the collagen sponge carrier) occurred during the course of the study.

Neurologic Outcomes

At 12 and 24 months, the investigational patients showed a higher rate of success than the control patients in their overall neurologic success scores (Table 3 and Figure 1). More than 87% of patients in the investigational group were considered to be a neurologic success (defined as equivalence or improvement from the preoperative condition) at 3 months after surgery. These results were maintained at the final 24-month follow-up. More than 95% of patients in the autograft control group were considered to be a neurologic success at 3 months postoperatively. However, these clinical results deteriorated to 73.3% at 24 months.

Back Pain Outcomes

Patients in the investigational group showed an improvement in back pain analog scores (maximum score = 20) of more than 7 points at their initial postoperative visit at 6 weeks (Table 4 and Figure 2). In this group, back pain continued to improve and averaged close to a 9-point improvement in pain scores at 24 months after surgery. The control group's improvement in back pain followed a similar pattern. However, at 24 months, average back pain scores improved only 5 points in this group. The mean improvement scores for low back pain in the investigational group were statistically

Deleted: 01/01/02

significantly greater than those reported in the control group at 3, 6, and 24 months postoperatively (p=0.038, p=0.034 and p=0.047, respectively).

Leg Pain Outcomes

The investigational group also showed greater of relief of leg pain when compared to the control group (Table 5 and Figure 3). In the investigational group, leg pain improved by more than five points within six weeks of surgery. These results remained virtually unchanged at the last follow-up of 24 months. However, while the autogenous graft group showed initial improvement of greater than 5 points, the improvement at 24 months decreased to 3.1 points.

General Health (SF-36)

The investigational (InFUSE Bone Graft) group showed higher mean scores at 24 months in both the Physical (PCS) and Mental (MCS) Components of the SF-36 than the control group (Figures 4 and 5). However, neither of these comparisons was found to be statistically significantly different.

Patient Satisfaction Questionnaire Outcomes

At 24 months the success rate was over 83% for all three questions. For the control group, the success rate for the three questions ranged from 55-65% (Table 6).

Oswestry Disability Questionnaire Outcomes

The Oswestry Disability Questionnaire assessed pain associated with activities (Table 7 and Figure 6). At all time periods, the investigational group had greater improvements in Oswestry scores than the control group. At 3, 6, and 24 months postoperatively, the improvement values were statistically significantly different

Deleted: 01/01/02

(p=0.032, p=0.039, and p=0.039 respectively). At 24 months, the mean improvement in Oswestry scores was 33.5 points.

Seventy-one percent (71%) of the patients in the investigational group showed an improvement of at least 15 points in their disability scores at 3 months. This improvement compared favorably with the 43% of patients who showed improvement in the control group ($P = 0.075$). At 12 months, 83% of the investigational group patients improved more than 15 points compared with 58% of the controls. This finding was similar at the 24-month follow-up.

Return to Work Status

Higher percentages of patients in the investigational group were also able to return to work (Figure 7). In the investigational group, 45.8% of patients were working prior to surgery. At 24 months postoperatively, 66.7% were working. These patients were also able to return to work earlier than those in the control group. In the control group, 40.9% were working preoperatively and at 24 months postoperatively 35.0% were working.

Iliac Crest Graft Site Pain Status

Autograft bone was not harvested from the iliac crest in the investigational group; therefore, bone graft site pain was not measured and was assumed to be zero in this group. In the control group, the intensity and frequency of pain and morbity from the graft site harvesting was measured on a 20-point numerical rating scale. At hospital discharge the mean graft site pain was the highest at 11.3. Graft site pain persisted at 24 months in these patients with a mean score of 2.2. (Figure 8).

Deleted: 01/01/02

Additional Surgery

No patients treated with InFUSE Bone Graft required an additional surgical procedure in the immediate perioperative period; 1 control patient required an early return to surgery to remove residual disc material (Table 8). Four patients underwent supplemental posterior fixation procedures after their primary surgery. One investigational patient continued to have persistent low back pain at 24 months. The patient's radiographs met the criterion for fusion; however, the attending physician elected to reoperate and supplement the interbody grafts with insertion of posterior pedicle fixation. The attending physician was able to identify "slight motion" in the posterior facet joints despite the presence of an adequate fusion anteriorly across the disc space. Three patients in the control group had supplemental posterior fixation inserted from 7 months to 20 months following their initial surgeries. In each of these cases, the patient reported persistent low back pain and in some instances referred leg pain.

Radiographic Outcomes

At 6 months after surgery, 19 patients (90.5%) who were treated with InFUSE Bone Graft had evidence of interbody fusion compared with 13 patients (65%) in the control group ($P = 0.067$) (Figure 9). At 12 months, all patients (100%) in the investigational group were found to have fusions compared with 17 patients (89.5%) in the control group. Based on their radiographs at the final 24-month follow-up, all patients (100%) in the investigational were considered to have remained fused (Figure 10).

One patient in the investigational group did meet the criteria for fusion but underwent supplemental posterior fixation after the 24-month follow-up period. In this patient, the attending physician identified motion within the facet joints and elected to

Deleted: 01/01/02

add supplemental posterior fixation to the spinal motion segment just after the 24-month visit. By the criteria of this study, this patient was recorded as having a successful interbody fusion at the 12- and 24 month follow-up examination and is not considered a failure until the 36-month follow-up. All patients were found to have bony integration of the allografts to the vertebral endplates and trabeculated new bone formation across the fused interspace. Considering this one investigational patient as fusion failure secondary to the use of supplemental posterior fixation, the fusion rate for the investigational group was 95.8%.

At 24 months in the control autograft group, 13 patients (68.4%) were considered to have fusions (Figure 11). In the control group, there were no failures of the allograft dowels. Three control patients underwent supplemental posterior fixation for pseudarthrosis. Radiographic lucencies developed at the interface of the allograft to the vertebral endplate between the 12 and 24-month follow-ups (Figure 12). This lead to the fall off in the fusion rate in the control group. There was no migration of the implants.

DISCUSSION

Recombinant human bone morphogenetic protein-2 (rhBMP-2) is an osteoinductive growth factor.[2,18] Urist discovered the capabilities of demineralized bone matrix to induce ectopic bone formation in a rat muscle pouch and introduced the concept that bone growth factors can induce new bone formation independent of the bone tissue environment.[20] Bone morphogenetic protein-2 is one of several proteins identified from bone tissue that acts a osteoinductive cytokine and induces the differentiation of pluripotential precursor cells along an osteogenic line. A pure form of this protein can be produced through standard recombinant technology. The human cDNA sequence is

Deleted: 01/01/02

created through the use of oligonucleotide probes, and these clones are then spliced into a viral vector and transfected into a carrier cell in a process called recombination. These production cells (Chinese hamster ovary cells) have the ability to produce large quantities of rhBMP-2. Creating recombinant human proteins in this manner avoids potential complications associated with disease transmission from allograft or xenograft sources.

The availability of rhBMP-2 in pure "unlimited" sources has the ability to greatly enhance spinal fusion results while lowering pain scores associated with a bone graft harvesting procedure. The purpose of this study was to assess the efficacy of this recombinant protein impregnated on a collagen sponge in a threaded cortical allograft dowel for the treatment of degenerative disc disease by an anterior interbody fusion.

To date, in both animal and human studies, rhBMP-2 has been shown to be capable of inducing new bone formation.[2,17] In a study of anterior lumbar interbody fusion in nonhuman primates, rhBMP-2 and an absorbable collagen sponge carrier was shown to promote fusion through osteoinduction.[10] New bone formation appeared to be superior to autogenous iliac crest graft with cortical dowel allograft. Similarly, in a preliminary clinical study involving the use of InFUSE Bone Graft™ and a tapered cylindrical titanium cage in humans, arthrodesis was found to occur more reliably in patients treated with rhBMP-2 than in controls treated with autogenous bone graft.[3]

This study is the first clinical report of the effectiveness of rhBMP-2 used with cortical allograft to promote anterior lumbar intervertebral fusion in humans. There were no unanticipated adverse events that were related to the use of InFUSE™ Bone Graft occurred during the course of the study. The investigational group did not undergo an

Deleted: 01/01/02

autogenous bone graft harvesting procedure. This lead to statistically significant reduction in operative time and in decreased blood loss during the surgical procedure.

Overall, the investigational group who received rhBMP-2 on a collagen sponge carrier (InFUSE Bone Graft™) showed higher rates of success in the reduction of painful symptoms of back and leg pain associated with degenerative lumbar disc disease than the control autograft group. Patients in the investigational group showed an improvement in back pain of more than 7 points at their initial postoperative visit. Back pain continued to improve throughout the study and averaged close to a 9-point improvement in pain scores at 24 months after surgery. The mean improvement scores for low back pain in the BMP group were statistically significantly greater than those reported in the autograft group. In the investigational group, leg pain improved by more than five points within six weeks of surgery and remained unchanged at the last clinical follow-up at 24 months. At all clinical evaluations, the BMP group showed greater relief of leg pain when compared to the control group. Similarly at 12 and 24 months, the investigational patients showed a higher rate of success than the control patients in their overall neurologic success scores. The use of rhBMP-2 obviates the need for autogenous bone graft. The investigational group had no complaints of iliac bone harvesting site pain while the control group had complaints of hip pain throughout the 2-year study period.

Coinciding with the reduction in painful symptoms, the investigational group also showed a greater and faster functional recovery. The Oswestry Low back Disability Questionnaire was used to measure the level of pain and dysfunction associated with various activities of patients enrolled in the clinical trial. At all time periods, the investigational group had greater improvements in Oswestry scores than the control

Deleted: 01/01/02

group. The mean improvements in Oswestry Disability scores at 12 and 24 months (31.6 and 33.5 points) are amongst the highest improvements in the literature. Return to work status was also assessed to evaluate functional recovery of the patients in the study. Similarly, higher percentages of patients in the investigational group were also able to return to work. In this group, 45.8% of patients were working prior to surgery and 66.7% were working at 24 moths postoperatively.

The investigational group also showed improved general health status following surgery. The Short Form SF-36 was used to measure specific health concepts related to physical and social functioning and limitations. In both the Physical (PCS) and Mental (MCS) Components of the SF-36, the BMP group showed higher mean scores at 24 months than the control group. As would be expected from these improved outcomes, patient satisfaction was higher in the BMP group. At 24 months, over 83% of patients in the BMP group responded that they were satisfied with their surgical outcome to all three questions that were asked.

The investigational BMP group showed higher rates of fusion when compared with the control group at 6, 12 and 24 months. The difference in fusion rates at 24 months was statistically different (p=0.004). However, one investigational patient underwent a supplemental fixation procedure after the 24-month visit. The findings from the 24-month radiographs and CT scans did meet the fusion criteria. The use of supplemental fixation in this patient reduced the fusion rate in the investigational group to 95.8%. The fusion rate in the autograft control group decreased from 89.5% to 68.4% between 12 and 24 months. This identification of these 4 new pseudarthroses during this time period was secondary to the development of lucencies surrounding the bone dowel and vertebral

Deleted: 01/01/02

body interface and loss contiguous bone across the disc space. None of these late radiographic findings occurred in the investigational group.

RhBMP-2 was shown to be a promising method of facilitating anterior intervertebral spinal fusion and of decreasing pain and improving clinical outcomes after anterior lumbar fusion surgery with allograft bone dowels. These improved outcomes are due, in part, to the successful combination of the anterior surgical approach, the use of threaded allograft dowels and a high rate of successful interbody fusion.

Deleted: 01/01/02

REFERENCES

1. Blumenthal SL, Baker J, Dossett A, Selby DK. The role of anterior lumbar fusion for internal disc disruption. Spine 1988;13:566-9.

2. Boden SD, Schimandle JH, Hutton WC. Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 1995;20:2633-44.

3. Boden SD, Zdeblick TA Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Spine 2000;25:376-81.

4. Boyd, L.M.; Estes, B.T. and Liu M. "Biomechanics of Lumbar Interbody Constructs, *Effect of Design and Materials.*" Chirurgie Endoscopique et Mini-invasive du Rachis. Ed. Husson JL, LeHuec JC. Sauramps Médical. Montpelier, France. pp 181-92, 1999.

5. Burkus JK, Dorchak JD, Sanders DL, Foor BD: Single-level anterior lumbar interbody fusion using threaded cortical bone allografts. North American Spine Society Meeting of the Americas, Miami, Florida, 1999.

6. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group -- radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. Neurosurg Focus 2001;10:1-9.

7. Crock HV. Anterior lumbar interbody fusion: indications for its use and notes on surgical technique. Clin Orthop 1982;165:157-63.

8. Flynn JC, Houque MA. Anterior fusion of the lumbar spine. J Bone Joint Surg 1979;61A:1143-50.

Deleted: 01/01/02

9. Harmon PH. Anterior excision and vertebral fusion operation for intervertebral disc syndromes of the lower lumbar spine: three to five year results in 244 cases. Clin Orthop 1963;26:107-27.

10. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A. The use of recombinant human bone morphogenetic protein-2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999;24:629-36.

11. Kumar A, Kozak JA, Doherty BJ, Dickson JH. Interspace distraction and graft subsidence after anterior lumbar fusion with femoral strut allograft. Spine 1993;18:2393-2400.

12. Lane JD, Moore ES. Transperitoneal approach to the intervertebral disc in the lumbar area. Annals of Surgery 1948;127:537-51.

13. Loguidice VA, Johnson RG, Guyer RD, Stith WJ, Ohnmeiss DD, Hochschuler SH, Rashbaum RF. Anterior lumbar interbody fusion. Spine 1988;13:366-9.

14. Leong JC, Chun SY, Grange WJ, Fang D: Long-term results of lumbar intervertebral disc prolapse. Spine 1983;8:793-9.

15. Morales RW, Pettine KA, Salib RM. A biomechanical study of bone allografts used in lumbar interbody fusions. North American Spine Society – 6th Annual Meeting, Keystone, Colorado 1991

16. Sacks S. Anterior interbody fusion of the lumbar spine. J Bone Joint Surg [Br] 1965;47:211-23.

17. Sandhu HS, Kanim LEA, Toth JM, et al. Experimental spinal fusion with recombinant human bone morphogenetic protein-2 without decortication of osseous elements. Spine 1997;22:1171-80.

Deleted: 01/01/02

18. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995; 20:1326-37.

19. Stauffer RN, Coventry MB. Anterior interbody lumbar spine fusion. J Bone Joint Surg [Am]1972;54:756-68.

20. Urist MR. Bone: Formation by autoinduction. Science 1965;150:893-9.

23 Deleted: 01/01/02

TABLE 1. Patient Demographic Data

Demographic Data	InFUSE Bone Graft™ Group	Autograft Group
Number of patients	24	22*
Age (years)	41.5	45.6
Weight (lbs)	172.7	176.0
Sex (male/female)	8/16	10/12
Workers' compensation (%)	5 (21)	7(32)
Spinal litigation (%)	4 (17)	4(18)
Tobacco use (%)	8 (33)	6(27)
Previous surgeries (%)	11 (46)	7 (32)

*One patient died an accidental death at 6 months after surgery.

Table 2. Intraoperative Data

Surgical Data	InFuse Bone Graft™ Group	Autograft Group
Operative time (min)	103	114
Blood loss (mL)	124.1	245.0
Levels (%)		
L4-L5	11 (46)	8 (36)
L5-S1	13 (54)	14 (64)
Hospital stay (days)	3.4	3.7

25

Deleted: 01/01/02

Table 3. Neurologic Outcomes

Period	Variable	Investigational (n=24)	Control (n=22)
6 Weeks	Overall		
	Success	21 (87.5)	18 (90.0)
	Failure	3 (12.5)	2 (10.0)
	p-value*	1.000	
3 Months	Overall		
	Success	21 (87.5)	20 (95.2)
	Failure	3 (12.5)	1 (4.8)
	p-value*	0.611	
6 Months	Overall		
	Success	21 (87.5)	17 (89.5)
	Failure	3 (12.5)	2 (10.5)
	p-value*	1.000	
12 Months	Overall		
	Success	23 (95.8)	16 (84.2)
	Failure	1 (4.2)	3 (15.8)
	p-value*	0.306	
24 Months	Overall		
	Success	21 (87.5)	11 (73.3)
	Failure	3 (12.5)	4 (26.7)
	p-value*	0.396	

*p-values are from Fisher's exact test.

Deleted: 01/01/02

Table 4. Back Pain Outcomes

Period	Variable	Investigational (n=24)	Control (n=22)
Preoperative	n	24	22
	Mean	16.3	16.3
	Std	2.6	2.2
6 Weeks	n	24	21
	Mean	8.9	10.4
	Std	4.5	4.2
	p-value**	0.297	
Improvement from Preoperative	Mean	-7.4	-6.0
	p-value*	<0.001	<0.001
3 Months	n	24	21
	Mean	7.9	10.9
	Std	4.3	4.5
	p-value**	0.038	
Improvement from Preoperative	Mean	-8.4	-5.4
	p-value*	<0.001	<0.001
6 Months	n	24	20
	Mean	6.8	9.9
	Std	4.3	5.1
	p-value**	0.034	
Improvement from Preoperative	Mean	-9.5	-6.4
	p-value*	<0.001	<0.001
12 Months	n	24	19
	Mean	7.4	9.2
	Std	5.3	6.3
	p-value**	0.338	
Improvement from Preoperative	Mean	-8.9	-7.2
	p-value*	<0.001	<0.001
24 Months	n	24	17
	Mean	7.4	10.9
	Std	6.0	6.0
	p-value**	0.047	
Improvement from Preoperative	Mean	-8.9	-5.2
	p-value*	<0.001	<0.001

*p-values for change from preoperative in each group are from paired test.
**p-values for difference between the treatment groups are from analysis of variance.

27

Deleted: 01/01/02

Table 5. Leg Pain Outcomes

Period	Variable	Investigational (n = 24)	Control (n = 22)
Preoperative	n	24	22
	Mean	12.8	14.6
	Std	5.7	4.1
6 Weeks	n	24	21
	Mean	7.0	8.8
	Std	5.9	5.9
	p-value**	0.933	
Improvement from Preoperative	Mean	-5.8	-5.6
	p-value*	0.001	0.001
3 Months	n	24	21
	Mean	6.2	8.3
	Std	4.4	5.8
	p-value**	0.874	
Improvement from Preoperative	Mean	-6.7	-6.4
	p-value*	<0.001	<0.001
6 Months	n	24	20
	Mean	5.0	6.1
	Std	4.7	4.4
	p-value**	0.654	
Improvement from Preoperative	Mean	-7.9	6.3
	p-value*	<0.001	<0.001
12 Months	n	24	19
	Mean	5.5	8.1
	Std	5.5	6.1
	p-value**	0.818	
Improvement from Preoperative	Mean	-7.3	-6.8
	p-value*	<0.001	<0.001
24 Months	n	24	17
	Mean	6.3	11.5
	Std	6.0	6.3
	p-value**	0.142	
Improvement from Preoperative	Mean	-6.5	-3.5

ALIF with InFUSE Bone Graft
Burkus et al.

28

Deleted: 01/01/02

	p-value*	<0.001	0.023

*p-values for change from preoperative in each group are from paired test.
**p-values for difference between the treatment groups are from analysis of variance.

Deleted: 01/01/02

Table 6. Patient Satisfaction

Period	Variable	Investigational (n=24)	Control (n=22)
6 Months	I am satisfied with the results of my surgery		
	Definitely True	17 (70.8)	12 (60.0)
	Mostly True	3 (12.5)	4 (20.0)
	p-value*	0.503	
	I was helped as much as I thought I would be by my surgery		
	Definitely True	14 (58.3)	6 (30.0)
	Mostly True	6 (25.0)	9 (45.0)
	p-value*	0.229	
	All things considered I would have the surgery again for the same condition		
	Definitely True	18 (75.0)	13 (65.0)
	Mostly True	1 (4.2)	3 (15.0)
	p-value*	0.312	
12 Months	I am satisfied with the results of my surgery		
	Definitely True	14 (58.3)	6 (30.0)
	Mostly True	6 (25.0)	9 (45.0)
	p-value*	0.229	
	I was helped as much as I thought I would be by my surgery		
	Definitely True	12 (50.0)	6 (30.0)
	Mostly True	7 (29.2)	4 (20.0)
	p-value*	0.169	
	All things considered I would have the surgery again for the same condition		
	Definitely True	15 (62.5)	11 (55.0)
	Mostly True	4 (16.7)	1 (5.0)
	p-value*	0.130	
24 Months	I am satisfied with the results of my surgery		
	Definitely True	13 (54.2)	6 (30.0)
	Mostly True	9 (37.5)	5 (25.0)
	p-value*	0.084	
	I was helped as much as I thought I would be by my surgery		
	Definitely True	13 (54.2)	6 (30.0)
	Mostly True	9 (37.5)	5 (25.0)
	p-value*	0.249	
	All things considered I would have the surgery again for the same condition		
	Definitely True	15 (62.5)	11 (55.0)
	Mostly True	6 (25.0)	2 (10.0)
	p-value*	0.137	

ALIF with InFUSE Bone Graft Burkus et al.	30	Deleted: 01/01/02

*p-values are from the Chi-square test.

Deleted: 01/01/02

Table 7. Oswestry Low Back Pain Disability Scores

Period	Variable	Investigational	Control
Preoperative			
	n	24	22
	Mean	52.4	55.3
	Std	13.1	13.5
7 Weeks			
	n	24	21
	Mean	39.9	47.2
	Std	16.8	18.8
	p-value**	0.307	
Improvement from Preoperative			
	Mean	-12.5	-7.9
	p-value*	<0.001	0.024
4 Months			
	n	24	21
	Mean	29.0	42.0
	Std	14.7	19.0
	p-value**	0.032	
Improvement from Preoperative			
	Mean	-23.4	-14.3
	p-value*	<0.001	<0.001
7 Months			
	n	24	20
	Mean	21.6	34.4
	Std	16.1	21.8
	p-value**	0.039	
Improvement from Preoperative			
	Mean	-31.0	-20.9
	p-value*	<0.001	<0.001
13 Months			
	n	24	19
	Mean	20.8	30.0
	Std	14.9	21.2
	p-value**	0.171	
Improvement from Preoperative			
	Mean	-31.6	-24.7
	p-value**	<0.001	<0.001
25 Months			
	n	24	17
	Mean	18.9	32.8
	Std	14.5	22.7
	p-value**	0.039	
Improvement from Preoperative			
	Mean	-33.5	-21.5
	p-value*	<0.001	<0.001

*p-values for change from preoperative in each group are from paired test.
**p-values for difference between the treatment groups are from analysis of variance.

32

Deleted: 01/01/02

Table 8. Additional Surgeries

Procedure	InFUSE Bone Graft™ Group	Autograft Group
Removals	0	0
Revisions	0	0
Supplemental fixation (%)	1 (4.2)	3 (13.6)
Reoperation (%)	0	1 (4.5)

Deleted: 01/01/02

LEGEND OF FIGURES

Figure 1. Comparison of neurologic outcomes in the investigational group (InFUSE Bone Graft) and the control group (iliac crest autograft). Success was based on postoperative neurologic condition being improved or no worse than the preoperative condition.

Figure 2. Comparison of back pain outcomes in the investigational group (InFUSE Bone Graft) and the control group (iliac crest autograft).

Figure 3. Comparison of leg pain outcomes in the investigational group (InFUSE Bone Graft) and the control group (iliac crest autograft).

Figure 4. Comparison of Short Form 36 Physical Component Scores in the investigational group (InFUSE Bone Graft) and the control group (iliac crest autograft).

Figure 5. Comparison of Short Form 36 Mental Component Scores in the investigational group (InFUSE Bone Graft) and the control group (iliac crest autograft).

Figure 6. Comparison of Oswestry Disability Questionnaire outcomes in the investigational group (InFUSE Bone Graft) and the control group (iliac crest autograft).

Figure 7. Comparison of return-to-work status in the investigational group (InFUSE Bone Graft) and the control group (iliac crest autograft).

Figure 8. Iliac crest bone graft harvest site pain in the control group.

Figure 9. Comparison of postoperative fusion outcomes in the investigational group (InFUSE Bone Graft) and the control group (iliac crest autograft).

Figure 10. Serial thin cut CT scans following a L5S1 fusion using InFUSE Bone Graft. Sagittal and frontal CT reconstructions through both the right and left dowels show the progression of the interbody fusion. The immediate postoperative reconstructions show

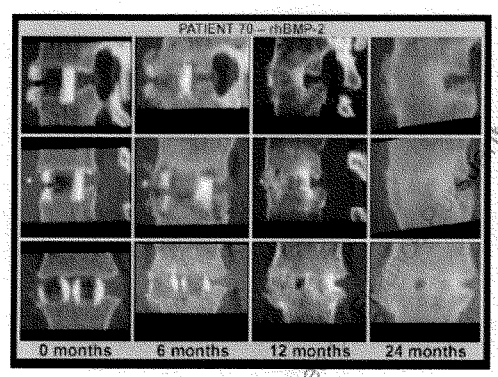
Deleted: 01/01/02

that the dowels have not been incorporated into the vertebral endplates and there is no bone formation in the central portion of the dowels. At six month the dowels are incorporated into the vertebral endplates and there is new formation within the dowels. At 12 months there is new bone formation connecting the adjacent vertebral bodies both inside and outside of the dowels. At 24 months the dowels have almost been completely reabsorbed and replaced with new trabecular bone formation.

Figure 11. Serial thin cut CT scans following a L5S1 fusion using autograft demonstrate the progression of the interbody fusion. Immediate postoperative scans show corticocancellous graft within the dowels. At six months, trabecular bone connects the adjacent vertebral bodies through the dowels and in anterior to the dowels. At 12 and 24 months, there is maturation of the interbody fusion with more bone formation and incorporation of the dowels to the vertebral endplates.

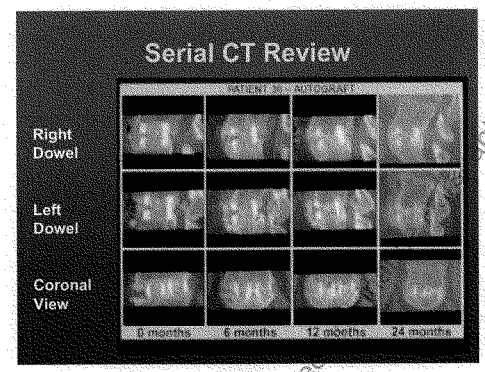
Figure 12. Serial thin cut CT scans following a L5S1 fusion using autograft show the development of a pseudarthrosis. At six months following surgery, the grafts with the dowels and the dowels themselves appear to have attached the adjacent vertebral endplates. At 12 months lucencies appear separating the dowels for the vertebral endplates. By 24 months, a radiolucent line involving the inferior portion of both dowels highlights noncontiguous bone formation between the vertebra consistent with a pseudarthrosis.

FIGURE # 10



Deleted: 01/01/02

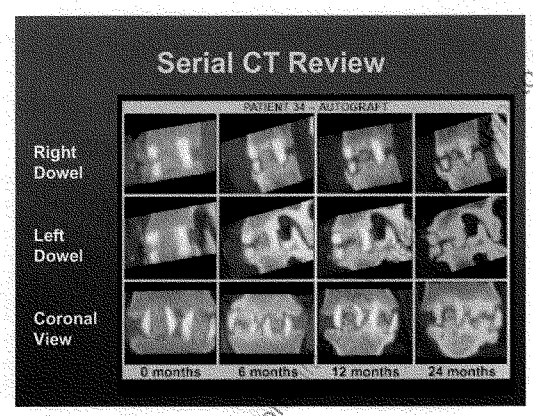
FIGURE #11



37

Deleted: 01/01/02

FIGURE #12



From: JKB[redacted]
Sent: Tuesday, January 1, 2002 04:11:02 PM
To: Peter Wehrly[redacted]
CC: Neil Beals[redacted]; Tara Hood[redacted]
Subject: Revised CT scan LT BMP manuscript

Attachments: Revised & reprinted CAT Scan BMP LT Cage.2.doc

Pete,

Here is number two. This is the revised CT Scan LT Cage paper. The SPINE criticisms were not that hard on this paper. I have incorporated suggested changes and have attached the revised paper.

Again, I will have the Hughston Foundation medical writing department review the paper before resubmitting.

I will begin reworking the Open LT BMP study manuscript once I watch Colorado beat up Oregon.

Best regards,

Ken Burkus

RADIOGRAPHIC ASSESSMENT OF INTERBODY FUSION USING rhBMP-2

J. Kenneth Burkus, M.D.*

John D. Dorchak, M.D.*

D. Lynn Sanders, CCRC†

From

The Hughston Clinic, PC

Columbus, Georgia

* Staff Physician, Spine Service, The Hughston Clinic, PC

† Spine Service, The Hughston Clinic, PC

Address correspondence and reprint requests to: J.K. Burkus, MD, The Hughston Clinic, [redacted]

Deleted: 12/29/01

ABSTRACT

Study Design. A prospective randomized study of the radiographic progress of fusion at 6, 12, and 24 months in 42 patients who underwent a single-level anterior lumbar interbody fusion using cylindrical interbody fusion cages.

Objectives. To determine the patterns and rates of osteoinduction associated with the use of recombinant human bone morphogenetic protein-2 (rhBMP-2) and an absorbable collagen sponge carrier in anterior lumbar interbody fusion with a tapered cylindrical fusion device.

Summary of Background Data. Studies have shown that rhBMP-2 used with allograft dowels increases the rate of interbody fusion by promoting osteoinduction and enhancing incorporation of the allograft. In a small series of human patients undergoing anterior lumbar interbody fusion with a tapered cylindrical fusion cage, rhBMP-2 has been shown to promote osteoinduction and fusion.

Methods. In this prospective nonblinded study, 42 patients were randomly divided into 2 groups: the investigational group underwent interbody fusion using two tapered cylindrical fusion cages (LT-CAGE™) and rhBMP-2 on an absorbable collagen sponge, and a control group underwent the procedure and received the devices and autogenous iliac crest bone graft. Plain radiographs and computed tomographic scans were used to evaluate the pattern of osteoinduction within the interbody space and the progression of fusion at 6, 12, and 24 months after surgery.

Deleted: 12/29/01

Results. All patients who received rhBMP-2 showed radiographic evidence of osteoinduction within the interbody cages at 6 months postoperatively. The density within the cages increased by an average of 142.0 Hounsfield units by 6 months and 228.7 units by 12 months. New bone formation occurred within the disc space outside of the cages by 6 months in 18 of the investigational group patients (18/22; 82%). By 24 months, all investigational patients showed new formation outside of the cages. In the autograft control group, the density within the cages increased by an average of 42 Hounsfield units and 10 (10/20; 50%) showed evidence of bone formation outside of the cages.

Conclusions. The use of rhBMP-2 is a promising method of facilitating anterior intervertebral spinal fusion in patients who have undergone anterior lumbar fusion surgery.

Key words: anterior lumbar interbody fusion, bone morphogenetic protein, osteoinduction, radiography, interbody fusion cages

Key points:

1. New bone formation occurs within a lumbar space with recombinant human bone morphogenetic protein-2 and an absorbable collagen sponge carrier in anterior lumbar interbody fusion with a tapered cylindrical fusion device.
2. New bone formation occurs inside and outside of the tapered cylindrical fusion device.
3. New bone formation outside of the cages occurs more rapidly in patients treated with rhBMP-2 that in patients treated with autograft.

Précis

Forty-two patients were followed for 24 months after undergoing ALIF and receiving autogenous bone graft or rhBMP-2 with the LT-CAGE device. In the rhBMP-2 group, bone formation as evidenced by progressive density on thin-cut CT scans more than doubled at 6 months and more than tripled by 24 months. In the rhBMP-2 group, new bone formation occurred outside of the cages in 82% of patients by 6 months and 100% by 24 months. Rates of new bone formation and fusion exceeded that of the autograft control group.

Deleted: 12/29/01

Introduction

Clinical studies of anterior lumbar interbody fusion have identified differing rates of fusion.[7,9,14] The variation in fusion outcome is in part determined by the surgical technique, bone graft material, and method of intervertebral fixation.[4] Recombinant human bone morphogenetic protein-2 (rhBMP-2) (Genetics Institute, Cambridge, MA) is an osteoinductive growth factor.[1] In both animal and human studies, it has been proven to be capable of consistently inducing new bone formation.[2,12,13] In a study of anterior lumbar interbody fusion in nonhuman primates, rhBMP-2 and an absorbable collagen sponge carrier was shown to promote fusion through osteoinduction.[10] New bone formation appeared to be superior to autogenous iliac crest graft with cortical dowel allograft.

In the preliminary report of an unpublished human clinical trial of the use of rhBMP-2 and threaded cortical bone dowels, high rates of fusion were achieved.[6] Similarly, in a small clinical study, rhBMP-2 and a tapered cylindrical titanium cage, arthrodesis was found to occur more reliably in patients treated with rhBMP-2 than in controls treated with autogenous bone graft.[3]

Radiographic imaging of a developing fusion mass after anterior lumbar surgery is challenging in patients who have metallic interbody implants.[8,11] Thin-cut CT imaging (1 mm) is the most efficacious method of identifying bone formation within second-generation cages.[5,8] Recombinant human bone morphogenetic protein-2 (rhBMP-2) has been shown to promote osteoinduction and fusion. To determine its osteoinductive capability with a threaded, cylindrical,

Deleted: 12/29/01

tapered interbody device and an absorbable collagen sponge, we evaluated the radiographic outcomes of 42 patients who underwent a single-level anterior interbody fusion with the LT-CAGE device. We compared the radiographic outcomes in the investigational patients (LT-CAGE with rhBMP-2) with the outcomes in the control patients (LT-CAGE with autogenous bone graft).

Materials and Methods

Patients. Between August 1998 and March 1999, 45 patients with symptomatic single-level degenerative disc disease were enrolled in this prospective, randomized, nonblinded study. All patients were between the ages of 18 and 65 years and had symptomatic degenerative lumbar spondylosis at the L4-5 or L5-S1 levels. All patients had disabling low back or leg pain, or both, that had lasted for at least 6 months and had not resolved with nonoperative treatment. All patients were considered candidates for a single-level stand-alone anterior lumbar interbody fusion. No patients had osteoporosis, which was considered a criterion for exclusion. Patients were excluded from the study if they had spinal conditions other than degenerative disc disease, multi-level spondylosis, or Grade II or higher spondylolisthesis. Other exclusion criteria were symptomatic spondylosis outside of the L4-5 or L5-S1 disc space levels, were 40% above ideal body weight, had a history of chronic use of steroidal or nonsteroidal anti-inflammatory medications, and had a history of disc space infection. Patients were randomly assigned from a table of random numbers to receive the LT-

Deleted: 12/29/01

CAGE device (LT-CAGE™, Medtronic Sofamor Danek, Memphis, TN) with recombinant human bone morphogenetic protein-2 (rhBMP-2) (Genetics Institute, Cambridge, MA) on an absorbable collagen sponge carrier (Colla-Tec, Inc., Plainsboro, NJ) or the device with autogenous iliac crest bone graft.

Of the 45 patients enrolled in the study, 42 patients were followed for 24 months after surgery. Three patients were eliminated from this study for failure to complete the 24-month follow-up. In the investigational rhBMP-2 group, 1 patient did not complete the 24-month follow-up and was lost to follow up after his 12-month radiographic assessment. In the control autograft group, 1 patient was lost to follow-up after the 6-month assessment and 1 patient died of an unrelated coronary event at 9 months after surgery.

The investigational rhBMP-2 group consisted of 22 patients (11 men, 11 women) whose average age at surgery was 41.7 years. The control autogenous bone graft group consisted of 20 patients (11 men, 9 women) whose average age was 44.2 years. Four patients (18%) in the rhBMP-2 group and 2 patients (10%) in the autograft group had used tobacco within 6 months before surgery.

Surgical Procedure. The patients underwent an anterior lumbar interbody fusion procedure through an open retroperitoneal approach at a single study site by the two surgeon authors. In each patient, a complete anterior discectomy was carried out. The nucleus pulposus and the cartilaginous endplates were circumferentially removed through and anterior annular incision. The bony endplates were preserved. Following precise reaming of the endplates, two LT-CAGE devices

Deleted: 12/29/91

were inserted into the disc space. The cages were placed in the disc space contacting the vertebral ring apophysis both anteriorly and posteriorly. No cages were placed in an anteriorly recessed position. All cages placed flush to the anterior cortical margins of the vertebral body but not protruding outside of the margins of the disc space.

The rhBMP-2 used was reconstituted using sterile water and was used as a "single dose" at 1.5mg/ml. This dosage was the same in all patients studied. The solution (1.5 mg rhBMP-2/ml) was applied to a bovine collagen sponge and allowed to bind to the sponge for 15 minutes. The rhBMP-2 soaked sponge was then placed in the hollow central portion of the LT-CAGE device before its insertion into the prepared disc space. No additional sponges were placed outside of the devices. No autogenous grafts were used in the investigational group.

The control group received morcellized autogenous iliac crest graft placed within the cages. The bone graft was harvested form the inner table of the right iliac wing. Cortical and cancellous bone graft was obtained using osteotomes and gouges. The graft was morcellized using a ronguer and tightly packed into the cages prior to insertion. Additional graft was uniformly placed within the disc space anterior to the cages.

Radiographic Outcome Measurements. Plain radiographs and thin-cut computed tomographic (CT) scans (1 mm) were used to evaluate patterns of osteoinduction at 2 days and at 6, 12, and 24 months after surgery. Fusion was

Deleted: 12/29/01

defined as an absence of radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation of less than 5° on flexion-extension lateral radiographs, and continuous trabecular bone growth connecting the vertebral bodies. Two independent radiologists interpreted all radiographs and computed tomography scans. In cases in which the fusion outcome interpretation differed, a third independent radiologist was consulted. The radiologists who were interpreting the data and rendering assessment of bone density and fusion were unaware of the status of each patient they were evaluating.

Thin-cut CT scans were used to assess new bone formation and bone remodeling within and around the fusion cages. On the CT scans, fusion was defined by increased density within the cages and the presence of continuous trabecular bone formation through both of the cages. The changes in density within the cages were determined by precisely measuring the Hounsfield units (HU) within each cage on the serial CT scans. To reduce imaging artifact,[8] Hounsfield units were recoded within the central portion of the cages (at least 3 mm from the metallic side wall of the cages) and were calibrated against known densities on each scan (Figure 1).

Results

Plain Radiographs. At 12 months after surgery, 1 patient in the control group was identified as having a pseudarthrosis. This patient's standing lateral

Deleted: 12/29/01

radiographs showed radiolucencies surrounding both implants; dynamic flexion and extension lateral radiographs showed motion of greater than 5°. This patient underwent a posterior instrumented fusion to stabilize the lumbar motion segment. No other patient in the investigational group or the control group was identified as having a pseudarthrosis on plain radiographic studies.

Computed Tomography.

Bone Density Changes within Cages. In the rhBMP-2 investigational group, immediate postoperative CT scans showed an average density of 179.0 HU (range, 94-226 HU) within the central portion of the LT-CAGE, and the control group showed an average 541.3 HU (range, 403-712 HU) (Table 1) (Figure 2). At 6 months, the rhBMP-2 group showed an average increase to 322.1 HU (range, 178-488 HU); at 12 months, an increase to an average of 427.1 HU (range, 303-703 HU); and at 24 months, an increase to 442.9 HU (range, 434-789 HU). In the investigational group at six months, the average increase in density from the immediate postoperative scans was 142.0 HU; and at 12 months the average increase was 228.7 HU (Table 2). At 24 months, the average difference in density was 213.9 HU when compared to the average initial postoperative density (Figure 3).

In the autograft control group, the average density within the cages at 6 months was 574.6 HU (range, 379-714 HU); at 1 year, the average density was 667.1 HU (range, 462-903 HU); and at 24 months, the average density was 628.1 HU (range, 474-933 HU) . At six months, the average increase in density compared with the initial postoperative scan was 42.0 HU; at 12 months, the

Deleted: 12/29/01

change in density compared with the immediate postoperative scans increased to 184.6 HU. By 24 months, the average difference from the immediate postoperative scan was reduced to 64.3 HU.

Progression of densities within the cages correlated with evidence of fusion on standard plain radiographic measurements. One patient in the control group developed a pseudarthrosis at one year. This patient showed an average increase in the density of the grafts within the cages of only 45 HU.

Bone Formation Outside of Cages. At 6 months after surgery, new bone formation was identified in the rhBMP-2 group outside of the cages in 18 patients (82%), at 12 months in 21 patients (95%), and at 24 months in 22 patients (100%) (Table 3) (Figure 4). In the autograft group at 6 months, new bone formation was identified outside of the cages in 10 patients (50%), at 12 months in sixteen patients (80%), and at 24 months in 19 patients (95%) (Figure 5). It is important to note that all bone growth was contained within the interbody space. No ectopic bone formation was noted.

The patient in the control (autograft) group who developed a pseudarthrosis at 12 months showed no new bone formation outside the cages.

Discussion

Osteoinduction has been shown to occur within the LT CAGE in both the rhBMP-2 and autograft treated patients. In the rhBMP-2 group, bone formation, as evidenced by progressive density on thin-cut CT scans, almost doubled within

Deleted: 12/29/01

6 months of surgery and increased almost two and one half times by 24 months. New bone formation within the cages occurred most markedly during the first 6 to 12 months after surgery. Once new bone formation began to occur outside of the cages, the rate of increase in density within the cage tapered off. In the autograft control group, increases in bone density were also found; however, the rates of change were less than in the rhBMP-2 group.

The radiographic densities within the cages of the rhBMP-2 group at 24 months postoperatively (442.9 HU) did not reach the density of the autograft group following initial implantation (541.3 HU). The autograft group did have cancellous graft alone packed into the cages. The autograft group had both cancellous and cortical bone packed into the cages. The autogenous graft mixture would lead to higher density recording within the cage than one would expect from cancellous graft alone. One would anticipate that the rhBMP-2 formed bone within the cages placed in the central part of the disc space would not reconstitute cortical bone but would rather reconstitute bone with a less dense cancellous pattern. This study does provide some evidence that there is remodeling of the cortical bone grafts within the cages in the autograft group. The densities within the cages in the autograft group actually decline by 39 HU between 12 and 24 months (667.1 HU vs. 628.1 HU).

In the rhBMP-2 group, new bone formation had occurred outside of the cages by 6 months after surgery, and it occurred in all patients by 24 months. Rates of new bone formation exceeded those of the autograft control group. All new bone formation outside of the cages occurred within the confines of the disc

space. All CT scan slices and all reconstructed images were studied to evaluate new bone formation. No new bone formation extended outside of the annulus fibrosus; no bone growth was observed extending posteriorly into the spinal canal or posterolaterally into the neuroforamina.

The rapid development of bone outside of the cages at the periphery of the disc space in the rhBMP-2 group may also lead to the reduced density within the cages. With peripheral bone formation spanning the disc space, the biomechanical loading of the central portion of the disc space is reduced. The reduced loads would result in bone remodeling within the cages to accommodated the changing physiologic loading pattern. The density within the autograft group is reduced between 12 and 24 months postoperatively.

No patient in the rhBMP-2 group developed a pseudarthrosis using standard plain radiographic criteria; no patient in this group required an additional surgery. One patient in autograft control group developed a pseudarthrosis and was the only patient in the study to require a posterior stabilization procedure.

High fusion rates associated with new bone formation inside and outside of the cages can be achieved without harvesting bone from the iliac crest and without device-related adverse events. The use of rhBMP-2 with the LT-CAGE device is a promising method of facilitating anterior intervertebral spinal fusion in patients who have degenerative lumbar disc disease.

References

1. Boden SD, Schimandle JH, Huttton WC. Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 1995;20: 2633-44.

2. Boden SD, Horton WC, Martin G, et al. Laproscopic anterior arthrodesis with rhBMP-2 in a titanium interbody threaded cage. J Spinal Disord 1998;11: 95-101.

3. Boden SD, Zdeblick TA Sandhu HS, et al. The use of rhBMP-2 in interbody fusion cages. Spine 2000;25: 376-81.

4. Boyd LM, Estes BT, Liu M. Biomechanics of lumbar interbody constructs: Effect of design and materials. In: Husson JL, LeHuec JC, eds. Chirurgie Endoscopique et Mini-invasive du Rachis. Montpelier, France: Sauramps Médical, 1999:181-192.

5. Burkus JK, Foley K, Haid R, et al.: Surgical Interbody Research Group—radiographic assessment of interbody fusion devices: fusion criteria for anterior lumbar interbody surgery. Neurosurg Focus [serial online] April 2001;10(4): Article 11.

6. Burkus JK, Transfeldt EE, Kitchel SH, et al. A prospective and randomized study assessing the clinical and radiographic outcomes of patients treated with rhBMP-2 and threaded cortical bone dowels in the lumbar spine. Proceedings of the 15th Annual meeting of the North American Spine Society. Rosemont, IL: North American Spine Society 2000:114.

7. Camissa FP, Dhawlikar SH, Parvataneni HK, et al. Radiolucencies surrounding allograft bone dowels in the early post-operative period. Proceedings of the 13th Annual meeting of the North American Spine Society. Rosemont, IL: North American Spine Society 1998:273.

8. Cizek GR, Boyd LM. Imaging pitfalls of interbody spinal implants. Spine 2000;25:2633-36.

9. Flynn JC, Houque MA. Anterior fusion of the lumbar spine. J Bone Joint Surg [Am] 1979;61:1143-50.

10. Hecht BP, Fischgrund JS, Herkowitz HN, et al. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999;7:629-36.

11. Heithoff KB, Mullin WJ, Holte D, et al. The failure of radiographic detection of pseudarthrosis in patients with titanium lumbar interbody fusion cages. Proceedings of the 14th Annual meeting of the North American Spine Society. Rosemont, IL; North American Spine Society 1999:14.

12. Sandhu HS, Kanim LEA, Toth JM, et al. Experimental spinal fusion with recombinant human bone morphogenetic protein 2 without decortication of osseous elements. Spine 1997;22:1171-80.

13. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995;20:1326-37.

14. Stauffer RN, Coventry MB. Anterior interbody lumbar spine fusion. J Bone Joint Surg [Am] 1972;54:756-68.

Table 1. Bone Density Measurements Within The Interbody Fusion Device.

Period	Bone density (HU)*	Investigational Group	Control Group
Immediate postoperative	n	16	12
	Mean ± SD	179.0 ± 87.7	541.3 ± 103.7
	n	20	18
6 months	Mean ± SD	322.1 ± 130.7	574.6 ± 139.8
	n	21	19
12 months	Mean ± SD	427.1 ± 166.8	667.1 ± 169.0
	n	20	18
24 months	Mean ± SD	442.9 ± 153.0	628.1 ± 211.5

*HU = Hounsfield units

Table 2. Bone Density Increases Within The Interbody Fusion Device From The Immediate Postoperative Scan.

Period	Bone density increase	Investigational (rhBMP) Group	Control (autograft) Group	p-value**
	n	16	11	
6 months	Mean ± SD	142.0 ± 143.3	42.0 ± 79.2	0.046
		(p = 0.001)*	(p = 0.109)*	
	n	15	12	
12 months	Mean ± SD	228.7 ± 199.3	184.6 ± 180.6	0.557
		(p = 0.001)*	(p = 0.005)*	
	n	14	12	
24 months	Mean ± SD	213.9 ± 186.5	64.3 ± 199.9	0.060
		(p = 0.001)	(p = 0.289)	

*P-values for changes from the immediate postoperative period in each group were from paired tests.

**P-values for differences between the treatment groups were from analysis of variance.

Deleted: 12/29/01

Table 3. Number Of Patients Who Had Bone Formation Outside Of Interbody Fusion Device.

Postoperative period	Investigational (rhBMP) Group	Control (autograft) Group	P-value*
6 months	18/22 (82%)	10/20 (50%)	0.049
12 months	21/22 (95%)	16/20 (80%)	0.174
24 months	22/22 (100%)	19/20 (95%)	0.476

*P-values were from Fisher's exact test for comparing the differences between the treatment groups.

Legend of Figures

Figure 1. Thin cut CT scan (1 mm) sagittal reconstruction through the central portion of the interbody fusion cage shows the elliptical outline of region 3 millimeter away from the cage sidewalls for determination of Hounsfield Units.

Figure 2. Comparison of the average bone density within the interbody fusion device between the rhBMP-2 group and the autograft group.

Figure 3. A. Thin cut CT scan (1 mm) sagittal reconstruction at 2 days after surgery shows good placement of the cage within the disc space. The rhBMP-2 soaked sponge occupies the central portion of the cage. There is no bone present with the cage or the disc space. B. CT image at 2 years postoperatively shows new bone formation inside and outside of the cage.

Figure 4. A. Thin cut CT scan (1 mm) sagittal reconstruction immediately after surgery with rhBMP-2 shows no bone present outside of the cage. B. CT image at 6 months after surgery shows new bone formation within the disc space both anterior and posterior to the cage. This sagittal reconstructed image is taken through a cage placed within the confine of the disc space but at its lateral margins. The bone seen outside of the confines of the disc space is a portion of the facet joint complex and does not represent bone growth extending beyond the disc space.

Fig. 5. Comparison of the percentage of new bone formation outside the interbody fusion device between the rhBMP-2 group and the autograft group.

From: JKB[redacted]
Sent: Monday, February 4, 2002 05:33:22 AM
To: Peter Wehrly[redacted]com]; Neil Beals[redacted]; Bailey Lipscomb[redacted]
CC: Mike DeMane[redacted]
Subject: BMP Bone Bowel Manuscript

Attachments: Revised Bone Dowel BMP Paper.5.doc; JKB resubmit letter2.doc

Pete, Neil, Bailey:

I thought that if I sent you the revised Bone Dowel BMP manuscript, you guys might give me some insight into how the FDA meeting went on Friday.

Tara Hood continued to provide information to the medical writers at the Hughston Foundation while I was away and carried this manuscript revision forward.

I hope this revision will be acceptable for publication at SPINE. Boden - though - is rather hard to predict.

OK, I know I am behind on the LT paper but I am also late for clinic.

It is really invigorating to have so much good quality clinical research material to work on.

Best regards,

Ken Burkus

Clinical and Radiographic Outcomes of Anterior Lumbar Interbody Fusion Using Recombinant Human Bone Morphogenetic Protein-2

J. Kenneth Burkus, MD*

Ensor Transfeldt, MD†

Scott H. Kitchel, MD‡

Robert Watkins, MD§

and

Richard Balderston, MD‖

* Hughston Spine Service, The Hughston Clinic, Columbus, Georgia

† Twin Cities Spine Service, Minneapolis, Minnesota

‡ Orthopedic Healthcare NW, Eugene, Oregon

§ The Center for Spinal Surgery, Los Angeles, California

‖ 3B Orthopedics, Philadelphia, Pennsylvania

This study was sponsored by Medtronic Sofamor Danek, Memphis, TN.

Address correspondence and reprint requests to: J.K. Burkus, MD, The Hughston Clinic, PC, [redacted]

ABSTRACT

Study Design. A prospective nonblinded multicenter study of outcomes in patients undergoing single-level anterior lumbar discectomy and interbody fusion with InFUSE™ Bone Graft (rhBMP-2).

Objective. To determine the safety and effectiveness of InFUSE™ Bone Graft applied to an absorbable collagen sponge in anterior lumbar interbody fusion with threaded cortical allografts.

Summary of Background Data. In primates, rhBMP-2 used with allograft dowels was shown to increase rates of interbody fusion by promoting osteoinduction and enhancing incorporation of the allograft. Recently, in a small series of human patients undergoing ALIF with a tapered cylindrical metal fusion cage, InFUSE™ Bone Graft has been shown to promote osteoinduction and fusion.

Methods. Forty-six patients underwent a single-level anterior lumbar discectomy and interbody fusion at five investigational sites. They were randomly assigned to one of two groups, and the results in the investigational patients who received threaded cortical allograft dowels with InFUSE™ Bone Graft were compared with those in the control patients who received threaded allograft dowels with autogenous iliac crest bone graft. Patients clinical outcomes were assessed using neurologic status, work status, and Oswestry Low Back Pain Disability, Short Form-36, and back and leg pain questionnaires. Anteroposterior, lateral, flexion-extension radiographs, and computed tomography scans were used to evaluate the progression of fusion at 6, 12, and 24 months after surgery.

Results. All patients who received InFUSE™ Bone Graft showed radiographic evidence of bony induction and early incorporation of the cortical allografts. All patients in this group had fusions at 12 months that remained fused at 24 months. At 12 and 24 months, the investigational group showed higher rates of fusion and improved neurologic status and back and leg pain when compared with the control group. There were no unanticipated adverse events related to the use of InFUSE™ Bone Graft.

Conclusion. The use of InFUSE™ Bone Graft is a promising method of facilitating anterior intervertebral spinal fusion, decreasing pain, and improving clinical outcomes in patients who have undergone anterior lumbar fusion surgery with structural threaded cortical allograft bone dowels.

Key words: anterior lumbar interbody fusion, bone morphogenetic protein, degenerative disc disease, lumbar spine

PRÉCIS

In 46 patients who underwent anterior lumbar interbody fusion with threaded cortical allografts and were followed for 2 years, the investigational group that received InFUSE™ Bone Graft on a collagen sponge carrier showed higher rates of fusion at 6, 12, and 24 months after surgery when compared with the group that received autogenous iliac crest bone graft. These patients demonstrated faster and greater functional recovery and greater reduction of back and leg pain than the controls, and a higher percentage of the investigational group than of the autogenous bone graft group was able to return to work.

INTRODUCTION

Cylindrical threaded allograft dowels can be used as stand-alone intervertebral implants that function as an instrumented anterior lumbar interbody fusion (ALIF). They are not intradiscal spacers that require additional segmental stabilization. The threaded cortical bone dowels can withstand lumbar compressive loads and can promote load sharing between the allograft and the host bone while maximizing device porosity.[4,17] These interbody constructs are implanted within the central portion of the disc space through a controlled insertion technique. Impacted allografts, when used alone for interbody fusion in the lumbar spine, have been reported to have a high rate of pseudarthrosis and subsidence.[9,12,21] Contemporary reports of large clinical series of ALIFs using impacted grafts have shown various rates of fusion and differing clinical outcomes.[1,7,10,13-15,18] The threaded dowels resist expulsion and stabilize the bone-implant interface.[4] In addition, threaded bone dowels offer increased strength to support cancellous graft material.[19] In one clinical series, 43 patients were followed for more than 1 year and had a high fusion rate and improved clinical outcomes.[5]

InFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, TN) is recombinant human bone morphogenetic protein applied to an absorbable collagen sponge. Its use replaces the need for autogenous bone grafts and eliminates the complications associated with iliac crest graft harvesting. In a clinical series of patients undergoing an ALIF procedure with a tapered cylindrical metal fusion cage, InFUSE™ Bone Graft has been shown to promote osteoinduction and increase rates of fusion.[3] Our report presents the 2-year clinical and radiographic results of the use of InFUSE™ Bone Graft (rhBMP-2) with

a collagen sponge carrier inside a cylindrical threaded cortical allograft dowel in patients undergoing anterior lumbar interbody fusion.

MATERIALS AND METHODS

Study Design. This prospective, randomized, non-blinded study was conducted under an approved investigational device exemption (IDE). Forty-six patients at five investigational sites had ALIF surgery between April and August 1998. The patients were randomly assigned to 1 of 2 study groups. The investigational group received InFUSE™ Bone Graft, recombinant human bone morphogenetic protein-2 (rhBMP-2) applied to an absorbable collagen sponge carrier, used in conjunction with the MD-II™ threaded cortical bone dowel (Regeneration Technologies, Inc., Alachua, FL). The control group received autogenous iliac crest bone graft. Data were collected preoperatively, intraoperatively, and at 6 weeks, 3, 6, 12 and 24 months postoperatively. Operative procedure details and adverse events were also recorded.

Degenerative Lumbar Disc Disease. Degenerative lumbar disc disease refers to a specific pain syndrome that originates from degenerative changes and instability patterns within the intervertebral disc. Diagnosed by a history of clinical complaints, physical findings, and neuroradiographic studies, this syndrome is characterized by chronic and, at times, incapacitating low back pain, which is often felt as referred pain in the buttock and posterior aspect of the thigh. The referred leg-pain pattern rarely extends below the knees and radiates in a nondermatomal distribution into the lower extremities. Pain is usually exacerbated by vigorous activities and relieved by rest. Prolonged sitting may be painful, and patients often have difficulty finding a comfortable position. Patients with this degenerative condition do not usually exhibit objective neurologic deficits. Positive

sciatic tension signs are also uncommon. Patients often have restricted range of motion of the lumbar spine, tenderness to palpation over the affected lumbar motion segment, and paravertebral muscle spasm.

The diagnosis is confirmed with neuroradiographic studies, including plain radiographs, magnetic resonance imaging (MRI), and discography. Plain radiographs often show signs of instability, such as disc space collapse, radial osteophytes, retrolithesis, spondylolisthesis, or a combination of these conditions. Dynamic flexion-extension lateral radiographs are sometimes necessary to show patterns of sagittal plane translation. In these degenerative conditions, MRI shows desiccation of the disc, sclerosis of the adjacent vertebral endplates, and radial protrusion of the annulus. Discography can identify radial tears in the annulus fibrosus and early degenerative changes in the disc. However, the diagnosis of painful degenerative lumbar disc disease is confirmed with a positive provocative pain response during discography. To identify the pain generator accurately, discography must elicit a concordant reproduction of the patient's painful symptoms at the time of the injection. The radiographic findings and the provocative pain response during discography must be correlated with other neuroradiographic studies and clinical findings. Discography cannot be used alone to select patients for surgery.

Patient Population. All patients were between the ages of 19 and 68 years and had symptomatic degenerative disc disease at the L4-L5 or L5-S1 levels. All patients had had low back pain for at least 6 months before their surgery that was recalcitrant to nonoperative treatment modalities, such as physical therapy, bed rest, and anti-inflammatory medications. Patients were included in the study if their plain radiographic findings documented single-level disc disease, and they had undergone at least one

additional confirmatory neuroradiographic study, such as MRI, CT-enhanced myelography, or discography. All patients were considered candidates for a single-level stand-alone anterior lumbar interbody fusion.

Patients were excluded from the study if they had spinal conditions other than single-level symptomatic degenerative disc disease or Grade 0 or 1 spondylolisthesis. Other exclusion criteria were symptomatic disc disease at a level other than the L4-L5 or L5-S1 disc space levels, obesity (more than 40% above ideal body weight), a history of discitis, or a medical condition that required medication, such as steroids or nonsteroidal anti-inflammatory medications, that could interfere with fusion.

The investigational group comprised 24 patients who were treated with InFUSE™ Bone Graft (Table 1). There were 22 patients in the control treatment group who were treated with autograft. In the control group, 1 patient was lost to follow-up and was excluded from the study; and 1 patient died in a house fire at 6 months after surgery leaving 20 patients in this group who were followed for a minimum of 24 months after surgery.

Surgical Technique. The patients underwent an open ALIF using either a transperitoneal or a retroperitoneal approach to the lumbosacral spine. In each patient, a complete discectomy was carried out. An incision was made in the annulus fibrosus, the nucleus pulposus and the cartilaginous endplates were circumferentially removed; however, the bony endplates were preserved prior to reaming and tapping of the endplate for receipt of the dowel. Two allograft bone dowels were then inserted into each disc space.

The rhBMP-2 was reconstituted using sterile water and a single dose at a concentration of 1.5 mg/mL was administered. The concentration was the same in all

patients. The solution was applied by syringe to an absorbable collagen sponge. Next, the collagen sponge was placed into the central portion of the bone dowel. The total dose (8 to 12 mL) depended on the capacity of the bone dowel (16, 18, or 20 mm) used. Additional InFUSE™ Bone Graft (or rhBMP-2 prepared sponges) was placed between the bone dowels. No autogenous grafts were used in the investigational group.

The control group received morcellized autogenous iliac crest graft in conjunction with the threaded cortical bone dowels. The iliac grafts were harvested through a separate incision directly over the iliac wing. The inner or outer table of the ilium was exposed subperiostealy and corticocancellous grafts were harvested. A single cortex was preserved in all grafts; no bicortical iliac grafts were obtained. The central opening of the dowels were packed with the bone graft before their insertion into the disc space. Additional bone graft was packed between and anterior to the dowels.

Postoperative Care. All patients were instructed to wear an external orthosis for 6 to 12 weeks after surgery. Patients were encouraged to ambulate immediately after surgery. Physical activities were advanced at the discretion of the attending surgeon.

Clinical Outcome Measurements. Assessments were completed preoperatively, during the patient's hospitalization, and postoperatively at 6 weeks and 3, 6, 12, and 24 months. Clinical outcomes were measured using well-established instruments: Oswestry Low Back Pain Disability Questionnaire,[8] Short Form 36 (SF-36),[16,23] and neurologic status, work status, patient satisfaction, and back, leg, and graft site pain questionnaires. The Oswestry Low Back Pain Disability Questionnaire was self-administered and was used to measure the level of pain and disability associated with various activities. Neurologic status assessment was based on four objective clinical measurements: motor, sensory,

reflexes, and sciatic tension signs. Neurologic outcome success was based on maintenance of or improvement in each variable tested. The SF-36 is a self-administered questionnaire that measures specific health concepts related to physical functioning, social functioning and health perceptions. It comprises a Physical Component Summary (PCS) and a Mental Component Summary (MCS). Three patient satisfaction questions were administered at each postoperative time period. A successful answer to each question was defined as either a "definitely true" or "mostly true" response. Low back, leg, and iliac graft site pain were evaluated using numerical rating scales that identified both pain intensity and duration. Standard visual analog scales were used for pain intensity and duration of the painful symptoms. The two scores were added together to derive a composite score.

Radiographic Outcome Measurements. Radiographs and CT scans were used to evaluate fusion at 6, 12 ,and 24 months after surgery.[6] Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent radiologist was used to adjudicate conflicting fusion findings.

Fusion was defined as bridging bone connecting the adjacent vertebral bodies either through the implants or around the implants, less than 5 degrees of angular motion, less than or equal to 3 mm of translation, and an absence of radiolucent lines around more than 50% of either of the implant surfaces. Stability and radiolucent lines were assessed on plain radiographs using anteroposterior, lateral, and flexion-extension views. Thin-slice (1 mm) computed tomography scans with sagittal reconstructions were evaluated at 6, 12, and 24 months. The presence of continuous trabecular bone formation between the vertebral bodies was assessed using radiographs and computed tomography scans. A

fusion was considered successful only if all four criteria were achieved: 1) bridging trabecular bone connecting the two vertebral bodies either through the dowels or around the dowels as evaluated by thin-cut CT scans and radiographs; 2) no angular motion of 5° or more on dynamic plain radiographs; 3) no sagittal translation of more than 3 mm on dynamic plain radiographs; and 4) no radiolucencies that involved more than half of the interfaces between the dowels and the host vertebral endplates.

Statistical Methods. The data from this clinical trial were analyzed using the statistical software package SAS® version 6.12. For continuous variables, *P* values are from ANOVA, and for categorical variables, they are from Fisher's exact test or chi-square test.

RESULTS

Surgery. In the investigational group, 11 patients (45.8%) had surgery at the L4-L5 level and 13 (54.2%) had surgery at the L5-S1 level (Table 2). In the control group, surgery was performed at the L4-L5 level in 8 patients (36.4%) and at the L5-S1 level in 14 patients (63.6%). The mean operative time was slightly longer in the control group. The investigational group had surgery more commonly at the L4-L5 level. This exposure of the L4-L5 disc space often involves a tedious mobilization of the iliac vessels and requires more time when compared with the exposure at the L5-S1 level. The average blood loss was less in the investigational group than in the control group ($P = 0.026$). The average hospital stay was similar in both groups.

Clinical Outcomes. No unanticipated adverse events that were related to the use of InFUSE™ Bone Graft (rhBMP-2 and the collagen sponge carrier) occurred during the course of the study.

Neurologic Outcomes. At 12 and 24 months, the investigational patients showed a higher rate of success than the control patients in their overall neurologic success scores (Table 3 and Figure 1). More than 87% of patients in the investigational group were considered to be a neurologic success (defined as equivalence or improvement from the preoperative condition) at 3 months after surgery. These results were maintained at the final 24-month follow-up. More than 95% of patients in the autograft control group were considered to be a neurologic success at 3 months after surgery. However, these clinical results deteriorated to 73.3% at 24 months.

Back Pain Outcomes. Patients in the investigational group showed an improvement in back pain analog scores (maximum score = 20) of more than 7 points at their initial postoperative visit at 6 weeks (Table 4 and Figure 2). In this group, back pain continued to improve and averaged close to a 9-point improvement in pain scores at 24 months after surgery. The control group's improvement in back pain followed a similar pattern. However, at 24 months, average back pain scores improved only 5 points in this group. The mean improvement scores for low back pain in the investigational group were significantly greater than those reported in the control group at 3, 6, and 24 months (P = 0.038, P = 0.034 and P = 0.047, respectively).

Leg Pain Outcomes. The investigational group also showed greater of relief of leg pain compared with the controls (Table 5 and Figure 3). In the investigational group, leg pain improved by more than 5 points within 6 weeks of surgery. These results remained

virtually unchanged at the last follow-up of 24 months. However, while the autogenous graft group showed initial improvement of greater than 5 points, the improvement at 24 months decreased to 3.1 points.

General Health (SF-36) Outcomes. In both the Physical (PCS) and Mental (MCS) Components of the SF-36, a successful outcome was defined as a maintenance or improvement in results from preoperative. The investigational group showed higher success at 24 months than the control group (Figures 4 and 5). However, these results were not found to be statistically significant.

Patient Satisfaction Outcomes. At 24 months the success rate was more than 83% in the investigational group for all three questions. For the control group, the success rate for the three questions ranged from 55% to 65% (Table 6).

Oswestry Disability Questionnaire Outcomes. The Oswestry Disability Questionnaire was used to assess pain with activity (Table 7 and Figure 6). At all follow-up intervals, the investigational group had greater improvements in Oswestry scores than the control group. At 3, 6, and 24 months, the differences in improvement scores were statistically significant ($P = 0.032$, $P = 0.039$, and $P = 0.039$, respectively). At 24 months, the mean improvement in Oswestry scores was 33.5 points.

Seventy-one percent (71%) of the patients in the investigational group showed an improvement of at least 15 points in their disability scores at 3 months. This improvement compared favorably with the 43% of patients who showed improvement in the control group ($P = 0.075$). At 12 months, 83% of the investigational group patients improved more than 15 points compared with 58% of the controls. This finding was similar at the 24-month follow-up.

Return-to-Work Status. Higher percentages of patients in the investigational group were also able to return to work (Figure 7). In the investigational group, 45.8% of patients were working before their surgery. At 24 months after surgery, 66.7% were working. These patients were also able to return to work earlier than those in the control group. In the control group, 40.9% were working before surgery and at 24 months, 35.0% were working.

Iliac Crest Graft Site Pain. Autograft bone was not harvested from the iliac crest in the investigational group; therefore, bone graft site pain was not measured and was assumed to be zero in this group. In the control group, the intensity and frequency of pain and morbidity from the graft harvesting was measured on a 20-point rating scale. At discharge from the hospital, the mean graft site pain was highest (11.3). Graft site pain persisted at 24 months in these patients with a mean score of 2.2 (Figure 8).

Additional Surgery. No patients treated with InFUSE™ Bone Graft required an additional surgical procedure in the immediate perioperative period; 1 control patient required an early return to surgery to remove residual disc material (Table 8). Four patients (1 investigational, 3 control) underwent supplemental posterior fixation procedures after their primary surgery. The investigational patient continued to have persistent low back pain at 24 months. The patient's radiographs met the criteria for fusion; however, the attending physician elected to reoperate and supplement the interbody grafts with insertion of posterior pedicle fixation. The attending physician was able to identify "slight motion" in the posterior facet joints despite the presence of an adequate fusion across the anterior disc space. The three patients in the control group had supplemental posterior fixation inserted from 7 months to 20 months following their

initial surgeries. In each of these cases, the patient reported persistent low back pain and in some instances referred leg pain.

Radiographic Outcomes. At 6-months after surgery, 21 patients in the investigational group were able to return for follow-up evaluation. Of these, 19 patients (90.5%) who were treated with InFUSE™ Bone Graft had evidence of interbody fusion compared with 13 of the 20 patients (65%) in the control group ($P = 0.067$) (Figure 9). At 12 months, all patients (24/24, 100%) in the investigational group had evidence of fusion compared with 17 patients (89.5%) in the control group. Based on their radiographs at the final follow up at 24 months after surgery, all patients (100%) in the investigational group showed evidence of remaining fused (Figure 10).

One patient in the investigational group did meet the criteria for fusion but underwent supplemental posterior fixation after the final 24-month follow-up examination. In this patient, the attending physician identified motion within the facet joints and elected to add supplemental posterior fixation to the spinal motion segment just after the 24-month visit. By the criteria of this study, this patient was recorded as having a successful interbody fusion at the 12- and 24-month follow-up examination and is not considered a failure until the 36-month follow-up examination. All patients were found to have bony integration of the allografts to the vertebral endplates and trabeculated new bone formation across the fused interspace. By considering this investigational patient as a fusion failure because of the need to use supplemental posterior fixation, the fusion rate for the investigational group was 95.8%.

At 24 months in the control autograft group, 19 patients were available for radiographic evaluation, and 13 of these patients (68.4%) were considered to have fusions

(Figure 11). In the control group, there were no failures of the allograft dowels. Three control group patients underwent supplemental posterior fixation for pseudarthrosis. Radiographic lucencies developed at the interface of the allograft to the vertebral endplate between the 12- and 24-month follow-up examinations (Figure 12). This led to the decrease in the fusion rate in the control group. There was no migration of the implants.

DISCUSSION

Recombinant human bone morphogenetic protein-2 (rhBMP-2) is an osteoinductive growth factor.[2,20] Urist discovered the capabilities of demineralized bone matrix to induce ectopic bone formation in a rat muscle pouch and introduced the concept that bone growth factors can induce new bone formation independent of the bone tissue environment.[22] Bone morphogenetic protein-2 is one of several proteins identified from bone tissue that acts a osteoinductive cytokine and induces the differentiation of pluripotential precursor cells along an osteogenic line. A pure form of this protein can be produced through standard recombinant technology. The human cDNA sequence is created through the use of oligonucleotide probes, and these clones are then spliced into a viral vector and transfected into a carrier cell in a process called recombination. These production cells (Chinese hamster ovary cells) have the ability to produce large quantities of rhBMP-2. Creating recombinant human proteins in this manner avoids potential complications associated with disease transmission from allograft or xenograft sources.

The availability of rhBMP-2 in pure "unlimited" sources has the ability to greatly enhance spinal fusion results while lowering pain scores associated with a bone graft harvesting procedure. The purpose of this study was to assess the efficacy of this

recombinant protein impregnated on a collagen sponge in a threaded cortical allograft dowel for the treatment of degenerative disc disease by an anterior interbody fusion.

To date, in both animal and human studies, rhBMP-2 has been shown to be capable of inducing new bone formation.[2,19] In a study of anterior lumbar interbody fusion in nonhuman primates, rhBMP-2 and an absorbable collagen sponge carrier was shown to promote fusion through osteoinduction.[11] New bone formation appeared to be superior to autogenous iliac crest graft with cortical dowel allograft. Similarly, in a preliminary clinical study involving the use of InFUSE™ Bone Graft and a tapered cylindrical titanium cage in humans, arthrodesis was found to occur more reliably in patients treated with rhBMP-2 than in controls treated with autogenous bone graft.[3]

This study is the first clinical report of the effectiveness of rhBMP-2 used with cortical allograft to promote anterior lumbar intervertebral fusion in humans. No unanticipated adverse events that were related to the use of InFUSE™ Bone Graft occurred during the course of the study. Because the investigational group did not undergo the bone graft harvesting procedure, there was a statistically significant reduction in operative time and decreased blood loss during the surgical procedure.

Overall, the investigational group, who received rhBMP-2 on a collagen sponge carrier (InFUSE™ Bone Graft), showed higher rates of success in the reduction of back and leg pain associated with degenerative lumbar disc disease than the control group. At their initial postoperative visit, patients in the investigational group showed an improvement in back pain of more than 7 points. Back pain scores continued to improve throughout the study period and averaged approximately a 9-point improvement at 24 months. In the investigational group, leg pain improved by more than five points within

six weeks of surgery and remained unchanged at the last clinical follow-up at 24 months. At all clinical folow-up intervals, the investigational group showed greater relief of leg pain when compared with the control group. Similarly, at 12 and 24 months, the investigational patients showed a higher rate of success than the control patients in their overall neurologic success scores. The use of rhBMP-2 obviates the need for autogenous bone graft and the potential for donor site morbidity. The control group had complaints of hip pain throughout the 24-month study period.

Coinciding with the reduction in painful symptoms was the investigational group's greater and faster functional recovery. At all time periods, the investigational group had greater improvements in Oswestry Low back Disability Questionnaire scores than the control group. The mean improvements in Oswestry scores at 12 and 24 months (31.6 and 33.5 points) are among the highest reported in the literature. Return-to-work status was also assessed to evaluate functional recovery of the patients in the study. Similarly, higher percentages of patients in the investigational group were also able to return to work. In this group, 45.8% of patients were working before surgery, and 66.7% were working at 24 months after surgery.

The investigational group also showed improved general health status after surgery. In both the Physical (PCS) and Mental (MCS) Components of the SF-36, which was used to measure specific health concepts related to physical and social functioning and limitations, the investigational group showed higher mean scores at 24 months than the control group. As would be expected from these improved outcomes, patient satisfaction was higher in this group. At 24 months, 83% of patients in the group

responded to all three questions that were asked that they were satisfied with their surgical outcome.

The investigational group showed higher rates of fusion when compared with the control group at 6, 12 and 24 months. The difference in fusion rates at 24 months was statistically significant ($P = 0.004$). However, one investigational patient underwent a supplemental fixation procedure after the 24-month visit. (The findings from the patient's 24-month radiographs and CT scans did meet the fusion criteria.) The use of supplemental fixation in this patient reduced the fusion rate in the investigational group to 95.8%. The fusion rate in the autograft control group decreased from 89.5% at 12 months to 68.4% at 24 months. The identification of these 4 new pseudarthroses during this time period was secondary to the development of lucencies surrounding the bone dowel and vertebral body interface and loss of contiguous bone across the disc space. None of these late radiographic findings occurred in the investigational group.

InFUSE™ Bone Graft was shown to be a promising method of facilitating anterior intervertebral spinal fusion and of decreasing pain and improving clinical outcomes after anterior lumbar fusion surgery with allograft bone dowels. These improved outcomes were due, in part, to the successful combination of the anterior surgical approach, the use of threaded allograft dowels, and a high rate of successful interbody fusion.

REFERENCES

1. Blumenthal SL, Baker J, Dossett A, Selby DK. The role of anterior lumbar fusion for internal disc disruption. Spine 1988;13:566-9.

2. Boden SD, Schimandle JH, Hutton WC. Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 1995;20:2633-44.

3. Boden SD, Zdeblick TA Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Spine 2000;25:376-81.

4. Boyd, L.M.; Estes, B.T. and Liu M. "Biomechanics of Lumbar Interbody Constructs, *Effect of Design and Materials*." Chirurgie Endoscopique et Mini-invasive du Rachis. Ed. Husson JL, LeHuec JC. Sauramps Médical. Montpelier, France. pp 181-92, 1999.

5. Burkus JK, Dorchak JD, Sanders DL, Foor BD: Single-level anterior lumbar interbody fusion using threaded cortical bone allografts. North American Spine Society Meeting of the Americas, Miami, Florida, 1999.

6. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. Neurosurg Focus 2001;10:1-9.

7. Crock HV. Anterior lumbar interbody fusion: indications for its use and notes on surgical technique. Clin Orthop 1982;165:157-63.

8. Fairbank JCT, Couper J, Davies JB, O'Brien JP. The Oswestry Low Back Pain Disability Questionnaire. Physiotherapy 1980;66:271-273.

9. Flynn JC, Houque MA. Anterior fusion of the lumbar spine. J Bone Joint Surg 1979;61A:1143-50.

10. Harmon PH. Anterior excision and vertebral fusion operation for intervertebral disc syndromes of the lower lumbar spine: three to five year results in 244 cases. Clin Orthop 1963;26:107-27.

11. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A. The use of recombinant human bone morphogenetic protein-2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999;24:629-36.

12. Kumar A, Kozak JA, Doherty BJ, Dickson JH. Interspace distraction and graft subsidence after anterior lumbar fusion with femoral strut allograft. Spine 1993;18:2393-2400.

13. Lane JD, Moore ES. Transperitoneal approach to the intervertebral disc in the lumbar area. Annals of Surgery 1948;127:537-51.

14. Loguidice VA, Johnson RG, Guyer RD, Stith WJ, Ohnmeiss DD, Hochschuler SH, Rashbaum RF. Anterior lumbar interbody fusion. Spine 1988;13:366-9.

15. Leong JC, Chun SY, Grange WJ, Fang D: Long-term results of lumbar intervertebral disc prolapse. Spine 1983;8:793-9.

16. McHorney CA, Ware JE Jr., Lu RJF, Sherbourne CD. The MOS 36-Item Short-From Health Survey (SF-36), III: tests of data quality, scling assumptions, and reliability across diverse patient groups. Med Care. 1994;32:40-66

17. Morales RW, Pettine KA, Salib RM. A biomechanical study of bone allografts used in lumbar interbody fusions. North American Spine Society – 6th Annual Meeting, Keystone, Colorado 1991

18. Sacks S. Anterior interbody fusion of the lumbar spine. J Bone Joint Surg [Br] 1965;47:211-23.

19. Sandhu HS, Kanim LEA, Toth JM, et al. Experimental spinal fusion with recombinant human bone morphogenetic protein-2 without decortication of osseous elements. Spine 1997;22:1171-80.

20. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995; 20:1326-37.

21. Stauffer RN, Coventry MB. Anterior interbody lumbar spine fusion. J Bone Joint Surg [Am]1972;54:756-68.

22. Urist MR. Bone: Formation by autoinduction. Science 1965;150:893-9.

23. Ware JE Jr, Sherbourne CD. The MOS 36-Item Short-From Health Survey (SF-36), I: conceptual framework and item selection. Med Care. 1992;30:473-483.

TABLE 1. Patient Demographic Data

Demographic Data	Investigational (InFUSE™ Bone Graft) Group	Control (Autograft) Group
Number of patients	24	22*
Age (years)	41.5	45.6
Weight (lbs)	172.7	175.9
Sex (male/female)	8/16	10/12
Workers' compensation (%)	5 (21)	7 (32)
Spinal litigation (%)	4 (17)	4 (18)
Tobacco use (%)	8 (33)	6 (27)
Previous surgeries (%)	11 (46)	7 (32)

*One patient died an accidental death at 6 months after surgery, and 1 patient was lost-to-follow up.

Table 2. Intraoperative Data

Surgical Data	Investigational (InFUSE™ Bone Graft) Group	Control (Autograft) Group
Operative time (min)	103	114
Blood loss (mL)	124.1	245.0
Levels (%)		
L4-L5	11 (46)	8 (36)
L5-S1	13 (54)	14 (64)
Hospital stay (days)	3.4	3.7

Table 3. Neurologic Outcomes

Period	Variable	Investigational n=24 (%)	Control n=22 (%)
6 Weeks	Overall		
	Success	21 (87.5)	18 (90.0)
	Failure	3 (12.5)	2 (10.0)
	P-value*	1.000	
3 Months	Overall		
	Success	21 (87.5)	20 (95.2)
	Failure	3 (12.5)	1 (4.8)
	P-value*	0.611	
6 Months	Overall		
	Success	21 (87.5)	17 (89.5)
	Failure	3 (12.5)	2 (10.5)
	P-value*	1.000	
12 Months	Overall		
	Success	23 (95.8)	16 (84.2)
	Failure	1 (4.2)	3 (15.8)
	P-value*	0.306	
24 Months	Overall		
	Success	21 (87.5)	11 (73.3)
	Failure	3 (12.5)	4 (26.7)
	P-value*	0.396	

**P*-values are from Fisher's exact test.

Table 4. Back Pain Outcomes

Period	Variable	Investigational n=24	Control n=22
Preoperative	n	24	22
	Mean	16.3	16.3
	SD	2.6	2.2
6 Weeks	n	24	21
	Mean	8.9	10.4
	SD	4.5	4.2
	P value**	0.297	
Improvement from Preoperative	Mean	-7.4	-6.0
	P value*	<0.001	<0.001
3 Months	N	24	21
	Mean	7.9	10.9
	SD	4.3	4.5
	P value**	0.038	
Improvement from Preoperative	Mean	-8.4	-5.4
	P value*	<0.001	<0.001
6 Months	N	24	20
	Mean	6.8	9.9
	SD	4.3	5.1
	P value**	0.034	
Improvement from Preoperative	Mean	-9.5	-6.4
	P value*	<0.001	<0.001
12 Months	N	24	19
	Mean	7.4	9.2
	SD	5.3	6.3
	P value**	0.338	
Improvement from Preoperative	Mean	-8.9	-7.2
	P value*	<0.001	<0.001
24 Months	N	24	17
	Mean	7.4	10.9
	SD	6.0	6.0
	P value**	0.047	
Improvement from Preoperative	Mean	-8.9	-5.2
	P value*	<0.001	<0.001

**P* values for change from preoperative in each group are from paired tests.
***P* values for difference between the treatment groups are from analysis of variance.

Table 5. Leg Pain Outcomes

Period	Variable	Investigational n = 24	Control n = 22
Preoperative	n	24	22
	Mean	12.8	14.6
	SD	5.7	4.1
6 Weeks	N	24	21
	Mean	7.0	8.8
	SD	5.9	5.9
	P value**	0.933	
Improvement from Preoperative	Mean	-5.8	-5.6
	P value*	0.001	0.001
3 Months	N	24	21
	Mean	6.2	8.3
	SD	4.4	5.8
	P value**	0.874	
Improvement from Preoperative	Mean	-6.7	-6.4
	P value*	<0.001	<0.001
6 Months	N	24	20
	Mean	5.0	6.1
	SD	4.7	4.4
	P value**	0.654	
Improvement from Preoperative	Mean	-7.9	8.7
	P value*	<0.001	<0.001
12 Months	N	24	19
	Mean	5.5	8.1
	SD	5.5	6.1
	P value**	0.818	
Improvement from Preoperative	Mean	-7.3	-6.8
	P value*	<0.001	0.001
24 Months	N	24	17
	Mean	6.3	11.5
	SD	6.0	6.3
	P value**	0.142	
Improvement from Preoperative	Mean	-6.5	-3.5
	P value*	<0.001	0.023

**P* values for change from preoperative in each group are from paired tests.
***P* values for difference between the treatment groups are from analysis of variance.

Table 6. Patient Satisfaction

Period	Variable	Investigational n=24 (%)	Control n=22 (%)
6 Months	I am satisfied with the results of my surgery		
	Definitely True	17 (70.8)	12 (60.0)
	Mostly True	3 (12.5)	4 (20.0)
	P value*	0.503	
	I was helped as much as I thought I would be by my surgery		
	Definitely True	14 (58.3)	6 (30.0)
	Mostly True	6 (25.0)	9 (45.0)
	P value*	0.229	
	All things considered I would have the surgery again for the same condition		
	Definitely True	18 (75.0)	13 (65.0)
	Mostly True	1 (4.2)	3 (15.0)
	P value*	0.312	
12 Months	I am satisfied with the results of my surgery		
	Definitely True	11 (45.8)	7 (35.0)
	Mostly True	8 (33.3)	7 (35.0)
	P value*	0.460	
	I was helped as much as I thought I would be by my surgery		
	Definitely True	12 (50.0)	6 (30.0)
	Mostly True	7 (29.2)	4 (20.0)
	P value*	0.169	
	All things considered I would have the surgery again for the same condition		
	Definitely True	15 (62.5)	11 (55.0)
	Mostly True	4 (16.7)	1 (5.0)
	P value*	0.130	
24 Months	I am satisfied with the results of my surgery		
	Definitely True	13 (54.2)	6 (30.0)
	Mostly True	7 (29.2)	5 (25.0)
	P value*	0.084	
	I was helped as much as I thought I would be by my surgery		
	Definitely True	13 (54.2)	6 (30.0)
	Mostly True	9 (37.5)	5 (25.0)
	P value*	0.249	
	All things considered I would have the surgery again for the same condition		
	Definitely True	15 (62.5)	11 (55.0)
	Mostly True	6 (25.0)	2 (10.0)
	P value*	0.137	

*P values are from the chi-square test.

Table 7. Oswestry Low Back Pain Disability Scores

Period	Variable	Investigational	Control
Preoperative			
	n	24	22
	Mean	52.4	55.3
	SD	13.1	13.5
6 Weeks			
	N	24	21
	Mean	39.9	47.2
	SD	16.8	18.8
	P value**	0.307	
Improvement from Preoperative			
	Mean	-12.5	-7.9
	P value*	<0.001	0.024
3 Months			
	N	24	21
	Mean	29.0	42.0
	SD	14.7	19.0
	P value**	0.032	
Improvement from Preoperative			
	Mean	-23.4	-14.3
	P value*	<0.001	<0.001
6 Months			
	N	24	20
	Mean	21.4	34.4
	SD	16.1	21.8
	P value**	0.039	
Improvement from Preoperative			
	Mean	-31.0	-20.9
	P value*	<0.001	<0.001
12 Months			
	N	24	19
	Mean	20.8	30.0
	SD	14.9	21.2
	P value**	0.171	
Improvement from Preoperative			
	Mean	-31.6	-24.7
	P value**	<0.001	<0.001
24 Months			
	N	24	17
	Mean	18.9	32.8
	SD	14.5	22.7
	P value**	0.039	
Improvement from Preoperative			
	Mean	-33.5	-21.5
	P value*	<0.001	<0.001

* *P* values for change from preoperative in each group are from paired tests.
***P* values for difference between the treatment groups are from analysis of variance.

Table 8. Additional Surgeries

Procedure	Investigational (InFUSE™ Bone Graft) Group	Control (Autograft) Group
Removals	0	0
Revisions	0	0
Supplemental fixation (%)	1 (4.2)	3 (13.6)
Reoperation (%)	0	1 (4.5)

LEGEND OF FIGURES

Figure 1. Comparison of neurologic outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft). Success was based on postoperative neurologic condition being improved or no worse than the preoperative condition.

Figure 2. Comparison of back pain outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Figure 3. Comparison of leg pain outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Figure 4. Comparison of Short Form 36 Physical Component Scores in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Figure 5. Comparison of Short Form 36 Mental Component Scores in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Figure 6. Comparison of Oswestry Disability Questionnaire outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Figure 7. Comparison of return-to-work status in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Figure 8. Iliac crest bone graft harvest site pain in the control group.

Figure 9. Comparison of postoperative fusion outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Figure 10. Serial thin-cut CT scans after an L5-S1 fusion using InFUSE™ Bone Graft. Sagittal and frontal CT reconstructions through both the right and left dowels show the progression of the interbody fusion. The immediate postoperative reconstructions show that the dowels have not been incorporated into the vertebral endplates, and there is no bone formation in the central portion of the dowels. At 6 months, the dowels are incorporated into the vertebral endplates and there is new bone formation within the dowels. At 12 months, there is new bone formation connecting the adjacent vertebral bodies both inside and outside of the dowels. At 24 months, the dowels have almost been completely reabsorbed and replaced with new trabecular bone formation.

Figure 11. Serial thin-cut CT scans after an L5-S1 fusion using autograft demonstrate the progression of the interbody fusion. Immediate postoperative scans show corticocancellous graft within the dowels. At 6 months, trabecular bone connects the adjacent vertebral bodies through the dowels and anterior to the dowels. At 12 and 24 months, there is maturation of the interbody fusion with more bone formation and incorporation of the dowels into the vertebral endplates.

Figure 12. Serial thin-cut CT scans after an L5-S1 fusion using autograft show the development of a pseudarthrosis. At 6 months, the grafts within the dowels and the dowels themselves appear to have become attached the adjacent vertebral endplates. At 12 months, lucencies appear separating the dowels from the vertebral endplates. By 24 months, a radiolucent line involving the inferior portion of both dowels highlights noncontiguous bone formation between the vertebrae consistent with a pseudarthrosis.

January 31, 2002

James N. Weinstein, D.O., Editor-in-Chief
Spine
Dartmouth College
[redacted]
Hanover, NH 03755-3863

RE: MS # 01520 Clinical and Radiographic Outcomes of Anterior Lumbar Interbody Fusion Using rhBMP-2

Dear Dr. Weinstein:

Enclosed are four copies of our revised manuscript. We appreciate the reviewers' comments and have revised the manuscript according to their suggestions. Our response to their comments and where changes are located in the text follows.

Reviewer #1

1-1. Page 8, para 5: Details of the rhBMP-2 dose have been added to Materials and Methods.

1-2. Page 10, para 2 and 3: We have expanded our definition of fusion.

1-3. Page 11, para 2: Statistical methods have been included. Deleted:

1-4. Table 3 (page 26) has been added to report *P* values of neurologic score differences.

1-5. Page 13, para 1, line 4: Statement and a new table (Table 4 on page 27) have been added to report *P* values of back pain score differences.

1-6. Table 5 on page 28 has been added to report *P* values of leg pain score differences.

1-7. Statements have been added under each subheading of the Results section of this revision regarding the significance of the pre- and postoperative comparisons.

1-8. Page 15, para 3: A statement has been added explaining that the investigational group patient who underwent supplemental posterior fixation due to "slight motion" detected within the facet joint was recorded as having a successful fusion at the 24-month follow-up. The fusion failure was not detected until after this follow-up.

1-9. Page 17, para 1: Change from "carrier" to "production" cells has been made as suggested.

1-10. All patients (100%) in the BMP group were evaluated as being fused at 12 and 24 months.At 6 months, all but 2 (90.5%) of the BMP patients were considered fused. With only 2 patients considered not fused at any given timepoint, there were not enough data available to evaluate the time to healing or fusion in any given set of patients, including smokers.

1-11. Pages 26 - 30: New Tables 3 through 7 have been added to complement data in Figs 1 through 7 (old Figs 2-8) that include P values and standard deviations.

1-12. New Figures 10 through 11 have been added as suggested by reviewer.

Reviewer #2

2-1. Figure 1 has been deleted as recommended.

2-2. Page 7, para 3 through page 8, para2: The description of inclusion and exclusion criteria have been expanded and clarified.

2-3. Page 6, para 3 through page 8, para 2: An expanded definition of degenerative disc disease along with the clinical features of the candidates for surgery has been included.

2-4. Page 8: A more complete description of the control group's surgical procedure including the graft harvesting procedure has been added.

2-5. Page 9, para 3: The postoperative care protocol has been included.

2-6. Picture was not available. Our manuscript is already very heavy on tables and figures.

2-7. Page 28: A new table, Table 5, has been added clarifying the amount of leg pain improvement each group experienced.

2-8. Page 19, para 3: A statement was added to the Discussion regarding the 4 pseudarthroses that developed in the control group between 12 and 24 months.

2-9. Additional emphasis has been placed on the advantages of BMPs throughout the Discussion.

Reviewer #3

3-1. A Précis has been added.

3-2. Page 5, para 2: InFuse Bone Graft manufacturer's information has been added.

3-3. Page 6, para 3: The definition of degenerative disc disease and the indications for surgery in our patients has been expanded.

3-4. The inclusion/exclusion criteria were the same for both the investigational and control groups. It was an inclusion criterion for all of the patients to have single level degenerative disc disease. Both groups were held to the same criteria; therefore, the results of one group should not be cause to question the criteria.

3-5. Page 8, para 4: Misspelled word corrected.

3-6. Page 8, para 5: Details of the rhBMP-2 dose have been added to Materials and Methods.

3-7. Fusion for this clinical trial was assessed per the FDA approved protocol. Some of this information has been provided to FDA on a confidential basis. These data have not been published and are not available yet.

3-8. Page 9, para 4: the description of neurologic outcome testing has been expanded. We have also expanded the description of the other scoring methods. Tables have been added showing the results of statistical analysis of the groups' differences.

3-9 and 3-10. Page 15, para 1: Statement has been added clarifying the attending physician's finding of slight motion in the posterior fact joints that led to the decision to reoperate.

3-11. Page 16, para 3: Rewritten as suggested.

3-12. Page 16: Discussion has been rewritten as suggested.

Thank you for your attention to our manuscript.

Sincerely,

J. Kenneth Burkus, M.D.
Enclosures

JKB/cmb

From: Tara Hood
Sent: Tuesday, March 12, 2002 03:50:23 PM
To: J. Kenneth Burkus; 'Dr. Thomas Zdeblick [redacted]
CC: Neil Beals; Bailey Lipscomb; Pete Wehrly; Bill Martin; Clark Charlton; Julie Bearcroft; [redacted]
Subject: FW: Open LT BMP manuscript

Attachments: Final revisions OPEN LTCAGE BMP.11.doc

I added in information on the antibodies. It is highlighted in blue and added at the end of results. I think I understood from Dr. Zdeblick that he recommended just adding in the rhBMP-2 antibody information. If this is incorrect and you would like to add in the bovine and human collagen antibody info, please just let me know.

Also, it looks as if there is a request for a p-value in relation to the fusion data. The p-values in the tables are looking at postoperative compared to preoperative measurements, not investigational to control. The probability of superiority is given for fusion because it is comparing the treatment groups and this is using Bayesian methods. Just to clarify the probability of superiority, this is a predictive measurement inclusive of 12 month data. Our statistician says this may be confusing, you may want to just end this sentence after .... "six percentage points higher than the fusion rate of the control group (88.7%)."

Just let me know if you need anything else.
Thanks,
Tara

-----Original Message-----
From: Dr. Thomas Zdeblick [SMTP:[redacted]
Sent: Sunday, March 10, 2002 7:49 PM
To: Tara Hood; Neil Beals; J. Kenneth Burkus
Cc: Tom Zdeblick M.D.; Bailey Lipscomb; Pete Wehrly; Bill Martin; Clark Charlton; Julie Bearcroft; [redacted]

Subject: RE: Open LT BMP manuscript

Enclosed is a revised manuscript. I have made a few edits. I think it looks great!
All we need is a short statement on antibodies. TAZ

At 04:21 PM 3/8/02 -0600, Tara Hood wrote:
>Dr. Burkus,
>I wanted to clarify some of the remaining questions/numbers that were
>identified in bold by you.

>
>Page 15/Table 11 - fusion data in table is correct, numbers in text should
>be changed to 127 investigational patients at 12 months, 112 control
>patients at 12 months.
>
>Table 5 - footnote = "P-values for change from preoperative in each group
>are from paired t-test." (this applies to all p-values in table)
>
>Table 7 - footnote = "P-values for change from preoperative in each group
>are from paired t-test." (this applies to all p-values in table)
>
>Table 9 - footnote should read "paired t-test"
>
>Hope this helps. Thanks for everything.
>Tara
>
>
>
>
>
>> -----Original Message-----
>> From: Neil Beals
>> Sent: Friday, March 08, 2002 4:05 PM
>> To: J. Kenneth Burkus
>> Cc: Tom Zdeblick M.D.; Tara Hood; Bailey Lipscomb; Pete Wehrly; Bill
>> Martin; Clark Charlton; Julie Bearcroft; [redacted]
>> Subject: FW: Open LT BMP manuscript
>>
>> Ken,
>>
>> I read over manuscript and I think it looks great. I have only a few
>> comments. I will get with Tara and see if we can get answers to your
>> questions in bold.
>>
>> My comments:
>> * would it be appropriate to make bigger deal out of donor site pain
>> and include more discussion and references?
>> * would it be helpful to add in verbiage on advantages of cage design
>> versus previous generations (page18)? this could help address reaction
>> from those who felt results would be better
>> * maybe a little more emphasis on the high quality of the study - not
>> sure a prospective randomized study of this magnitude has ever been
>> conducted before, particularly for spine?
>> * LT CAGE name is used in discussion; it may be best to use generic
>> descriptors and limit tradenames to materials and methods
>> * is FDA criteria of success for back and leg pain (3 point reduction)
>> accepted?
>> * I didn't see mention of antibody results - should that be included

>> for completeness? also other potential safety issues? not sure of how
>> much to put out there
>> * 15 point reduction is mentioned on pg 21 - is this FDA Oswestry
>> reference?
>> * not sure last sentence is needed
>>
>> Again, it looks great - thanks, Ken.
>>
>> Neil
>>
>>
>> -----Original Message-----
>> From: JKB[redacted]
>> Sent: Friday, March 08, 2002 7:32 AM
>> To: Tom Zdeblick; Peter Wehrly; Bill Martin; Neil Beals; Clark Charlton
>> Subject: Open LT BMP manuscript
>>
>> Sirs.
>>
>> Here is the latest edition of the OPEN LT BMP Manuscript.
>>
>> I have questions written in BOLD in the text regarding: Tables 5, 7, 9 and
>> 11. Also the text on page 15 (radiographic assessment) with be altered
>> when I get the table questions answered. Please give me some feedback -
>> cannot find my red book (LT data Book) here at home - I will get into the
>> office later today.
>>
>> The manuscript will be ready for submission in 24 hours.
>>
>> Best.
>> Ken << File: Final revisions OPEN LTCAGE BMP.1.doc >>

A Prospective, Randomized Lumbar Fusion Study using rhBMP-2 with Tapered Interbody Cages

J. Kenneth Burkus MD [†]

Matthew F. Gornet MD*

Curtis Dickman, MD[‡]

Thomas A. Zdeblick MD[§]

[†]Staff Physician, Spine Service, The Hughston Clinic, P.C., Columbus, Georgia

*Staff Physician, Missouri Bone and Joint Institute, St. Louis, Missouri

[‡]Barrows Institute, Phoenix, Arizona

[§]Chairman, Department of **Orthopedics and Rehabilitation**, University of Wisconsin, Madison, Wisconsin

Address correspondence and reprint requests to J.K. Burkus, MD, The Hughston Clinic, [redacted]

ABSTRACT

Study Design. In a multi-center, prospective, randomized, nonblinded, 2-year study, 279 patients who underwent a single-level anterior lumbar interbody fusion with tapered threaded titanium fusion device were randomized into two groups: one received autogenous iliac crest bone graft, the other, recombinant human bone morphogenetic protein-2 (rhBMP-2) on a collagen sponge carrier.

Objectives. The objective of the study was to determine the clinical and radiographic outcomes in patients treated for single-level degenerative lumbar disc disease with a stand-alone anterior interbody fusion using tapered threaded titanium fusion cages with autogenous bone graft or rhBMP-2 and an absorbable collagen sponge carrier.

Summary of Background Data. In a small series of human patients undergoing anterior lumbar interbody fusion with a tapered titanium fusion cage, rhBMP-2 has been shown to promote osteoinduction and fusion.

Methods. In this prospective nonblinded study, 279 patients were randomly divided into 2 groups that underwent interbody fusion using two tapered threaded fusion cages: the investigational group (143 patients) that received rhBMP-2 on an absorbable collagen sponge and a control group (136 patients) that received autogenous iliac crest bone graft. Assessment of a patient's clinical outcome was based on neurologic status, work status, and Oswestry Low Back Pain Disability scores and back and leg pain questionnaires. Plain radiographs and computed tomographic scans were used to evaluate fusion at 6,12 and 24 months postoperatively.

Results. Mean operative time (1.6 hours) and blood loss (109.8 mL) was less in the investigational rhBMP-2 group than in the autograft control group (2.0 hours and 153.1

mL). At 24 months, the investigational group's fusion rate of 94.5% remained higher than the control's at 88.7%. New bone formation occurred in all patients treated with rhBMP-2. At all postoperative intervals, the mean Oswestry, back pain, and leg pain scores and neurologic status improved in both treatment groups compared with the preoperative scores and were similar in both groups. In the control group, 8 adverse events related to harvesting of the iliac crest graft occurred in 8 patients (5.9%), and, at 24 months after surgery, 32% patients still reported graft site discomfort and 16% were bothered by the appearance of graft site.

Conclusions. The investigational group had shorter operative times and less blood loss. At 24 months, this group had a fusion rate that was nearly 6 percentage points greater than the control group with a probability of superiority of 90.2%. Overall results show that the use of rhBMP-2 can eliminate the need for harvesting iliac crest graft for successful lumbar fusions.

Key words: anterior lumbar interbody fusion, bone morphogenetic protein, osteoinduction, radiography, interbody fusion cages

Key points:

- Fusion rates for both treatment groups were high at all studied intervals. At 24 months, the average rate of fusion for patients treated with rhBMP-2 was nearly 6 percentage points higher (94.5% vs. 88.7%) than for patients treated with autograft with a probability of superiority of 90.2 percent.
- The average operative time was1.6 hours for patients treated with rhBMP-2 compared with 2.0 hours in the autograft group. This difference was statistically significant.
- Blood loss was less for patients treated with rhBMP-2 than for patients who underwent iliac crest bone graft harvesting.
- At all postoperative assessment intervals, patients in both treatment groups showed improvement in Oswestry disability scores, in neurologic status, and in back and leg pain outcomes.
- The use of rhBMP-2 in anterior lumbar interbody fusion procedures eliminates the complications of iliac crest bone harvesting.

Précis

In a 2-year prospective randomized study of 279 patients, the investigational group that received rhBMP-2 with the tapered cage device had a higher rate of fusion, reduced operative times, and decreased blood loss when compared with the control group that received autogenous bone graft with the LT-CAGE™ device. The rhBMP-2 group avoided the complications that can arise from an iliac crest bone harvesting procedure.

INTRODUCTION

Degenerative changes within a lumbar spinal motion segment are, in part, evidenced by the presence of radial tears or fissures in the annulus fibrosus, disc space desiccation and collapse, and the formation of radial osteophytes. These morphologic changes within the spinal motion segment can lead to loss of the intervertebral disc's ability to accommodate normal biomechanical stresses and can cause pain. Fusion of the degenerative and unstable spinal motion segment can give significant relief from this disabling and often progressive condition (2,7,9).

Anterior lumbar interbody fusion (ALIF) is an effective treatment for patients with symptomatic degenerative disc disease. Lumbar spine stabilization procedures that do not interfere with the posterior spinal muscles have some significant advantages (9,10,14-16,19). The anterior approach to the lumbosacral spine enables the surgeon to expand the disc space and re-establish the normal anatomic alignment and relationships of the spinal motion segment while avoiding injury to the posterior paravertebral muscles. The anterior approach also retains all posterior stabilizing structures and avoids epidural scarring and perineural fibrosis. Adjacent segment degeneration in the lumbar spine after anterior interbody fusion can also be reduced (17).

Stand-alone ALIF procedures using autogenous bone grafts alone have been associated with high rates of pseudarthrosis, graft subsidence, and graft extrusion (8,23). Supplemental posterior segmental spinal instrumentation has been advocated to stabilize interbody grafts and increase rates of fusion. Recently, cylindrical threaded

intervertebral devices with autogenous bone grafts have been shown to stabilize a lumbar motion segment after anterior discectomy. Their use has lead to high rates of fusion and to improved clinical outcomes (4).

In non-human primate animal models, recombinant human bone morphogenetic protein 2 (rhBMP-2) applied to an absorbable collagen sponge carrier has been shown to promote osteoinduction and fusion after ALIF (11). Recently, this technique was used in a small series of human patients who underwent stand-alone ALIF with tapered fusion cages. In these patients, the use of rhBMP-2 applied to a collagen sponge was also shown to promote osteoinduction and fusion (4). To further evaluate this method, we evaluated the clinical and radiographic outcomes at 24 months of 279 patients who underwent a single level ALIF. We compared the outcomes in the investigational patients (rhBMP-2) with those in the control patients (autogenous bone).

MATERIALS AND METHODS

Study Design. Between August 1998 and July 1999, 279 patients completed surgery in this prospective, randomized, nonblinded, FDA approved study at 16 investigational sites. All patients underwent a single-level anterior lumbar fusion with the LT-CAGE™ device (Medtronic Sofamor Danek, Memphis, TN). Patients were randomly assigned in a 1:1 manner to one of two groups: the investigational group received rhBMP-2 on an absorbable collagen sponge carrier and the control group received autogenous iliac crest bone graft. InFUSE Bone Graft™ (Medtronic Sofamor Danek, Memphis, TN) is the

trademarked name for recombinant human bone morphogenetic protein 2 applied to an absorbable collagen sponge.

Patient Data. Preoperatively, all patients had symptomatic, single-level degenerative lumbar disc disease and symptoms of disabling low back or leg pain, or both, of at least 6 months' duration that had not responded to nonoperative treatments. The two treatment groups were very similar demographically, and there were no statistically significant differences ($P < 0.05$) for any of the variables (Table 1). The rhBMP-2 group consisted of 143 patients and the control group consisted of 136 patients. The average age at surgery was 43.3 years for the rhBMP-2 group and 42.3 years for the control group. In the rhBMP-2 group, 47 patients (32.9%) had used tobacco within 6 months before surgery compared with 49 patients (36%) in the control group. The percentage of patients with pending litigation was 12.6% and 16.2% in the rhBMP-2 and control groups, respectively. The percentage of patients seeking worker's compensation was 32.9% in the rhBMP-2 group and 34.6% in the control group.

Clinical and Radiographic Outcome Measurements. Patient assessments were completed preoperatively, during hospitalization, and postoperatively at 6 weeks and at 3, 6, 12, and 24 months. Clinical outcomes were assessed using neurologic status, work status, patient satisfaction, and Oswestry Low Back Pain Disability, back, leg, and graft site pain questionnaires.

Radiographs and computed tomography (CT) scans were used to evaluate fusion at 6, 12, and 24 months after surgery. Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent, blinded radiologist was used to adjudicate conflicting fusion findings. Fusion was defined as an absence of

radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation less than 5° on flexion-extension radiographs, and continuous trabecular bone growth connecting the vertebral bodies (6). There was good agreement between the radiologists reviewing the studies. At 6, 12, and 24 months after surgery, agreement between the independent reviewers was more than 98%. Patients who had secondary surgeries because of persistent low back symptoms and clinically suspected nonunions were considered as having failed fusions and were classified as failures in all fusion calculations, regardless of their independent radiological assessment.

Clinical and Radiographic Follow-up. The rate of patient return for follow-up was high at all postoperative periods (Table 2). At 12 months, the rate of patient return for both treatment groups exceeded 96%. At 24 months, the follow-up rate for the investigational group was 92.5% and the control group rate was 90.8%.

Surgical Technique. All patients underwent the ALIF procedure through an open approach. Patients were placed in the supine position on the operating room table. Fluoroscopy was used throughout the surgical procedure. A vertical or transverse incision was made over the lumbosacral spine. A retroperitoneal exposure was carried out in 81% (226/279) of patients, and a transperitoneal exposure was used in 19% (53/279) of patients. The parasympathetic nerve complex was bluntly mobilized and retracted from the surgical field: electrocautery was not used during this portion of the surgical procedure. Segmental vessels were sequentially identified, ligated, and divided. The great vessels were mobilized exposing the anterior surface and lateral borders of the disc space. The midpoint of the disc space was identified with radiographic markers and fluoroscopy.

An incision was made in the anterior portion of the annulus, removing the anterior longitudinal ligament and the anteriolateral borders of the annulus fibrosus. Under direct visualization the entire contents of the disc space were removed including the nucleus pulposis and the cartilaginous endplates. Great care was taken to protect and preserve the bony vertebral endplates. The disc space was sequentially distracted to the height of normal adjacent disc space height. A double barrel guide was inserted into the disc space and the bony endplates were precisely prepared with a reamer.

In the investigational group, each cage was filled with a rhBMP-2 soaked collagen sponge. No autogenous bone grafts or local reamings were used in this group. The cages were sequentially inserted through the guide tube into the prepared intervertebral disc space. Cage placement was evaluated with fluoroscopy in both the anteroposterior and lateral dimensions. In the control group, two cage devices were packed with morcellized autogenous bone graft harvested from the iliac crest.

Postoperatively, patients were placed in a soft lumbar corset. Activities were advanced by the treating physician. Isometric strengthening and exercise program were started at six weeks postoperatively.

Statistical Methods. The data from this clinical trial were analyzed using the statistical software package SAS® version 6.12. For continuous variables, *P* values are from ANOVA, and for categorical variables, they are from Fisher's exact test or chi-square test.

RESULTS

Surgery

The mean operative time in the investigational rhBMP-2 group (1.6 hours) was less than in the control group (2.0 hours) (Table 3). The average blood loss in the rhBMP-2 group was 109.3 ml as compared with 153.8 ml in the control group. The operative time and blood loss was less in the investigational group despite the fact that the more technically demanding and time consuming approach to the L4-L5 level was performed more frequently in the investigational group (25.9%, 37/143) than in the control group (23.5%, 32/136). The average hospital stay was similar in both groups (3.1 days for the investigational group vs. 3.3 days for the control group). There were no unanticipated device-related adverse events in either treatment group.

Complications

Vascular events. Eleven intraoperative vascular events occurred: 6 were in the rhBMP-2 group (4.2%) and 5, in the autograft group (3.7%). The most common injury (6/11) was a laceration of the iliac vein. Two control group patients developed deep venous thrombosis and were treated with anticoagulation medications.

Retrograde ejaculation. Six male patients (4.1%, 6/146) complained of retrograde ejaculation after surgery. In these patients, the L5-S1 disc space was approached 5 times (83.3%, 5/6). A transperitoneal approach was used in 4 of the 6 patients (66.6%). This complication occurred in 13.3% (4/30) of the men who underwent a transperitoneal approach and occurred in only 1.8% (2/116) of men who underwent a retroperitoneal approach. In two patients, the retrograde ejaculation resolved by 12 months after

surgery; one patient underwent a retroperitoneal approach, the other a transperitoneal approach.

Iliac crest graft site. In the control group, 8 adverse events related to harvesting of the iliac crest graft were identified in 8 patients (5.9%). These events included 3 injuries to the lateral femoral cutaneous nerve, 2 avulsion fractures of the anterior superior iliac spine, 1 infection and 1 hematoma. None required an additional surgery. There were no graft site adverse events in the investigational group since the use of rhBMP-2 precluded the need to harvest bone graft.

The level of postoperative pain and morbidity associated with the iliac crest graft harvesting was measured using numeric rating scales for pain intensity and duration (Table 4). After surgery, all of the control patients experienced hip donor site pain. The highest levels of pain were noted immediately after surgery with a mean score of 12.7 points out of 20 points. The percentage of patients experiencing pain decreased over time. However, at 24 months after surgery, nearly one-third of the control patients (32%) still experienced pain. At two years, the graft site pain scores averaged 1.8 points, and 16% of the control patients were bothered by the appearance of the graft site.

Antibody Testing

Antibody results. Antibodies to rhBMP-2 were evaluated preoperatively and postoperatively using enzyme-linked immunosorbent assays (ELISAs). The results were similar between the investigational and control groups (0.7% and 0.8%, respectively). There appeared to be no negative clinical consequence to positive antibody test results.

Clinical Outcomes

Oswestry Disability Questionnaire scores. The Oswestry Low Back Pain Disability Questionnaire measured pain associated with activities. The Oswestry Questionnaire was administered preoperatively as well as at each postoperative visit. At all postoperative time periods for both the investigational and the control treatment groups, the mean overall Oswestry scores were similar at the time periods for both treatment groups. At all postoperative visits, both treatment groups demonstrated statistical improvements as compared with the preoperative scores that were maintained through two years (Table 5). At 24 months, the mean improvements in the Oswestry scores were 29.0 points in the investigational group and 29.5 points in the controls. In the rhBMP-2 group, 84.6% of patients showed an improvement of at least 15% in their disability scores at 12 months after surgery and compared favorably with 85.6% of patients in the control group. (At 24 months, 84.4% of the investigational group was improved compared with 82.4% of the control group.)

Neurologic Status. Neurologic status of the patients was determined by evaluating four neurologic measurements: motor function, sensory function, deep tendon reflexes and sciatic tension signs. Values for each of the 4 subsets of objective findings were totaled and expressed as a percentage of the maximum possible score. Each measurement was compared with the patient's preoperative score. Neurologic success was based on demonstrating maintenance of or improvement in all four neurologic measurements. At 12 and 24 months after surgery, the overall neurologic

success rates for the investigational group were 81.8% and 82.8% respectively compared with 84.7% and 83.3% rates for the control group (Table 6).

Back Pain. Back pain intensity and duration were assessed using a 20-point numeric rating scale. Adding the numeric rating scores for back pain intensity and pain duration allowed examiners to derive a composite back pain score (Table 7). The mean back pain scores at all postoperative periods were improved from the preoperative mean values for both treatment groups. The mean improvements in back pain scores at both 12 and 24 months were greater for the investigational group than for the control autograft group.

Back pain success was determined for each patient by comparing the postoperative score with the preoperative score. Success was based on the patient's having at least a 3-point improvement in back pain score after surgery (Table 8). At 12 and 24 months after surgery, the investigational group had back pain success rates of 79.1% and 74.6%, respectively. These rates were similar to the respective rates in the control group of 72.8% and 78.7%.

Leg Pain. Leg pain was assessed in a similar manner using a numeric rating scale for both the intensity and duration of painful symptoms. Mean leg pain scores improved significantly after surgery (Table 9). Outcomes were similar in both treatment groups. Leg pain success was defined as a function of the patient's preoperative complaints. If a patient had a preoperative pain score of 10 points or more, success was defined as a 3-point improvement in his or her postoperative scores. In patients who had preoperative leg pain scores of less than 10 points, success was defined as maintenance of or improvement in scores when compared with their preoperative

condition. At 12 months after surgery, the leg pain success rates were similar in both treatment groups. The investigational group had a success rate of 72.1% and the control group had success rate of 72.8%. At 24 months, the success rate in the investigational group improved to 80.3% and was higher than the 74.1% result in the control group.

Work Status. Many factors affect a patient's work status, such as the nature of the work performed and ability of the work place to accommodate work restrictions. The work status of the investigational patients **was similar** to that of the control patients at most postoperative follow-up intervals (Table 10). For patients who were working before surgery, the median return to work time was 63.5 days in the investigational group and 64.5 days in the control group. More people in both treatment groups were working at the two-year follow-up than were working before their surgery. At last follow-up, in the investigational group, 80 patients were employed while only 54 were employed before surgery. Similarly, in the control group, 38 were working before surgery and 60 were working at two years after surgery.

Patient Satisfaction. At 12 and 24 months after surgery, the results were similar in each treatment group. At 24 months, 81.2% of the investigational patients and 80.4% of the controls were satisfied with their surgical outcomes. In the investigational group, 82% said they would undergo surgery again compared with 76.7% of the control patients who would undergo surgery again. In the investigational group, 74.6% believed that they were helped as much as they had expected to be from the surgery; 76.6% of the control group felt they had been.

Radiographic Outcomes

Fusion status of the study patients was evaluated on plain radiographs and CT scans (Figs. 1-3). At six months after surgery, 97.0% of patients in the investigational group had evidence of interbody fusion compared with 115 patients (95.8 %) in the control group (Table 11). **QQ AU: Data in table do not agree with data in text. XQQ** At 12 months, 125 patients (96.9 %) in the investigational group showed evidence of fusion. **QQ AU: Table 11 says 127 pts. XQQ** In the control group, 111 patients (92.5%) showed evidence of fusion at one year. **QQ AU: Table 11 says 112 pts. XQQ** At 24 months, the investigational group had a 94.5% fusion rate, which was approximately six percentage points higher than that of the control group (88.7%).

Secondary Surgical Procedures

In the investigational group, 11 patients (7.0%) had a second surgery and 14 patients (10.3%) in the control group had second surgeries. In the investigational group, 2 patients had implant removals: One removal occurred at 5 days after surgery, and the other at 4months. The removal at 5 days was due to a vertebral bone fracture and implant displacement. The removal at 4 months was due to implant displacement and possible failed fusion. Seven investigational patients underwent supplemental fixation for presumed pseudarthrosis, 1 underwent supplemental fixation after posterior decompression for persistent radicular symptoms after the initial surgery, and 1 underwent a panlumbar fusion for discogenic back pain. Two of the supplemental fixations for presumed pseudarthrosis occurred before the 6-month follow-up evaluation. Fusion was not evaluated until 6 months after surgery; therefore, these patients cannot be classified as fusion failures. They are second surgery failures.

In the control group, 12 patients underwent supplemental posterior fixation for a presumed pseudarthrosis and 2 underwent supplemental posterior fixation for persistent discogenic pain. One patient underwent supplemental fixation for presumed pseudarthrosis before the 6-month follow up.

In 90% (18/20) of these patients (7/7 in the investigational group and 11/13 in the control group) the fusion was radiographically solid at the visit prior to the supplemental fixation, but posterior instrumentation was inserted by the treating physician based on clinical symptoms of persistent pain. In 53.3% of these patients, pain improved after the secondary posterior surgical procedure.

DISCUSSION

Spinal fusions can be performed anteriorly, posteriorly, or posterolaterally. Instrumentation can also be used to stabilize the spinal motion segment and to promote fusion. Traditionally, fusions in the lumbar spine have been performed through a posterior approach. After a successful posterolateral lumbar spinal fusion, patients often have significant relief of their painful symptoms. However, the posterolateral approach and the lateral exposure of the transverse processes of the lumbar spine can compromise the patient's functional outcome (13). The paraspinal muscles must be detached from the posterior spinal elements and transverse processes during the surgical exposure for the lateral fusion. This injury to the spinal muscles of the lumbar spine limits the patient's ultimate rehabilitation potential (1). Several studies have demonstrated significant loss of paraspinal muscle strength and muscle atrophy in patients with persistent back pain after posterolateral lumbar spinal fusion (12,18,22).

The surgeon strips the paraspinal muscles from their anatomic attachments to the spine and then reattaches them to the midline fascia and retained spinal elements. However, postoperative healing and scar tissue formation interferes with the normal independent function of the paravertebral muscle groups. The loss of their normal anatomic attachment sites, formation of scar tissue, and loss of independent muscle function compromise the paravertebral muscles.

Stand-alone anterior lumbar interbody fusion allows the complications of posterior "fusion disease" to be avoided. The anterior approach retains all posterior-stabilizing structures and avoids epidural scarring and perineural fibrosis. There is no need for paraspinal muscle stripping, retraction, or denervation of the adjacent facet joint. The muscle-splitting approach is one that does not compromise existing posterior spinal elements, and it allows the surgeon to reestablish normal disc space height and restore the normal sagittal contours of the lumbar spine. This technique allows a faster and often a more complete functional recovery of the patient. Long-term follow-up studies have not shown significant rates of adjacent segment degeneration after anterior interbody fusion (17).

Numerous clinical studies have documented the efficacy and improved outcomes with this procedure. Femoral ring allografts have been widely used; however, these intradiscal spacers alone do not provide enough stability to promote fusion consistently, and they have been associated with high rates of postoperative subsidence (2). Anterior femoral ring allografts often require an additional instrumented posterior spinal fusion to stabilize the spinal motion segment. Recent advances in metallic interbody fusion

devices have been introduced to stabilize intervertebral grafts and have been used to encourage fusion and prevent disc space collapse during the healing process (5).

This study is one of the largest prospective clinical evaluations of stand alone ALIF procedures. The randomized patient groups had no statistically significant differences in the variables assessed. Clinical and radiographic follow-up exceeded 90% at all intervals.

Because the investigational, or rhBMP-2, group did not undergo an autogenous bone graft harvesting procedure, there was a statistically significant reduction in operative time and in decreased blood loss during the procedure in these patients. In our patients, retrograde ejaculation was associated with the transabdominal approach to the lumbosacral spine.

The difficulty in achieving anterior interbody fusion through the use of fusion cages lies in the preparation of the endplate. The endplate must be partially removed to allow healing of the vertebral bodies. However, if resection of the endplate is excessive, subsidence can occur and, ultimately, pseudarthrosis. The procedure used in our study patients helps to enhance this fusion in two separate ways. With the LT-CAGE™ device, there is minimal endplate resection, thus preserving the weight-bearing portions of the endplate, which allows greater restoration of lordosis and prevents subsidence. The use of recombinant human bone morphogenetic protein has been shown to accelerate fusion in animal models (3,20,21). Its use should also allow the fusion procedure to more rapidly and more thoroughly occur in humans, as well. Indeed, from a radiographic standpoint this was true in our patients: 97% of patients with the LT-CAGE™ device and rhBMP-2 had radiographic evidence of a solid fusion at one year.

Our study's fusion assessment protocol is one of the first to use thin-cut CT scans to evaluate new bone formation (6). The thin-walled second-generation LT-CAGE™ device reduced imaging artifact in the instrumented disc space, and new bone formation was identified reliably inside and outside of the intervertebral cages on these CT scans. New bone formation was identified in all patients who received cages filled with rhBMP-2 that remained implanted for more than 6 months. Fusion failure was documented in the rhBMP-2 treated group because of a secondary surgical procedure not because of lack of new bone formation. All new bone formation was found within the instrumented disc space. **Areas between the cages, lateral to the cages, and anterior and posterior to the cages did often ossify. However,** there was no ectopic bone formation outside of the annular confines of the disc space, and there was no bone formation extending posteriorly into the spinal canal or laterally into the neuroforamina.

Recombinant human bone morphogenetic protein is an osteoinductive growth factor that stimulates pleuripotential cells to form bone (24). We believe that exposure of bleeding cancellous bone allowed influx of pleuripotential cells that were affected by the rhBMP-2 bound to the collagen carrier sponge. The investigational, or rhBMP-2, group had a 96.9% fusion rate at 12 months compared with 92.6% in the control group. At 24 months, the investigational group had a 94.5% fusion rate, which was almost six percentage points higher than the fusion rate of the control group (88.7%) with a probability of superiority of 90.2 %. **(p = ???)Deleted redundant sentence.** No metastatic calcifications were seen in these study patients.

The final assessment of a successful interbody fusion is difficult. Independent radiologists carefully scrutinized the plain x-rays, flexion-extension films, and CT scans of each patient. The reconstructed CT scans proved to be the most useful method of determining the success of the arthrodesis. Bridging trabecular bone seen on the coronal and sagittal reconstructed images was the final arbiter for determining whether a successful fusion had occurred. Only gross motion from a pseudarthrosis could be seen on the flexion-extension films and was seen best as a change in lucency between vertebral body and cage during the flexion-extension sequence. Finally, the question of how a patient with an arthrodesis that appears solid radiographically but who has persistent pain should be treated remains undetermined. In several instances in this study, the treating surgeon elected to proceed with a posterior instrumented fusion in the face of persistent pain and a successful arthrodesis. By the treating clinician's statement, these patients were noted to have pseudarthrosis. However, there is no accurate way to determine whether these were true radiographic pseudarthroses. In fact, only approximately half of the patients who went on to have posterior instrumentation for a presumed pseudarthrosis achieved significant pain relief. Less than half (40%) achieved pain improvement of 15 points or greater. Despite these rigorous criteria for determining successful fusion, we were able to obtain a very high rate of radiographic success.

The mean improvements in Oswestry score (29.0 and 29.5 points) are among the highest improvements reported in the literature. We believe this is due in part to the successful combination of anterior approach, threaded tapered titanium fusion cages, and a high degree of successful arthrodesis.

RhBMP-2 is a promising method of facilitating anterior intervertebral spinal fusion and of decreasing pain and improving clinical outcomes after anterior lumbar fusion when used with the LT-CAGE™ device. The combination of the threaded tapered fusion cage and rhBMP-2 may be efficacious in the treatment of challenging patients, such as smokers and those with associated medical disabilities. **The use of rhBMP-2 is associated with high fusion rates without the need for harvesting bone from the iliac crest and exposing the patient to the adverse effects associated with that procedure.(note: this is a better final line)**

REFERENCES

1. Beimborn DS, Morrissey MC: A review of the literature related to trunk muscle performance. *Spine* 13:655-660, 1988.

2. Blumenthal SL, Baker J, Dossett A, Selby DK. The role of anterior lumbar fusion for internal disc disruption. Spine 1988;13:566-9.

3. Boden SD, Schimandle JH, Hutton WC. 1995 Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 1995;20:2633-44.

4. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25:376-81.

5. Boyd, L.M.; Estes, B.T. and Liu M. "Biomechanics of Lumbar Interbody Constructs, *Effect of Design and Materials.*" Chirurgie Endoscopique et Mini-invasive du Rachis. Ed. Husson JL, LeHuec JC. Sauramps Médical. Montpelier, France. pp 181-92, 1999.

6. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. Neurosurg Focus 2001;10:1-9.

7. Crock HV. Anterior lumbar interbody fusion: indications for its use and notes on surgical technique. Clin Orthop 1982;165:157-63.

8. Flynn JC, Hoque MA. Anterior fusion of the lumbar spine. End result study with long-term follow-up. J Bone Joint Surg 1979;61A:1143-50.

9. Goldner JL, Urbaniak JR, McCollom DE: Anterior excision and interbody spinal fusion for chronic low back pain. *Orthop Clin North Am* 2:543-568, 1971

10. Harmon PH. Anterior excision and vertebral fusion operation for intervertebral disc syndromes of the lower lumbar spine: three to five year results in 244 cases. Clin Orthop 1963;26:107-27.

11. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999;24:629-36.

12. Jonsson B: The functions of individual muscles in the lumbar part of the spinae muscle. *Electromyography* 10:5-21, 1970.

13. Kahanovitz N, Viola K, Gallagher M: Long term strength assessment of postoperative diskectomy patients. *Spine* 14:402-403,1989.

14. Lane JD, Moore ES. Transperitoneal approach to the intervertebral disc in the lumbar area. Annals of Surgery 1948;127:537-51.

15. Loguidice VA, Johnson RG, Guyer RD, Stith WJ, Ohnmeiss DD, Hochschuler SH, Rashbaum RF. Anterior lumbar interbody fusion. Spine 1988;13:366-9.

16. Leong JC, Chun SY, Grange WJ, Fang D: Long-term results of lumbar intervertebral disc prolapse. Spine 1983;8:793-9.

17. Penta M, Sandhu A, Fraser RD: Magnetic resonance imaging assessment of disc degeneration 10 years after anterior lumbar interbody fusion. *Spine* 20: 743-747, 1995.

18. Rantanen J, Hurme M, Falck B, Alaranta H, Nykvist F, Lehto M, Einola S, Kalimo H: The lumbar multifidus muscle five years after surgery for a lumbar intervertebral disc herniation. *Spine* 18:568-574, 1993.

19. Sacks S. Anterior interbody fusion of the lumbar spine. J Bone Joint Surg [Br] 1965;47:211-23.

20. Sandhu HS, Kanim LEA, Toth JM, et al. Experimental spinal fusion with recombinant human bone morphogenetic protein-2 without decortication of osseous elements. Spine 1997;22:1171-80.

21. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995; 20:1326-37.

22. Sihvonen T, Herno A, Paljarvi L, Airaksinen O, Partanen J, Tapaninaho A: Local denervation atrophy of paraspinal muscles in postoperative failed back syndrome. *Spine* 18:575-581, 1993.

23. Stauffer RN, Coventry MB. Anterior interbody lumbar spine fusion. J Bone Joint Surg [Am]1972;54:756-68.

24. Urist MR. Bone: Formation by autoinduction. Science 1965;150:893-9.

Table 1. Patient Data

Variable	Investigational (n=143)	Control (n=136)	P value *
Age (yrs.)			
n	143	136	0.369
Mean	43.3	42.3	
Weight (lbs.)			
n	143	134	0.639
Mean	179.1	181.1	
Sex [n (%)]			
Male	78 (54.5)	68 (50.0)	0.473
Female	65 (45.5)	68 (50.0)	
Workers' Compensation [n (%)]	47 (32.9)	47 (34.6)	0.801
Spinal Litigation [n (%)]	18 (12.6)	22 (16.2)	0.400
Tobacco Used [n (%)]	47 (32.9)	49 (36.0)	0.615
Preop Work Status [n (%)]	68 (47.6)	50 (36.8)	0.071
Working			

*For continuous variables, P values are from ANOVA. For categorical variables, P values are from Fisher's exact test or chi-square test.

Table 2. Patient Accountability

Investigational Group

	Preop	Surgery	6 Weeks	3 Months	6 Months	12 Months	24 Months
Theoretical							
Follow-up[1]	143	143	143	143	143	143	143
Deaths	0	0	0	0	0	0	0
(Cumulative)							
Failures[2]	0	0	1 (1)	0 (1)	3 (4)	1 (5)	4 (9)
(Cumulative)							
Expected[3]	143	143	142	142	139	138	133
Number Evaluated	143	143	141	141	137	133	123
Percent Follow-up	100.0%	100.0%	99.3%	99.3%	98.6%	96.4%	92.5%

Control Group

	Preop	Surgery	6 Weeks	3 Months	6 Months	12 Months	24 Months
Theoretical							
Follow-up[1]	136	136	136	136	136	136	136
Deaths	0	0	0	0	0	1	1
(Cumulative)							
Failures[2]	0	0	0	0	1 (1)	4 (5)	7 (12)
(Cumulative)							
Expected[3]	136	136	136	136	135	130	120
Number Evaluated	136	136	134	134	133	126	109
Percent Follow-up	100.0%	100.0%	98.5%	98.5%	98.5%	96.9%	90.8%

[1] Theoretical = Patients who have entered the follow-up window.
[2] Failures include device removals, revisions and supplemental fixations.
[3] Expected = Theoretical – Cumulative Deaths – Cumulative Failures

Table 3. Surgery Information

Variable	Investigational (n=143)	Control (n=136)
Operative Time (hrs)		
n	143	136
Mean	1.6	2.0
Blood Loss (ml)		
n	142	136
Mean	109.8	153.1
Hospital Stay (days)		
n	143	136
Mean	3.1	3.3
Treatment Levels [n (%)]		
L4-L5	37 (25.9)	32 (23.5)
L5-S1	106 (74.1)	103 (75.7)
L5-L6	0 (0.0)	1 (0.7)
Operative Approach [n (%)]		
Retroperitoneal	116 (81.1)	110 (80.1)
Transperitoneal	27 (18.9)	26 (19.1)

Table 4. Iliac Crest Graft Site Pain and Appearance Scores

Period	Variable	Control
Discharge	Pain Score	
	n	134
	Mean	12.7
	P value[1]	<0.001
	Appearance of Graft Site	
	Poor[2]	13 (9.8)
6 Weeks	Pain Score	
	n	132
	Mean	6.7
	P value	<0.001
	Appearance of Graft Site	
	Poor	5 (3.8)
3 Months	Pain Score	
	n	134
	Mean	3.5
	P value	<0.001
	Appearance of Graft Site	
	Poor	3 (2.3)
6 Months	Pain Score	
	n	132
	Mean	2.6
	P value	<0.001
	Appearance of Graft Site	
	Poor	5 (3.8)
12 Months	Pain Score	
	n	130
	Mean	2.1
	P value	<0.001
	Appearance of Graft Site	
	Poor	5 (3.8)
24 Months	Pain Score	
	n	117
	Mean	1.8
	P value	<0.001
	Appearance of Graft Site	
	Poor	3 (2.6)

[1] P values are from Student's *t* test comparing mean with zero.
[2] Poor= "It bothers me very much."

Table 5 – Oswestry Low Back Pain Disability Scores

Period	Variable	Investigational	Control
Preoperative			
	n	143	136
	Mean	53.7	55.1
6 Weeks			
	n	140	131
	Mean	42.1	41.4
Improvement from Preoperative			
	Mean	11.4	13.6
	P value[1]	<0.001	<0.001
3 Months			
	n	141	134
	Mean	33.5	34.2
Improvement from Preoperative			
	Mean	19.9	20.8
	P value	<0.001	<0.001
6 Months			
	n	136	131
	Mean	29.3	29.4
Improvement from Preoperative			
	Mean	24.4	25.4
	P value	<0.001	<0.001
12 Months			
	n	130	125
	Mean	25.5	25.6
Improvement from Preoperative			
	Mean	27.7	28.9
	P value	<0.001	<0.001
24 Months			
	n	122	108
	Mean	23.9	23.8
Improvement from Preoperative			
	Mean	29.0	29.5
	P value	<0.001	<0.001

[1] **QQ AU: What does the footnote symbol by P value indicate? XQQ**

Table 6. Neurologic Outcomes

Period	Variable	Investigational (n=143) n (%)	Control (n=136) n (%)
6 Weeks	Overall		
	Success	110 (80.3)	108 (83.7)
	Failure	27 (19.7)	21 (16.3)
3 Months	Overall		
	Success	119 (84.4)	103 (77.4)
	Failure	22 (15.6)	30 (22.6)
6 Months	Overall		
	Success	106 (77.9)	106 (80.9)
	Failure	30 (22.1)	25 (19.1)
12 Months	Overall		
	Success	108 (81.8)	105 (84.7)
	Failure	24 (18.2)	19 (15.3)
24 Months	Overall		
	Success	101 (82.8)	90 (83.3)
	Failure	21 (17.2)	18 (16.7)

Table 7. Back Pain Outcomes

Period	Variable	Investigational	Control
Preoperative	n	143	136
	Mean	15.8	16.1
6 Weeks	n	139	132
	Mean	9.3	8.8
Improvement from Preoperative	Mean	6.5	7.4
	P value[1]	<0.001	<0.001
3 Months	n	140	134
	Mean	8.7	9.0
Improvement from Preoperative	Mean	7.1	7.1
	P value	<0.001	<0.001
6 Months	n	136	131
	Mean	8.6	8.9
Improvement from Preoperative	Mean	7.3	7.1
	P value	<0.001	<0.001
12 Months	n	129	125
	Mean	8.0	8.4
Improvement from Preoperative	Mean	7.8	7.6
	P value	<0.001	<0.001
24 Months	n	122	108
	Mean	7.3	7.9
Improvement from Preoperative	Mean	8.4	8.1
	P value	<0.001	<0.001

[1] **QQ AU: What does the footnote symbol by P value indicate? XQQ**

Table 8. Back Pain Success Rates

Variable	Investigational n (%)	Control n (%)
6 Weeks		
Success	107/139 (77.0)	101/132 (76.5)
Failure	32/139 (23.0)	31/132 (23.5)
3 Months		
Success	103/140 (73.6)	105/134 (78.4)
Failure	37/140 (26.4)	29/134 (21.6)
6 Months		
Success	106/136 (77.9)	94/131 (71.8)
Failure	30/136 (22.1)	37/131 (28.2)
12 Months		
Success	102/129 (79.1)	91/125 (72.8)
Failure	27/129 (20.9)	34/125 (27.2)
24 Months		
Success	91/122 (74.6)	85/108 (78.7)
Failure	31/122 (25.4)	23/108 (21.3)

Table 9. Leg Pain Scores

Period	Variable	Investigational n = 143	Control n = 136
Preoperative			
	n	143	136
	Mean	12.5	12.5
6 Weeks			
	n	139	132
	Mean	7.5	8.4
Improvement from Preoperative	n	139	132
	Mean	5.1	4.1
	P value[1]	<0.001	<0.001
3 Months			
	n	140	134
	Mean	6.8	6.8
Improvement from Preoperative	n	140	134
	Mean	5.6	5.6
	P value	<0.001	<0.001
6 Months			
	n	136	131
	Mean	6.3	6.3
Improvement from Preoperative	n	136	131
	Mean	6.4	6.3

	P value	<0.001	<0.001
12 Months			
	n	129	125
	Mean	6.3	6.6
Improvement from Preoperative	n	129	125
	Mean	6.4	5.6
	P value	<0.001	<0.001
24 Months			
	n	122	108
	Mean	6.3	6.3
Improvement from Preoperative	n	122	108
	Mean	6.5	5.9
	P value	<0.001	<0.001

[1] P values for change from preoperative in each group are from paired test.
QQ AU: Should this be "paired tests" or "paired *t* tests"?

Table 10. Return-To-Work Status

Period	Variable	Investigational n (%)	Control n (%)
3 Months	Working	54 (38.3)	38 (28.4)
	Not Working	42 (29.8)	43 (32.1)
	Was Not Working Before Surgery	45 (31.9)	53 (39.6)
6 Months	Working	69 (50.7)	60 (45.5)
	Not Working	25 (18.4)	29 (22.0)
	Was Not Working Before Surgery	42 (30.9)	43 (32.6)
12 Months	Working	72 (55.0)	63 (50.4)
	Not Working	20 (15.3)	19 (15.2)
	Was Not Working Before Surgery	39 (29.8)	43 (34.4)
24 Months	Working	80 (66.1)	60 (56.1)
	Not Working	11 (9.1)	13 (12.1)
	Was Not Working Before Surgery	30 (24.8)	34 (31.8)

Table 11. Rates of Radiographic Fusion [Number (%) of Patients]
QQ AU: Text says at 12 months there are 125 investigational pts., which would be 95.4% and 111 control pts., which would be 91.7%. Which is correct? Check accuracy of fusion data given in Discussion section.

Variable	Investigational (n=143) n (%)	Control (n=136) n (%)
6 Months		
Success	128/132 (97.0)	115/120 (95.8)
Failure	4/132 (3.0)	5/120 (4.2)
12 Months		
Success	127/131 (96.9)	112/121 (92.6)
Failure	4/131 (3.1)	9/121 (7.4)
24 Months		
Success	120/127 (94.5)	102/115 (88.7)
Failure	7/127 (5.5)	13/115 (11.3)

LEGEND OF FIGURES

Figure 1: Standing lateral radiograph of the lumbosacral spine shows disc space collapse at L5-S1 and early radial osteophyte formation. There is loss of segmental lordosis at the disc space to 15°.

Figure 2: Standing lateral radiograph at 24 months after surgery shows restoration of anatomic disc space height at the L5-S1 interspace and improvement of segmental lordosis to 27°. New bone formation can be seen anterior to the cages.

Figure 3: Thin-cut 1-mm CT scan sagittal reconstruction at 24 months after surgery shows new bone formation within the LT-CAGE™ device and new bone formation anterior to the cage but within the confines of the disc space.

From: JKE[redacted]
Sent: Thursday, April 4, 2002 07:10:18 AM
To: Neil Beals[redacted]
Subject: BMP Manuscripts

Attachments: Revised Bone Dowel BMP Paper.6.doc; Revised CAT Scan BMP LT Cage.2.doc; Final revisions OPEN LTCAGE BMP.4.doc

Clinical and Radiographic Outcomes of Anterior Lumbar Interbody Fusion Using Recombinant Human Bone Morphogenetic Protein-2

J. Kenneth Burkus, MD*

Ensor Transfeldt, MD†

Scott H. Kitchel, MD‡

Robert Watkins, MD§

and

Richard Balderston, MD||

* Hughston Spine Service, The Hughston Clinic, Columbus, Georgia

† Twin Cities Spine Service, Minneapolis, Minnesota

‡ Orthopedic Healthcare NW, Eugene, Oregon

§ The Center for Spinal Surgery, Los Angeles, California

|| 3B Orthopedics, Philadelphia, Pennsylvania

This study was sponsored by Medtronic Sofamor Danek, Memphis, TN.

Address correspondence and reprint requests to: J.K. Burkus, MD, The Hughston Clinic, PC. [redacted]

Deleted: 01/31/02

ABSTRACT

Study Design. A prospective nonblinded multicenter study of outcomes in patients undergoing single-level anterior lumbar discectomy and interbody fusion with InFUSE™ Bone Graft (rhBMP-2).

Objective. To determine the safety and effectiveness of InFUSE™ Bone Graft applied to an absorbable collagen sponge in anterior lumbar interbody fusion with threaded cortical allografts.

Summary of Background Data. In primates, rhBMP-2 used with allograft dowels was shown to increase rates of interbody fusion by promoting osteoinduction and enhancing incorporation of the allograft. Recently, in a small series of human patients undergoing ALIF with a tapered cylindrical metal fusion cage, InFUSE™ Bone Graft has been shown to promote osteoinduction and fusion.

Methods. Forty-six patients underwent a single-level anterior lumbar discectomy and interbody fusion at five investigational sites. They were randomly assigned to one of two groups, and the results in the investigational patients who received threaded cortical allograft dowels with InFUSE™ Bone Graft were compared with those in the control patients who received threaded allograft dowels with autogenous iliac crest bone graft. Patients clinical outcomes were assessed using neurologic status, work status, and Oswestry Low Back Pain Disability, Short Form-36, and back and leg pain questionnaires. Anteroposterior, lateral, flexion-extension radiographs, and computed tomography scans were used to evaluate the progression of fusion at 6, 12, and 24 months after surgery.

Deleted: 01/31/02

Results. All patients who received InFUSE™ Bone Graft showed radiographic evidence of bony induction and early incorporation of the cortical allografts. All patients in this group had fusions at 12 months that remained fused at 24 months. At 12 and 24 months, the investigational group showed higher rates of fusion and improved neurologic status and back and leg pain when compared with the control group. There were no unanticipated adverse events related to the use of InFUSE™ Bone Graft.

Conclusion. The use of InFUSE™ Bone Graft is a promising method of facilitating anterior intervertebral spinal fusion, decreasing pain, and improving clinical outcomes in patients who have undergone anterior lumbar fusion surgery with structural threaded cortical allograft bone dowels.

Key words: anterior lumbar interbody fusion, bone morphogenetic protein, degenerative disc disease, lumbar spine

Deleted: 01/31/02

PRÉCIS

In 46 patients who underwent anterior lumbar interbody fusion with threaded cortical allografts and were followed for 2 years, the investigational group that received InFUSE™ Bone Graft on a collagen sponge carrier showed higher rates of fusion at 6, 12, and 24 months after surgery when compared with the group that received autogenous iliac crest bone graft. These patients demonstrated faster and greater functional recovery and greater reduction of back and leg pain than the controls, and a higher percentage of the investigational group than of the autogenous bone graft group was able to return to work.

Deleted: 01/31/02

INTRODUCTION

Cylindrical threaded allograft dowels can be used as stand-alone intervertebral implants that function as an instrumented anterior lumbar interbody fusion (ALIF). They are not intradiscal spacers that require additional segmental stabilization. The threaded cortical bone dowels can withstand lumbar compressive loads and can promote load sharing between the allograft and the host bone while maximizing device porosity.[4,17] These interbody constructs are implanted within the central portion of the disc space through a controlled insertion technique. Impacted allografts, when used alone for interbody fusion in the lumbar spine, have been reported to have a high rate of pseudarthrosis and subsidence.[9,12,21] Contemporary reports of large clinical series of ALIFs using impacted grafts have shown various rates of fusion and differing clinical outcomes.[1,7,10,13-15,18] The threaded dowels resist expulsion and stabilize the bone-implant interface.[4] In addition, threaded bone dowels offer increased strength to support cancellous graft material.[19] In one clinical series, 43 patients were followed for more than 1 year and had a high fusion rate and improved clinical outcomes.[5]

InFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, TN) is recombinant human bone morphogenetic protein applied to an absorbable collagen sponge. Its use replaces the need for autogenous bone grafts and eliminates the complications associated with iliac crest graft harvesting. In a clinical series of patients undergoing an ALIF procedure with a tapered cylindrical metal fusion cage, InFUSE™ Bone Graft has been shown to promote osteoinduction and increase rates of fusion.[3] Our report presents the 2-year clinical and radiographic results of the use of InFUSE™ Bone Graft (rhBMP-2) with

Deleted: 01/31/02

a collagen sponge carrier inside a cylindrical threaded cortical allograft dowel in patients undergoing anterior lumbar interbody fusion.

MATERIALS AND METHODS

Study Design. This prospective, randomized, non-blinded study was conducted under an approved investigational device exemption (IDE). Forty-six patients at five investigational sites had ALIF surgery between April and August 1998. The patients were randomly assigned to 1 of 2 study groups. The investigational group received InFUSE™ Bone Graft, recombinant human bone morphogenetic protein-2 (rhBMP-2) applied to an absorbable collagen sponge carrier, used in conjunction with the MD-II™ threaded cortical bone dowel (Regeneration Technologies, Inc., Alachua, FL). The control group received autogenous iliac crest bone graft. Data were collected preoperatively, intraoperatively, and at 6 weeks, 3, 6, 12 and 24 months postoperatively. Operative procedure details and adverse events were also recorded.

Degenerative Lumbar Disc Disease. Degenerative lumbar disc disease refers to a specific pain syndrome that originates from degenerative changes and instability patterns within the intervertebral disc. Diagnosed by a history of clinical complaints, physical findings, and neuroradiographic studies, this syndrome is characterized by chronic and, at times, incapacitating low back pain, which is often felt as referred pain in the buttock and posterior aspect of the thigh. The referred leg-pain pattern rarely extends below the knees and radiates in a nondermatomal distribution into the lower extremities. Pain is usually exacerbated by vigorous activities and relieved by rest. Prolonged sitting may be painful, and patients often have difficulty finding a comfortable position. Patients with this degenerative condition do not usually exhibit objective neurologic deficits. Positive

Deleted: 01/31/02

sciatic tension signs are also uncommon. Patients often have restricted range of motion of the lumbar spine, tenderness to palpation over the affected lumbar motion segment, and paravertebral muscle spasm.

The diagnosis is confirmed with neuroradiographic studies, including plain radiographs, magnetic resonance imaging (MRI), and discography. Plain radiographs often show signs of instability, such as disc space collapse, radial osteophytes, retrolithesis, spondylolisthesis, or a combination of these conditions. Dynamic flexion-extension lateral radiographs are sometimes necessary to show patterns of sagittal plane translation. In these degenerative conditions, MRI shows desiccation of the disc, sclerosis of the adjacent vertebral endplates, and radial protrusion of the annulus. Discography can identify radial tears in the annulus fibrosus and early degenerative changes in the disc. However, the diagnosis of painful degenerative lumbar disc disease is confirmed with a positive provocative pain response during discography. To identify the pain generator accurately, discography must elicit a concordant reproduction of the patient's painful symptoms at the time of the injection. The radiographic findings and the provocative pain response during discography must be correlated with other neuroradiographic studies and clinical findings. Discography cannot be used alone to select patients for surgery.

Inclusion and Exclusion Criteria. Patients with single level lumbar degenerative disc disease were included in the study. This diagnosis was based upon the patient history and symptoms, physical findings, functional deficits and radiographic finding. Patients with primary complaints of low back pain were included in the study. Patients may also have experienced low back pain with or without referred leg pain; patients may also have experienced low back pain with or without sciatica. Patients were included with these

Deleted: 01/31/02

primary symptoms and had a preoperative Oswestry Low Back Pain Disability Index score of 35 points or more. Patients were included with and without objective neurologic deficits. All patients included in the study had these disabling symptoms for a minimum of six months and had failed to respond a non-operative treatment regimen that included aerobic conditioning, medications, spinal injections, and/or manipulation.

Correlative radiographic findings necessary for inclusion in the study were: instability as defined by segmental angulation ≥ 5° and/or translation ≥ 4mm, osteophyte formation, decreased disc height of at least 50%, thickening of ligamentous tissue, and/or disc protrusion and herniation. The radiographic inclusion criteria did not require patients to have discography, even though some were performed. These radiographic findings could be established on one or more studies including either plain radiographs, MR imaging, CT scanning and/or discography. Isolated "facet joint syndromes" were not evaluated.

Patients were excluded from the study that had a medical condition, which requires postoperative medications that interfere with fusion, such as steroids or nonsteroidal anti-inflammatory drugs (this did not include low dose aspirin for prophylactic anticoagulation). NSAIDS were used as part of the preoperative treatment regimen; however, these medications were avoided during the clinical trial.

Patient Population. All patients were between the ages of 19 and 68 years and had symptomatic degenerative disc disease at the L4-L5 or L5-S1 levels. All patients had had low back pain for at least 6 months before their surgery that was recalcitrant to

Deleted: 01/31/02

nonoperative treatment modalities, such as physical therapy, bed rest, and anti-inflammatory medications. Patients were included in the study if their plain radiographic findings documented single-level disc disease, and they had undergone at least one additional confirmatory neuroradiographic study, such as MRI, CT-enhanced myelography, or discography. All patients were considered candidates for a single-level stand-alone anterior lumbar interbody fusion.

Patients were excluded from the study if they had spinal conditions other than single-level symptomatic degenerative disc disease or Grade 0 or 1 spondylolisthesis. Other exclusion criteria were symptomatic disc disease at a level other than the L4-L5 or L5-S1 disc space levels, obesity (more than 40% above ideal body weight), a history of discitis, or a medical condition that required medication, such as steroids or nonsteroidal anti-inflammatory medications, that could interfere with fusion.

The investigational group comprised 24 patients who were treated with InFUSE™ Bone Graft (Table 1). There were 22 patients in the control treatment group who were treated with autograft. In the control group, 1 patient was lost to follow-up and was excluded from the study; and 1 patient died in a house fire at 6 months after surgery leaving 20 patients in this group who were followed for a minimum of 24 months after surgery.

Surgical Technique. The patients underwent an open ALIF using either a transperitoneal or a retroperitoneal approach to the lumbosacral spine. In each patient, a complete discectomy was carried out. An incision was made in the annulus fibrosus, the nucleus pulposus and the cartilaginous endplates were circumferentially removed; however, the

Deleted: 01/31/02

bony endplates were preserved prior to reaming and tapping of the endplate for receipt of the dowel. Two allograft bone dowels were then inserted into each disc space.

The rhBMP-2 was reconstituted using sterile water and a single dose at a concentration of 1.5 mg/mL was administered. The concentration was the same in all patients. The solution was applied by syringe to an absorbable collagen sponge. Next, the collagen sponge was placed into the central portion of the bone dowel. The total dose (8 to 12 mL) depended on the capacity of the bone dowel (16, 18, or 20 mm) used. Additional InFUSE™ Bone Graft (or rhBMP-2 prepared sponges) was placed between the bone dowels. No autogenous grafts were used in the investigational group.

The control group received morcellized autogenous iliac crest graft in conjunction with the threaded cortical bone dowels. The iliac grafts were harvested through a separate incision directly over the iliac wing. The inner or outer table of the ilium was exposed subperiostealy and corticocancellous grafts were harvested. A single cortex was preserved in all grafts; no bicortical iliac grafts were obtained. The central opening of the dowels were packed with the bone graft before their insertion into the disc space. Additional bone graft was packed between and anterior to the dowels.

Postoperative Care. All patients were instructed to wear an external orthosis for 6 to 12 weeks after surgery. Patients were encouraged to ambulate immediately after surgery. Physical activities were advanced at the discretion of the attending surgeon.

Clinical Outcome Measurements. Assessments were completed preoperatively, during the patient's hospitalization, and postoperatively at 6 weeks and 3, 6, 12, and 24 months. Clinical outcomes were measured using well-established instruments: Oswestry Low Back Pain Disability Questionnaire,[8] Short Form 36 (SF-36),[16,23] and neurologic status,

Deleted: 01/31/02

work status, patient satisfaction, and back, leg, and graft site pain questionnaires. The Oswestry Low Back Pain Disability Questionnaire was self-administered and was used to measure the level of pain and disability associated with various activities. Neurologic status assessment was based on four objective clinical measurements: motor, sensory, reflexes, and sciatic tension signs. Neurologic outcome success was based on maintenance of or improvement in each variable tested. The SF-36 is a self-administered questionnaire that measures specific health concepts related to physical functioning, social functioning and health perceptions. It comprises a Physical Component Summary (PCS) and a Mental Component Summary (MCS). Three patient satisfaction questions were administered at each postoperative time period. A successful answer to each question was defined as either a "definitely true" or "mostly true" response. Low back, leg, and iliac graft site pain were evaluated using numerical rating scales that identified both pain intensity and duration. Standard visual analog scales were used for pain intensity and duration of the painful symptoms. The two scores were added together to derive a composite score.

Radiographic Outcome Measurements. Radiographs and CT scans were used to evaluate fusion at 6, 12 ,and 24 months after surgery.[6] Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent radiologist was used to adjudicate conflicting fusion findings.

Fusion was defined as bridging bone connecting the adjacent vertebral bodies either through the implants or around the implants, less than 5 degrees of angular motion, less than or equal to 3 mm of translation, and an absence of radiolucent lines around more than 50% of either of the implant surfaces. Stability and radiolucent lines were assessed

Deleted: 01/31/02

on plain radiographs using anteroposterior, lateral, and flexion-extension views. Thin-slice (1 mm) computed tomography scans with sagittal reconstructions were evaluated at 6, 12, and 24 months. The presence of continuous trabecular bone formation between the vertebral bodies was assessed using radiographs and computed tomography scans. A fusion was considered successful only if all four criteria were achieved: 1) bridging trabecular bone connecting the two vertebral bodies either through the dowels or around the dowels as evaluated by thin-cut CT scans and radiographs; 2) no angular motion of 5° or more on dynamic plain radiographs; 3) no sagittal translation of more than 3 mm on dynamic plain radiographs; and 4) no radiolucencies that involved more than half of the interfaces between the dowels and the host vertebral endplates.

Statistical Methods. The data from this clinical trial were analyzed using the statistical software package SAS® version 6.12. For continuous variables, *P* values are from ANOVA, and for categorical variables, they are from Fisher's exact test or chi-square test.

RESULTS

Surgery. In the investigational group, 11 patients (45.8%) had surgery at the L4-L5 level and 13 (54.2%) had surgery at the L5-S1 level (Table 2). In the control group, surgery was performed at the L4-L5 level in 8 patients (36.4%) and at the L5-S1 level in 14 patients (63.6%). The mean operative time was slightly longer in the control group. The investigational group had surgery more commonly at the L4-L5 level. This exposure of the L4-L5 disc space often involves a tedious mobilization of the iliac vessels and requires more time when compared with the exposure at the L5-S1 level. The average

Deleted: 01/31/02

blood loss was less in the investigational group than in the control group ($P = 0.026$). The average hospital stay was similar in both groups.

Clinical Outcomes. No unanticipated adverse events that were related to the use of InFUSE™ Bone Graft (rhBMP-2 and the collagen sponge carrier) occurred during the course of the study.

Neurologic Outcomes. At 12 and 24 months, the investigational patients showed a higher rate of success than the control patients in their overall neurologic success scores (Table 3 and Figure 1). More than 87% of patients in the investigational group were considered to be a neurologic success (defined as equivalence or improvement from the preoperative condition) at 3 months after surgery. These results were maintained at the final 24-month follow-up. More than 95% of patients in the autograft control group were considered to be a neurologic success at 3 months after surgery. However, these clinical results deteriorated to 73.3% at 24 months.

Back Pain Outcomes. Patients in the investigational group showed an improvement in back pain analog scores (maximum score = 20) of more than 7 points at their initial postoperative visit at 6 weeks (Table 4 and Figure 2). In this group, back pain continued to improve and averaged close to a 9-point improvement in pain scores at 24 months after surgery. The control group's improvement in back pain followed a similar pattern. However, at 24 months, average back pain scores improved only 5 points in this group. The mean improvement scores for low back pain in the investigational group were significantly greater than those reported in the control group at 3, 6, and 24 months ($P = 0.038$, $P = 0.034$ and $P = 0.047$, respectively).

Deleted: 01/31/02

Leg Pain Outcomes. There was no difference in the preoperative leg pain scores between the invitational and control groups (investigational 12.8; control 14.6 p=0.2291).The investigational group also showed greater of relief of leg pain compared with the controls (Table 5 and Figure 3). In the investigational group, leg pain improved by more than 5 points within 6 weeks of surgery. These results remained virtually unchanged at the last follow-up of 24 months. However, while the autogenous graft group showed initial improvement of greater than 5 points, the improvement at 24 months decreased to 3.1 points.

General Health (SF-36) Outcomes. In both the Physical (PCS) and Mental (MCS) Components of the SF-36, a successful outcome was defined as a maintenance or improvement in results from preoperative. The investigational group showed higher success at 24 months than the control group (Figures 4 and 5). However, these results were not found to be statistically significant.

Patient Satisfaction Outcomes. At 24 months the success rate was more than 83% in the investigational group for all three questions. For the control group, the success rate for the three questions ranged from 55% to 65% (Table 6).

Oswestry Disability Questionnaire Outcomes. The Oswestry Disability Questionnaire was used to assess pain with activity (Table 7 and Figure 6). At all follow-up intervals, the investigational group had greater improvements in Oswestry scores than the control group. At 3, 6, and 24 months, the differences in improvement scores were statistically significant ($P = 0.032$, $P = 0.039$, and $P = 0.039$, respectively). At 24 months, the mean improvement in Oswestry scores was 33.5 points.

Deleted: 01/31/02

Seventy-one percent (71%) of the patients in the investigational group showed an improvement of at least 15 points in their disability scores at 3 months. This improvement compared favorably with the 43% of patients who showed improvement in the control group ($P = 0.075$). At 12 months, 83% of the investigational group patients improved more than 15 points compared with 58% of the controls. This finding was similar at the 24-month follow-up.

Return-to-Work Status. Higher percentages of patients in the investigational group were also able to return to work (Figure 7). In the investigational group, 45.8% of patients were working before their surgery. At 24 months after surgery, 66.7% were working. These patients were also able to return to work earlier than those in the control group. In the control group, 40.9% were working before surgery and at 24 months, 35.0% were working.

Iliac Crest Graft Site Pain. Autograft bone was not harvested from the iliac crest in the investigational group; therefore, bone graft site pain was not measured and was assumed to be zero in this group. In the control group, the intensity and frequency of pain and morbidity from the graft harvesting was measured on a 20-point rating scale. At discharge from the hospital, the mean graft site pain was highest (11.3). Graft site pain persisted at 24 months in these patients with a mean score of 2.2 (Figure 8).

Additional Surgery. No patients treated with InFUSE™ Bone Graft required an additional surgical procedure in the immediate perioperative period; 1 control patient required an early return to surgery to remove residual disc material (Table 8). Four patients (1 investigational, 3 control) underwent supplemental posterior fixation procedures after their primary surgery. The investigational patient continued to have

Deleted: 01/31/02

persistent low back pain at 24 months. The patient's radiographs met the criteria for fusion; however, the attending physician elected to reoperate and supplement the interbody grafts with insertion of posterior pedicle fixation. The attending physician was able to identify "slight motion" in the posterior facet joints despite the presence of an adequate fusion across the anterior disc space. The three patients in the control group had supplemental posterior fixation inserted from 7 months to 20 months following their initial surgeries. In each of these cases, the patient reported persistent low back pain and in some instances referred leg pain.

Radiographic Outcomes. At 6-months after surgery, 21 patients in the investigational group were able to return for follow-up evaluation. Of these, 19 patients (90.5%) who were treated with InFUSE™ Bone Graft had evidence of interbody fusion compared with 13 of the 20 patients (65%) in the control group ($P = 0.067$) (Figure 9). At 12 months, all patients (24/24, 100%) in the investigational group had evidence of fusion compared with 17 patients (89.5%) in the control group. Based on their radiographs at the final follow up at 24 months after surgery, all patients (100%) in the investigational group showed evidence of remaining fused (Figure 10).

One patient in the investigational group did meet the criteria for fusion but underwent supplemental posterior fixation after the final 24-month follow-up examination. In this patient, the attending physician identified motion within the facet joints and elected to add supplemental posterior fixation to the spinal motion segment just after the 24-month visit. By the criteria of this study, this patient was recorded as having a successful interbody fusion at the 12- and 24-month follow-up examination and is not considered a failure until the 36-month follow-up examination. All patients were found to

Deleted: 01/31/02

have bony integration of the allografts to the vertebral endplates and trabeculated new bone formation across the fused interspace. By considering this investigational patient as a fusion failure because of the need to use supplemental posterior fixation, the fusion rate for the investigational group was 95.8%.

At 24 months in the control autograft group, 19 patients were available for radiographic evaluation, and 13 of these patients (68.4%) were considered to have fusions (Figure 11). In the control group, there were no failures of the allograft dowels. Three control group patients underwent supplemental posterior fixation for pseudarthrosis. Radiographic lucencies developed at the interface of the allograft to the vertebral endplate between the 12- and 24-month follow-up examinations (Figure 12). This led to the decrease in the fusion rate in the control group. There was no migration of the implants.

Fusion Rate. In this study, **fusion** is defined as the radiographic identification of: bridging bone, no motion (<5° angulation, <3mm translation), and absence of radiolucent lines around more than 50% of either implant. In the control group, there were patients who were felt to be radiographically fused at 12 months, and then later at 24 months, they were felt to be radiographically not fused. This was due to the radiolucent line criteria. The patients had bridging bone and no motion at 12 & 24 months, however, at 12 months radiolucent lines were not evident; it was not until 24 months postoperatively that these lucencies around the cortical implants were seen. This is very likely due to the nature of the control implant. The dowels were packed solid with autograft bone and lucencies resulting from failure of the allograft to fully incorporate to the vertebral endplates is not evident early on but is a fining that is seen overtime. After all, that is why the

Deleted: 01/31/02

radiographic follow-up was carried out to two years Due to early incorporation of the allograft to the vertebral endplates in the rhBMP group, issue was not seen postoperatively in the investigational group.

Factors other than those in the radiographic criteria were used in determining the **rate of fusion** or **fusion success**. The rate of fusion or fusion success is, in part, defined by secondary surgeries. In he investigational group, a patient had undergone a secondary surgery (i.e. supplemental fixation); that patient was called a fusion failure from that time forward. We did not go back and call this patient a fusion failure at previous visits. At these previous visits the patients met the protocol-required elements of radiographic fusion. The pseudarthrosis diagnosis may have been in response to persistent low back pain not a deviation from the fusion criteria. At the time of surgery on this investigational patient the attending surgeon found that the spinal motion segment "was extremely stable and contained only micro-motion noted after the facet joints were debrided".

DISCUSSION

Recombinant human bone morphogenetic protein-2 (rhBMP-2) is an osteoinductive growth factor.[2,20] Urist discovered the capabilities of demineralized bone matrix to induce ectopic bone formation in a rat muscle pouch and introduced the concept that bone growth factors can induce new bone formation independent of the bone tissue environment.[22] Bone morphogenetic protein-2 is one of several proteins identified from bone tissue that acts a osteoinductive cytokine and induces the differentiation of pluripotential precursor cells along an osteogenic line. A pure form of this protein can be produced through standard recombinant technology. The human cDNA sequence is

Deleted: 01/31/02

created through the use of oligonucleotide probes, and these clones are then spliced into a viral vector and transfected into a carrier cell in a process called recombination. These production cells (Chinese hamster ovary cells) have the ability to produce large quantities of rhBMP-2. Creating recombinant human proteins in this manner avoids potential complications associated with disease transmission from allograft or xenograft sources.

The availability of rhBMP-2 in pure "unlimited" sources has the ability to greatly enhance spinal fusion results while lowering pain scores associated with a bone graft harvesting procedure. The purpose of this study was to assess the efficacy of this recombinant protein impregnated on a collagen sponge in a threaded cortical allograft dowel for the treatment of degenerative disc disease by an anterior interbody fusion.

To date, in both animal and human studies, rhBMP-2 has been shown to be capable of inducing new bone formation.[2,19] In a study of anterior lumbar interbody fusion in nonhuman primates, rhBMP-2 and an absorbable collagen sponge carrier was shown to promote fusion through osteoinduction.[11] New bone formation appeared to be superior to autogenous iliac crest graft with cortical dowel allograft. Similarly, in a preliminary clinical study involving the use of InFUSE™ Bone Graft and a tapered cylindrical titanium cage in humans, arthrodesis was found to occur more reliably in patients treated with rhBMP-2 than in controls treated with autogenous bone graft.[3]

This study is the first clinical report of the effectiveness of rhBMP-2 used with cortical allograft to promote anterior lumbar intervertebral fusion in humans. No unanticipated adverse events that were related to the use of InFUSE™ Bone Graft occurred during the course of the study. Because the investigational group did not

undergo the bone graft harvesting procedure, there was a statistically significant reduction in operative time and decreased blood loss during the surgical procedure.

Overall, the investigational group, who received rhBMP-2 on a collagen sponge carrier (InFUSE™ Bone Graft), showed higher rates of success in the reduction of back and leg pain associated with degenerative lumbar disc disease than the control group. At their initial postoperative visit, patients in the investigational group showed an improvement in back pain of more than 7 points. Back pain scores continued to improve throughout the study period and averaged approximately a 9-point improvement at 24 months. In the investigational group, leg pain improved by more than five points within six weeks of surgery and remained unchanged at the last clinical follow-up at 24 months. At all clinical follow-up intervals, the investigational group showed greater relief of leg pain when compared with the control group. Similarly, at 12 and 24 months, the investigational patients showed a higher rate of success than the control patients in their overall neurologic success scores. The use of rhBMP-2 obviates the need for autogenous bone graft and the potential for donor site morbidity. The control group had complaints of hip pain throughout the 24-month study period.

Coinciding with the reduction in painful symptoms was the investigational group's greater and faster functional recovery. At all time periods, the investigational group had greater improvements in Oswestry Low back Disability Questionnaire scores than the control group. The mean improvements in Oswestry scores at 12 and 24 months (31.6 and 33.5 points) are among the highest reported in the literature. Return-to-work status was also assessed to evaluate functional recovery of the patients in the study. Similarly, higher percentages of patients in the investigational group were also able to

Deleted: 01/31/02

return to work. In this group, 45.8% of patients were working before surgery, and 66.7% were working at 24 months after surgery.

The investigational group also showed improved general health status after surgery. In both the Physical (PCS) and Mental (MCS) Components of the SF-36, which was used to measure specific health concepts related to physical and social functioning and limitations, the investigational group showed higher mean scores at 24 months than the control group. As would be expected from these improved outcomes, patient satisfaction was higher in this group. At 24 months, 83% of patients in the group responded to all three questions that were asked that they were satisfied with their surgical outcome.

The investigational group showed higher rates of fusion when compared with the control group at 6, 12 and 24 months. The difference in fusion rates at 24 months was statistically significant ($P = 0.004$). However, one investigational patient underwent a supplemental fixation procedure after the 24-month visit. (The findings from the patient's 24-month radiographs and CT scans did meet the fusion criteria.) The use of supplemental fixation in this patient reduced the fusion rate in the investigational group to 95.8%. The fusion rate in the autograft control group decreased from 89.5% at 12 months to 68.4% at 24 months. The identification of these 4 new pseudarthroses during this time period was secondary to the development of lucencies surrounding the bone dowel and vertebral body interface and loss of contiguous bone across the disc space. None of these late radiographic findings occurred in the investigational group.

InFUSE™ Bone Graft was shown to be a promising method of facilitating anterior intervertebral spinal fusion and of decreasing pain and improving clinical

Deleted: 01/31/02

outcomes after anterior lumbar fusion surgery with allograft bone dowels. These improved outcomes were due, in part, to the successful combination of the anterior surgical approach, the use of threaded allograft dowels, and a high rate of successful interbody fusion.

Deleted: 01/31/02

REFERENCES

1. Blumenthal SL, Baker J, Dossett A, Selby DK. The role of anterior lumbar fusion for internal disc disruption. Spine 1988;13:566-9.

2. Boden SD, Schimandle JH, Hutton WC. Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 1995;20:2633-44.

3. Boden SD, Zdeblick TA Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Spine 2000;25:376-81.

4. Boyd, L.M.; Estes, B.T. and Liu M. "Biomechanics of Lumbar Interbody Constructs, *Effect of Design and Materials*." Chirurgie Endoscopique et Mini-invasive du Rachis. Ed. Husson JL, LeHuec JC. Sauramps Médical. Montpelier, France. pp 181-92, 1999.

5. Burkus JK, Dorchak JD, Sanders DL, Foor BD: Single-level anterior lumbar interbody fusion using threaded cortical bone allografts. North American Spine Society Meeting of the Americas, Miami, Florida, 1999.

6. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. Neurosurg Focus 2001;10:1-9.

7. Crock HV. Anterior lumbar interbody fusion: indications for its use and notes on surgical technique. Clin Orthop 1982;165:157-63.

8. Fairbank JCT, Couper J, Davies JB, O'Brien JP. The Oswestry Low Back Pain Disability Questionnaire. Physiotherapy 1980;66:271-273.

9. Flynn JC, Houque MA. Anterior fusion of the lumbar spine. J Bone Joint Surg 1979;61A:1143-50.

10. Harmon PH. Anterior excision and vertebral fusion operation for intervertebral disc syndromes of the lower lumbar spine: three to five year results in 244 cases. Clin Orthop 1963;26:107-27.

11. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A. The use of recombinant human bone morphogenetic protein-2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999;24:629-36.

12. Kumar A, Kozak JA, Doherty BJ, Dickson JH. Interspace distraction and graft subsidence after anterior lumbar fusion with femoral strut allograft. Spine 1993;18:2393-2400.

13. Lane JD, Moore ES. Transperitoneal approach to the intervertebral disc in the lumbar area. Annals of Surgery 1948;127:537-51.

14. Loguidice VA, Johnson RG, Guyer RD, Stith WJ, Ohnmeiss DD, Hochschuler SH, Rashbaum RF. Anterior lumbar interbody fusion. Spine 1988;13:366-9.

15. Leong JC, Chun SY, Grange WJ, Fang D: Long-term results of lumbar intervertebral disc prolapse. Spine 1983;8:793-9.

16. McHorney CA, Ware JE Jr., Lu RJF, Sherbourne CD. The MOS 36-Item Short-From Health Survey (SF-36), III: tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994;32:40-66

17. Morales RW, Pettine KA, Salib RM. A biomechanical study of bone allografts used in lumbar interbody fusions. North American Spine Society – 6th Annual Meeting, Keystone, Colorado 1991

18. Sacks S. Anterior interbody fusion of the lumbar spine. J Bone Joint Surg [Br] 1965;47:211-23.

Deleted: 01/31/02

19. Sandhu HS, Kanim LEA, Toth JM, et al. Experimental spinal fusion with recombinant human bone morphogenetic protein-2 without decortication of osseous elements. Spine 1997;22:1171-80.

20. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995; 20:1326-37.

21. Stauffer RN, Coventry MB. Anterior interbody lumbar spine fusion. J Bone Joint Surg [Am]1972;54:756-68.

22. Urist MR. Bone: Formation by autoinduction. Science 1965;150:893-9.

23. Ware JE Jr, Sherbourne CD. The MOS 36-Item Short-From Health Survey (SF-36), I: conceptual framework and item selection. Med Care. 1992;30:473-483.

Deleted: 01/31/02

TABLE 1. Patient Demographic Data

Demographic Data	Investigational (InFUSE™ Bone Graft) Group	Control (Autograft) Group
Number of patients	24	22*
Age (years)	41.5	45.6
Weight (lbs)	172.7	175.9
Sex (male/female)	8/16	10/12
Workers' compensation (%)	5 (21)	7 (32)
Spinal litigation (%)	4 (17)	4 (18)
Tobacco use (%)	8 (33)	6 (27)
Previous surgeries (%)	11 (46)	7 (32)

*One patient died an accidental death at 6 months after surgery, and 1 patient was lost-to-follow up.

27

Deleted: 01/31/02

Table 2. Intraoperative Data

Surgical Data	Investigational (InFUSE™ Bone Graft) Group	Control (Autograft) Group
Operative time (min)	103	114
Blood loss (mL)	124.1	245.0
Levels (%)		
L4-L5	11 (46)	8 (36)
L5-S1	13 (54)	14 (64)
Hospital stay (days)	3.4	3.7

Deleted: 01/31/02

Table 3. Neurologic Outcomes

Period	Variable	Investigational n=24 (%)	Control n=22 (%)
6 Weeks	Overall		
	Success	21 (87.5)	18 (90.0)
	Failure	3 (12.5)	2 (10.0)
	P-value*	1.000	
3 Months	Overall		
	Success	21 (87.5)	20 (95.2)
	Failure	3 (12.5)	1 (4.8)
	P-value*	0.611	
6 Months	Overall		
	Success	21 (87.5)	17 (89.5)
	Failure	3 (12.5)	2 (10.5)
	P-value*	1.000	
12 Months	Overall		
	Success	23 (95.8)	16 (84.2)
	Failure	1 (4.2)	3 (15.8)
	P-value*	0.306	
24 Months	Overall		
	Success	21 (87.5)	11 (73.3)
	Failure	3 (12.5)	4 (26.7)
	P-value*	0.396	

**P*-values are from Fisher's exact test.

Deleted: 01/31/02

Table 4. Back Pain Outcomes

Period	Variable	Investigational n=24	Control n=22
Preoperative	n	24	22
	Mean	16.3	16.3
	SD	2.6	2.2
6 Weeks	n	24	21
	Mean	8.9	10.4
	SD	4.5	4.2
	P value**	0.297	
Improvement from Preoperative	Mean	-7.4	-6.0
	P value*	<0.001	<0.001
3 Months	N	24	21
	Mean	7.9	10.9
	SD	4.3	4.5
	P value**	0.038	
Improvement from Preoperative	Mean	-8.4	-5.4
	P value*	<0.001	<0.001
6 Months	N	24	20
	Mean	6.8	9.9
	SD	4.3	5.1
	P value**	0.034	
Improvement from Preoperative	Mean	-9.5	-6.4
	P value*	<0.001	<0.001
12 Months	N	24	19
	Mean	7.4	9.2
	SD	5.3	6.3
	P value**	0.338	
Improvement from Preoperative	Mean	-8.9	-7.2
	P value*	<0.001	<0.001
24 Months	N	24	17
	Mean	7.4	10.9
	SD	6.0	6.0
	P value**	0.047	
Improvement from Preoperative	Mean	-8.9	-5.2
	P value*	<0.001	<0.001

**P* values for change from preoperative in each group are from paired tests.
***P* values for difference between the treatment groups are from analysis of variance.

Deleted: 01/31/02

Table 5. Leg Pain Outcomes

Period	Variable	Investigational n = 24	Control n = 22	*P*-Value**
Preoperative	n	24	22	
	Mean	12.8	14.6	
	SD	5.7	4.1	
6 Weeks	n	24	21	
	Mean	7.0	8.8	
	SD	5.9	5.9	
Improvement from Preoperative	Mean	-5.8	-5.6	0.933
	P value*	0.001	0.001	
3 Months	n	24	21	
	Mean	6.2	8.3	
	SD	4.4	5.8	
Improvement from Preoperative	Mean	-6.7	-6.4	0.874
	P value*	<0.001	<0.001	
6 Months	n	24	20	
	Mean	5.0	6.1	
	SD	4.7	4.4	
Improvement from Preoperative	Mean	-7.9	-8.7	0.654
	P value*	<0.001	<0.001	
12 Months	N	24	19	
	Mean	5.5	8.1	
	SD	5.5	6.1	
Improvement from Preoperative	Mean	-7.3	-6.8	0.818
	P value*	<0.001	0.001	
24 Months	N	24	17	
	Mean	6.3	11.5	
	SD	6.0	6.3	
Improvement from Preoperative	Mean	-6.5	-3.5	0.142
	P value*	<0.001	0.023	

**P* values for change from preoperative in each group are from paired tests.
***P* values for difference between the treatment groups are from analysis of variance.

Deleted: 01/31/02

Table 6. Patient Satisfaction

Period	Variable	Investigational n=24 (%)	Control n=22 (%)
6 Months	I am satisfied with the results of my surgery		
	Definitely True	17 (70.8)	12 (60.0)
	Mostly True	3 (12.5)	4 (20.0)
	P value*	0.503	
	I was helped as much as I thought I would be by my surgery		
	Definitely True	14 (58.3)	6 (30.0)
	Mostly True	6 (25.0)	9 (45.0)
	P value*	0.229	
	All things considered I would have the surgery again for the same condition		
	Definitely True	18 (75.0)	13 (65.0)
	Mostly True	1 (4.2)	3 (15.0)
	P value*	0.312	
12 Months	I am satisfied with the results of my surgery		
	Definitely True	11 (45.8)	7 (35.0)
	Mostly True	8 (33.3)	7 (35.0)
	P value*	0.460	
	I was helped as much as I thought I would be by my surgery		
	Definitely True	12 (50.0)	6 (30.0)
	Mostly True	7 (29.2)	4 (20.0)
	P value*	0.169	
	All things considered I would have the surgery again for the same condition		
	Definitely True	15 (62.5)	11 (55.0)
	Mostly True	4 (16.7)	1 (5.0)
	P value*	0.130	
24 Months	I am satisfied with the results of my surgery		
	Definitely True	13 (54.2)	6 (30.0)
	Mostly True	7 (29.2)	5 (25.0)
	P value*	0.084	
	I was helped as much as I thought I would be by my surgery		
	Definitely True	13 (54.2)	6 (30.0)
	Mostly True	9 (37.5)	5 (25.0)
	P value*	0.249	
	All things considered I would have the surgery again for the same condition		
	Definitely True	15 (62.5)	11 (55.0)
	Mostly True	6 (25.0)	2 (10.0)
	P value*	0.137	

**P* values are from the chi-square test.

32

Deleted: 01/31/02

Table 7. Oswestry Low Back Pain Disability Scores

Period	Variable	Investigational	Control
Preoperative			
	n	24	22
	Mean	52.4	55.3
	SD	13.1	13.5
6 Weeks			
	N	24	21
	Mean	39.9	47.2
	SD	16.8	18.8
	P value**	0.307	
Improvement from Preoperative			
	Mean	-12.5	-7.9
	P value*	<0.001	0.024
3 Months			
	N	24	21
	Mean	29.0	42.0
	SD	14.7	19.0
	P value**	0.032	
Improvement from Preoperative			
	Mean	-23.4	-14.3
	P value*	<0.001	<0.001
6 Months			
	N	24	20
	Mean	21.4	34.4
	SD	16.1	21.8
	P value**	0.039	
Improvement from Preoperative			
	Mean	-31.0	-20.9
	P value*	<0.001	<0.001
12 Months			
	N	24	19
	Mean	20.8	30.0
	SD	14.9	21.2
	P value**	0.171	
Improvement from Preoperative			
	Mean	-31.6	-24.7
	P value**	<0.001	<0.001
24 Months			
	N	24	17
	Mean	18.9	32.8
	SD	14.5	22.7
	P value**	0.039	
Improvement from Preoperative			
	Mean	-33.5	-21.5
	P value*	<0.001	<0.001

* *P* values for change from preoperative in each group are from paired tests.
** *P* values for difference between the treatment groups are from analysis of variance.

33

Deleted: 01/31/02

Table 8. Additional Surgeries

Procedure	Investigational (InFUSE™ Bone Graft) Group	Control (Autograft) Group
Removals	0	0
Revisions	0	0
Supplemental fixation (%)	1 (4.2)	3 (13.6)
Reoperation (%)	0	1 (4.5)

Deleted: 01/31/02

LEGEND OF FIGURES

Figure 1. Comparison of neurologic outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft). Success was based on postoperative neurologic condition being improved or no worse than the preoperative condition.

Figure 2. Comparison of back pain outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Figure 3. Comparison of leg pain outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Figure 4. Comparison of Short Form 36 Physical Component Scores in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Figure 5. Comparison of Short Form 36 Mental Component Scores in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Figure 6. Comparison of Oswestry Disability Questionnaire outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Figure 7. Comparison of return-to-work status in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Figure 8. Iliac crest bone graft harvest site pain in the control group.

Figure 9. Comparison of postoperative fusion outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

35

Deleted: 01/31/02

Figure 10. Serial thin-cut CT scans after an L5-S1 fusion using InFUSE™ Bone Graft. Sagittal and frontal CT reconstructions through both the right and left dowels show the progression of the interbody fusion. The immediate postoperative reconstructions show that the dowels have not been incorporated into the vertebral endplates, and there is no bone formation in the central portion of the dowels. At 6 months, the dowels are incorporated into the vertebral endplates and there is new bone formation within the dowels. At 12 months, there is new bone formation connecting the adjacent vertebral bodies both inside and outside of the dowels. At 24 months, the dowels have almost been completely reabsorbed and replaced with new trabecular bone formation.

Figure 11. Serial thin-cut CT scans after an L5-S1 fusion using autograft demonstrate the progression of the interbody fusion. Immediate postoperative scans show corticocancellous graft within the dowels. At 6 months, trabecular bone connects the adjacent vertebral bodies through the dowels and anterior to the dowels. At 12 and 24 months, there is maturation of the interbody fusion with more bone formation and incorporation of the dowels into the vertebral endplates.

Figure 12. Serial thin-cut CT scans after an L5-S1 fusion using autograft show the development of a pseudarthrosis. At 6 months, the grafts within the dowels and the dowels themselves appear to have become attached the adjacent vertebral endplates. At 12 months, lucencies appear separating the dowels from the vertebral endplates. By 24 months, a radiolucent line involving the inferior portion of both dowels highlights noncontiguous bone formation between the vertebrae consistent with a pseudarthrosis.

RADIOGRAPHIC ASSESSMENT OF INTERBODY FUSION USING rhBMP-2

J. Kenneth Burkus, M.D.*

John D. Dorchak, M.D.*

D. Lynn Sanders, CCRC†

From

The Hughston Clinic, PC

Columbus, Georgia

* Staff Physician, Spine Service, The Hughston Clinic, PC

† Spine Service, The Hughston Clinic, PC

Address correspondence and reprint requests to: J.K. Burkus, MD, The Hughston Clinic, [redacted]

Deleted: 12/29/01

ABSTRACT

Study Design. A prospective randomized study of the radiographic progress of fusion at 6, 12, and 24 months in 42 patients who underwent a single-level anterior lumbar interbody fusion using cylindrical interbody fusion cages.

Objectives. To determine the patterns and rates of osteoinduction associated with the use of recombinant human bone morphogenetic protein-2 (rhBMP-2) and an absorbable collagen sponge carrier in anterior lumbar interbody fusion with a tapered cylindrical fusion device.

Summary of Background Data. Studies have shown that rhBMP-2 used with allograft dowels increases the rate of interbody fusion by promoting osteoinduction and enhancing incorporation of the allograft. In a small series of human patients undergoing anterior lumbar interbody fusion with a tapered cylindrical fusion cage, rhBMP-2 has been shown to promote osteoinduction and fusion.

Methods. In this prospective nonblinded study, 42 patients were randomly divided into 2 groups: the investigational group underwent interbody fusion using two tapered cylindrical fusion cages (LT-CAGE™) and rhBMP-2 on an absorbable collagen sponge, and a control group underwent the procedure and received the devices and autogenous iliac crest bone graft. Plain radiographs and computed tomographic scans were used to evaluate the pattern of osteoinduction within the interbody space and the progression of fusion at 6, 12, and 24 months after surgery.

Deleted: 12/29/01

Results. All patients who received rhBMP-2 showed radiographic evidence of osteoinduction within the interbody cages at 6 months postoperatively. The density within the cages increased by an average of 142.0 Hounsfield units by 6 months and 228.7 units by 12 months. New bone formation occurred within the disc space outside of the cages by 6 months in 18 of the investigational group patients (18/22; 82%). By 24 months, all investigational patients showed new formation outside of the cages. In the autograft control group, the density within the cages increased by an average of 42 Hounsfield units and 10 (10/20; 50%) showed evidence of bone formation outside of the cages.

Conclusions. The use of rhBMP-2 is a promising method of facilitating anterior intervertebral spinal fusion in patients who have undergone anterior lumbar fusion surgery.

Key words: anterior lumbar interbody fusion, bone morphogenetic protein, osteoinduction, radiography, interbody fusion cages

Key points:

1. New bone formation occurs within a lumbar space with recombinant human bone morphogenetic protein-2 and an absorbable collagen sponge carrier in anterior lumbar interbody fusion with a tapered cylindrical fusion device.
2. New bone formation occurs inside and outside of the tapered cylindrical fusion device.
3. New bone formation outside of the cages occurs more rapidly in patients treated with rhBMP-2 that in patients treated with autograft.

Précis

Forty-two patients were followed for 24 months after undergoing ALIF and receiving autogenous bone graft or rhBMP-2 with the LT-CAGE device. In the rhBMP-2 group, bone formation as evidenced by progressive density on thin-cut CT scans more than doubled at 6 months and more than tripled by 24 months. In the rhBMP-2 group, new bone formation occurred outside of the cages in 82% of patients by 6 months and 100% by 24 months. Rates of new bone formation and fusion exceeded that of the autograft control group.

Deleted: 12/29/01

Introduction

Clinical studies of anterior lumbar interbody fusion have identified differing rates of fusion.[7,9,14] The variation in fusion outcome is in part determined by the surgical technique, bone graft material, and method of intervertebral fixation.[4] Recombinant human bone morphogenetic protein-2 (rhBMP-2) (Genetics Institute, Cambridge, MA) is an osteoinductive growth factor.[1] In both animal and human studies, it has been proven to be capable of consistently inducing new bone formation.[2,12,13] In a study of anterior lumbar interbody fusion in nonhuman primates, rhBMP-2 and an absorbable collagen sponge carrier was shown to promote fusion through osteoinduction.[10] New bone formation appeared to be superior to autogenous iliac crest graft with cortical dowel allograft.

In the preliminary report of an unpublished human clinical trial of the use of rhBMP-2 and threaded cortical bone dowels, high rates of fusion were achieved.[6] Similarly, in a small clinical study, rhBMP-2 and a tapered cylindrical titanium cage, arthrodesis was found to occur more reliably in patients treated with rhBMP-2 than in controls treated with autogenous bone graft.[3]

Radiographic imaging of a developing fusion mass after anterior lumbar surgery is challenging in patients who have metallic interbody implants.[8,11] Thin-cut CT imaging (1 mm) is the most efficacious method of identifying bone formation within second-generation cages.[5,8] Recombinant human bone morphogenetic protein-2 (rhBMP-2) has been shown to promote osteoinduction and fusion. To determine its osteoinductive capability with a threaded, cylindrical,

Deleted: 12/29/01

tapered interbody device and an absorbable collagen sponge, we evaluated the radiographic outcomes of 42 patients who underwent a single-level anterior interbody fusion with the LT-CAGE device. We compared the radiographic outcomes in the investigational patients (LT-CAGE with rhBMP-2) with the outcomes in the control patients (LT-CAGE with autogenous bone graft).

Materials and Methods

Patients. Between August 1998 and March 1999, 45 patients with symptomatic single-level degenerative disc disease were enrolled in this prospective, randomized, nonblinded study. All patients were between the ages of 18 and 65 years and had symptomatic degenerative lumbar spondylosis at the L4-5 or L5-S1 levels. All patients had disabling low back or leg pain, or both, that had lasted for at least 6 months and had not resolved with nonoperative treatment. All patients were considered candidates for a single-level stand-alone anterior lumbar interbody fusion. No patients had osteoporosis, which was considered a criterion for exclusion. Patients were excluded from the study if they had spinal conditions other than degenerative disc disease, multi-level spondylosis, or Grade II or higher spondylolisthesis. Other exclusion criteria were symptomatic spondylosis outside of the L4-5 or L5-S1 disc space levels, were 40% above ideal body weight, had a history of chronic use of steroidal or nonsteroidal anti-inflammatory medications, and had a history of disc space infection. Patients were randomly assigned from a table of random numbers to receive the LT-

Deleted: 12/29/01

CAGE device (LT-CAGE™, Medtronic Sofamor Danek, Memphis, TN) with recombinant human bone morphogenetic protein-2 (rhBMP-2) (Genetics Institute, Cambridge, MA) on an absorbable collagen sponge carrier (Colla-Tec, Inc., Plainsboro, NJ) or the device with autogenous iliac crest bone graft.

Of the 45 patients enrolled in the study, 42 patients were followed for 24 months after surgery. Three patients were eliminated from this study for failure to complete the 24-month follow-up. In the investigational rhBMP-2 group, 1 patient did not complete the 24-month follow-up and was lost to follow up after his 12-month radiographic assessment. In the control autograft group, 1 patient was lost to follow-up after the 6-month assessment and 1 patient died of an unrelated coronary event at 9 months after surgery.

The investigational rhBMP-2 group consisted of 22 patients (11 men, 11 women) whose average age at surgery was 41.7 years. The control autogenous bone graft group consisted of 20 patients (11 men, 9 women) whose average age was 44.2 years. Four patients (18%) in the rhBMP-2 group and 2 patients (10%) in the autograft group had used tobacco within 6 months before surgery.

Surgical Procedure. The patients underwent an anterior lumbar interbody fusion procedure through an open retroperitoneal approach at a single study site by the two surgeon authors. In each patient, a complete anterior discectomy was carried out. The nucleus pulposus and the cartilaginous endplates were circumferentially removed through and anterior annular incision. The bony endplates were preserved. Following precise reaming of the endplates, two LT-

Deleted: 12/29/01

CAGE devices were inserted into the disc space. The cages were placed in the disc space contacting the vertebral ring apophysis both anteriorly and posteriorly. No cages were placed in an anteriorly recessed position. All cages placed flush to the anterior cortical margins of the vertebral body but not protruding outside of the margins of the disc space.

The rhBMP-2 used was reconstituted using sterile water and was used as a "single dose" at 1.5mg/ml. This dosage was the same in all patients studied. The solution (1.5 mg rhBMP-2/ml) was applied to a bovine collagen sponge and allowed to bind to the sponge for 15 minutes. The rhBMP-2 soaked sponge was then placed in the hollow central portion of the LT-CAGE device before its insertion into the prepared disc space. No additional sponges were placed outside of the devices. No autogenous grafts were used in the investigational group.

The control group received morcellized autogenous iliac crest graft placed within the cages. The bone graft was harvested form the inner table of the right iliac wing. Cortical and cancellous bone graft was obtained using osteotomes and gouges. The graft was morcellized using a ronguer and tightly packed into the cages prior to insertion. Additional graft was uniformly placed within the disc space anterior to the cages.

Radiographic Outcome Measurements. Plain radiographs and thin-cut computed tomographic (CT) scans (1 mm) were used to evaluate patterns of osteoinduction at 2 days and at 6, 12, and 24 months after surgery. Fusion was

defined as an absence of radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation of less than 5° on flexion-extension lateral radiographs, and continuous trabecular bone growth connecting the vertebral bodies. Two independent radiologists interpreted all radiographs and computed tomography scans. In cases in which the fusion outcome interpretation differed, a third independent radiologist was consulted. The radiologists who were interpreting the data and rendering assessment of bone density and fusion were unaware of the status of each patient they were evaluating.

Thin-cut CT scans were used to assess new bone formation and bone remodeling within and around the fusion cages. On the CT scans, fusion was defined by increased density within the cages and the presence of continuous trabecular bone formation through both of the cages. The changes in density within the cages were determined by precisely measuring the Hounsfield units (HU) within each cage on the serial CT scans. To reduce imaging artifact,[8] Hounsfield units were recoded within the central portion of the cages (at least 3 mm from the metallic side wall of the cages) and were calibrated against known densities on each scan (Figure 1).

Results

Plain Radiographs. At 12 months after surgery, 1 patient in the control group was identified as having a pseudarthrosis. This patient's standing lateral

Deleted: 12/29/01

radiographs showed radiolucencies surrounding both implants; dynamic flexion and extension lateral radiographs showed motion of greater than 5°. This patient underwent a posterior instrumented fusion to stabilize the lumbar motion segment. No other patient in the investigational group or the control group was identified as having a pseudarthrosis on plain radiographic studies.

Computed Tomography.

Bone Density Changes within Cages. In the rhBMP-2 investigational group, immediate postoperative CT scans showed an average density of 179.0 HU (range, 94-226 HU) within the central portion of the LT-CAGE, and the control group showed an average 541.3 HU (range, 403-712 HU) (Table 1) (Figure 2). At 6 months, the rhBMP-2 group showed an average increase to 322.1 HU (range, 178-488 HU); at 12 months, an increase to an average of 427.1 HU (range, 303-703 HU); and at 24 months, an increase to 442.9 HU (range, 434-789 HU). In the investigational group at six months, the average increase in density from the immediate postoperative scans was 142.0 HU; and at 12 months the average increase was 228.7 HU (Table 2). At 24 months, the average difference in density was 213.9 HU when compared to the average initial postoperative density (Figure 3).

In the autograft control group, the average density within the cages at 6 months was 574.6 HU (range, 379-714 HU); at 1 year, the average density was 667.1 HU (range, 462-903 HU); and at 24 months, the average density was 628.1 HU (range, 474-933 HU) . At six months, the average increase in density compared with the initial postoperative scan was 42.0 HU; at 12 months, the

change in density compared with the immediate postoperative scans increased to 184.6 HU. By 24 months, the average difference from the immediate postoperative scan was reduced to 64.3 HU.

Progression of densities within the cages correlated with evidence of fusion on standard plain radiographic measurements. One patient in the control group developed a pseudarthrosis at one year. This patient showed an average increase in the density of the grafts within the cages of only 45 HU.

Bone Formation Outside of Cages. At 6 months after surgery, new bone formation was identified in the rhBMP-2 group outside of the cages in 18 patients (82%), at 12 months in 21 patients (95%), and at 24 months in 22 patients (100%) (Table 3) (Figure 4). In the autograft group at 6 months, new bone formation was identified outside of the cages in 10 patients (50%), at 12 months in sixteen patients (80%), and at 24 months in 19 patients (95%) (Figure 5). It is important to note that all bone growth was contained within the interbody space. No ectopic bone formation was noted.

The patient in the control (autograft) group who developed a pseudarthrosis at 12 months showed no new bone formation outside the cages.

Discussion

Osteoinduction has been shown to occur within the LT CAGE in both the rhBMP-2 and autograft treated patients. In the rhBMP-2 group, bone formation, as evidenced by progressive density on thin-cut CT scans, almost doubled within

Deleted: 12/29/01

6 months of surgery and increased almost two and one half times by 24 months. New bone formation within the cages occurred most markedly during the first 6 to 12 months after surgery. Once new bone formation began to occur outside of the cages, the rate of increase in density within the cage tapered off. In the autograft control group, increases in bone density were also found; however, the rates of change were less than in the rhBMP-2 group.

The radiographic densities within the cages of the rhBMP-2 group at 24 months postoperatively (442.9 HU) did not reach the density of the autograft group following initial implantation (541.3 HU). The autograft group did have cancellous graft alone packed into the cages. The autograft group had both cancellous and cortical bone packed into the cages. The autogenous graft mixture would lead to higher density recording within the cage than one would expect from cancellous graft alone. One would anticipate that the rhBMP-2 formed bone within the cages placed in the central part of the disc space would not reconstitute cortical bone but would rather reconstitute bone with a less dense cancellous pattern. This study does provide some evidence that there is remodeling of the cortical bone grafts within the cages in the autograft group. The densities within the cages in the autograft group actually decline by 39 HU between 12 and 24 months (667.1 HU vs. 628.1 HU).

In the rhBMP-2 group, new bone formation had occurred outside of the cages by 6 months after surgery, and it occurred in all patients by 24 months. Rates of new bone formation exceeded those of the autograft control group. All new bone formation outside of the cages occurred within the confines of the disc

Deleted: 12/29/01

space. All CT scan slices and all reconstructed images were studied to evaluate new bone formation. No new bone formation extended outside of the annulus fibrosus; no bone growth was observed extending posteriorly into the spinal canal or posterolaterally into the neuroforamina.

The rapid development of bone outside of the cages at the periphery of the disc space in the rhBMP-2 group may also lead to the reduced density within the cages. With peripheral bone formation spanning the disc space, the biomechanical loading of the central portion of the disc space is reduced. The reduced loads would result in bone remodeling within the cages to accommodated the changing physiologic loading pattern. The density within the autograft group is reduced between 12 and 24 months postoperatively.

No patient in the rhBMP-2 group developed a pseudarthrosis using standard plain radiographic criteria; no patient in this group required an additional surgery. One patient in autograft control group developed a pseudarthrosis and was the only patient in the study to require a posterior stabilization procedure.

High fusion rates associated with new bone formation inside and outside of the cages can be achieved without harvesting bone from the iliac crest and without device-related adverse events. The use of rhBMP-2 with the LT-CAGE device is a promising method of facilitating anterior intervertebral spinal fusion in patients who have degenerative lumbar disc disease.

References

1. Boden SD, Schimandle JH, Huttton WC. Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 1995;20: 2633-44.

2. Boden SD, Horton WC, Martin G, et al. Laproscopic anterior arthrodesis with rhBMP-2 in a titanium interbody threaded cage. J Spinal Disord 1998;11: 95-101.

3. Boden SD, Zdeblick TA Sandhu HS, et al. The use of rhBMP-2 in interbody fusion cages. Spine 2000;25: 376-81.

4. Boyd LM, Estes BT, Liu M. Biomechanics of lumbar interbody constructs: Effect of design and materials. In: Husson JL, LeHuec JC, eds. Chirurgie Endoscopique et Mini-invasive du Rachis. Montpelier, France: Sauramps Médical, 1999:181-192.

5. Burkus JK, Foley K, Haid R, et al.: Surgical Interbody Research Group—radiographic assessment of interbody fusion devices: fusion criteria for anterior lumbar interbody surgery. Neurosurg Focus [serial online] April 2001;10(4): Article 11.

6. Burkus JK, Transfeldt EE, Kitchel SH, et al. A prospective and randomized study assessing the clinical and radiographic outcomes of patients treated with rhBMP-2 and threaded cortical bone dowels in the lumbar spine. Proceedings of the 15th Annual meeting of the North American Spine Society. Rosemont, IL: North American Spine Society 2000:114.

7. Camissa FP, Dhawlikar SH, Parvataneni HK, et al. Radiolucencies surrounding allograft bone dowels in the early post-operative period. Proceedings of the 13th Annual meeting of the North American Spine Society. Rosemont, IL: North American Spine Society 1998:273.

8. Cizek GR, Boyd LM. Imaging pitfalls of interbody spinal implants. Spine 2000;25:2633-36.

9. Flynn JC, Houque MA. Anterior fusion of the lumbar spine. J Bone Joint Surg [Am] 1979;61:1143-50.

10. Hecht BP, Fischgrund JS, Herkowitz HN, et al. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999;7:629-36.

11. Heithoff KB, Mullin WJ, Holte D, et al. The failure of radiographic detection of pseudarthrosis in patients with titanium lumbar interbody fusion cages. Proceedings of the 14th Annual meeting of the North American Spine Society. Rosemont, IL; North American Spine Society 1999:14.

12. Sandhu HS, Kanim LEA, Toth JM, et al. Experimental spinal fusion with recombinant human bone morphogenetic protein 2 without decortication of osseous elements. Spine 1997;22:1171-80.

13. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995;20:1326-37.

14. Stauffer RN, Coventry MB. Anterior interbody lumbar spine fusion. J Bone Joint Surg [Am] 1972;54:756-68.

Deleted: 12/29/01

Table 1. Bone Density Measurements Within The Interbody Fusion Device.

Period	Bone density (HU)*	Investigational Group	Control Group
Immediate postoperative	n	16	12
	Mean ± SD	179.0 ± 87.7	541.3 ± 103.7
	n	20	18
6 months	Mean ± SD	322.1 ± 130.7	574.6 ± 139.8
	n	21	19
12 months	Mean ± SD	427.1 ± 166.8	667.1 ± 169.0
	n	20	18
24 months	Mean ± SD	442.9 ± 153.0	628.1 ± 211.5

*HU = Hounsfield units

Deleted: 12/29/01

Table 2. Bone Density Increases Within The Interbody Fusion Device From The Immediate Postoperative Scan.

Period	Bone density increase	Investigational (rhBMP) Group	Control (autograft) Group	p-value**
	n	16	11	
6 months	Mean ± SD	142.0 ± 143.3	42.0 ± 79.2	0.046
		(p = 0.001)*	(p = 0.109)*	
	n	15	12	
12 months	Mean ± SD	228.7 ± 199.3	184.6 ± 180.6	0.557
		(p = 0.001)*	(p = 0.005)*	
	n	14	12	
24 months	Mean ± SD	213.9 ± 186.5	64.3 ± 199.9	0.060
		(p = 0.001)	(p = 0.289)	

*P-values for changes from the immediate postoperative period in each group were from paired tests.

**P-values for differences between the treatment groups were from analysis of variance.

Table 3. Number Of Patients Who Had Bone Formation Outside Of Interbody Fusion Device.

Postoperative period	Investigational (rhBMP) Group	Control (autograft) Group	P-value*
6 months	18/22 (82%)	10/20 (50%)	0.049
12 months	21/22 (95%)	16/20 (80%)	0.174
24 months	22/22 (100%)	19/20 (95%)	0.476

*P-values were from Fisher's exact test for comparing the differences between the treatment groups.

Deleted: 12/29/01

Legend of Figures

Figure 1. Thin cut CT scan (1 mm) sagittal reconstruction through the central portion of the interbody fusion cage shows the elliptical outline of region 3 millimeter away from the cage sidewalls for determination of Hounsfield Units.

Figure 2. Comparison of the average bone density within the interbody fusion device between the rhBMP-2 group and the autograft group.

Figure 3. A. Thin cut CT scan (1 mm) sagittal reconstruction at 2 days after surgery shows good placement of the cage within the disc space. The rhBMP-2 soaked sponge occupies the central portion of the cage. There is no bone present with the cage or the disc space. B. CT image at 2 years postoperatively shows new bone formation inside and outside of the cage.

Figure 4. A. Thin cut CT scan (1 mm) sagittal reconstruction immediately after surgery with rhBMP-2 shows no bone present outside of the cage. B. CT image at 6 months after surgery shows new bone formation within the disc space both anterior and posterior to the cage. This sagittal reconstructed image is taken through a cage placed within the confine of the disc space but at its lateral margins. The bone seen outside of the confines of the disc space is a portion of the facet joint complex and does not represent bone growth extending beyond the disc space.

Fig. 5. Comparison of the percentage of new bone formation outside the interbody fusion device between the rhBMP-2 group and the autograft group.

A Prospective, Randomized Lumbar Fusion Study using rhBMP-2 with Tapered Interbody Cages

J. Kenneth Burkus MD [†]

Matthew F. Gornet MD*

Curtis Dickman, MD[‡]

Thomas A. Zdeblick MD[§]

[†]Staff Physician, Spine Service, The Hughston Clinic, P.C., Columbus, Georgia

*Staff Physician, Missouri Bone and Joint Institute, St. Louis, Missouri

[‡]Barrows Institute, Phoenix, Arizona

[§]Chairman, Department of Orthopedics and Rehabilitation, University of Wisconsin, Madison, Wisconsin

Address correspondence and reprint requests to J.K. Burkus, MD, The Hughston Clinic, [redacted]

ABSTRACT

Study Design. In a multi-center, prospective, randomized, nonblinded, 2-year study, 279 patients who underwent a single-level anterior lumbar interbody fusion with tapered threaded titanium fusion device were randomized into two groups: one received autogenous iliac crest bone graft, the other, recombinant human bone morphogenetic protein-2 (rhBMP-2) on a collagen sponge carrier.

Objectives. The objective of the study was to determine the clinical and radiographic outcomes in patients treated for single-level degenerative lumbar disc disease with a stand-alone anterior interbody fusion using tapered threaded titanium fusion cages with autogenous bone graft or rhBMP-2 and an absorbable collagen sponge carrier.

Summary of Background Data. In a small series of human patients undergoing anterior lumbar interbody fusion with a tapered titanium fusion cage, rhBMP-2 has been shown to promote osteoinduction and fusion.

Methods. In this prospective nonblinded study, 279 patients were randomly divided into 2 groups that underwent interbody fusion using two tapered threaded fusion cages: the investigational group (143 patients) that received rhBMP-2 on an absorbable collagen sponge and a control group (136 patients) that received autogenous iliac crest bone graft. Assessment of a patient's clinical outcome was based on neurologic status, work status, and Oswestry Low Back Pain Disability scores and back and leg pain questionnaires. Plain radiographs and computed tomographic scans were used to evaluate fusion at 6,12 and 24 months postoperatively.

Results. Mean operative time (1.6 hours) and blood loss (109.8 mL) was less in the investigational rhBMP-2 group than in the autograft control group (2.0 hours and 153.1

mL). At 24 months, the investigational group's fusion rate of 94.5% remained higher than the control's at 88.7%. New bone formation occurred in all patients treated with rhBMP-2. At all postoperative intervals, the mean Oswestry, back pain, and leg pain scores and neurologic status improved in both treatment groups compared with the preoperative scores and were similar in both groups. In the control group, 8 adverse events related to harvesting of the iliac crest graft occurred in 8 patients (5.9%), and, at 24 months after surgery, 32% patients still reported graft site discomfort and 16% were bothered by the appearance of graft site.

Conclusions. The investigational group had shorter operative times and less blood loss. At 24 months, this group had a fusion rate that was nearly 6 percentage points greater than the control group with a probability of superiority of 90.2%. Overall results show that the use of rhBMP-2 can eliminate the need for harvesting iliac crest graft for successful lumbar fusions.

Key words: anterior lumbar interbody fusion, bone morphogenetic protein, osteoinduction, radiography, interbody fusion cages

Key points:

- Fusion rates for both treatment groups were high at all studied intervals. At 24 months, the average rate of fusion for patients treated with rhBMP-2 was nearly 6 percentage points higher (94.5% vs. 88.7%) than for patients treated with autograft with a probability of superiority of 90.2 percent.
- The average operative time was1.6 hours for patients treated with rhBMP-2 compared with 2.0 hours in the autograft group. This difference was statistically significant.
- Blood loss was less for patients treated with rhBMP-2 than for patients who underwent iliac crest bone graft harvesting.
- At all postoperative assessment intervals, patients in both treatment groups showed improvement in Oswestry disability scores, in neurologic status, and in back and leg pain outcomes.
- The use of rhBMP-2 in anterior lumbar interbody fusion procedures eliminates the complications of iliac crest bone harvesting including postoperative pain and scarring.

Précis

In a 2-year prospective randomized study of 279 patients, the investigational group that received rhBMP-2 with the tapered cage device had a higher rate of fusion, reduced operative times, and decreased blood loss when compared with the control group that received autogenous bone graft with the LT-CAGE™ device. The rhBMP-2 group avoided the complications that can arise from an iliac crest bone harvesting procedure.

INTRODUCTION

Degenerative changes within a lumbar spinal motion segment are, in part, evidenced by the presence of radial tears or fissures in the annulus fibrosus, disc space desiccation and collapse, and the formation of radial osteophytes. These morphologic changes within the spinal motion segment can lead to loss of the intervertebral disc's ability to accommodate normal biomechanical stresses and can cause pain. Fusion of the degenerative and unstable spinal motion segment can give significant relief from this disabling and often progressive condition (2,7,9).

Anterior lumbar interbody fusion (ALIF) is an effective treatment for patients with symptomatic degenerative disc disease. Lumbar spine stabilization procedures that do not interfere with the posterior spinal muscles have some significant advantages (9,10,14-16,19). The anterior approach to the lumbosacral spine enables the surgeon to expand the disc space and re-establish the normal anatomic alignment and relationships of the spinal motion segment while avoiding injury to the posterior paravertebral muscles. The anterior approach also retains all posterior stabilizing structures and avoids epidural scarring and perineural fibrosis. Adjacent segment degeneration in the lumbar spine after anterior interbody fusion can also be reduced (17).

Stand-alone ALIF procedures using autogenous bone grafts alone have been associated with high rates of pseudarthrosis, graft subsidence, and graft extrusion (8,23). Supplemental posterior segmental spinal instrumentation has been advocated to stabilize interbody grafts and increase rates of fusion. Recently, cylindrical threaded

intervertebral devices with autogenous bone grafts have been shown to stabilize a lumbar motion segment after anterior discectomy. Their use has lead to high rates of fusion and to improved clinical outcomes (4).

In non-human primate animal models, recombinant human bone morphogenetic protein 2 (rhBMP-2) applied to an absorbable collagen sponge carrier has been shown to promote osteoinduction and fusion after ALIF (11). Recently, this technique was used in a small series of human patients who underwent stand-alone ALIF with tapered fusion cages. In these patients, the use of rhBMP-2 applied to a collagen sponge was also shown to promote osteoinduction and fusion (4). To further evaluate this method, we evaluated the clinical and radiographic outcomes at 24 months of 279 patients who underwent a single level ALIF. We compared the outcomes in the investigational patients (rhBMP-2) with those in the control patients (autogenous bone).

MATERIALS AND METHODS

Study Design. Between August 1998 and July 1999, 279 patients completed surgery in this prospective, randomized, nonblinded, FDA approved study at 16 investigational sites. All patients underwent a single-level anterior lumbar fusion with the LT-CAGE™ device (Medtronic Sofamor Danek, Memphis, TN). Patients were randomly assigned in a 1:1 manner to one of two groups: the investigational group received rhBMP-2 on an absorbable collagen sponge carrier and the control group received autogenous iliac crest bone graft. InFUSE Bone Graft™ (Medtronic Sofamor Danek, Memphis, TN) is the

trademarked name for recombinant human bone morphogenetic protein 2 applied to an absorbable collagen sponge.

Patient Data. Preoperatively, all patients had symptomatic, single-level degenerative lumbar disc disease and symptoms of disabling low back or leg pain, or both, of at least 6 months' duration that had not responded to nonoperative treatments. The two treatment groups were very similar demographically, and there were no statistically significant differences ($P < 0.05$) for any of the variables (Table 1). The rhBMP-2 group consisted of 143 patients and the control group consisted of 136 patients. The average age at surgery was 43.3 years for the rhBMP-2 group and 42.3 years for the control group. In the rhBMP-2 group, 47 patients (32.9%) had used tobacco within 6 months before surgery compared with 49 patients (36%) in the control group. The percentage of patients with pending litigation was 12.6% and 16.2% in the rhBMP-2 and control groups, respectively. The percentage of patients seeking worker's compensation was 32.9% in the rhBMP-2 group and 34.6% in the control group.

Clinical and Radiographic Outcome Measurements. Patient assessments were completed preoperatively, during hospitalization, and postoperatively at 6 weeks and at 3, 6, 12, and 24 months. Clinical outcomes were assessed using neurologic status, work status, patient satisfaction, and Oswestry Low Back Pain Disability, back, leg, and graft site pain questionnaires.

Radiographs and computed tomography (CT) scans were used to evaluate fusion at 6, 12, and 24 months after surgery. Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent, blinded radiologist was used to adjudicate conflicting fusion findings. Fusion was defined as an absence of

radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation less than 5° on flexion-extension radiographs, and continuous trabecular bone growth connecting the vertebral bodies (6). There was good agreement between the radiologists reviewing the studies. At 6, 12, and 24 months after surgery, agreement between the independent reviewers was more than 98%. Patients who had secondary surgeries because of persistent low back symptoms and clinically suspected nonunions were considered as having failed fusions and were classified as failures in all fusion calculations, regardless of their independent radiological assessment.

Clinical and Radiographic Follow-up. The rate of patient return for follow-up was high at all postoperative periods (Table 2). At 12 months, the rate of patient return for both treatment groups exceeded 96%. At 24 months, the follow-up rate for the investigational group was 92.5% and the control group rate was 90.8%.

Surgical Technique. All patients underwent the ALIF procedure through an open approach. Patients were placed in the supine position on the operating room table. Fluoroscopy was used throughout the surgical procedure. A vertical or transverse incision was made over the lumbosacral spine. A retroperitoneal exposure was carried out in 81% (226/279) of patients, and a transperitoneal exposure was used in 19% (53/279) of patients. The parasympathetic nerve complex was bluntly mobilized and retracted from the surgical field: electrocautery was not used during this portion of the surgical procedure. Segmental vessels were sequentially identified, ligated, and divided. The great vessels were mobilized exposing the anterior surface and lateral borders of the disc space. The midpoint of the disc space was identified with radiographic markers and fluoroscopy.

An incision was made in the anterior portion of the annulus, removing the anterior longitudinal ligament and the anteriolateral borders of the annulus fibrosus. Under direct visualization the entire contents of the disc space were removed including the nucleus pulposis and the cartilaginous endplates. Great care was taken to protect and preserve the bony vertebral endplates. The disc space was sequentially distracted to the height of normal adjacent disc space height. A double barrel guide was inserted into the disc space and the bony endplates were precisely prepared with a reamer.

In the investigational group, each cage was filled with a rhBMP-2 soaked collagen sponge. No autogenous bone grafts or local reamings were used in this group. The cages were sequentially inserted through the guide tube into the prepared intervertebral disc space. Cage placement was evaluated with fluoroscopy in both the anteroposterior and lateral dimensions. In the control group, two cage devices were packed with morcellized autogenous bone graft harvested from the iliac crest.

The rhBMP-2 used was reconstituted using sterile water and was used as a single dose of 1.5 mg/mL in all study patients. The 1.5 mg rhBMP-2/mL solution was applied to a bovine collagen sponge and allowed to bind to the sponge for 15 minutes. The dosage of rhBMP-2 varied by patient depending on cage size, with the total dose ranging from 4.2 mg to 8.4mg. The rhBMP-2 soaked sponge was then placed in the hollow central portion of the LT-CAGE device before its insertion into the prepared disc space. No additional sponges were placed outside of the devices. No autogenous grafts were used in the investigational group.

The control group received morcellized autogenous iliac crest graft placed within the cages. The bone graft was harvested from the inner table of the right iliac wing.

Cortical and cancellous bone graft was obtained using osteotomes and gouges. The graft was morcellized using a rongeur and was tightly packed into the cages before their insertion.

Postoperatively, patients were placed in a soft lumbar corset. Activities were advanced by the treating physician. Isometric strengthening and exercise program were started at six weeks postoperatively.

Statistical Methods. The data from this clinical trial were analyzed using the statistical software package SAS® version 6.12. For continuous variables, *P* values are from ANOVA, and for categorical variables, they are from Fisher's exact test or chi-square test.

RESULTS

Surgery

The mean operative time in the investigational rhBMP-2 group (1.6 hours) was less than in the control group (2.0 hours) (Table 3). The average blood loss in the rhBMP-2 group was 109.3 ml as compared with 153.8 ml in the control group. The operative time and blood loss was less in the investigational group despite the fact that the more technically demanding and time consuming approach to the L4-L5 level was performed more frequently in the investigational group (25.9%, 37/143) than in the control group (23.5%, 32/136). The average hospital stay was similar in both groups

(3.1 days for the investigational group vs. 3.3 days for the control group). There were no unanticipated device-related adverse events in either treatment group.

Complications

Vascular events. Eleven intraoperative vascular events occurred: 6 were in the rhBMP-2 group (4.2%) and 5, in the autograft group (3.7%). The most common injury (6/11) was a laceration of the iliac vein. Two control group patients developed deep venous thrombosis and were treated with anticoagulation medications. No patients in the investigational group developed a deep venous thrombosis. This may, in part, be secondary to the reduced surgical times in the investigational group and reduction in time the great vessels were manipulated and retracted during the surgical procedure.

Retrograde ejaculation. Six male patients (4.1%, 6/146) complained of retrograde ejaculation after surgery. In these patients, the L5-S1 disc space was approached 5 times (83.3%, 5/6). A transperitoneal approach was used in 4 of the 6 patients (66.6%). This complication occurred in 13.3% (4/30) of the men who underwent a transperitoneal approach and occurred in only 1.8% (2/116) of men who underwent a retroperitoneal approach. In two patients, the retrograde ejaculation resolved by 12 months after surgery; one patient underwent a retroperitoneal approach, the other a transperitoneal approach.

Iliac crest graft site. In the control group, 8 adverse events related to harvesting of the iliac crest graft were identified in 8 patients (5.9%). These events included 3 injuries to the lateral femoral cutaneous nerve, 2 avulsion fractures of the anterior superior iliac spine, 1 infection and 1 hematoma. None required an additional surgery.

There were no graft site adverse events in the investigational group since the use of rhBMP-2 precluded the need to harvest bone graft.

The level of postoperative pain and morbidity associated with the iliac crest graft harvesting was measured using numeric rating scales for pain intensity and duration (Table 4; Figure 1). After surgery, all of the control patients experienced hip donor site pain. The highest levels of pain were noted immediately after surgery with a mean score of 12.7 points out of 20 points. The percentage of patients experiencing pain decreased over time; however, at 24 months after surgery, nearly one-third of the control patients (32%) still experienced pain (Figure 2). At two years, the graft site pain scores averaged 1.8 points, and 16% of the control patients were bothered by the appearance of the graft site.

Antibody Testing

Antibody results. Antibodies to rhBMP-2 were evaluated preoperatively and 3 months postoperatively using enzyme-linked immunosorbent assays (ELISAs). The results were similar between the investigational and control groups (0.7% and 0.8%, respectively). There appeared to be no negative clinical consequence to positive antibody test results.

Clinical Outcomes

Oswestry Disability Questionnaire scores. The Oswestry Low Back Pain Disability Questionnaire measured pain associated with activities. The Oswestry Questionnaire was administered preoperatively as well as at each postoperative visit. At all postoperative time periods for both the investigational and the control treatment

groups, the mean overall Oswestry scores were similar at the time periods for both treatment groups. At all postoperative visits, both treatment groups demonstrated statistical improvements as compared with the preoperative scores that were maintained through two years (Table 5). At 24 months, the mean improvements in the Oswestry scores were 29.0 points in the investigational group and 29.5 points in the controls (Figure 3). In the rhBMP-2 group, 84.6% of patients showed an improvement of at least 15% in their disability scores at 12 months after surgery as compared with 85.6% of patients in the control group. At 24 months, the 84.4% of the investigational group was improved and compared favorably with 82.4% improved in the control group.

Neurologic Status. Neurologic status of the patients was determined by evaluating four neurologic measurements: motor function, sensory function, deep tendon reflexes and sciatic tension signs. Values for each of the 4 subsets of objective findings were totaled and expressed as a percentage of the maximum possible score. Each measurement was compared with the patient's preoperative score. Neurologic success was based on demonstrating maintenance of or improvement in all four neurologic measurements. At 12 and 24 months after surgery, the overall neurologic success rates for the investigational group were 81.8% and 82.8% respectively compared with 84.7% and 83.3% rates for the control group (Table 6).

Back Pain. Back pain intensity and duration were assessed using a 20-point numeric rating scale. Adding the numeric rating scores for back pain intensity and pain duration allowed examiners to derive a composite back pain score (Table 7). The mean back pain scores at all postoperative periods were improved from the preoperative mean values for both treatment groups. The mean improvements in back pain scores at

both 12 and 24 months were greater for the investigational group than for the control autograft group (Figure 4).

Back pain success was determined for each patient by comparing the postoperative score with the preoperative score. Success was based on the patient's having at least a 3-point improvement in back pain score after surgery (Table 8). At 12 and 24 months after surgery, the investigational group had back pain success rates of 79.1% and 74.6%, respectively. These rates were similar to the respective rates in the control group of 72.8% and 78.7%.

Leg Pain. Leg pain was assessed in a similar manner using a numeric rating scale for both the intensity and duration of painful symptoms. Mean leg pain scores improved significantly after surgery (Table 9). Outcomes were similar in both treatment groups (Figure 5). Leg pain success was defined as a function of the patient's preoperative complaints. If a patient had a preoperative pain score of 10 points or more, success was defined as a 3-point improvement in his or her postoperative scores. In patients who had preoperative leg pain scores of less than 10 points, success was defined as maintenance of or improvement in scores when compared with their preoperative condition. At 12 months after surgery, the leg pain success rates were similar in both treatment groups. The investigational group had a success rate of 72.1% and the control group had success rate of 72.8%. At 24 months, the success rate in the investigational group improved to 80.3% and was higher than the 74.1% result in the control group.

Work Status. Many factors affect a patient's work status, such as the nature of the work performed and ability of the work place to accommodate work restrictions. The

work status of the investigational patients was similar to that of the control patients at most postoperative follow-up intervals (Table 10). For patients who were working before surgery, the median return to work time was 63.5 days in the investigational group and 64.5 days in the control group. More people in both treatment groups were working at the two-year follow-up than were working before their surgery. At last follow-up, in the investigational group, 80 patients were employed while only 54 were employed before surgery. Similarly, in the control group, 38 were working before surgery and 60 were working at two years after surgery (Figure 6).

Patient Satisfaction. At 12 and 24 months after surgery, the results were similar in each treatment group. At 24 months, 81.2% of the investigational patients and 80.4% of the controls were satisfied with their surgical outcomes. In the investigational group, 82% said they would undergo surgery again compared with 76.7% of the control patients who would undergo surgery again. In the investigational group, 74.6% believed that they were helped as much as they had expected to be from the surgery; 76.6% of the control group felt they had been.

Radiographic Outcomes

Fusion status of the study patients was evaluated on plain radiographs and CT scans. At six months after surgery, 97.0% of patients in the investigational group had evidence of interbody fusion compared with 115 patients (95.8 %) in the control group (Table 11). At 12 months, 127 patients (96.9 %) in the investigational group showed evidence of fusion. In the control group, 112 patients (92.5%) showed evidence of fusion at one year. At 24 months, the investigational group had a 94.5% fusion rate,

which was approximately six percentage points higher than that of the control group (88.7%) (Figure 7)

Secondary Surgical Procedures

In the investigational group, 11 patients (7.0%) had a second surgery and 14 patients (10.3%) in the control group had second surgeries. In the investigational group, 2 patients had implant removals: One removal occurred at 5 days after surgery, and the other at 4months. The removal at 5 days was due to a vertebral bone fracture and implant displacement. The removal at 4 months was due to implant displacement and possible failed fusion. Seven investigational patients underwent supplemental fixation for presumed pseudarthrosis, 1 underwent supplemental fixation after posterior decompression for persistent radicular symptoms after the initial surgery, and 1 underwent a panlumbar fusion for discogenic back pain. Two of the supplemental fixations for presumed pseudarthrosis occurred before the 6-month follow-up evaluation. Fusion was not evaluated until 6 months after surgery; therefore, these patients cannot be classified as fusion failures. They are second surgery failures.

In the control group, 12 patients underwent supplemental posterior fixation for a presumed pseudarthrosis and 2 underwent supplemental posterior fixation for persistent discogenic pain. One patient underwent supplemental fixation for presumed pseudarthrosis before the 6-month follow up.

In 90% (18/20) of these patients (7/7 in the investigational group and 11/13 in the control group) the fusion was radiographically solid at the visit prior to the supplemental fixation, but posterior instrumentation was inserted by the treating physician based on

clinical symptoms of persistent pain. In 53.3% of these patients, pain improved after the secondary posterior surgical procedure.

DISCUSSION

Spinal fusions can be performed anteriorly, posteriorly, or posterolaterally. Instrumentation can also be used to stabilize the spinal motion segment and to promote fusion. Traditionally, fusions in the lumbar spine have been performed through a posterior approach. After a successful posterolateral lumbar spinal fusion, patients often have significant relief of their painful symptoms. However, the posterolateral approach and the lateral exposure of the transverse processes of the lumbar spine can compromise the patient's functional outcome (13). The paraspinal muscles must be detached from the posterior spinal elements and transverse processes during the surgical exposure for the lateral fusion. This injury to the spinal muscles of the lumbar spine limits the patient's ultimate rehabilitation potential (1). Several studies have demonstrated significant loss of paraspinal muscle strength and muscle atrophy in patients with persistent back pain after posterolateral lumbar spinal fusion (12,18,22). The surgeon strips the paraspinal muscles from their anatomic attachments to the spine and then reattaches them to the midline fascia and retained spinal elements. However, postoperative healing and scar tissue formation interferes with the normal independent function of the paravertebral muscle groups. The loss of their normal anatomic attachment sites, formation of scar tissue, and loss of independent muscle function compromise the paravertebral muscles.

Stand-alone anterior lumbar interbody fusion allows the complications of posterior "fusion disease" to be avoided. The anterior approach retains all posterior-stabilizing structures and avoids epidural scarring and perineural fibrosis. There is no need for paraspinal muscle stripping, retraction, or denervation of the adjacent facet joint. The muscle-splitting approach is one that does not compromise existing posterior spinal elements, and it allows the surgeon to reestablish normal disc space height and restore the normal sagittal contours of the lumbar spine. This technique allows a faster and often a more complete functional recovery of the patient. Long-term follow-up studies have not shown significant rates of adjacent segment degeneration after anterior interbody fusion (17).

Numerous clinical studies have documented the efficacy and improved outcomes with this procedure(7,9,10,14,16,19). Femoral ring allografts have been widely used; however, these intradiscal spacers alone do not provide enough stability to promote fusion consistently, and they have been associated with high rates of postoperative subsidence (2). Anterior femoral ring allografts often require an additional instrumented posterior spinal fusion to stabilize the spinal motion segment. Recent advances in metallic interbody fusion devices have been introduced to stabilize intervertebral grafts and have been used to encourage fusion and prevent disc space collapse during the healing process (5). The LT-CAGE™ represents a significant technological advance over first generation cylindrical cages. The insertional torque on implantation of the fusion device is greater, there is less scatter and artifact on postoperative imaging and the cage achieves segmental lordosis without asymmetric endplate reaming.

This study is one of the largest prospective clinical evaluations of stand alone ALIF procedures. The randomized patient groups had no statistically significant differences in the variables assessed. Clinical and radiographic follow-up exceeded 90% at all intervals.

Since the investigational, or rhBMP-2, group did not undergo an autogenous bone graft harvesting procedure, there was a statistically significant reduction in operative time and in decreased blood loss during the procedure in these patients. Retrograde ejaculation was associated with the transabdominal approach to the lumbosacral spine.

The difficulty in achieving anterior interbody fusion through the use of fusion cages lies in the preparation of the endplate. The endplate must be partially removed to allow healing of the vertebral bodies. However, if resection of the endplate is excessive, subsidence can occur and, ultimately, pseudarthrosis. The procedure used in our study patients helps to enhance this fusion in two separate ways. With the LT-CAGE™ device, there is minimal endplate resection, thus preserving the weight-bearing portions of the endplate, which allows greater restoration of lordosis and prevents subsidence. The use of recombinant human bone morphogenetic protein has been shown to accelerate fusion in animal models (3,20,21). Its use should also allow the fusion procedure to more rapidly and more thoroughly occur in humans, as well. Indeed, from a radiographic standpoint this was true in our patients: 97% of patients with the LT-CAGE™ device and rhBMP-2 had radiographic evidence of a solid fusion at one year.

Our study's fusion assessment protocol is one of the first to use thin-cut CT scans to evaluate new bone formation (6). The thin-walled second-generation LT-

CAGE™ device reduced imaging artifact in the instrumented disc space, and new bone formation was identified reliably inside and outside of the intervertebral cages on these CT scans. New bone formation was identified in all patients who received cages filled with rhBMP-2 that remained implanted for more than 6 months. Fusion failure was documented in the rhBMP-2 treated group because of a secondary surgical procedure not because of lack of new bone formation. All new bone formation was found within the instrumented disc space. Areas between the cages, lateral to the cages, and anterior and posterior to the cages did often ossify (Figures 8 and 9). However, there was no ectopic bone formation outside of the annular confines of the disc space, and there was no bone formation extending posteriorly into the spinal canal or laterally into the neuroforamina.

Recombinant human bone morphogenetic protein is an osteoinductive growth factor that stimulates pleuripotential cells to form bone (24). We believe that exposure of bleeding cancellous bone allowed influx of pleuripotential cells that were affected by the rhBMP-2 bound to the collagen carrier sponge. The investigational, or rhBMP-2, group had a 96.9% fusion rate at 12 months compared with 92.6% in the control group. At 24 months, the investigational group had a 94.5% fusion rate, which was almost six percentage points higher than the fusion rate of the control group (88.7 This range of effect was essentially limited to the disc space. Areas between the cages, lateral to the cages, and anterior and posterior to the cages did ossify, but in no case did this ossification extend outside of the confines of the vertebral column. No heterotopic ossification occurred in the epidural space or within the peritoneal cavity or retroperitoneal space. No metastatic calcifications were seen in these study patients.

The final assessment of a successful interbody fusion is difficult. Independent radiologists carefully scrutinized the plain x-rays, flexion-extension films, and CT scans of each patient. The reconstructed CT scans proved to be the most useful method of determining the success of the arthrodesis. Bridging trabecular bone seen on the coronal and sagittal reconstructed images was the final arbiter for determining whether a successful fusion had occurred (Figures 10 and 11). Only gross motion from a pseudarthrosis could be seen on the flexion-extension films and was seen best as a change in lucency between vertebral body and cage during the flexion-extension sequence. Finally, the question of how a patient with an arthrodesis that appears solid radiographically but who has persistent pain should be treated remains undetermined. In several instances in this study, the treating surgeon elected to proceed with a posterior instrumented fusion in the face of persistent pain and a successful arthrodesis. By the treating clinician's statement, these patients were noted to have pseudarthrosis. However, there is no accurate way to determine whether these were true radiographic pseudarthroses. In fact, only approximately half of the patients who went on to have posterior instrumentation for a presumed pseudarthrosis achieved significant pain relief. Less than half (40%) achieved pain improvement of 15 points or greater. Despite these rigorous criteria for determining successful fusion, we were able to obtain a very high rate of radiographic success.

The mean improvements in Oswestry score (29.0 and 29.5 points) are among the highest improvements reported in the literature. We believe this is due in part to the successful combination of anterior approach, threaded tapered titanium fusion cages, and a high degree of successful arthrodesis.

rhBMP-2 is a promising method of facilitating anterior intervertebral spinal fusion and of decreasing pain and improving clinical outcomes after anterior lumbar fusion when used with the LT-CAGE™ device. The use of rhBMP-2 is associated with high fusion rates without the need for harvesting bone from the iliac crest and exposing the patient to the adverse effects associated with that procedure. The combination of the threaded tapered fusion cage and rhBMP-2 may be efficacious in the treatment of challenging patients, such as smokers and those with associated medical disabilities. The use of rhBMP-2 is associated with high fusion rates without the need for harvesting bone graft from the iliac crest and exposing the patient t the adverse effects associated with that procedure.

REFERENCES

1. Beimborn DS, Morrissey MC: A review of the literature related to trunk muscle performance. *Spine* 13:655-660, 1988.

2. Blumenthal SL, Baker J, Dossett A, Selby DK. The role of anterior lumbar fusion for internal disc disruption. Spine 1988;13:566-9.

3. Boden SD, Schimandle JH, Hutton WC. 1995 Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 1995;20:2633-44.

4. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25:376-81.

5. Boyd, L.M.; Estes, B.T. and Liu M. "Biomechanics of Lumbar Interbody Constructs, *Effect of Design and Materials.*" Chirurgie Endoscopique et Mini-invasive du Rachis. Ed. Husson JL, LeHuec JC. Sauramps Medical. Montpelier, France. pp 181-92, 1999.

6. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. Neurosurg Focus 2001;10:1-9.

7. Crock HV. Anterior lumbar interbody fusion: indications for its use and notes on surgical technique. Clin Orthop 1982;165:157-63.

8. Flynn JC, Hoque MA. Anterior fusion of the lumbar spine. End result study with long-term follow-up. J Bone Joint Surg 1979;61A:1143-50.

9. Goldner JL, Urbaniak JR, McCollom DE: Anterior excision and interbody spinal fusion for chronic low back pain. *Orthop Clin North Am* 2:543-568, 1971

10. Harmon PH. Anterior excision and vertebral fusion operation for intervertebral disc syndromes of the lower lumbar spine: three to five year results in 244 cases. Clin Orthop 1963;26:107-27.

11. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999;24:629-36.

12. Jonsson B: The functions of individual muscles in the lumbar part of the spinae muscle. *Electromyography* 10:5-21, 1970.

13. Kahanovitz N, Viola K, Gallagher M: Long term strength assessment of postoperative diskectomy patients. *Spine* 14:402-403,1989.

14. Lane JD, Moore ES. Transperitoneal approach to the intervertebral disc in the lumbar area. Annals of Surgery 1948;127:537-51.

15. Loguidice VA, Johnson RG, Guyer RD, Stith WJ, Ohnmeiss DD, Hochschuler SH, Rashbaum RF. Anterior lumbar interbody fusion. Spine 1988;13:366-9.

16. Leong JC, Chun SY, Grange WJ, Fang D: Long-term results of lumbar intervertebral disc prolapse. Spine 1983;8:793-9.

17. Penta M, Sandhu A, Fraser RD: Magnetic resonance imaging assessment of disc degeneration 10 years after anterior lumbar interbody fusion. *Spine* 20: 743-747, 1995.

18. Rantanen J, Hurme M, Falck B, Alaranta H, Nykvist F, Lehto M, Einola S, Kalimo H: The lumbar multifidus muscle five years after surgery for a lumbar intervertebral disc herniation. *Spine* 18:568-574, 1993.

19. Sacks S. Anterior interbody fusion of the lumbar spine. J Bone Joint Surg [Br] 1965;47:211-23.

20. Sandhu HS, Kanim LEA, Toth JM, et al. Experimental spinal fusion with recombinant human bone morphogenetic protein-2 without decortication of osseous elements. Spine 1997;22:1171-80.

21. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995; 20:1326-37.

22. Sihvonen T, Herno A, Paljarvi L, Airaksinen O, Partanen J, Tapaninaho A: Local denervation atrophy of paraspinal muscles in postoperative failed back syndrome. *Spine* 18:575-581, 1993.

23. Stauffer RN, Coventry MB. Anterior interbody lumbar spine fusion. J Bone Joint Surg [Am]1972;54:756-68.

24. Urist MR. Bone: Formation by autoinduction. Science 1965;150:893-9.

Table 1. Patient Data

Variable	Investigational (n=143)	Control (n=136)	P value *
Age (yrs.)			
n	143	136	0.369
Mean	43.3	42.3	
Weight (lbs.)			
n	143	134	0.639
Mean	179.1	181.1	
Sex [n (%)]			
Male	78 (54.5)	68 (50.0)	0.473
Female	65 (45.5)	68 (50.0)	
Workers' Compensation [n (%)]	47 (32.9)	47 (34.6)	0.801
Spinal Litigation [n (%)]	18 (12.6)	22 (16.2)	0.400
Tobacco Used [n (%)]	47 (32.9)	49 (36.0)	0.615
Preop Work Status [n (%)]	68 (47.6)	50 (36.8)	0.071
Working			

*For continuous variables, P values are from ANOVA. For categorical variables, P values are from Fisher's exact test or chi-square test.

Table 2. Patient Accountability

Investigational Group	Preop	Surgery	6 Weeks	3 Months	6 Months	12 Months	24 Months
Theoretical							
Follow-up[1]	143	143	143	143	143	143	143
Deaths	0	0	0	0	0	0	0
(Cumulative)							
Failures[2]	0	0	1 (1)	0 (1)	3 (4)	1 (5)	4 (9)
(Cumulative)							
Expected[3]	143	143	142	142	139	138	133
Number Evaluated	143	143	141	141	137	133	123
Percent Follow-up	100.0%	100.0%	99.3%	99.3%	98.6%	96.4%	92.5%

Control Group	Preop	Surgery	6 Weeks	3 Months	6 Months	12 Months	24 Months
Theoretical							
Follow-up[1]	136	136	136	136	136	136	136
Deaths	0	0	0	0	0	1	1
(Cumulative)							
Failures[2]	0	0	0	0	1 (1)	4 (5)	7 (12)
(Cumulative)							
Expected[3]	136	136	136	136	135	130	120
Number Evaluated	136	136	134	134	133	126	109
Percent Follow-up	100.0%	100.0%	98.5%	98.5%	98.5%	96.9%	90.8%

[1] Theoretical = Patients who have entered the follow-up window.
[2] Failures include device removals, revisions and supplemental fixations.
[3] Expected = Theoretical – Cumulative Deaths – Cumulative Failures

Table 3. Surgery Information

Variable	Investigational (n=143)	Control (n=136)
Operative Time (hrs)		
n	143	136
Mean	1.6	2.0
Blood Loss (ml)		
n	142	136
Mean	109.8	153.1
Hospital Stay (days)		
n	143	136
Mean	3.1	3.3
Treatment Levels [n (%)]		
L4-L5	37 (25.9)	32 (23.5)
L5-S1	106 (74.1)	103 (75.7)
L5-L6	0 (0.0)	1 (0.7)
Operative Approach [n (%)]		
Retroperitoneal	116 (81.1)	110 (80.1)
Transperitoneal	27 (18.9)	26 (19.1)

Table 4. Iliac Crest Graft Site Pain and Appearance Scores

Period	Variable	Control
Discharge	Pain Score	
	n	134
	Mean	12.7
	P value[1]	<0.001
	Appearance of Graft Site	
	Poor[2]	13 (9.8)
6 Weeks	Pain Score	
	n	132
	Mean	6.7
	P value	<0.001
	Appearance of Graft Site	
	Poor	5 (3.8)
3 Months	Pain Score	
	n	134
	Mean	3.5
	P value	<0.001
	Appearance of Graft Site	
	Poor	3 (2.3)
6 Months	Pain Score	
	n	132
	Mean	2.6
	P value	<0.001
	Appearance of Graft Site	
	Poor	5 (3.8)
12 Months	Pain Score	
	n	130
	Mean	2.1
	P value	<0.001
	Appearance of Graft Site	
	Poor	5 (3.8)
24 Months	Pain Score	
	n	117
	Mean	1.8
	P value	<0.001
	Appearance of Graft Site	
	Poor	3 (2.6)

[1] P values are from Student's *t* test comparing mean with zero.
[2] Poor= "It bothers me very much."

Table 5 – Oswestry Low Back Pain Disability Scores

Period	Variable	Investigational	Control
Preoperative			
	n	143	136
	Mean	53.7	55.1
6 Weeks			
	n	140	131
	Mean	42.1	41.4
Improvement from Preoperative			
	Mean	11.4	13.6
	P value[1]	<0.001	<0.001
3 Months			
	n	141	134
	Mean	33.5	34.2
Improvement from Preoperative			
	Mean	19.9	20.8
	P value	<0.001	<0.001
6 Months			
	n	136	131
	Mean	29.3	29.4
Improvement from Preoperative			
	Mean	24.4	25.4
	P value	<0.001	<0.001
12 Months			
	n	130	125
	Mean	25.5	25.6
Improvement from Preoperative			
	Mean	27.7	28.9
	P value	<0.001	<0.001
24 Months			
	n	122	108
	Mean	23.9	23.8
Improvement from Preoperative			
	Mean	29.0	29.5
	P value	<0.001	<0.001

[1] P-values for change from preoperative in each group are from paired t-test

Table 6. Neurologic Outcomes

Period	Variable	Investigational (n=143) n (%)	Control (n=136) n (%)
6 Weeks	Overall		
	Success	110 (80.3)	108 (83.7)
	Failure	27 (19.7)	21 (16.3)
3 Months	Overall		
	Success	119 (84.4)	103 (77.4)
	Failure	22 (15.6)	30 (22.6)
6 Months	Overall		
	Success	106 (77.9)	106 (80.9)
	Failure	30 (22.1)	25 (19.1)
12 Months	Overall		
	Success	108 (81.8)	105 (84.7)
	Failure	24 (18.2)	19 (15.3)
24 Months	Overall		
	Success	101 (82.8)	90 (83.3)
	Failure	21 (17.2)	18 (16.7)

Table 7. Back Pain Outcomes

Period	Variable	Investigational	Control
Preoperative	n	143	136
	Mean	15.8	16.1
6 Weeks	n	139	132
	Mean	9.3	8.8
Improvement from Preoperative	Mean	6.5	7.4
	P value[1]	<0.001	<0.001
3 Months	n	140	134
	Mean	8.7	9.0
Improvement from Preoperative	Mean	7.1	7.1
	P value	<0.001	<0.001
6 Months	n	136	131
	Mean	8.6	8.9
Improvement from Preoperative	Mean	7.3	7.1
	P value	<0.001	<0.001
12 Months	n	129	125
	Mean	8.0	8.4
Improvement from Preoperative	Mean	7.8	7.6
	P value	<0.001	<0.001
24 Months	n	122	108
	Mean	7.3	7.9
Improvement from Preoperative	Mean	8.4	8.1
	P value	<0.001	<0.001

[1] P-values for change from preoperative in each group are from paired t-test

Table 8. Back Pain Success Rates

Variable	Investigational n (%)	Control n (%)
6 Weeks		
Success	107/139 (77.0)	101/132 (76.5)
Failure	32/139 (23.0)	31/132 (23.5)
3 Months		
Success	103/140 (73.6)	105/134 (78.4)
Failure	37/140 (26.4)	29/134 (21.6)
6 Months		
Success	106/136 (77.9)	94/131 (71.8)
Failure	30/136 (22.1)	37/131 (28.2)
12 Months		
Success	102/129 (79.1)	91/125 (72.8)
Failure	27/129 (20.9)	34/125 (27.2)
24 Months		
Success	91/122 (74.6)	85/108 (78.7)
Failure	31/122 (25.4)	23/108 (21.3)

Table 9. Leg Pain Scores

Period	Variable	Investigational n = 143	Control n = 136
Preoperative			
	n	143	136
	Mean	12.5	12.5
6 Weeks			
	n	139	132
	Mean	7.5	8.4
Improvement from Preoperative	n	139	132
	Mean	5.1	4.1
	P value[1]	<0.001	<0.001
3 Months			
	n	140	134
	Mean	6.8	6.8
Improvement from Preoperative	n	140	134
	Mean	5.6	5.6
	P value	<0.001	<0.001
6 Months			
	n	136	131
	Mean	6.3	6.3
Improvement from Preoperative	n	136	131
	Mean	6.4	6.3

	P value	<0.001	<0.001
12 Months			
	n	129	125
	Mean	6.3	6.6
Improvement from Preoperative	n	129	125
	Mean	6.4	5.6
	P value	<0.001	<0.001
24 Months			
	n	122	108
	Mean	6.3	6.3
Improvement from Preoperative	n	122	108
	Mean	6.5	5.9
	P value	<0.001	<0.001

[1] P values for change from preoperative in each group are from paired t-test.

Table 10. Return-To-Work Status

Period	Variable	Investigational n (%)	Control n (%)
3 Months	Working	54 (38.3)	38 (28.4)
	Not Working	42 (29.8)	43 (32.1)
	Was Not Working Before Surgery	45 (31.9)	53 (39.6)
6 Months	Working	69 (50.7)	60 (45.5)
	Not Working	25 (18.4)	29 (22.0)
	Was Not Working Before Surgery	42 (30.9)	43 (32.6)
12 Months	Working	72 (55.0)	63 (50.4)
	Not Working	20 (15.3)	19 (15.2)
	Was Not Working Before Surgery	39 (29.8)	43 (34.4)
24 Months	Working	80 (66.1)	60 (56.1)
	Not Working	11 (9.1)	13 (12.1)
	Was Not Working Before Surgery	30 (24.8)	34 (31.8)

Table 11. Rates of Radiographic Fusion [Number (%) of Patients]

Variable	Investigational (n=143) n (%)	Control (n=136) n (%)
6 Months		
Success	128/132 (97.0)	115/120 (95.8)
Failure	4/132 (3.0)	5/120 (4.2)
12 Months		
Success	127/131 (96.9)	112/121 (92.6)
Failure	4/131 (3.1)	9/121 (7.4)
24 Months		
Success	120/127 (94.5)	102/115 (88.7)
Failure	7/127 (5.5)	13/115 (11.3)

LEGEND OF FIGURES

Figure 1. Hip Donor Site Pain

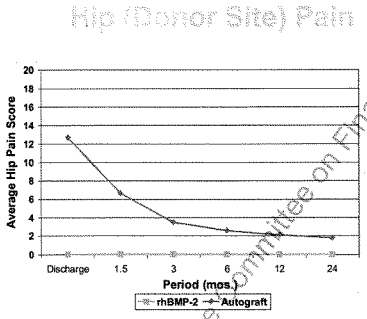


Figure 2. Incidence of Donor Site Pain

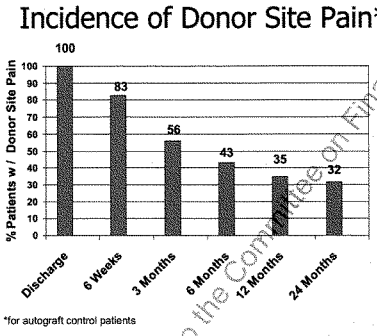


Figure 3. Average Oswestry Disability Scores

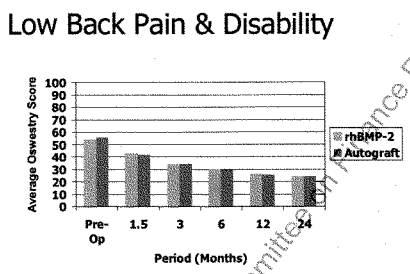


Figure 4. Average Low Back Pain Sores

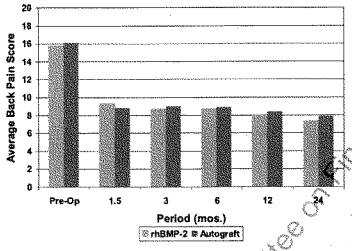


Figure 5. Average Leg Pain Scores

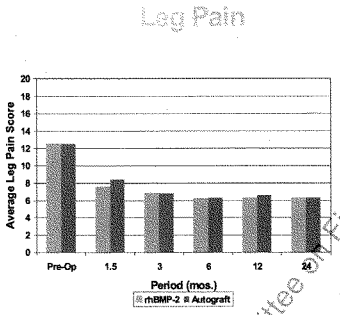


Figure 6. Average Return to Work Status

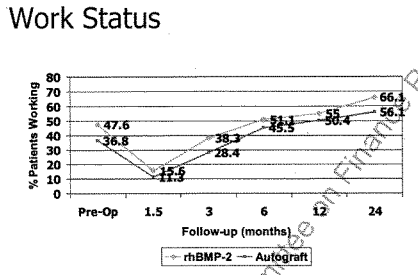


Figure 7.

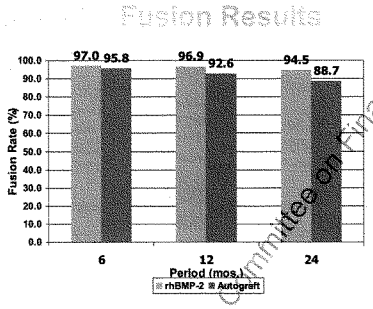


Figure 8: Postoperative standing lateral radiograph shows central placed LT-CAGE™ fusion devices in the L5S1 disc space and restoration of disc space height.

Figure 10: Thin-cut 1-mm CT scan sagittal reconstruction immediately following surgery shows no bone formation within the LT-CAGE™.

Figure 9: Standing lateral radiograph at 24 months after surgery shows anatomic disc space height at the L5-S1 interspace with no evidence of subsidence of the implants. New bone formation is seen anterior to the implants (arrows).

Figure 11: Thin-cut 1-mm CT scan sagittal reconstruction at 24 months after surgery shows new bone formation within the LT-CAGE™ device and new bone formation anterior and posterior to the cage but within the confines of the disc space.

From: JKE[redacted]
Sent: Tuesday, April 16, 2002 07:42:31 PM
To: Peter Wehrly[redacted]; Neil Beals[redacted]; Bill[redacted]
Subject: Bowel Dowel BMP manuscript

Attachments: Revised Bone Dowel BMP Paper.9.doc; resubmit letter3.doc

Pete, Neil, Bill

I have attached the ltest revision of the Bone Dowel BMP paper.

This should be it.

ALL I NEED IS FOR THE OTHER ASSHOLES ON THE PAPER TO SIGN THE COPYRIGHT RELEASE FORM. Maybe they feel bad because they did not write one word. So much for being a nice guy and includig everyone.

Of course, that means Watkins and Balderton.

Can you call them and get them to sign it?

Best
Ken

Clinical and Radiographic Outcomes of Anterior Lumbar Interbody Fusion Using Recombinant Human Bone Morphogenetic Protein-2

J. Kenneth Burkus, MD*

Ensor Transfeldt, MD†

Scott H. Kitchel, MD‡

Robert Watkins, MD§

and

Richard Balderston, MD‖

* Hughston Spine Service, The Hughston Clinic, Columbus, Georgia

† Twin Cities Spine Service, Minneapolis, Minnesota

‡ Orthopedic Healthcare NW, Eugene, Oregon

§ The Center for Spinal Surgery, Los Angeles, California

‖ 3B Orthopedics, Philadelphia, Pennsylvania

This study was sponsored by Medtronic Sofamor Danek, Memphis, TN.

Address correspondence and reprint requests to: J.K. Burkus, MD, The Hughston Clinic, PC, [redacted]

ABSTRACT

Study Design. A prospective nonblinded multicenter study of outcomes in patients undergoing single-level anterior lumbar discectomy and interbody fusion with InFUSE™ Bone Graft (rhBMP-2).

Objective. To determine the safety and effectiveness of InFUSE™ Bone Graft applied to an absorbable collagen sponge in anterior lumbar interbody fusion with threaded cortical allografts.

Summary of Background Data. In primates, rhBMP-2 used with allograft dowels was shown to increase rates of interbody fusion by promoting osteoinduction and enhancing incorporation of the allograft. Recently, in a small series of human patients undergoing ALIF with a tapered cylindrical metal fusion cage, InFUSE™ Bone Graft has been shown to promote osteoinduction and fusion.

Methods. Forty-six patients underwent a single-level anterior lumbar discectomy and interbody fusion at five investigational sites. They were randomly assigned to one of two groups, and the results in the investigational patients who received threaded cortical allograft dowels with InFUSE™ Bone Graft were compared with those in the control patients who received threaded allograft dowels with autogenous iliac crest bone graft. Patients clinical outcomes were assessed using neurologic status, work status, and Oswestry Low Back Pain Disability, Short Form-36, and back and leg pain questionnaires. Anteroposterior, lateral, flexion-extension radiographs, and computed tomography scans were used to evaluate the progression of fusion at 6, 12, and 24 months after surgery.

Results. All patients who received InFUSE™ Bone Graft showed radiographic evidence of bony induction and early incorporation of the cortical allografts. All patients in this group had fusions at 12 months that remained fused at 24 months. At 12 and 24 months, the investigational group showed higher rates of fusion and improved neurologic status and back and leg pain when compared with the control group. There were no unanticipated adverse events related to the use of InFUSE™ Bone Graft.

Conclusion. The use of InFUSE™ Bone Graft is a promising method of facilitating anterior intervertebral spinal fusion, decreasing pain, and improving clinical outcomes in patients who have undergone anterior lumbar fusion surgery with structural threaded cortical allograft bone dowels.

Key words: anterior lumbar interbody fusion, bone morphogenetic protein, degenerative disc disease, lumbar spine

Key points:

- At 6, 12, and 24 months after surgery, fusion rates in the rhBMP-2 group were higher than in the control group.
- At all follow-up intervals, the investigational rhBMP-2 group had greater improvements in Oswestry scores than the control group. At 3, 6, and 24 months, the differences in improvement scores were statistically significant ($P = 0.032$, $P = 0.039$, and $P = 0.039$, respectively)
- At all postoperative assessment intervals, patients in both treatment groups showed improvement in back and leg pain outcomes.
- The use of rhBMP-2 in anterior lumbar interbody fusion procedures eliminates the complications of iliac crest bone harvesting including postoperative pain and scarring.

PRÉCIS

In 46 patients who underwent anterior lumbar interbody fusion with threaded cortical allografts and were followed for 2 years, the investigational group that received InFUSE™ Bone Graft on a collagen sponge carrier showed higher rates of fusion at 6, 12, and 24 months after surgery when compared with the group that received autogenous iliac crest bone graft. These patients demonstrated faster and greater functional recovery.

INTRODUCTION

Cylindrical threaded allograft dowels can be used as stand-alone intervertebral implants that function as an instrumented anterior lumbar interbody fusion (ALIF). They are not intradiscal spacers that require additional segmental stabilization. The threaded cortical bone dowels can withstand lumbar compressive loads and can promote load sharing between the allograft and the host bone while maximizing device porosity.[4,17] These interbody constructs are implanted within the central portion of the disc space through a controlled insertion technique. Impacted allografts, when used alone for interbody fusion in the lumbar spine, have been reported to have a high rate of pseudarthrosis and subsidence.[9,12,21] Contemporary reports of large clinical series of ALIFs using impacted grafts have shown various rates of fusion and differing clinical outcomes.[1,7,10,13-15,18] The threaded dowels resist expulsion and stabilize the bone-implant interface.[4] In addition, threaded bone dowels offer increased strength to support cancellous graft material.[19] In one clinical series, 43 patients were followed for more than 1 year and had a high fusion rate and improved clinical outcomes.[5]

InFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, TN) is recombinant human bone morphogenetic protein applied to an absorbable collagen sponge. Its use replaces the need for autogenous bone grafts and eliminates the complications associated with iliac crest graft harvesting. In a clinical series of patients undergoing an ALIF procedure with a tapered cylindrical metal fusion cage, InFUSE™ Bone Graft has been shown to promote osteoinduction and increase rates of fusion.[3] Our report presents the 2-year clinical and radiographic results of the use of InFUSE™ Bone Graft (rhBMP-2) with

a collagen sponge carrier inside a cylindrical threaded cortical allograft dowel in patients undergoing anterior lumbar interbody fusion.

MATERIALS AND METHODS

Study Design. This prospective, randomized, non-blinded study was conducted under an approved investigational device exemption (IDE).

Patient Selection Criteria. Patients with single-level lumbar degenerative disc disease were included in the study. This diagnosis was based on the patient's history and symptoms, physical findings, functional deficits and radiographic findings. Patients with primary symptoms of low back pain were included in the study. Patients may also have experienced low back pain with or without referred leg pain or sciatica. Patients also had a preoperative Oswestry Low Back Pain Disability Index score of 35 points or more. Patients were included with and without objective neurologic deficits. All patients had had these disabling symptoms for a minimum of six months and had failed to respond to a nonoperative treatment regimen that included aerobic conditioning, medications, spinal injections, and in some patients spinal manipulation.

The following correlative radiographic findings were necessary for inclusion in the study: instability as defined by segmental angulation of 5° or translation of 4mm, or both; osteophyte formation; decreased disc height of at least 50%; thickening of ligamentous tissue or disc protrusion and herniation, or both. The radiographic inclusion criteria did not require patients to have discography, although some were performed. Radiographic findings could be established on one or more studies: plain radiographs, MR imaging, CT scanning, or discography. Isolated "facet joint syndromes" were not evaluated.

Patients were excluded from the study if they had a medical condition that required postoperative medications such as steroids or nonsteroidal anti-inflammatory drugs that interfere with fusion. (Low-dose aspirin for prophylactic anticoagulation was allowed.) NSAIDS were used as part of the preoperative treatment regimen; however, these medications were avoided during the clinical trial.

Patient Population. Forty-six patients at 5 investigational sites had ALIF surgery between April and August 1998. All patients were between the ages of 19 and 68 years and had symptomatic degenerative disc disease at the L4-L5 or L5-S1 levels. The patients were randomly assigned to 1 of 2 study groups. The investigational group (24 patients) received InFUSE™ Bone Graft, which is recombinant human bone morphogenetic protein-2 (rhBMP-2) applied to an absorbable collagen sponge carrier, used in conjunction with the MD-II™ threaded cortical bone dowel (Regeneration Technologies, Inc., Alachua, FL) (Table 1). The control group (22 patients) received autogenous iliac crest bone graft. All patients were between the ages of 19 and 68 years and had symptomatic degenerative disc disease at the L4-L5 or L5-S1 levels. In the control group, 1 patient was lost to follow-up and was excluded from the study; and 1 patient died in a house fire at 6 months after surgery leaving 20 patients in this group who were followed for a minimum of 24 months after surgery.

Data were collected preoperatively, intraoperatively, and at 6 weeks, 3, 6, 12 and 24 months postoperatively. Operative procedure details and adverse events were also recorded.

Surgical Technique. The patients underwent an open ALIF using either a transperitoneal or a retroperitoneal approach to the lumbosacral spine. In each patient, a

complete discectomy was carried out. An incision was made in the annulus fibrosus, the nucleus pulposus and the cartilaginous end plates were circumferentially removed; however, the bony end plates were preserved before reaming and tapping of the end plate for receipt of the dowel. Two allograft bone dowels were then inserted into each disc space.

The rhBMP-2 was reconstituted using sterile water and a single dose at a concentration of 1.5 mg/mL was administered. The concentration was the same in all patients. The solution was applied by syringe to an absorbable collagen sponge. Next, the collagen sponge was placed into the central portion of the bone dowel. The total dose (8 to 12 mL) depended on the capacity of the bone dowel (16, 18, or 20 mm) used. Additional InFUSE™ Bone Graft (or rhBMP-2 prepared sponges) was placed between the bone dowels. No autogenous grafts were used in the investigational group.

The control group received morcellized autogenous iliac crest graft in conjunction with the threaded cortical bone dowels. The iliac grafts were harvested through a separate incision directly over the iliac wing. The inner or outer table of the ilium was exposed subperiostealy and corticocancellous grafts were harvested. A single cortex was preserved in all grafts; no bicortical iliac grafts were obtained. The central opening of the dowels were packed with the bone graft before their insertion into the disc space. Additional bone graft was packed between and anterior to the dowels.

Postoperative Care. All patients were instructed to wear an external orthosis for 6 to 12 weeks after surgery. Patients were encouraged to ambulate immediately after surgery. Physical activities were advanced at the discretion of the attending surgeon.

Clinical Outcome Measurements. Assessments were completed preoperatively, during the patient's hospitalization, and postoperatively at 6 weeks and 3, 6, 12, and 24 months. Clinical outcomes were measured using well-established instruments: Oswestry Low Back Pain Disability Questionnaire,[8] Short Form 36 (SF-36),[16,23] and neurologic status, work status, patient satisfaction, and back, leg, and graft site pain questionnaires. The Oswestry Low Back Pain Disability Questionnaire was self-administered and was used to measure the level of pain and disability associated with various activities. Neurologic status assessment was based on four objective clinical measurements: motor, sensory, reflexes, and sciatic tension signs. Neurologic outcome success was based on maintenance of or improvement in each variable tested. The SF-36 is a self-administered questionnaire that measures specific health concepts related to physical functioning, social functioning and health perceptions. It comprises a Physical Component Summary (PCS) and a Mental Component Summary (MCS). Three patient satisfaction questions were administered at each postoperative time period. A successful answer to each question was defined as either a "definitely true" or "mostly true" response. Low back, leg, and iliac graft site pain were evaluated using numerical rating scales that identified both pain intensity and duration. Standard visual analog scales were used for pain intensity and duration of the painful symptoms. The two scores were added together to derive a composite score.

Radiographic Outcome Measurements. Radiographs and CT scans were used to evaluate fusion at 6, 12 ,and 24 months after surgery.[6] Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent radiologist was used to adjudicate conflicting fusion findings.

Fusion was defined as bridging bone connecting the adjacent vertebral bodies either through the implants or around the implants, less than 5 degrees of angular motion, less than or equal to 3 mm of translation, and an absence of radiolucent lines around more than 50% of either of the implant surfaces. Stability and radiolucent lines were assessed on plain radiographs using anteroposterior, lateral, and flexion-extension views. Thin-slice (1 mm) computed tomography scans with sagittal reconstructions were evaluated at 6, 12, and 24 months. The presence of continuous trabecular bone formation between the vertebral bodies was assessed using radiographs and computed tomography scans. A fusion was considered successful only if all four criteria were achieved: 1) bridging trabecular bone connecting the two vertebral bodies either through the dowels or around the dowels as evaluated by thin-cut CT scans and radiographs; 2) no angular motion of 5° or more on dynamic plain radiographs; 3) no sagittal translation of more than 3 mm on dynamic plain radiographs; and 4) no radiolucencies that involved more than half of the interfaces between the dowels and the host vertebral end plates.

Statistical Methods. The data from this clinical trial were analyzed using the statistical software package SAS® version 6.12. For continuous variables, *P* values are from ANOVA, and for categorical variables, they are from Fisher's exact test or chi-square test.

RESULTS

Surgery. In the investigational group, 11 patients (45.8%) had surgery at the L4-L5 level and 13 (54.2%) had surgery at the L5-S1 level (Table 2). In the control group, surgery was performed at the L4-L5 level in 8 patients (36.4%) and at the L5-S1 level in 14 patients (63.6%). The mean operative time was slightly longer in the control group. The

investigational group had surgery more commonly at the L4-L5 level. This exposure of the L4-L5 disc space often involves a tedious mobilization of the iliac vessels and requires more time when compared with the exposure at the L5-S1 level. The average blood loss was less in the investigational group than in the control group ($P = 0.026$). The average hospital stay was similar in both groups.

Clinical Outcomes. No unanticipated adverse events that were related to the use of InFUSE™ Bone Graft (rhBMP-2 and the collagen sponge carrier) occurred during the course of the study.

Neurologic Outcomes. At 12 and 24 months, the investigational patients showed a higher rate of success than the control patients in their overall neurologic success scores (Table 3 and Figure 1). More than 87% of patients in the investigational group were considered to be a neurologic success (defined as equivalence or improvement from the preoperative condition) at 3 months after surgery. These results were maintained at the final 24-month follow-up. More than 95% of patients in the autograft control group were considered to be a neurologic success at 3 months after surgery. However, these clinical results deteriorated to 73.3% at 24 months.

Back Pain Outcomes. Patients in the investigational group showed an improvement in back pain analog scores (maximum score = 20) of more than 7 points at their initial postoperative visit at 6 weeks (Table 4 and Figure 2). In this group, back pain continued to improve and averaged close to a 9-point improvement in pain scores at 24 months after surgery. The control group's improvement in back pain followed a similar pattern. However, at 24 months, average back pain scores improved only 5 points in this group. The mean improvement scores for low back pain in the investigational group were

significantly greater than those reported in the control group at 3, 6, and 24 months (P = 0.038, P = 0.034 and P = 0.047, respectively).

Leg Pain Outcomes. Preoperatively, there was no difference between the leg pain scores of the two groups (investigational, 12.8; control, 14.6 [P = 0.2291]. Postoperatively, the investigational group showed greater of relief of leg pain compared with the controls (Table 5 and Figure 3). In the investigational group, leg pain improved by more than 5 points within 6 weeks of surgery. These results remained virtually unchanged at the last follow-up of 24 months. However, while the autogenous graft group showed initial improvement of greater than 5 points, the improvement at 24 months decreased to 3.1 points.

General Health (SF-36) Outcomes. In both the Physical (PCS) and Mental (MCS) Components of the SF-36, a successful outcome was defined as a maintenance or improvement in results from preoperative. The investigational group showed higher success at 24 months than the control group (Figures 4 and 5). However, these results were not found to be statistically significant.

Patient Satisfaction Outcomes. At 24 months the success rate was more than 83% in the investigational group for all three questions. For the control group, the success rate for the three questions ranged from 55% to 65% (Table 6).

Oswestry Disability Questionnaire Outcomes. The Oswestry Disability Questionnaire was used to assess pain with activity (Table 7 and Figure 6). At all follow-up intervals, the investigational group had greater improvements in Oswestry scores than the control group. At 3, 6, and 24 months, the differences in improvement scores were statistically

significant ($P = 0.032$, $P = 0.039$, and $P = 0.039$, respectively). At 24 months, the mean improvement in Oswestry scores was 33.5 points.

Seventy-one percent (71%) of the patients in the investigational group showed an improvement of at least 15 points in their disability scores at 3 months. This improvement compared favorably with the 43% of patients who showed improvement in the control group ($P = 0.075$). At 12 months, 83% of the investigational group patients improved more than 15 points compared with 58% of the controls. This finding was similar at the 24-month follow-up.

Return-to-Work Status. Higher percentages of patients in the investigational group were also able to return to work (Figure 7). In the investigational group, 45.8% of patients were working before their surgery. At 24 months after surgery, 66.7% were working. These patients were also able to return to work earlier than those in the control group. In the control group, 40.9% were working before surgery and at 24 months, 35.0% were working.

Iliac Crest Graft Site Pain. Autograft bone was not harvested from the iliac crest in the investigational group; therefore, bone graft site pain was not measured and was assumed to be zero in this group. In the control group, the intensity and frequency of pain and morbidity from the graft harvesting was measured on a 20-point rating scale. At discharge from the hospital, the mean graft site pain was highest (11.3). Graft site pain persisted at 24 months in these patients with a mean score of 2.2 (Figure 8).

Additional Surgery. No patients treated with InFUSE™ Bone Graft required an additional surgical procedure in the immediate perioperative period; 1 control patient required an early return to surgery to remove residual disc material (Table 8). Four

patients (1 investigational, 3 control) underwent supplemental posterior fixation procedures after their primary surgery. The investigational patient continued to have persistent low back pain at 24 months. The patient's radiographs met the criteria for fusion; however, the attending physician elected to reoperate and supplement the interbody grafts with insertion of posterior pedicle fixation. The attending physician was able to identify "slight motion" in the posterior facet joints despite the presence of an adequate fusion across the anterior disc space. The three patients in the control group had supplemental posterior fixation inserted from 7 months to 20 months following their initial surgeries. In each of these cases, the patient reported persistent low back pain and in some instances referred leg pain.

Radiographic Outcomes. At 6-months after surgery, 21 patients in the investigational group were able to return for follow-up evaluation. Of these, 19 patients (90.5%) who were treated with InFUSE™ Bone Graft had evidence of interbody fusion compared with 13 of the 20 patients (65%) in the control group ($P = 0.067$) (Figure 9). At 12 months, all patients (24/24, 100%) in the investigational group had evidence of fusion compared with 17 patients (89.5%) in the control group. Based on their radiographs at the final follow up at 24 months after surgery, all patients (100%) in the investigational group showed evidence of remaining fused (Figure 10).

One patient in the investigational group did meet the criteria for fusion but underwent supplemental posterior fixation after the final 24-month follow-up examination. In this patient, the attending physician identified motion within the facet joints and elected to add supplemental posterior fixation to the spinal motion segment just after the 24-month visit. By the criteria of this study, this patient was recorded as having

a successful interbody fusion at the 12- and 24-month follow-up examination and is not considered a failure until the 36-month follow-up examination. All patients were found to have bony integration of the allografts to the vertebral end plates and trabeculated new bone formation across the fused interspace. By considering this investigational patient as a fusion failure because of the need to use supplemental posterior fixation, the fusion rate for the investigational group was 95.8%.

At 24 months in the control autograft group, 19 patients were available for radiographic evaluation, and 13 of these patients (68.4%) were considered to have fusions (Figure 11). In the control group, there were no failures of the allograft dowels. Three control group patients underwent supplemental posterior fixation for pseudarthrosis. Radiographic lucencies developed at the interface of the allograft to the vertebral end plate between the 12- and 24-month follow-up examinations (Figure 12). This led to the decrease in the fusion rate in the control group. There was no migration of the implants.

DISCUSSION

Recombinant human bone morphogenetic protein-2 (rhBMP-2) is an osteoinductive growth factor.[2,20] Urist discovered the capabilities of demineralized bone matrix to induce ectopic bone formation in a rat muscle pouch and introduced the concept that bone growth factors can induce new bone formation independent of the bone tissue environment.[22] Bone morphogenetic protein-2 is one of several proteins identified from bone tissue that acts a osteoinductive cytokine and induces the differentiation of pluripotential precursor cells along an osteogenic line. A pure form of this protein can be produced through standard recombinant technology. The human cDNA sequence is created through the use of oligonucleotide probes, and these clones are then spliced into a

viral vector and transfected into a carrier cell in a process called recombination. These production cells (Chinese hamster ovary cells) have the ability to produce large quantities of rhBMP-2. Creating recombinant human proteins in this manner avoids potential complications associated with disease transmission from allograft or xenograft sources.

The availability of rhBMP-2 in pure "unlimited" sources has the ability to greatly enhance spinal fusion results while lowering pain scores associated with a bone graft harvesting procedure. The purpose of this study was to assess the efficacy of this recombinant protein impregnated on a collagen sponge in a threaded cortical allograft dowel for the treatment of degenerative disc disease by an anterior interbody fusion.

To date, in both animal and human studies, rhBMP-2 has been shown to be capable of inducing new bone formation.[2,19] In a study of anterior lumbar interbody fusion in nonhuman primates, rhBMP-2 and an absorbable collagen sponge carrier was shown to promote fusion through osteoinduction.[11] New bone formation appeared to be superior to autogenous iliac crest graft with cortical dowel allograft. Similarly, in a preliminary clinical study involving the use of InFUSE™ Bone Graft and a tapered cylindrical titanium cage in humans, arthrodesis was found to occur more reliably in patients treated with rhBMP-2 than in controls treated with autogenous bone graft.[3]

This study is the first clinical report of the effectiveness of rhBMP-2 used with cortical allograft to promote anterior lumbar intervertebral fusion in humans. No unanticipated adverse events that were related to the use of InFUSE™ Bone Graft occurred during the course of the study. Because the investigational group did not undergo the bone graft harvesting procedure, there was a statistically significant reduction in operative time and decreased blood loss during the surgical procedure.

Overall, the investigational group, who received rhBMP-2 on a collagen sponge carrier (InFUSE™ Bone Graft), showed higher rates of success in the reduction of back and leg pain associated with degenerative lumbar disc disease than the control group. At their initial postoperative visit, patients in the investigational group showed an improvement in back pain of more than 7 points. Back pain scores continued to improve throughout the study period and averaged approximately a 9-point improvement at 24 months. In the investigational group, leg pain improved by more than five points within six weeks of surgery and remained unchanged at the last clinical follow-up at 24 months. When compared with the control group, the investigational group showed greater relief of leg pain at all clinical follow-up intervals. Similarly, at 12 and 24 months, the investigational patients showed a higher rate of success than the control patients did in their overall neurologic success scores. The use of rhBMP-2 obviates the need for autogenous bone graft and the potential for donor site morbidity. The control group had complaints of hip pain throughout the 24-month study period.

Coinciding with the reduction in painful symptoms was the investigational group's greater and faster functional recovery. At all time periods, the investigational group had greater improvements in Oswestry Disability Questionnaire scores than the control group. The mean improvements in Oswestry scores at 12 and 24 months (31.6 and 33.5 points) are among the highest reported in the literature. Return-to-work status was also assessed to evaluate functional recovery of the patients in the study. Similarly, higher percentages of patients in the investigational group were also able to return to work. In this group, 45.8% of patients were working before surgery, and 66.7% were working at 24 months after surgery.

The investigational group also showed improved general health status after surgery. In both the Physical (PCS) and Mental (MCS) Components of the SF-36, which was used to measure specific health concepts related to physical and social functioning and limitations, the investigational group showed higher mean scores at 24 months than the control group. As would be expected from these improved outcomes, patient satisfaction was higher in this group. At 24 months, 83% of patients in the group responded to all three questions that were asked that they were satisfied with their surgical outcome.

Fusion rate. The investigational group showed higher rates of fusion when compared with the control group at 6, 12 and 24 months. In our study, *fusion* was defined as radiographically identified bridging bone, no motion (<5° angulation, <3mm translation), and absence of radiolucent lines around more than 50% of either implant. In the control group, there were patients who were thought to be fused radiographically at 12 months, and later, at 24 months, they were thought not to be fused radiographically. This confusion regarding fusion was due to the radiolucent line criteria. Although there was bridging bone and no motion at 12 and 24 months in these patients, radiolucent lines were not evident at 12 months. It was not until 24 months after surgery that these lucencies around the cortical implants were seen. This occurrence is very likely due to the nature of the control group's implant. The dowels were packed solid with autograft bone and lucencies resulting from failure of the allograft to fully incorporate to the vertebral end plates is not evident early on but is seen overtime. After all, that is why the radiographic follow-up evaluations were carried out to two years. Because of early incorporation of the

allograft to the vertebral end plates in the BMP group, this radiolucent line issue was not seen postoperatively in the investigational group.

Criteria other than radiographic were used to determine the *rate of fusion,* or *fusion success*. Fusion success was, in part, defined by the need for secondary surgeries. If a patient in the investigational group had a secondary surgery (i.e., supplemental fixation), that patient was called a fusion failure from that time forward. We did not go back and classify this patient as a fusion failure at earlier visits. At these visits, the patient met the protocol requirements of radiographic fusion. The pseudarthrosis diagnosis may have been in response to persistent low back pain not a deviation from the fusion criteria. At the time of surgery on this investigational patient, the attending surgeon found that the spinal motion segment "was extremely stable and contained only micro-motion noted after the facet joints were debrided."

InFUSE™ Bone Graft was shown to be a promising method of facilitating anterior intervertebral spinal fusion and of decreasing pain and improving clinical outcomes after anterior lumbar fusion surgery with allograft bone dowels. These improved outcomes were due, in part, to the successful combination of the anterior surgical approach, the use of threaded allograft dowels, and a high rate of successful interbody fusion.

REFERENCES

1. Blumenthal SL, Baker J, Dossett A, Selby DK. The role of anterior lumbar fusion for internal disc disruption. Spine 1988;13:566-9.

2. Boden SD, Schimandle JH, Hutton WC. Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 1995;20:2633-44.

3. Boden SD, Zdeblick TA Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Spine 2000;25:376-81.

4. Boyd, L.M.; Estes, B.T. and Liu M. "Biomechanics of Lumbar Interbody Constructs, *Effect of Design and Materials*." Chirurgie Endoscopique et Mini-invasive du Rachis. Ed. Husson JL, LeHuec JC. Sauramps Médical. Montpelier, France. pp 181-92, 1999.

5. Burkus JK, Dorchak JD, Sanders DL, Foor BD: Single-level anterior lumbar interbody fusion using threaded cortical bone allografts. North American Spine Society Meeting of the Americas, Miami, Florida, 1999.

6. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. Neurosurg Focus 2001;10:1-9.

7. Crock HV. Anterior lumbar interbody fusion: indications for its use and notes on surgical technique. Clin Orthop 1982;165:157-63.

8. Fairbank JCT, Couper J, Davies JB, O'Brien JP. The Oswestry Low Back Pain Disability Questionnaire. Physiotherapy 1980;66:271-273.

9. Flynn JC, Houque MA. Anterior fusion of the lumbar spine. J Bone Joint Surg 1979;61A:1143-50.

10. Harmon PH. Anterior excision and vertebral fusion operation for intervertebral disc syndromes of the lower lumbar spine: three to five year results in 244 cases. Clin Orthop 1963;26:107-27.

11. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A. The use of recombinant human bone morphogenetic protein-2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999;24:629-36.

12. Kumar A, Kozak JA, Doherty BJ, Dickson JH. Interspace distraction and graft subsidence after anterior lumbar fusion with femoral strut allograft. Spine 1993;18:2393-2400.

13. Lane JD, Moore ES. Transperitoneal approach to the intervertebral disc in the lumbar area. Annals of Surgery 1948;127:537-51.

14. Loguidice VA, Johnson RG, Guyer RD, Stith WJ, Ohnmeiss DD, Hochschuler SH, Rashbaum RF. Anterior lumbar interbody fusion. Spine 1988;13:366-9.

15. Leong JC, Chun SY, Grange WJ, Fang D: Long-term results of lumbar intervertebral disc prolapse. Spine 1983;8:793-9.

16. McHorney CA, Ware JE Jr., Lu RJF, Sherbourne CD. The MOS 36-Item Short-From Health Survey (SF-36). III: tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994;32:40-66

17. Morales RW, Pettine KA, Salib RM. A biomechanical study of bone allografts used in lumbar interbody fusions. North American Spine Society – 6th Annual Meeting, Keystone, Colorado 1991

18. Sacks S. Anterior interbody fusion of the lumbar spine. J Bone Joint Surg [Br] 1965;47:211-23.

19. Sandhu HS, Kanim LEA, Toth JM, et al. Experimental spinal fusion with recombinant human bone morphogenetic protein-2 without decortication of osseous elements. Spine 1997;22:1171-80.

20. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995; 20:1326-37.

21. Stauffer RN, Coventry MB. Anterior interbody lumbar spine fusion. J Bone Joint Surg [Am]1972;54:756-68.

22. Urist MR. Bone: Formation by autoinduction. Science 1965;150:893-9.

23. Ware JE Jr, Sherbourne CD. The MOS 36-Item Short-From Health Survey (SF-36), I: conceptual framework and item selection. Med Care. 1992;30:473-483.

TABLE 1. Patient Demographic Data

Demographic Data	Investigational (InFUSE™ Bone Graft) Group	Control (Autograft) Group
Number of patients	24	22*
Age (years)	41.5	45.6
Weight (lbs)	172.7	175.9
Sex (male/female)	8/16	10/12
Workers' compensation (%)	5 (21)	7 (32)
Spinal litigation (%)	4 (17)	4 (18)
Tobacco use (%)	8 (33)	6 (27)
Previous surgeries (%)	11 (46)	7 (32)

*One patient died an accidental death at 6 months after surgery, and 1 patient was lost-to-follow up.

Table 2. Intraoperative Data

Surgical Data	Investigational (InFUSE™ Bone Graft) Group	Control (Autograft) Group
Operative time (min)	103	114
Blood loss (mL)	124.1	245.0
Levels (%)		
L4-L5	11 (46)	8 (36)
L5-S1	13 (54)	14 (64)
Hospital stay (days)	3.4	3.7

Table 3. Neurologic Outcomes

Period	Variable	Investigational n=24 (%)	Control n=22 (%)
6 Weeks	Overall		
	Success	21 (87.5)	18 (90.0)
	Failure	3 (12.5)	2 (10.0)
	P-value*	1.000	
3 Months	Overall		
	Success	21 (87.5)	20 (95.2)
	Failure	3 (12.5)	1 (4.8)
	P-value*	0.611	
6 Months	Overall		
	Success	21 (87.5)	17 (89.5)
	Failure	3 (12.5)	2 (10.5)
	P-value*	1.000	
12 Months	Overall		
	Success	23 (95.8)	16 (84.2)
	Failure	1 (4.2)	3 (15.8)
	P-value*	0.306	
24 Months	Overall		
	Success	21 (87.5)	11 (73.3)
	Failure	3 (12.5)	4 (26.7)
	P-value*	0.396	

**P*-values are from Fisher's exact test.

Table 4. Back Pain Outcomes

Period	Variable	Investigational n=24	Control n=22
Preoperative	n	24	22
	Mean	16.3	16.3
	SD	2.6	2.2
6 Weeks	n	24	21
	Mean	8.9	10.4
	SD	4.5	4.2
	P value**	0.297	
Improvement from Preoperative	Mean	-7.4	-6.0
	P value*	<0.001	<0.001
3 Months	N	24	21
	Mean	7.9	10.9
	SD	4.3	4.5
	P value**	0.038	
Improvement from Preoperative	Mean	-8.4	-5.4
	P value*	<0.001	<0.001
6 Months	N	24	20
	Mean	6.8	9.9
	SD	4.3	5.1
	P value**	0.034	
Improvement from Preoperative	Mean	-9.5	-6.4
	P value*	<0.001	<0.001
12 Months	N	24	19
	Mean	7.4	9.2
	SD	5.3	6.3
	P value**	0.338	
Improvement from Preoperative	Mean	-8.9	-7.2
	P value*	<0.001	<0.001
24 Months	N	24	17
	Mean	7.4	10.9
	SD	6.0	6.0
	P value**	0.047	
Improvement from Preoperative	Mean	-8.9	-5.2
	P value*	<0.001	<0.001

**P* values for change from preoperative in each group are from paired tests.
***P* values for difference between the treatment groups are from analysis of variance.

Table 5. Leg Pain Outcomes

Period	Variable	Investigational n = 24	Control n = 22
Preoperative	n	24	22
	Mean	12.8	14.6
	SD	5.7	4.1
6 Weeks	N	24	21
	Mean	7.0	8.8
	SD	5.9	5.9
	P value**	0.933	
Improvement from Preoperative	Mean	-5.8	-5.6
	P value*	0.001	0.001
3 Months	N	24	21
	Mean	6.2	8.3
	SD	4.4	5.8
	P value**	0.874	
Improvement from Preoperative	Mean	-6.7	-6.4
	P value*	<0.001	<0.001
6 Months	N	24	20
	Mean	5.0	6.1
	SD	4.7	4.4
	P value**	0.654	
Improvement from Preoperative	Mean	-7.9	8.7
	P value*	<0.001	<0.001
12 Months	N	24	19
	Mean	5.5	8.1
	SD	5.5	6.1
	P value**	0.818	
Improvement from Preoperative	Mean	-7.3	-6.8
	P value*	<0.001	0.001
24 Months	N	24	17
	Mean	6.3	11.5
	SD	6.0	6.3
	P value**	0.142	
Improvement from Preoperative	Mean	-6.5	-3.5
	P value*	<0.001	0.023

*P values for change from preoperative in each group are from paired tests.
**P values for difference between the treatment groups are from analysis of variance.

Table 6. Patient Satisfaction

Period	Variable	Investigational n=24 (%)	Control n=22 (%)
6 Months	I am satisfied with the results of my surgery		
	Definitely True	17 (70.8)	12 (60.0)
	Mostly True	3 (12.5)	4 (20.0)
	P value*	0.503	
	I was helped as much as I thought I would be by my surgery		
	Definitely True	14 (58.3)	6 (30.0)
	Mostly True	6 (25.0)	9 (45.0)
	P value*	0.229	
	All things considered I would have the surgery again for the same condition		
	Definitely True	18 (75.0)	13 (65.0)
	Mostly True	1 (4.2)	3 (15.0)
	P value*	0.312	
12 Months	I am satisfied with the results of my surgery		
	Definitely True	11 (45.8)	7 (35.0)
	Mostly True	8 (33.3)	7 (35.0)
	P value*	0.460	
	I was helped as much as I thought I would be by my surgery		
	Definitely True	12 (50.0)	6 (30.0)
	Mostly True	7 (29.2)	4 (20.0)
	P value*	0.169	
	All things considered I would have the surgery again for the same condition		
	Definitely True	15 (62.5)	11 (55.0)
	Mostly True	4 (16.7)	1 (5.0)
	P value*	0.130	
24 Months	I am satisfied with the results of my surgery		
	Definitely True	13 (54.2)	6 (30.0)
	Mostly True	7 (29.2)	5 (25.0)
	P value*	0.084	
	I was helped as much as I thought I would be by my surgery		
	Definitely True	13 (54.2)	6 (30.0)
	Mostly True	9 (37.5)	5 (25.0)
	P value*	0.249	
	All things considered I would have the surgery again for the same condition		
	Definitely True	15 (62.5)	11 (55.0)
	Mostly True	6 (25.0)	2 (10.0)
	P value*	0.137	

**P* values are from the chi-square test.

Table 7. Oswestry Low Back Pain Disability Scores

Period	Variable	Investigational	Control
Preoperative			
	n	24	22
	Mean	52.4	55.3
	SD	13.1	13.5
6 Weeks			
	N	24	21
	Mean	39.9	47.2
	SD	16.8	18.8
	P value**	0.307	
Improvement from Preoperative			
	Mean	-12.5	-7.9
	P value*	<0.001	0.024
3 Months			
	N	24	21
	Mean	29.0	42.0
	SD	14.7	19.0
	P value**	0.032	
Improvement from Preoperative			
	Mean	-23.4	-14.3
	P value*	<0.001	<0.001
6 Months			
	N	24	20
	Mean	21.4	34.4
	SD	16.1	21.8
	P value**	0.039	
Improvement from Preoperative			
	Mean	-31.0	-20.9
	P value*	<0.001	<0.001
12 Months			
	N	24	19
	Mean	20.8	30.0
	SD	14.9	21.2
	P value**	0.171	
Improvement from Preoperative			
	Mean	-31.6	-24.7
	P value**	<0.001	<0.001
24 Months			
	N	24	17
	Mean	18.9	32.8
	SD	14.5	22.7
	P value**	0.039	
Improvement from Preoperative			
	Mean	-33.5	-21.5
	P value*	<0.001	<0.001

* *P* values for change from preoperative in each group are from paired tests.
** *P* values for difference between the treatment groups are from analysis of variance.

Table 8. Additional Surgeries

Procedure	Investigational (InFUSE™ Bone Graft) Group	Control (Autograft) Group
Removals	0	0
Revisions	0	0
Supplemental fixation (%)	1 (4.2)	3 (13.6)
Reoperation (%)	0	1 (4.5)

LEGEND OF FIGURES

Figure 1. Comparison of neurologic outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft). Success was based on postoperative neurologic condition being improved or no worse than the preoperative condition.

Figure 2. Comparison of back pain outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Figure 3. Comparison of leg pain outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Figure 4. Comparison of Short Form 36 Physical Component Scores in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Figure 5. Comparison of Short Form 36 Mental Component Scores in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Figure 6. Comparison of Oswestry Disability Questionnaire outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Figure 7. Comparison of return-to-work status in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Figure 8. Iliac crest bone graft harvest site pain in the control group.

Figure 9. Comparison of postoperative fusion outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Figure 10. Serial thin-cut CT scans after an L5-S1 fusion using InFUSE™ Bone Graft. Sagittal and frontal CT reconstructions through both the right and left dowels show the progression of the interbody fusion. The immediate postoperative reconstructions show that the dowels have not been incorporated into the vertebral end plates, and there is no bone formation in the central portion of the dowels. At 6 months, the dowels are incorporated into the vertebral end plates and there is new bone formation within the dowels. At 12 months, there is new bone formation connecting the adjacent vertebral bodies both inside and outside of the dowels. At 24 months, the dowels have almost been completely reabsorbed and replaced with new trabecular bone formation.

Figure 11. Serial thin-cut CT scans after an L5-S1 fusion using autograft demonstrate the progression of the interbody fusion. Immediate postoperative scans show corticocancellous graft within the dowels. At 6 months, trabecular bone connects the adjacent vertebral bodies through the dowels and anterior to the dowels. At 12 and 24 months, there is maturation of the interbody fusion with more bone formation and incorporation of the dowels into the vertebral end plates.

Figure 12. Serial thin-cut CT scans after an L5-S1 fusion using autograft show the development of a pseudarthrosis. At 6 months, the grafts within the dowels and the dowels themselves appear to have become attached to the adjacent vertebral end plates. At 12 months, lucencies appear separating the dowels from the vertebral end plates. By 24 months, a radiolucent line involving the inferior portion of both dowels highlights noncontiguous bone formation between the vertebrae consistent with a pseudarthrosis.

From: Mark Marchan
Sent: Tuesday, July 16, 2002 09:19:00 AM
To: Neil Beals
CC: Jim Van Hoeck; Brad Winn; Newt Metcalf
Subject: Baskin BMP Paper

Attachments: Resubmission Cervical BMP Paper 051602.doc; Cervical BMP Paper Revisions.doc

Neil,

Attached for your reference is a list of your requested additions/changes to the Baskin paper and excerpts that relate to these changes. I have also included a copy of Dr. Baskin's resubmitted manuscript. We will check with his office to see if they can make any additional changes to the manuscript since it has been resubmitted. If you have any questions or comments regarding this info please contact me. Thanks.

Mark

A Prospective, Randomized, Controlled Cervical Fusion Study using rhBMP-2 with the CORNERSTONE-SR™ Allograft Ring and the ATLANTIS™ Anterior Cervical Plate

David S. Baskin, M.D.*†
Patrick Ryan, M.D.‡
Volker Sonntag, M.D.§
Richard Westmark, M.D.‖
Marsha A. Widmayer, M.A.*

* Departments of Neurosurgery and †Anesthesiology, Baylor College of Medicine, and *Veterans Affairs Medical Center, Houston, TX

‡Jackson Hospital, Montgomery, AL

§Division of Neurological Surgery, Barrow Neurological Institute, and St. Joseph's Hospital and Medical Center, Phoenix, AZ

‖Clear Lake Regional Medical Center, Webster, TX

Corresponding author: David S. Baskin, M.D.
Department of Neurosurgery
Baylor College of Medicine
[redacted]
Houston, TX 77030

[redacted] (voice)
(fax)
[redacted] (email)

This research was sponsored by Medtronic Sofamor Danek.

ABSTRACT

Study Design: A prospective, randomized, pilot clinical trial was performed comparing recombinant human bone morphogenetic protein (rhBMP-2) with autograft bone for the treatment of human cervical disc disease.

Objective: To examine the safety of using rhBMP-2 in an absorbable collagen sponge (ACS) compared to autogenous bone graft inside the CORNERSTONE-SR™ fibular allograft in anterior cervical discectomy and interbody fusion.

Summary of Background Data: rhBMP-2 is an osteoinductive protein that induces a reliable fusion in the lumbar spine, but it has not been studied in patients with degenerative cervical disc disease.

METHODS: Thirty-three patients with degenerative cervical disc disease were randomly assigned to investigational or control groups. The investigational group received a fibular allograft (CORNERSTONE-SR™) with a rhBMP-2-laden carrier ACS inside the graft, with an ATLANTIS™ anterior cervical plate. The control group received a fibular allograft with cancellous iliac crest autograft placed inside of it, with an ATLANTIS™ anterior cervical plate.

Patients underwent plain x-rays at 6 weeks and at 3, 6, 12, and 24 months, and CT scans at 3 and 6 months postoperatively, and completed general health profiles and self-evaluation scales. Adverse events were evaluated for severity, duration, association with the implant, and the need for a second surgical procedure.

RESULTS: All patients had solid fusions at 6 and 12 months after surgery. There were no device related adverse events. There were no significant group differences

postoperatively in any outcome measure. However, there was a trend for the investigational patients to have superior improvement in neck disability and in neck and arm pain and to have higher patient satisfaction at the end of one year compared to controls.

CONCLUSIONS: This pilot study demonstrates the feasibility of using rhBMP-2 safely and effectively in the cervical spine.

Key words: anterior cervical fusion, bone morphogenetic protein, osteoinduction, radiography, allograft, anterior cervical plating

Key points:

- The fusion rates for all control and investigational groups were 100% at 6 and 12 months postoperative.
- There were no device related adverse events.
- Investigational and control groups both had significant improvement in neck disability and in neck and arm pain following surgery.
- There was a trend for the investigational patients to have higher patient satisfaction at the end of one year and to have superior improvement in neck disability and in neck and arm pain compared to controls.
- The use of rhBMP-2 in anterior cervical fusion procedures eliminates the pain, scarring, and morbidity of iliac crest bone harvesting.

Précis

A prospective, randomized, trial compared rhBMP-2 to autograft in anterior cervical fusions. Successful fusion occurred in 100% of the patients. Investigational patients had a trend toward better results than controls in several outcome measures. Investigational group patients required no iliac crest graft harvest, and therefore experienced no graft site pain or complications.

INTRODUCTION

Anterior cervical discectomy and fusion is an effective and extensively practiced treatment for degenerative cervical disc disease. Smith and Robinson (10), and Cloward (2) first described the technique in the 1950's. Initially, autogenous bone, typically harvested from the iliac crest, was used for the interbody graft. The procedure has developed to include alternatives to autograft; allograft and interbody fusion devices avoid the pain, scarring, and morbidity associated with autograft harvest, yet maintain high fusion rates. Anterior cervical plating has become an accepted component of the procedure, as it has been shown to provide immediate stability, maintain sagittal alignment, and increase the fusion rate (9,11).

Recombinant human bone morphogenetic protein-2 (rhBMP-2) has been shown to initiate osteoinduction and achieve spinal arthrodesis in a non-human primate model (5,8). The application of rhBMP-2 in humans has been explored in a lumbar fusion indication. Human clinical studies have demonstrated that patients treated with rhBMP-2, when soaked onto an absorbable collagen sponge and placed into the central cavity of the LT-CAGE™ interbody fusion device, had consistent and clear osteoinduction (1,6).

The use of rhBMP-2 in an anterior cervical fusion application was previously unexplored. The authors took part in a prospective, randomized, controlled clinical trial in which rhBMP-2 was compared to autograft as an interbody graft filler. A total of 33 patients suffering from 1 or 2-level cervical disc disease were enrolled into the study and have been followed to 1 year postoperatively. Clinical and radiographic

comparisons have been made between the 2 treatments groups at the 6 week, 3 month, 6 month, and 1 year postoperative intervals.

MATERIALS AND METHODS

Study Design. Between September 1999 and May 2000, 33 patients were enrolled in this prospective, randomized, controlled FDA approved pilot clinical trial. The clinical trial was conducted at 4 investigational centers in the United States. All patients enrolled into the study met the prescribed inclusion/exclusion criteria and signed an informed consent. The patients were randomized into their treatment group on a 1:1 basis. After randomization, neither the surgeon nor the patient was blinded to the treatment. All patients received a standard 1 or 2 level anterior cervical discectomy and the disc spaces were prepared for a Smith-Robinson style interbody allograft (in this study, a CORNERSTONE-SR™ Allograft Ring, Regeneration Technologies Incorporated, Alachua, FL). At this point the interbody allografts were prepared according to the patient's treatment randomization (see surgical technique).

Patient Data. Preoperatively, all patients suffered from one or two levels of cervical disc disease producing radiculopathy and/or myelopathy. Preoperative imaging studies demonstrated herniated disc and/or posterior osteophyte formation at the involved level(s). All patients underwent a minimum of 6 weeks of conservative therapy prior to surgery, unless symptoms progressed to require surgery earlier. The investigational and control treatment groups were very similar, and did not significantly differ in any of the demographic parameters measured. Eighteen patients were enrolled in the

investigational group and 15 patients in the control group. Mean age was 51.3 years (investigational) or 47.1 years (control). Mean weight was 169.6 pounds (investigational) or 173.7 pounds (control). Eight of 18 (44%) investigational patients were male, and 7 of 15 (47%) control patients were male. Tobacco was used by 5 of 18 investigational patients and by 7 of 15 control patients.

Clinical and Radiographic Outcome Measurements. Patients were evaluated clinically and radiographically preoperatively, immediately postoperatively, and at 6 weeks, and 3, 6, and 12 months postoperative. The patients will be evaluated again at 24 months. The clinical outcome measures utilized in the clinical study were neurological status, the Neck Disability Index, the SF-36, Neck, Arm, and Graft Site pain visual analog scales, and patient satisfaction questionnaires.

Dynamic flexion/extension x-rays were used to determine fusion status at 6 weeks and 3, 6, and 12 months postoperative. CT scans were utilized at 3 and 6 months postoperatively to further assess fusion status. Two independent, blinded radiologists reviewed all x-rays and CT scans. A third independent, blinded radiologist was used to resolve conflicting fusion findings. Fusion was defined as less than 4 degrees difference in angular motion between flexion and extension as seen on lateral flexion extension radiographs, no radiolucency greater than 2 mm in thickness covering more than 50% of the superior or inferior surface of the graft(s) and evidence of bridging trabecular bone seen on radiographs and CT scans.

Clinical and Radiographic Follow-up. The rate of patient return for follow-up was high at all postoperative periods. One investigational and one control patient were lost to follow-up at 12 months. Of the patients not lost to follow-up, the rate of patient return at 12 months for the investigational group was 88% and for the control group was 100%. The follow-up rate did not drop below 86% at any postoperative interval.

Antibody Assessment. Patient blood samples were collected preoperatively and at 3 months postoperatively to determine titers for antibodies against rhBMP-2 and against the bovine Type 1 collagen in the sponge. A patient was considered to have an authentic elevated immune response if the preoperative sample for a patient was negative (titer < 50) while the postoperative sample was positive (titer ≥ 50), or if the preoperative sample was positive and the postoperative sample was 3-fold higher than the preoperative titer.

Surgical Technique. All patients received the standard ACDF procedure. Patients were placed in the supine position on the operating room table. A transverse incision was made over the cervical spine. An avascular dissection plane was developed between the trachea and esophagus medially and the carotid sheath laterally. After the anterior vertebral column was exposed, the longus colli muscles were elevated, and retraction was achieved via self-retaining retractors placed underneath the longus colli muscles. The appropriate level(s) were identified radiographically. Vertebral body distraction was often applied at this time. A discectomy and/or osteophytectomy was then completed to achieve neural decompression.

The disc space was then prepared for the interbody graft. A parallel cavity was made for the graft by shaping the end plates with a high-speed drill. The extent of endplate and bone removal was left to the discretion of the individual surgeon. Sizing trial tools were used to determine the appropriate graft size to select. For investigational patients, once the appropriate size of allograft was determined, the central cavity of the allograft was then filled with rhBMP-2. The carrier matrix was prepared to a concentration of 1.5 mg/ml rhBMP (InFUSE™ Bone Graft; Medtronic Sofamor Danek, Memphis, TN) by reconstituting with 3.2 ml sterile water. Then, 0.4 ml reconstituted rhBMP-2 solution was uniformly distributed on a 1.5 cm x 2.5 cm piece of collagen sponge. The sponge was placed inside the fibular allograft, which was gently tapped into the prepared disc space for each level fused. Irrigation after implantation was contraindicated.

Deleted: high-speed drill was utilized to create a

For patients in the control group, a small incision was made over the iliac crest, and blunt dissection was performed to expose the crest. A trephine was then used to take a core of cancellous bone, which was then packed into the central cavity of the allograft. The filled allograft was then gently tapped into the prepared disc space. For two level cases, the second disc space and interbody graft were prepared using the same method.

All patients received an appropriately sized anterior cervical plate (ATLANTIS™ Anterior Cervical Plate; Medtronic Sofamor Danek, Memphis, TN) to provide increased stability to the construct. The plate construct utilized either all fixed angle screws, all variable angle screws, or a hybrid construct using both fixed angle and variable angel screws. The screws were secured by an attached locking mechanism, which was

engaged after final screw seating. The appropriate placement of the construct was then confirmed radiographically.

A postoperative regimen which prohibited bone growth stimulators, and recommended against steroids, athletic activities, lifting and bending was recommended. Postoperative bracing requirements were left to the discretion of the individual surgeons.

RESULTS

As there were no differences in preoperative, operative, or outcome variables between the one-level and the two-level patients, their data was combined to form two treatment groups, investigational and control.

Surgery Information. One level arthrodesis was performed on 10 of 18 (56%) investigational patients, and eight of 15 (53%) control patients. The remaining patients received two level arthrodesis. Mean operative time for investigational and control groups was 1.8 hours each. Mean blood loss was 91.4 mL for investigational and 123.3 mL for control patients. Mean hospital stay was 1.4 days (investigational) or 1.1 days (control). There were no unanticipated device-related adverse events in either treatment group.

Graft Site

The level of postoperative pain and morbidity associated with the iliac crest graft harvesting was measured using numeric rating scales for pain intensity and duration. At

discharge and 6 weeks after surgery, control patients had significantly high levels of pain at the graft site ($p < 0.007$, student's t - test) and complained about the appearance of the graft site. By 12 months after surgery, the patients graft-site pain had resolved ($p < 0.165$) and no patients complained about the graft-site appearance.

Antibody Production

No patients produced detectable antibodies to the rhBMP. One investigational and one control patient had elevated titers to bovine Type 1 collagen at 3 months. These patients were not positive for antibodies to human Type 1 collagen.

Clinical Outcomes

Neck Disability Index Questionnaire scores. The Neck Disability Index (NDI) Questionnaire measures cervical pain and disability associated with activities of daily living. The NDI questionnaire was administered preoperatively and at each postoperative interval. At all postoperative intervals, both treatment groups demonstrated statistical improvements as compared with the preoperative scores (Table 1). The investigational group had a trend toward greater mean improvement than the control group at all postoperative intervals, although the investigational group began with slightly worse NDI preoperatively than did controls. At 12 months, the mean improvements in the NDI scores were 45.7 points in the investigational group and 40.8 points in the control group. 93% of patients in both groups showed an improvement of at least 15 points in their disability scores at 12 months postoperative.

Neurologic Status. Neurologic status of the patients was determined by evaluating motor and sensory function. Values for each of the subsets of objective findings were totaled and expressed as a percentage of the maximum possible score. Measurements were then compared with the patient's preoperative score. Neurologic success was based on demonstrating maintenance or improvement in both subsets. At 12 months after surgery, the overall neurologic success rates for the investigational group was 100% as compared with 93% for the control group (Table 2).

Neck Pain. Neck pain frequency and intensity were measured using a 20-point numeric rating scale. Adding the numeric rating scores for neck pain frequency and intensity created a composite neck pain score (Table 3). The mean neck pain scores at all postoperative periods were improved from the preoperative mean values for both treatment groups. The mean improvement in neck pain scores tended to be greater for the investigational group than for the control group at each postoperative interval, although the investigational group began with slightly worse neck pain preoperatively than did controls.

Neck pain success on an individual patient basis was determined by comparing the postoperative score with the preoperative score. Success was based on the patient having at least a 3-point improvement in neck pain score after surgery (Table 3). At 12 months postoperative, the investigational group had a neck pain success rate of 100% and the control group had a success rate of 79%.

Arm Pain. Arm pain was also assessed using a numeric rating scale for both the frequency and intensity of the pain. Mean arm pain scores improved significantly after surgery in both treatment groups (Table 4). Arm pain success was defined according to the following algorithm. If a patient had a preoperative pain score of 10 points or more, success was defined as a 3-point improvement on his or her postoperative scores. In those patients who had preoperative arm pain scores of less than 10 points, success was defined as maintenance or improvement in scores when compared with their preoperative condition. At each postoperative interval, the investigational group had a trend toward greater mean improvement in arm pain than the control group, although the investigational group began with slightly worse arm pain preoperatively than did controls (Table 4). At 12 months postoperative, the investigational group had a success rate of 100% and the control group had success rate of 93%.

General Health. The SF-36 questionnaire was used to measure the patients' general health status. The SF-36 questionnaire was administered preoperatively and at each postoperative interval. The SF-36 was analyzed according to its physical (PCS) and mental (MCS) components. The investigational group showed similar mean improvement to the control group at all postoperative intervals in both the PCS and MCS (Table 5). At 12 months, the mean improvements in the PCS and MCS scores were 14.3 points and 6.8 points respectively for the investigational group. The control group showed a mean improvement of 16 points in the PCS and a worsening of 1.3 points in the MCS at 12 months postoperative. SF-36 success was defined as maintenance or improvement in scores when compared to preoperative scores. At 12

months postoperative, the investigational group success rates for the PCS and MCS were 92% and 77% respectively (Table 5). The control group success rates for the PCS and MCS were 93% and 36% respectively at the 12-month interval.

Patient Satisfaction. Patient satisfaction was assessed by three questions inquiring whether the patients were satisfied with the results, were helped as much as they thought they would be, and whether they would have the surgery again for the same condition. At the 12-month postoperative interval, the investigational group patients had a trend toward greater satisfaction with the results of their procedure than did the control group patients.

Radiographic Outcomes. Fusion status of the study patients was evaluated with lateral flexion and extension radiographs and CT scans. Fusion was based on evidence of bridging bone, angular motion stability, and lucent line criteria (see methods for exact criteria). At 6 and 12 months postoperative, 100% of the patients in both the investigational and the control group that were not lost to follow-up were deemed fused (6 months investigational 15/15 = 100%, control 13/13 = 100%, 12 months 14/14 investigational = 100%, 12/12 control = 100%).

Two patients in the investigational group and one patient in the control group demonstrated bone formation immediately anterior to segments adjacent to the treated level. The ossification is clearly visible on the 12 month postoperative x-rays (Fig.1). All 3 patients were treated by the same surgeon.

Secondary Surgical Procedures. One patient in the investigational group required surgical intervention at an adjacent segment to the original two-level fusion. The surgery was unrelated to the original procedure. However, to perform the operation the anterior cervical plate was removed. No other subsequent cervical procedures were performed.

DISCUSSION

This pilot study is the first prospective clinical evaluation of rhBMP-2 for a cervical spine fusion indication. The primary purpose of this pilot study was to assess the feasibility of using rhBMP-2 when used in an anterior cervical fusion application. As expected with the low sample size of the study, there were no statistically significant differences between treatment groups in any parameters assessed. However, both groups showed significant postoperative improvement in neck disability and in neck and arm pain. Both groups had fusion rates of 100%, indicating these treatments for cervical degenerative disc disease are particularly successful. The investigational group also avoided the pain and morbidity of iliac crest graft harvest.

Deleted: Clinical improvement trends favored the investigational group.

In the current study, the Investigational group received rhBMP together with allograft bone. There is a small risk of disease transmission associated with the use of allograft bone (3). This risk is outweighed, however, by the elimination of the bone harvesting surgery.

Recombinant human bone morphogenetic protein is an osteoinductive growth factor that stimulates stem cells to form bone (12). A number of animal and human studies have been conducted to evaluate the effectiveness of this substance in promoting spinal

fusion, and in many cases, the success rate and quality or quantity of the fusion mass has been superior to autograft (see 4, 7 for reviews).

Anterior bone formation in immediately adjacent segments was demonstrated in two investigational and one control patient. As this occurred in both groups, and the same surgeon treated all three patients, the ossification may be technique related. Furthermore, the general incidence of anterior bone formation in immediately adjacent segments is unknown, and has been observed anecdotally by a number of experienced spine surgeons using standard allograft and autograft constructs. The pathophysiology of spondylosis relates to disc degeneration and segmental instability, to which the response is overgrowth of ligament and bone. It may be that in these cases and in others like them, the adjacent disc and/or facets are already degenerated, and that fusion accelerates the spondylitic process, which includes bony growth.

Deleted: . In this study, the investigational group received rhBMP-2 soaked onto an absorbable collagen sponge and placed into the central cavity of an allograft ring. At 6 and 12 months postoperative, the investigational group was determined to have a fusion rate of 100% by two independent blinded radiologists.¶

The presence of blood and surgical trauma may be associated with ectopic bone formation, and are also factors to consider. In this regard, blood may serve as a sink to extract BMP from its carrier. Meticulous hemostasis and use of drains will be important aspects of technique to consider when using rhBMP-2 in all spinal applications, despite the fact that evidence is lacking in this study to implicate BMP as the cause of adjacent segment anterior bone overgrowth.

rhBMP-2 has been shown in clinical trials to be safe and effective when used in a lumbar interbody fusion application (1,6). The use of rhBMP-2 is associated with high fusion rates without the need for harvesting bone from the iliac crest, avoiding the pain and morbidity of that procedure. This pilot study demonstrates that the use of rhBMP-2 in an anterior cervical fusion application is sufficiently safe to study its use in a larger

clinical trial. Further clinical studies are underway to evaluate the safety and effectiveness of rhBMP-2 for this indication.

ACKNOWLEDGEMENTS

This research was sponsored by Medtronic Sofamor Danek. The authors thank Newt Metcalf, Missy Taylor and Mark Marchan for the important role they played in the creation of this manuscript.

REFERENCES

1. Boden SD, Zdeblick TA, Sandhu HS, et al. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25:376-81.

2. Cloward RB. The anterior approach for removal of rupture cervical disks. J Neurosurg 1958;15:601-617.

3. Hardin CK. Banked bone. Otolaryngol Clin North Am 1994; 27:911-925.

4. Harvinder S, Sandhu MD. Anterior lumbar interbody fusion with osteoinductive growth factors. Clin Orthop 2000; 2000:56-60.

5. Hecht BP, Fischgrund JS, Herkowitz HN, et al. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999; 24:629-36.

6. Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2. A prospective study of clinical and radiographic outcomes. Spine 2001; 26:2751-2756.

7. Ludwig SC, Kowalski JM, Boden SD. Osteoinductive bone graft substitutes. Eur Spine J 2000; 9:S119-125.

8. Martin GJ Jr, Boden SD, Marone MA, et al. Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: important lessons learned regarding dose, carrier, and safety. J Spinal Disord. 1999; 12:179-186.

9. Schulte K, Clark CR, Goel VK. Kinematics of the cervical spine following discectomy and stabilization. Spine 1989; 14:1116-1121.

10. Smith GW, Robinson RA. The treatment of certain cervical spinal disorders by anterior removal of the intervertebral disc and interbody fusion. J Bone Joint Surg 1958; 40:607-624.

11. Spivak JM, Balderston RA. Spinal instrumentation. Curr Opin Rheumatol 1994; 6:187-94.

12. Urist MR. Bone: Formation by autoinduction. Science 1965; 150:893-899.

Figure Legend

Figure 1. Twelve Month Postoperative Lateral X-rays.

Panel A - Investigational Patient #2.

Panel B - Control Patient #6.

Panel C - Investigational Patient #9.

Note the formation of anterior bone in segments immediately adjacent to the fused vertebra in these three patients (white arrows).

TABLE 1 – Neck Disability Index Scores

Period	Variable	Investigational	Control
Preoperative			
	n	18	15
	Mean	61.3	55.4
6 Weeks			
	n	18	15
	Mean	23.9	22.8
Improvement from Preoperative	Mean	37.4	32.6
	P value[1]	<0.001	<0.001
3 Months			
	n	17	15
	Mean	21.3	21.9
Improvement from Preoperative	Mean	39.2	33.5
	P value	<0.001	<0.001
6 Months			
	n	17	13
	Mean	12.9	13.4
Improvement from Preoperative	Mean	47.8	38.8
	P value	<0.001	<0.001
12 Months			
	n	14	14
	Mean	17.3	12.3
Improvement from Preoperative	Mean	45.7	40.8
	P value	<0.001	<0.001

[1] P values for change from preoperative in each group are from paired T-tests
Patients in both treatment groups experienced significant improvement in neck disability following surgery.

TABLE 2. Neurologic Outcomes

Period	Variable	Investigational n (%)	Control n (%)
6 Weeks			
	Success	17 (94)	15 (100)
	Failure	1 (6)	0 (0)
3 Months			
	Success	18 (100)	15 (100)
	Failure	0 (0)	0 (0)
6 Months			
	Success	15 (88)	13 (100)
	Failure	2 (12)	0 (0)
12 Months			
	Success	15 (100)	13 (93)
	Failure	0 (0)	1 (7)

Patients in both treatment groups maintained or improved in motor function, sensory function and reflexes, indicating successful neurologic outcome.

TABLE 3. Neck Pain and Neck Pain Success

Period	Variable	Investigational	Control
Preoperative	n	18	15
	Mean	16.1	14.3
6 Weeks	n	18	15
	Mean	5.2	6.9
Improvement from Preoperative	Mean	10.9	7.4
	P value[1]	<0.001	<0.001
3 Months	n	17	15
	Mean	6.2	6.7
Improvement from Preoperative	Mean	10.6	7.6
	P value	<0.001	<0.001
6 Months	n	17	13
	Mean	4.6	4.1
Improvement from Preoperative	Mean	11.4	9.6
	P value	<0.001	<0.001
12 Months	n	15	14
	Mean	3.5	5.4
Improvement from Preoperative	Mean	12.1	8.6
	P value	<0.001	<0.001

[1] P values for change from preoperative in each group are from paired T-test.
Patients in both treatment groups experienced significant improvement in neck pain frequency and intensity.

Deleted: <#>Weeks¶
¶
¶
¶
Improvement from Preoperative¶
¶
¶
¶
... [1]
Formatted: Bullets and Numbering

Deleted: <#>Months¶
¶
¶
¶
Improvement from Preoperativ ... [2]
Formatted: Bullets and Numbering

Deleted: <#>Months¶
¶
¶
¶
Improvement from Preoperativ ... [3]
Formatted: Bullets and Numbering

Deleted: <#>Months¶
¶
¶
¶
Improvement from Preoperativ ... [4]
Formatted: Bullets and Numbering

TABLE 4. Arm Pain and Arm Pain Success

Period	Variable	Investigational	Control
Preoperative	n	18	15
	Mean	17.3	11.5
6 Weeks	n	18	15
	Mean	3.4	2.6
Improvement from Preoperative	Mean	13.9	8.9
	P value[1]	<0.001	<0.001
3 Months	n	17	15
	Mean	3.6	2.90
Improvement from Preoperative	Mean	14.1	8.5
	P value[1]	<0.001	<0.001
6 Months	n	17	13
	Mean	2.6	0.8
Improvement from Preoperative	Mean	14.8	10.0
	P value[1]	<0.001	<0.001
12 Months	n	15	14
	Mean	2.9	1.5
Improvement from Preoperative	Mean	14.5	9.7
	P value[1]	<0.001	<0.001

[1] P values for change from preoperative in each group are from paired test.
Patients in both treatment groups experienced significant improvement in arm pain frequency and intensity.

Deleted: <#>Weeks¶ ¶ ¶ ¶ Improvement from Preoperative¶ ¶ ¶ ¶ ... [5]
Formatted: Bullets and Numbering

Deleted: <#>Months¶ ¶ ¶ ¶ Improvement from Preoperative¶ ¶ ¶ ¶ ... [6]
Formatted: Bullets and Numbering

Deleted: <#> Months¶ ¶ ¶ ¶ Improvement from Preoperative¶ ¶ ¶ ¶ ... [7]
Formatted: Bullets and Numbering

Deleted: <#>Months¶ ¶ ¶ ¶ Improvement from Preoperative¶ ¶ ¶ ¶ ... [8]
Formatted: Bullets and Numbering

TABLE 5. SF-36 and SF-36 Success

Period	Variable	Investigational	Control
Preoperative	n	16	15
PCS	Mean	31.5	32.6
MCS	Mean	39.5	44.9
6 Weeks	n	18	15
PCS	Mean	40.5	39.7
MCS	Mean	47.0	48.2
3 Months	n	16	15
PCS	Mean	44.6	44.7
MCS	Mean	42.8	41.6
6 Months	n	15	12
PCS	Mean	45.8	46.7
MCS	Mean	47.7	45.3
12 Months	n	15	14
PCS	Mean	45.9	48.9
MCS	Mean	46.0	43.6

PCS = physical component score. MCS = mental component score
SF-36 is a measure of general physical and mental health. Note that both investigational and control patients improved in physical health following surgery. The investigational group consistently showed improvement in mental health following surgery. The control group, however, did not show consistent improvement in mental health following surgery.

Deleted: 6 Weeks¶ . PCS¶ ¶ ¶ . MCS¶ ... [9]

Deleted: 3 Months¶ . . PCS¶ ¶ ¶ . . MCS¶ ... [10]

Deleted: 6 Months¶ . . PCS¶ ¶ ¶ . . MCS¶ ... [11]

Deleted: 12 Months¶ . . PCS¶ ¶ ¶ . . MCS¶ ... [12]

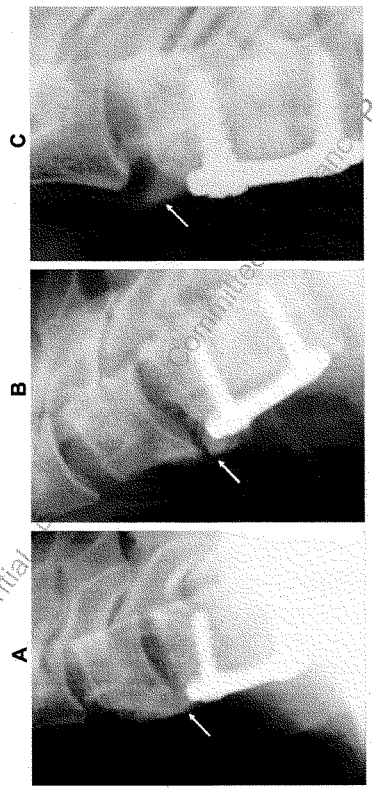


FIGURE 1

Page 24: [1] Deleted	widmayer		5/17/2002 3:19:00 PM
Weeks	n	18	15
	Mean	5.2	6.9
Improvement from Preoperative	Mean	10.9	7.4
	P value[1]	<0.001	<0.001
	Success	16/18 (89%)	10/15 (67%)

Page 24: [2] Deleted	widmayer		5/17/2002 3:19:00 PM
Months	n	17	15
	Mean	6.2	6.7
Improvement from Preoperative	Mean	10.6	7.6
	P value	<0.001	<0.001
	Success	15/17 (88%)	12/15 (80%)

Page 24: [3] Deleted	widmayer		5/17/2002 3:19:00 PM
Months	n	17	13
	Mean	4.6	4.1
Improvement from Preoperative	Mean	11.4	9.6
	P value	<0.001	<0.001
	Success	16/17 (94%)	11/13 (85%)

Page 24: [4] Deleted	widmayer		5/17/2002 3:19:00 PM
Months	n	15	14
	Mean	3.5	5.4
Improvement from Preoperative	Mean	12.1	8.6
	P value	<0.001	<0.001
	Success	15/15 (100%)	11/14 (79%)

Page 25: [5] Deleted	widmayer	5/17/2002 3:19:00 PM

Weeks	n	18	15
	Mean	3.4	2.6
Improvement from Preoperative	Mean	13.9	8.9
	P value[1]	<0.001	<0.001
	Success	16/18 (89%)	15/15 (100%)

Page 25: [6] Deleted widmayer 5/17/2002 3:19:00 PM

Months	n	17	15
	Mean	3.6	2.90
Improvement from Preoperative	Mean	14.1	8.5
	P value[1]	<0.001	<0.001
	Success	16/17 (94%)	13/15 (87%)

Page 25: [7] Deleted widmayer 5/17/2002 3:19:00 PM

Months	n	17	13
	Mean	2.6	0.8
Improvement from Preoperative	Mean	14.8	10.0
	P value[1]	<0.001	<0.001
	Success	17/17 (100%)	13/13 (100%)

Page 25: [8] Deleted widmayer 5/17/2002 3:19:00 PM

Months	n	15	14
	Mean	2.9	1.5
Improvement from Preoperative	Mean	14.5	9.7
	P value[1]	<0.001	<0.001
	Success	15/15 (100%)	13/14 (93%)

Page 26: [9] Deleted widmayer 5/17/2002 3:19:00 PM

6 Weeks		n	18	15
	PCS	Mean	40.5	39.7
		Success	13/16 (81%)	9/15 (60%)
	MCS	Mean	47.0	48.2
		Success	11/16 (69%)	9/15 (60%)

Page 26: [10] Deleted widmayer 5/17/2002 3:19:00 PM

3 Months		n	16	15
	PCS	Mean	44.6	44.7
		Success	14/14 (100%)	12/15 (80%)
	MCS	Mean	42.8	41.6
		Success	8/14 (57%)	5/15 (33%)

Page 26: [11] Deleted widmayer 5/17/2002 3:19:00 PM

6 Months		n	15	12
	PCS	Mean	45.8	46.7
		Success	11/13 (85%)	10/12 (83%)
	MCS	Mean	47.7	45.3
		Success	10/13 (77%)	6/12 (50%)

Page 26: [12] Deleted widmayer 5/17/2002 3:19:00 PM

12 Months		n	15	14
	PCS	Mean	45.9	48.9
		Success	12/13 (92%)	13/14 (93%)
	MCS	Mean	46.0	43.6
		Success	10/13 (77%)	5/14 (36%)

Suggested Changes	Revised Draft
We seem to be very reluctant to use brand name, InFUSE Bone Graft, while it is used frequently for all other constructs - I would suggest more consistency here.	Surgical Technique: "The carrier matrix was prepared to a concentration of 1.5 mg/ml rhBMP (InFUSE™ Bone Graft; Medtronic Sofamor Danek, Memphis, TN)"
No Conclusions - should these be defined and included?	Abstract Conclusion: "This pilot study demonstrates the feasibility of using rhBMP-2 safely and effectively in the cervical spine."
Introduction refers to LT Cage study showing higher fusion rates with InFUSE - this is not true (only trend at 24 months, not stat sig)	Removed from manuscript.
Methods indicate that radiographic data was collected at 3 months - this is not included in results - do we have data?	Only 6 and 12 month radiographic data was analyzed. We have 3 month data but it is unremarkable and was not included.
Technique section should include 15 minute soak of sponge and other aspects of protocol - e.g., no irrigation, no use of Gelfoam, etc	Surgical Technique: "Irrigation after implantation was contraindicated." Discussion: "The presence of blood and surgical trauma may be associated with ectopic bone formation, and are also factors to consider. In this regard, blood may serve as a sink to extract BMP from its carrier. Meticulous hemostasis and use of drains will be important aspects of technique to consider when using rhBMP-2 in all spinal applications…" No references were made to the soak time or gel foam
Different constructs were used (fixed, variable angle, hybrid) - may want to confirm that these do not have effect (even if not stat sig)	We do not have enough information to address this issue.
In results, statement is made that there is no difference between one and two level cases; given small number and lack of stat sig for any results, do you want to combine these? I recall fairly large differences between them and I believe FDA did not allow us to include both in pivotal study - my feeling is that this should be addressed more.	1 and 2 level cases were combined.
mention is made that hospital stay is higher - is this stat sig? I doubt it - if not, I would not include that statement	Removed from manuscript.

one investigational patient required surgical intervention - was this related to BMP? - it is unclear as currently written	Secondary Surgical Procedures: "One patient in the investigational group required surgical intervention at an adjacent segment to the original two-level fusion. The surgery was unrelated to the original procedure. However, to perform the operation the anterior cervical plate was removed. No other subsequent cervical procedures were performed."
Discussion is relatively brief - is this by design? I would think that many issues could be addressed here - e.g., potential future benefits of technology, some special considerations for use of BMP, effect/importance of instrumentation, etc	Discussion covers the following issues: disease transmission, iliac crest harvest, anterior bone formation, and surgical considerations.
reference to heterotopic bone formation is brief and, in my opinion should be expanded on if it is raised in this paper - one suggestion is to include a listing and explanation of possible contributing factors - in our brief review we quickly came up with a number of things to consider when using BMP in ACDF (hemostasis control, amount of BMP in allograft ("overstuffing"), bleeding at screw holes, irrigation after implanting, implanting gelfoam, etc). the reassuring thing is that this bone is not concerning due to its location	Discussion: "As this occurred in both groups, and the same surgeon treated all three patients, the ossification may be technique related… The presence of blood and surgical trauma may be associated with ectopic bone formation, and are also factors to consider. In this regard, blood may serve as a sink to extract BMP from its carrier. Meticulous hemostasis and use of drains will be important aspects of technique to consider when using rhBMP-2 in all spinal applications, despite the fact that evidence is lacking in this study to implicate BMP as the cause of adjacent segment anterior bone overgrowth."
is this first study to follow this type patient with CTs? if so, you may want to expand on this	This is part of fusion criteria and is mentioned in Radiographic Outcomes.

From: Mark Marchan
Sent: Tuesday, August 27, 2002 03:24:52 PM
To: Neil Beals
Subject: FW: Revised BMP paper and response

Attachments: Resubmission Cervical BMP Paper 082302.doc; Response letter 2.doc; Rev 1.jpg

Neil,

Attached is the latest revision of the Baskin BMP manuscript that has been submitted to *Spine*. I will need any of your comments ASAP so that they can get it resubmitted before Marsha goes on leave. Thanks.

Mark

-----Original Message-----
From: widmayer [SMTP[redacted]
Sent: Monday, August 26, 2002 1:46 PM
To: newt Metcalf; Mark Marchan
Subject: Revised BMP paper and response

Please run this by whomever needs to see it. I'll be in tomorrow, and then will be out for 10 days for medical reasons. I'll do whatever I can to get it submitted tomorrow. I've included the paper, response letter and reviewer's comments.

THANKS!!!

Marsha A. Widmayer
Department of Neurosurgery
Baylor College of Medicine
[redacted]
Houston, TX 77030
[redacted]

A Prospective, Randomized, Controlled Cervical Fusion Study using rhBMP-2 with the CORNERSTONE-SR™ Allograft Ring and the ATLANTIS™ Anterior Cervical Plate

David S. Baskin, M.D.*†
Patrick Ryan, M.D.‡
Volker Sonntag, M.D.§
Richard Westmark, M.D.‖
Marsha A. Widmayer, M.A.*

* Departments of Neurosurgery and †Anesthesiology, Baylor College of Medicine, and *Veterans Affairs Medical Center, Houston, TX

‡Jackson Hospital, Montgomery, AL

§Division of Neurological Surgery, Barrow Neurological Institute, and St. Joseph's Hospital and Medical Center, Phoenix, AZ

‖Clear Lake Regional Medical Center, Webster, TX

Corresponding author: David S. Baskin, M.D.
Department of Neurosurgery
Baylor College of Medicine
[redacted]
Houston, TX 77030

[redacted] (voice)
[redacted] (fax)
[redacted] (email)

This research was sponsored by Medtronic Sofamor Danek.

ABSTRACT

Study Design: A prospective, randomized, pilot clinical trial was performed comparing recombinant human bone morphogenetic protein (rhBMP-2) with autograft bone for the treatment of human cervical disc disease.

Objective: To examine the safety of using rhBMP-2 in an absorbable collagen sponge (ACS) compared to autogenous bone graft inside the CORNERSTONE-SR™ fibular allograft in anterior cervical discectomy and interbody fusion.

Summary of Background Data: rhBMP-2 is an osteoinductive protein that induces a reliable fusion in the lumbar spine, but it has not been studied in patients with degenerative cervical disc disease.

METHODS: Thirty-three patients with degenerative cervical disc disease were randomly assigned to investigational or control groups. The investigational group received a fibular allograft (CORNERSTONE-SR™) with an rhBMP-2-laden carrier ACS inside the graft, with an ATLANTIS™ anterior cervical plate. The control group received a fibular allograft with cancellous iliac crest autograft placed inside of it, with an ATLANTIS™ anterior cervical plate.

Patients underwent plain x-rays at 6 weeks and at 3, 6, 12, and 24 months, and CT scans at 3 and 6 months postoperatively, and completed general health profiles and self-evaluation scales. Adverse events were evaluated for severity, duration, association with the implant, and the need for a second surgical procedure.

RESULTS: All patients had solid fusions at 6, 12 and 24 months after surgery. There were no device related adverse events. At 24 months the investigational patients had significantly better improvement in Neck Disability and Arm Pain than did the controls. **CONCLUSIONS:** This pilot study demonstrates the feasibility of using rhBMP-2 safely and effectively in the cervical spine.

Key words: anterior cervical fusion, bone morphogenetic protein, osteoinduction, radiography, allograft, anterior cervical plating

Key points:

- The fusion rates for all control and investigational groups were 100% at 6, 12 and 24 months postoperative.
- There were no device related adverse events.
- Investigational and control groups both had significant improvement in neck disability and in neck and arm pain following surgery.
- Investigational patients had statistically significant improvement in Neck Disability and Arm Pain compared to controls, although the small sample size precludes concluding that the investigational treatment is superior.
- The use of rhBMP-2 in anterior cervical fusion procedures eliminates the pain, scarring, and morbidity of iliac crest bone harvesting.

Précis

A prospective, randomized, trial compared rhBMP-2 to autograft in anterior cervical fusions. Successful fusion occurred in 100% of the patients. Investigational patients had better results than controls in several outcome measures. Investigational group patients required no iliac crest graft harvest, and therefore experienced no graft site pain or complications.

INTRODUCTION

Anterior cervical discectomy and fusion is an effective and extensively practiced treatment for degenerative cervical disc disease. Smith and Robinson (11), and Cloward (2) first described the technique in the 1950's. Initially, autogenous bone, typically harvested from the iliac crest, was used for the interbody graft. The procedure has developed to include alternatives to autograft; allograft and interbody fusion devices avoid the pain, scarring, and morbidity associated with autograft harvest, yet maintain high fusion rates. Anterior cervical plating has become an accepted component of the procedure, as it has been shown to provide immediate stability, maintain sagittal alignment, and increase the fusion rate (10,12).

Recombinant human bone morphogenetic protein-2 (rhBMP-2) has been shown to initiate osteoinduction and achieve spinal arthrodesis in a non-human primate model (5,9). The application of rhBMP-2 in humans has been explored in a lumbar fusion indication. Human clinical studies have demonstrated that patients treated with rhBMP-2, when soaked onto an absorbable collagen sponge and placed into the central cavity of the LT-CAGE™ interbody fusion device, had consistent and clear osteoinduction (1,7).

The use of rhBMP-2 in an anterior cervical fusion application was previously unexplored. The authors took part in a prospective, randomized, controlled clinical trial in which rhBMP-2 was compared to autograft as an interbody graft filler. A total of 33 patients suffering from 1 or 2-level cervical disc disease were enrolled into the study and have been followed to 2 years postoperatively. Clinical and radiographic

comparisons have been made between the 2 treatments groups at the 6 week, 3 month, 6 month, 1 year and 2 year postoperative intervals.

MATERIALS AND METHODS

Study Design. Between September 1999 and May 2000, 33 patients were enrolled in this prospective, randomized, controlled FDA approved pilot clinical trial. The clinical trial was conducted at 4 investigational centers in the United States. All patients enrolled into the study met the prescribed inclusion/exclusion criteria and signed an informed consent. The patients were randomized into their treatment group on a 1:1 basis. After randomization, neither the surgeon nor the patient was blinded to the treatment. All patients received a standard 1 or 2 level anterior cervical discectomy and the disc spaces were prepared for a Smith-Robinson style interbody allograft (in this study, a CORNERSTONE-SR™ Allograft Ring, Regeneration Technologies Incorporated, Alachua, FL). At this point the interbody allografts were prepared according to the patient's treatment randomization (see surgical technique).

Patient Data. Preoperatively, all patients suffered from one or two levels of cervical disc disease producing radiculopathy and/or myelopathy. Preoperative imaging studies demonstrated herniated disc and/or posterior osteophyte formation at the involved level(s). All patients underwent a minimum of 6 weeks of conservative therapy prior to surgery, unless symptoms progressed to require surgery earlier. The investigational and control treatment groups were very similar, and did not significantly differ in any of the demographic parameters measured. Eighteen patients were enrolled in the

investigational group and 15 patients in the control group. Mean age was 51.3 years (investigational) or 47.1 years (control). Mean weight was 169.6 pounds (investigational) or 173.7 pounds (control). Eight of 18 (44%) investigational patients were male, and 7 of 15 (47%) control patients were male. Tobacco was used by 5 of 18 investigational patients and by 7 of 15 control patients.

Clinical and Radiographic Outcome Measurements. Patients were evaluated clinically and radiographically preoperatively, immediately postoperatively, and at 6 weeks, and 3, 6, 12 and 24 months postoperative. The clinical outcome measures were neurological status, the Neck Disability Index, the SF-36, Neck, Arm, and Graft Site pain visual analog scales, and patient satisfaction questionnaires.

Dynamic flexion/extension x-rays were used to determine fusion status at 6 weeks and 3, 6, 12 and 24 months postoperative. CT scans were used at 3 and 6 months postoperatively to further assess fusion status. Two independent, blinded radiologists reviewed all x-rays and CT scans. A third independent, blinded radiologist was used to resolve conflicting fusion findings. Fusion was defined as less than 4 degrees difference in angular motion between flexion and extension as seen on lateral flexion extension radiographs, no radiolucency greater than 2 mm in thickness covering more than 50% of the superior or inferior surface of the graft(s) and evidence of bridging trabecular bone seen on radiographs and CT scans.

Clinical and Radiographic Follow-up. The rate of patient return for follow-up was high at all postoperative periods. Three investigational and one control patient were lost to

follow-up at 24 months. Of the patients not lost to follow-up, the rate of patient return at 24 months for the investigational group was 86% and for the control group was 85%. The follow-up rate did not drop below 85% at any postoperative interval.

Antibody Assessment. Patient blood samples were collected preoperatively and at 3 months postoperatively to determine titers for antibodies against rhBMP-2 and against the bovine Type 1 collagen in the sponge. A patient was considered to have an authentic elevated immune response if the preoperative sample for a patient was negative (titer < 50) while the postoperative sample was positive (titer ≥ 50), or if the preoperative sample was positive and the postoperative sample was 3-fold higher than the preoperative titer.

Surgical Technique. All patients received the standard ACDF procedure. Patients were placed in the supine position on the operating room table. A transverse incision was made over the cervical spine. An avascular dissection plane was developed between the trachea and esophagus medially and the carotid sheath laterally. After the anterior vertebral column was exposed, the longus colli muscles were elevated, and retraction was achieved via self-retaining retractors placed underneath the longus colli muscles. The appropriate level(s) were identified radiographically. Vertebral body distraction was often applied at this time. A discectomy and/or osteophytectomy was then completed to achieve neural decompression.

The disc space was then prepared for the interbody graft. A parallel cavity was made for the graft by shaping the end plates with a high-speed drill. The extent of

Deleted: high-speed drill was utilized to create a

endplate and bone removal was left to the discretion of the individual surgeon. Sizing trial tools were used to determine the appropriate graft size to select. For investigational patients, once the appropriate size of allograft was determined, the central cavity of the allograft was then filled with rhBMP-2. The carrier matrix was prepared to a concentration of 1.5 mg/ml rhBMP-2 (InFUSE™ Bone Graft; Medtronic Sofamor Danek, Memphis, TN) by reconstituting with 3.2 ml sterile water. Then, 0.4 ml reconstituted rhBMP-2 solution was uniformly distributed on a 1.5 cm x 2.5 cm piece of collagen sponge. The sponge was allowed to soak for 15 minutes and then was placed inside the fibular allograft, which was gently tapped into the prepared disc space for each level fused. Irrigation after implantation was contraindicated.

For patients in the control group, a small incision was made over the iliac crest, and blunt dissection was performed to expose the crest. A trephine was then used to take a core of cancellous bone, which was then packed into the central cavity of the allograft. The filled allograft was then gently tapped into the prepared disc space. For two level cases, the second disc space and interbody graft were prepared using the same method.

All patients received an appropriately sized anterior cervical plate (ATLANTIS™ Anterior Cervical Plate; Medtronic Sofamor Danek, Memphis, TN) to provide increased stability to the construct. The plate construct utilized either all fixed angle screws, all variable angle screws, or a hybrid construct using both fixed angle and variable angel screws. The screws were secured by an attached locking mechanism, which was engaged after final screw seating. The appropriate placement of the construct was then confirmed radiographically.

A postoperative regimen that prohibited bone growth stimulators, and recommended against steroids, athletic activities, lifting and bending was recommended. Postoperative bracing requirements were left to the discretion of the individual surgeons.

RESULTS

As there were no differences in preoperative, operative, or outcome variables between the one-level and the two-level patients, their data was combined to form two treatment groups, investigational and control.

Surgery Information. One level arthrodesis was performed on 10 of 18 (56%) investigational patients, and eight of 15 (53%) control patients. The remaining patients received two level arthrodesis. Mean operative time for investigational and control groups was 1.8 hours each. Mean blood loss was 91.4 mL for investigational and 123.3 mL for control patients (N.S.). Mean hospital stay was 1.4 days (investigational) or 1.1 days (control) (N.S.). There were no unanticipated device-related adverse events in either treatment group.

Graft Site

The level of postoperative pain and morbidity associated with the iliac crest graft harvesting was measured using numeric rating scales for pain intensity and duration. At discharge and 6 weeks after surgery, control patients had significantly high levels of pain at the graft site ($p < 0.007$, student's t - test) and complained about the appearance

of the graft site. By 12 months after surgery, the patients graft-site pain had resolved ($p < 0.165$) and no patients complained about the graft-site appearance.

Antibody Production

No patients produced detectable antibodies to the rhBMP-2. One investigational and one control patient had elevated titers to bovine Type 1 collagen at 3 months. These patients were not positive for antibodies to human Type 1 collagen.

Clinical Outcomes

Neck Disability Index Questionnaire scores. The Neck Disability Index (NDI) Questionnaire measures cervical pain and disability associated with activities of daily living. The NDI questionnaire was administered preoperatively and at each postoperative interval. At all postoperative intervals, both treatment groups demonstrated statistical improvement compared with their preoperative scores (Table 1).

The investigational group demonstrated superior mean improvement than the control group at 24 months ($p < 0.03$), although this group began with slightly worse NDI preoperatively than did controls.

Neurologic Status. Neurologic status of the patients was determined by evaluating motor and sensory function. Values for each of the subsets of objective findings were totaled and expressed as a percentage of the maximum possible score. Measurements were then compared with the patient's preoperative score. Neurologic success was

based on demonstrating maintenance or improvement in both subsets. At 24 months after surgery, the overall neurologic success rate for each group was 100% (Table 2).

Neck Pain. Neck pain frequency and intensity were measured using a 20-point numeric rating scale. Adding the numeric rating scores for neck pain frequency and intensity created a composite neck pain score (Table 3). The mean neck pain scores at all postoperative periods were improved from the preoperative mean values for both treatment groups. At 24 months the mean change was 13 points for the Investigational group and 9 points for the control group, which was not statistically significant ($p < 0.055$).

Neck pain success on an individual patient basis was determined by comparing the postoperative score with the preoperative score. Success was based on the patient having at least a 3-point improvement in neck pain score after surgery (Table 3). At 24 months after surgery, the overall neck pain success rate for each group was 100%.

Arm Pain. Arm pain was also assessed using a numeric rating scale for both the frequency and intensity of the pain. Mean arm pain scores improved significantly after surgery in both treatment groups (Table 4). At all postoperative intervals, both treatment groups demonstrated statistical improvement compared with their preoperative scores (Table 4). Furthermore, the investigational group had superior mean improvement than the control group at 24 months ($p < 0.03$), although the investigational group began with slightly worse Arm Pain preoperatively than did controls.

Arm pain success was defined according to the following algorithm. If a patient had a preoperative pain score of 10 points or more, success was defined as a 3-point improvement on his or her postoperative scores. In those patients who had preoperative arm pain scores of less than 10 points, success was defined as maintenance or improvement in scores when compared with their preoperative condition.

General Health. The SF-36 questionnaire was used to measure the patients' general health status. The SF-36 questionnaire was administered preoperatively and at each postoperative interval. The SF-36 was analyzed according to its physical (PCS) and mental (MCS) components. The investigational group showed similar mean improvement to the control group at all postoperative intervals in both the PCS and MCS (Table 5). At 24 months, the mean improvements in the PCS and MCS scores were 16.7 points and 21.8 points, respectively, for the investigational group. The control group showed a mean improvement of 14.7 points in the PCS and an improvement of 7.2 in the MCS at 24 months postoperative.

SF-36 success was defined as maintenance or improvement in scores when compared to preoperative scores. At 24 months postoperative, the investigational group success rates for the PCS and MCS were 92% each. The control group success rates for the PCS and MCS were 100% and 75% respectively at the 24-month interval.

Patient Satisfaction. Patient satisfaction was assessed by three questions inquiring whether the patients were satisfied with the results, were helped as much as they thought they would be, and whether they would have the surgery again for the same

condition. At the 24-month postoperative interval, greater than 90% of each group responded favorably for each of the three questions.

Radiographic Outcomes. Fusion status of the study patients was evaluated with lateral flexion and extension radiographs and CT scans. Fusion was based on evidence of bridging bone, angular motion stability, and lucent line criteria (see methods for exact criteria). At 6, 12 and 24 months postoperative, 100% of the patients in both the investigational and the control group that were not lost to follow-up were deemed fused (6 months investigational 15/15 = 100%, control 13/13 = 100%, 12 months 14/14 investigational = 100%, 12/12 control = 100%, 24 months 10/10 investigational, 10/10 control).

Two patients in the investigational group and one patient in the control group demonstrated bone formation immediately anterior to segments adjacent to the treated level. This ossification became clearly visible on the 12 month postoperative x-rays (Fig.1). All 3 patients were treated by the same surgeon.

Secondary Surgical Procedures. One patient in the investigational group required surgical intervention at an adjacent segment to the original two-level fusion. The surgery was unrelated to the original procedure. However, to perform the operation the anterior cervical plate was removed. No other subsequent cervical procedures were performed.

DISCUSSION

This pilot study is the first prospective clinical evaluation of rhBMP-2 for a cervical spine fusion indication. The primary purpose of this pilot study was to assess the feasibility of using rhBMP-2 in an anterior cervical fusion application. Both groups showed significant postoperative improvement in neck disability and in neck and arm pain and both groups had fusion rates of 100%. The investigational group also avoided the pain and morbidity of iliac crest graft harvest. rhBMP-2 treatment was at least equally successful compared to the use of autograft bone. On some measures, rhBMP-2 provided superior improvement to standard autograft bone, although the small sample size precludes concluding superiority of treatment.

Generally, a 91 – 97% cervical fusion rate can be expected when spinal instrumentation is used (6). However, in the present study, all radiographs beginning at the 6-month follow-up indicated successful fusion. The fusion rate in the present study is likely due to the fusion criteria utilized. Fusion was defined as less than 4 degrees difference in angular motion between flexion and extension, no radiolucency greater than 2 mm in thickness covering more than 50% of the superior or inferior surface of the graft(s), and evidence of bridging trabecular bone seen on radiographs and CT scans. While some might use more conservative criteria, these criteria were adopted following discussions with the FDA and were applied equally across treatment groups.

In the current study, the Investigational group received rhBMP-2 together with allograft bone. There is a small risk of disease transmission associated with the use of allograft bone (3). In our opinion, this risk is outweighed by the elimination of bone harvesting surgery and its associated morbidity.

Recombinant human bone morphogenetic protein is an osteoinductive growth factor that stimulates stem cells to form bone (13). A number of animal and human studies have been conducted to evaluate the effectiveness of this substance in promoting spinal fusion, and in many cases, the success rate and quality or quantity of the fusion mass has been superior to autograft (see 4, 8 for reviews).

Anterior bone formation in immediately adjacent segments was demonstrated in two investigational and one control patient. As this occurred in both groups, and the same surgeon treated all three patients, the ossification may be technique related. Furthermore, the general incidence of anterior bone formation in immediately adjacent segments is unknown, and has been observed anecdotally by a number of experienced spine surgeons using standard allograft and autograft constructs. The pathophysiology of spondylosis relates to disc degeneration and segmental instability, to which the response is overgrowth of ligament and bone. It may be that in these cases and in others like them, the adjacent disc and/or facets are already degenerated, and that fusion accelerates the spondylitic process, which includes bony growth.

Deleted: . In this study, the investigational group received rhBMP-2 soaked onto an absorbable collagen sponge and placed into the central cavity of an allograft ring. At 6 and 12 months postoperative, the investigational group was determined to have a fusion rate of 100% by two independent blinded radiologists.¶

The presence of blood and surgical trauma may be associated with ectopic bone formation, and are also factors to consider. In this regard, blood may serve as a sink to extract BMP from its carrier. Meticulous hemostasis and use of drains will be important aspects of technique to consider when using rhBMP-2 in all spinal applications, despite the fact that evidence is lacking in this study to implicate rhBMP-2 as the cause of adjacent segment anterior bone overgrowth.

rhBMP-2 has been shown in clinical trials to be safe and effective when used in a lumbar interbody fusion application (1,7). The use of rhBMP-2 is associated with high

fusion rates without the need for harvesting bone from the iliac crest, avoiding the pain and morbidity of that procedure. This pilot study demonstrates that the use of rhBMP-2 in an anterior cervical fusion application is sufficiently safe to study its use in a larger clinical trial. Further clinical studies are underway to evaluate the safety and effectiveness of rhBMP-2 for this indication.

ACKNOWLEDGEMENTS

This research was sponsored by Medtronic Sofamor Danek. The authors thank Newt Metcalf, Missy Taylor and Mark Marchan for the important role they played in the creation of this manuscript.

REFERENCES

1. Boden SD, Zdeblick TA, Sandhu HS, et al. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25:376-81.

2. Cloward RB. The anterior approach for removal of rupture cervical disks. J Neurosurg 1958;15:601-617.

3. Hardin CK. Banked bone. Otolaryngol Clin North Am 1994; 27:911-925.

4. Harvinder S, Sandhu MD. Anterior lumbar interbody fusion with osteoinductive growth factors. Clin Orthop 2000; 2000:56-60.

5. Hecht BP, Fischgrund JS, Herkowitz HN, et al. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999; 24:629-36.

6. Kaiser MG, Haid RW Jr, Subach BR, Barnes B, Rodts GE Jr: Anterior cervical plating enhances arthrodesis after discectomy and fusion with cortical allograft. Neurosurgery 2002; 50:229-236.

7. Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2. A prospective study of clinical and radiographic outcomes. Spine 2001; 26:2751-2756.

8. Ludwig SC, Kowalski JM, Boden SD. Osteoinductive bone graft substitutes. Eur Spine J 2000; 9:S119-125.

9. Martin GJ Jr, Boden SD, Marone MA, et al. Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: important lessons learned regarding dose, carrier, and safety. J Spinal Disord. 1999; 12:179-186.

10. Schulte K, Clark CR, Goel VK. Kinematics of the cervical spine following discectomy and stabilization. Spine 1989; 14:1116-1121.

11. Smith GW, Robinson RA. The treatment of certain cervical spinal disorders by anterior removal of the intervertebral disc and interbody fusion. J Bone Joint Surg 1958; 40:607-624.

12. Spivak JM, Balderston RA. Spinal instrumentation. Curr Opin Rheumatol 1994; 6:187-94.

13. Urist MR. Bone: Formation by autoinduction. Science 1965; 150:893-899.

Figure Legend

Figure 1. Twelve Month Postoperative Lateral X-rays.

Panel A - Investigational Patient #2.

Panel B - Control Patient #6.

Panel C - Investigational Patient #9.

Note the formation of anterior bone in segments immediately adjacent to the fused vertebra in these three patients (white arrows).

TABLE 1 – Neck Disability Index Scores

Period	Variable	Investigational	Control
Preoperative			
	n	18	15
	Mean	61.3	55.4
6 Weeks			
	n	18	15
	Mean	23.9	22.8
Improvement from Preoperative	Mean	37.4	32.6
	P value[1]	<0.001	<0.001
3 Months			
	n	17	15
	Mean	21.3	21.9
Improvement from Preoperative	Mean	39.2	33.5
	P value	<0.001	<0.001
6 Months			
	n	17	13
	Mean	12.9	13.4
Improvement from Preoperative	Mean	47.8	38.8
	P value	<0.001	<0.001
12 Months			
	n	15	14
	Mean	16.3	12.3
Improvement from Preoperative	Mean	45.7	40.8
	P value	<0.001	<0.001
24 Months			
	n	14	12
	Mean	10.1	14.5
*Improvement from Preoperative	Mean	52.7	36.9
	P value	<0.001	<0.001

[1] P values for change from preoperative in each group are from paired T-tests
Patients in both treatment groups experienced significant improvement in neck disability following surgery.
* At 24 months, improvement was superior in the Investigational patients compared to Controls ($p < 0.03$, Student's t-test).

TABLE 2. Neurologic Outcomes

Period	Variable	Investigational n (%)	Control n (%)
6 Weeks			
	Success	17 (94)	15 (100)
	Failure	1 (6)	0 (0)
3 Months			
	Success	18 (100)	15 (100)
	Failure	0 (0)	0 (0)
6 Months			
	Success	15 (88)	13 (100)
	Failure	2 (12)	0 (0)
12 Months			
	Success	15 (100)	13 (93)
	Failure	0 (0)	1 (7)
24 Months			
	Success	14 (100)	12 (100)
	Failure	0 (0)	0 (0)

Patients in both treatment groups maintained or improved in motor function, sensory function and reflexes, indicating successful neurologic outcome.

TABLE 3. Neck Pain

Period	Variable	Investigational	Control
Preoperative	n	18	15
	Mean	16.1	14.3
6 Weeks	n	18	15
	Mean	5.2	6.9
Improvement from Preoperative	Mean	10.9	7.4
	P value[1]	<0.001	<0.001
3 Months	n	17	15
	Mean	6.2	6.7
Improvement from Preoperative	Mean	10.6	7.6
	P value	<0.001	<0.001
6 Months	n	17	13
	Mean	4.6	4.1
Improvement from Preoperative	Mean	11.4	9.6
	P value	<0.001	<0.001
12 Months	n	15	14
	Mean	3.5	5.4
Improvement from Preoperative	Mean	12.1	8.6
	P value	<0.001	<0.001
24 Months	n	14	12
	Mean	2.8	5.3
Improvement from Preoperative	Mean	13.0	9.0
	P value	<0.001	<0.001

[1] P values for change from preoperative in each group are from paired T-test.
Patients in both treatment groups experienced significant improvement in neck pain frequency and intensity. At 24 months the difference between groups in improvement approached statistical significance ($p < 0.055$)

Deleted: <#>Weeks¶ ¶ ¶ ¶ Improvement from Preoperative¶ ¶ ¶ ... [1]
Formatted: Bullets and Numbering

Deleted: <#>Months¶ ¶ ¶ ¶ Improvement from Preoperative ... [2]
Formatted: Bullets and Numbering

Deleted: <#>Months¶ ¶ ¶ ¶ Improvement from Preoperative ... [3]
Formatted: Bullets and Numbering

Deleted: <#>Months¶ ¶ ¶ ¶ Improvement from Preoperative ... [4]
Formatted: Bullets and Numbering

TABLE 4. Arm Pain

Period	Variable	Investigational	Control
Preoperative	n	18	15
	Mean	17.3	11.5
6 Weeks	n	18	15
	Mean	3.4	2.6
Improvement from Preoperative	Mean	13.9	8.9
	P value[1]	<0.001	<0.001
3 Months	n	17	15
	Mean	3.6	2.9
Improvement from Preoperative	Mean	14.1	8.5
	P value[1]	<0.001	<0.001
6 Months	n	17	13
	Mean	2.6	0.8
Improvement from Preoperative	Mean	14.8	10.0
	P value[1]	<0.001	<0.001
12 Months	n	15	14
	Mean	2.9	1.5
Improvement from Preoperative	Mean	14.5	9.7
	P value[1]	<0.001	<0.001
24 Months	n	14	12
	Mean	3.3	1.7
*Improvement from Preoperative	Mean	14.0	8.5
	P value[1]	<0.001	<0.001

[1] P values for change from preoperative in each group are from paired test.
Patients in both treatment groups experienced significant improvement in arm pain frequency and intensity.
* At 24 months, improvement was superior in the Investigational patients compared to Controls ($p < 0.03$, Student's t-test).

Deleted: <#>Weeks¶ ¶ ¶ Improvement from Preoperative¶ ¶ ¶ ... [5]
Formatted: Bullets and Numbering
Deleted: <#>Months¶ ¶ ¶ ¶ Improvement from Preoperative¶ ¶ ¶ ¶ ... [6]
Formatted: Bullets and Numbering
Deleted: <#> Months¶ ¶ ¶ ¶ Improvement from Preoperative¶ ¶ ¶ ¶ ... [7]
Formatted: Bullets and Numbering
Deleted: <#>Months¶ ¶ ¶ ¶ Improvement from Preoperative¶ ¶ ¶ ¶ ... [8]
Formatted: Bullets and Numbering

TABLE 5. SF-36

Period	Variable	Investigational	Control
Preoperative	n	16	15
PCS	Mean	31.7	32.6
MCS	Mean	32.4	42.5
6 Weeks	n	18	15
PCS	Mean	40.4	39.6
MCS	Mean	51.4	52.6
3 Months	n	16	15
PCS	Mean	44.4	44.6
MCS	Mean	48.4	47.6
6 Months	n	15	12
PCS	Mean	45.6	46.5
MCS	Mean	54.9	54.4
12 Months	n	15	14
PCS	Mean	45.7	48.7
MCS	Mean	54.1	50.4
24 Months	n	14	12
PCS	Mean	48.6	48.7
MCS	Mean	54.6	49.0

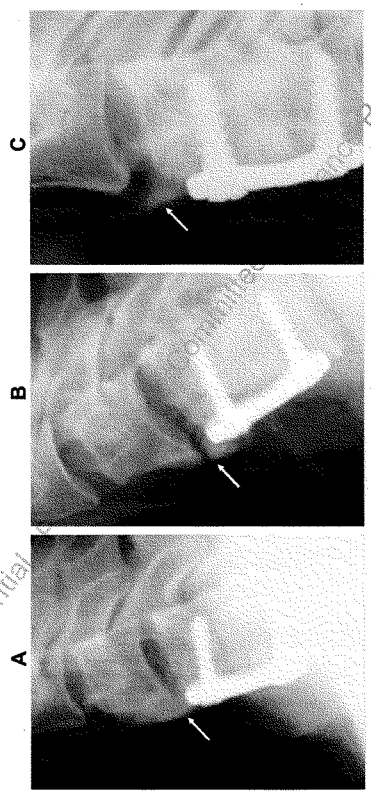
PCS = physical component score. MCS = mental component score
SF-36 is a measure of general physical and mental health. Note that both investigational and control patients improved in physical and mental health following surgery.

Deleted: 6 Weeks¶
... PCS¶
¶
¶
... MCS¶ ... [9]

Deleted: 3 Months¶
... PCS¶
¶
¶
... MCS¶ ... [10]

Deleted: 6 Months¶
... PCS¶
¶
¶
... MCS¶ ... [11]

Deleted: 12 Months¶
... PCS¶
¶
¶
... MCS¶ ... [12]



Page 24: [1] Deleted	widmayer		5/17/2002 3:19:00 PM
Weeks	n	18	15
	Mean	5.2	6.9
Improvement from Preoperative	Mean	10.9	7.4
	P value[1]	<0.001	<0.001
	Success	16/18 (89%)	10/15 (67%)

Page 24: [2] Deleted	widmayer		5/17/2002 3:19:00 PM
Months	n	17	15
	Mean	6.2	6.7
Improvement from Preoperative	Mean	10.6	7.6
	P value	<0.001	<0.001

Page 24: [3] Deleted	widmayer		5/17/2002 3:19:00 PM
Months	n	17	13
	Mean	4.6	4.1
Improvement from Preoperative	Mean	11.4	9.6
	P value	<0.001	<0.001

Page 24: [4] Deleted	widmayer		5/17/2002 3:19:00 PM
Months	n	15	14
	Mean	3.5	5.4
Improvement from Preoperative	Mean	12.1	8.6
	P value	<0.001	<0.001

Page 25: [5] Deleted	widmayer		5/17/2002 3:19:00 PM
Weeks	n	18	15
	Mean	3.4	2.6
Improvement from Preoperative	Mean	13.9	8.9
	P value[1]	<0.001	<0.001
	Success	16/18 (89%)	15/15 (100%)

Page 25: [6] Deleted	widmayer	5/17/2002 3:19:00 PM

Months	n	17	15
	Mean	3.6	2.90
Improvement from Preoperative	Mean	14.1	8.5
	P value[1]	<0.001	<0.001
	Success	16/17 (94%)	13/15 (87%)

Page 25: [7] Deleted widmayer 5/17/2002 3:19:00 PM

Months	n	17	13
	Mean	2.6	0.8
Improvement from Preoperative	Mean	14.8	10.0
	P value[1]	<0.001	<0.001

Page 25: [8] Deleted widmayer 5/17/2002 3:19:00 PM

Months	n	15	14
	Mean	2.9	1.5
Improvement from Preoperative	Mean	14.5	9.7
	P value[1]	<0.001	<0.001

Page 26: [9] Deleted widmayer 5/17/2002 3:19:00 PM

6 Weeks	n	18	15
PCS	Mean	40.5	39.7
	Success	13/16 (81%)	9/15 (60%)

Page 26: [10] Deleted widmayer 5/17/2002 3:19:00 PM

3 Months	n	16	15
PCS	Mean	44.6	44.7
	Success	14/14 (100%)	12/15 (80%)

Page 26: [11] Deleted widmayer 5/17/2002 3:19:00 PM

6 Months	n	15	12
PCS	Mean	45.8	46.7
	Success	11/13 (85%)	10/12 (83%)

Page 26: [12] Deleted widmayer 5/17/2002 3:19:00 PM

12 Months	n	15	14
PCS	Mean	45.9	48.9
	Success	12/13 (92%)	13/14 (93%)

August 27, 2002

Dr. James N. Weinstein
Editor-in-Chief
Spine
Dartmouth College
[redacted]
Hanover, NH 03755-3863

[redacted]

Dear Dr. Weinstein:

Enclosed is a revised original and three copies of the manuscript, *A Prospective, Randomized, Controlled Cervical Fusion Study using rhBMP-2 with the Cornerstone-SR™ Allograft Ring and the Atlantis™ Anterior Cervical Plate*. Where appropriate, I have made changes in the manuscript to address the reviewers' concerns, and a detailed description of these changes appears below.

Reviewer #1.

1. Reviewer #1 requested further explanation of the 100% fusion rate.

If the same criteria used in many publications were utilized in the present study, the success rate would likely be 91 – 97%, as seen in publications describing clinical practice (see refs). However, the criteria agreed upon by the sponsor and the FDA were different, and resulted in a 100% fusion rate. We have added a paragraph explaining this on page 15.

Reviewer #2.

1. Reviewer #2 pointed out that no trend analyses were done, and that references to trends in the text need to be removed.

We have removed these references. The 2-year follow-up data demonstrate statistically significant differences on two measures, which have been added to the text. However, we have also stated that the small sample size precludes concluding that one treatment is superior to the other.

Reviewer #3.

1. Reviewer #3 requests a 2-year follow-up period for publication in *Spine*.
   We now have 2-year follow-up data, which had been added to the manuscript.

Thank you again for your consideration of this manuscript. I look forward to its publication.

Sincerely,

David S. Baskin, M.D., F.A.C.S.
Corresponding Author
Professor of Neurosurgery
and Anesthesiology

REVIEWERS' COMMENTS

#1

I appreciate the changes the authors have made and believe they have more than accomplished their objective of demonstrating the efficacy of rh BMP-2 for at least one one year.

However, I am still unhappy with their explanation of the 100% fusion rate in both groups. Perhaps it reflects my inability to achieve such outstanding results. May I suggest possible explanations, at least as I see them:

1. The four surgeons involved are the best in the country.
   Corollary – they never had a bad result.
2. The four surgeons are very lucky.
3. The patient group was very carefully selected.
4. The numbers in each group are too small to accurately reflect a true non-fusion fusion rate.

Perhaps the authors could chose one or more of the above, unless there are other reasons. I think most people who do cervical spine surgery accept the fact that the anterior approach is good in properly selected patients, even without plating, especially in one level procedures.

The above comments are made, tongue in cheek. I've already said that this is a well done important piece of work. I know it's personal, but I'm unhappy about that 100% fusion rate and hope the authors will indulge me with more explanation.

#2

Spine A0217

The authors have presented the preliminary data relating to a randomized cervical fusion study using rhBMP-2. The manuscript has been revised and the issues are important. The journal is eager to have this preliminary data out for the readership. All the issues have been resolved except for one recurring theme. The authors continue to emphasize a trend in favor of the BMP throughout. Unless there is a critical trend analysis, trends remain non-statistical. Either there is inadequate power or there is "no" difference. I believe the authors should just relate the data and let the readership make their own conclusions. Consequently remove the trend sentence from the abstract, the key points, the precis, page 11 last paragraph, page 12 middle paragraph, page 13 first paragraph, and page 14 middle paragraph. This is an important first start but do not make claims that are not there. It weakens the credibility of the investigation.

#3

Reference: #A0217

The study design and manuscript preparation are outstanding, but I still have a criticism of short follow-up period. The author should read the article regarding the collaboration of SPINE and Journal of Spinal Disorders & Traumatology (see SPINE 2002:27;1253). I recommend that this excellent but premature study should be submitted to JSDT.

From: Neil Beals
Sent: Friday, August 30, 2002 01:22:55 PM
To: Mark Marchan
CC: Jim Van Hoeck; Missy Taylor; Bill McKay; Julie Bearcroft
Subject: FW: Revised BMP paper and response

comments attached FYI - I agree with Julie's comments

Neil

-----Original Message-----
From: Julie Bearcroft
Sent: Thursday, August 29, 2002 5:23 PM
To: Neil Beals
Subject: RE: Revised BMP paper and response

I have had a chance to read through this document and I would like to raise a couple issues. I realize that I may be sounding picky here but please hear me out...

--- #1 ---
On page 15, the authors report that fusion rates are expected to be 91 - 97% and that in this study they are 100%. They go on to comment that our criteria was not as conservative inferring that this is the reason for the hi rate. This argument does not align with our interpretation of the lumbar studies where the use of CT scans is considered to be a more critical fusion assessment tool compared to previous studies.

Furthermore, I had a chance to look up the reference cited (Kaiser et al.) for the lower fusion rates and it is unclear to me that our criteria are less conservative. In Kaiser's study, the authors report 91% success for 2-level fusions and 96% success for 1-level (a distinction that is not clear in this manuscript). The criteria used was "complete trabecular bridging of the graft-bone interface on static images and demonstration of lack of motion on dynamic images. Failure was diagnosed when a lucency was observed between the graft and vertebral endplate or when motion was detected across the treated segment." Is this different from our criteria?

Furthermore, the Kaiser study had 251 patients and this one had only 20 at 24 months. I think it is dangerous to directly compare these values and draw any conclusions as the authors have done. This is really a pilot and does simply demonstrate feasibility.

--- #2 ---
On page 16, the authors state, "In this regard, blood may serve as a sink to extract BMP from its carrier." This statement is much stronger than previous descriptions about the potential for blood clots to act as an exogenous carrier. I personally think the statement is too strong given our limited understanding about their relative affinity for BMP and the mechanism and kinetics of binding/release.

The authors go on to suggest that the use of drains may be helpful. Do we have a rationale for why this is suggested? Are drains typically used in cervical fusions?

--- #3 ---
last statement on page 17 should probably be modified - "Further clinical studies are underway to evaluation the safety and effectiveness of rhBMP-2 for this indication."

thoughts?
julie

-----Original Message-----
From: Neil Beals
Sent: Wednesday, August 28, 2002 4:33 PM
To: Mark Marchan
Cc: Julie Bearcroft
Subject: FW: Revised BMP paper and response
Importance: High

Mark,

I'll try to provide comments back to you in next day or so. Also, I would like for Julie Bearcroft to review briefly and provide her comments (time permitting).

Based upon a very brief review, it appears that very few, if any, of my comments provided on the draft manuscript back in March (email to Brad Winn on March 22) have been addressed in this paper. While those were provided on very short notice, I think it would be worthwhile to perhaps review those again (I'll probably end up repeating same comments in this review)

Neil

-----Original Message-----
From: Mark Marchan
Sent: Tuesday, August 27, 2002 3:25 PM
To: Neil Beals
Subject: FW: Revised BMP paper and response
Importance: High

Neil,

Attached is the latest revision of the Baskin BMP manuscript that has been submitted to *Spine*. I will need any of your comments ASAP so that they can get it resubmitted before Marsha goes on leave. Thanks.

Mark

-----Original Message-----

From: widmayer [SMTP[redacted]
Sent: Monday, August 26, 2002 1:46 PM
To: newt Metcalf; Mark Marchan
Subject: Revised BMP paper and response

Please run this by whomever needs to see it. I'll be in tomorrow, and then will be out for 10 days for medical reasons. I'll do whatever I can to get it submitted tomorrow. I've included the paper, response letter and reviewer's comments.

THANKS!!!

Marsha A. Widmayer
Department of Neurosurgery
Baylor College of Medicine
[redacted]
Houston, TX 77030

[redacted]<< File: Resubmission Cervical BMP Paper 082302.doc >> << File: Response letter 2.doc >> << File: Rev 1.jpg >>

From: Neil Beals
Sent: Friday, August 30, 2002 01:23:35 PM
To: Mark Marchan
CC: Julie Bearcroft; Jim Van Hoeck; Bill McKay; Missy Taylor
Subject: FW: Revised BMP paper and response

Attachments: Resubmission Cervical BMP Paper 082902.doc; Resubmission Cervical BMP Paper 082302.doc; Response letter 2.doc; Rev 1.jpg

Mark,

I have included some comments in attached paper.

Some other general comments:

- Reference to INFUSE is confusing; it is combination of rhbmp2 and acs, not just rhbmp2 (important to recognize the role and importance of the carrier)
- reference to "graft" throughout paper is somewhat confusing (at least to me) - graft is referenced as the autograft (which we should specify as iliac crest) and the allograft construct (Cornerstone construct); you may want to clarify in some wording
- I read comments from reviewer (#2) and understand his sensitivity to reading too much into this small series but he does indicate to just present the data and let reader decide which I totally agree with

  after looking at data again, I would suggest showing it in graph form and comparing outcome (NDI, neck pain, arm pain, SF-36 MCS, SF-36 PCS) by noting change from preop ; the starting scores were different for the 2 groups and by showing change from pre-op, it will normalize results and provide better comparison(and INFUSE group looks pretty impressive); also graph forms would be better to interpret

- I would also add in more discussion on donor site pain and need for osteogenic graft material (plant seed of doubt for just using allograft by itself)
- what are implications of this study vs other ACDF procedures? e.g., use of tri-cortical autograft instead of allograft construct? will donor site pain be greater?

Neil

-----Original Message-----
From: Mark Marchan
Sent: Tuesday, August 27, 2002 3:25 PM
To: Neil Beals
Subject: FW: Revised BMP paper and response

Importance: High

Neil,

Attached is the latest revision of the Baskin BMP manuscript that has been submitted to *Spine*. I will need any of your comments ASAP so that they can get it resubmitted before Marsha goes on leave. Thanks.

Mark

-----Original Message-----
From: widmayer [SMTP[redacted]
Sent: Monday, August 26, 2002 1:46 PM
To: newt Metcalf; Mark Marchan
Subject: Revised BMP paper and response

Please run this by whomever needs to see it. I'll be in tomorrow, and then will be out for 10 days for medical reasons. I'll do whatever I can to get it submitted tomorrow. I've included the paper, response letter and reviewer's comments.

THANKS!!!

Marsha A. Widmayer
Department of Neurosurgery
Baylor College of Medicine
[redacted]
Houston, TX 77030
[redacted]

A Prospective, Randomized, Controlled Cervical Fusion Study using rhBMP-2 with the CORNERSTONE-SR™ Allograft Ring and the ATLANTIS™ Anterior Cervical Plate

David S. Baskin, M.D.*†
Patrick Ryan, M.D.‡
Volker Sonntag, M.D.§
Richard Westmark, M.D.‖
Marsha A. Widmayer, M.A.*

* Departments of Neurosurgery and †Anesthesiology, Baylor College of Medicine, and *Veterans Affairs Medical Center, Houston, TX

‡Jackson Hospital, Montgomery, AL

§Division of Neurological Surgery, Barrow Neurological Institute, and St. Joseph's Hospital and Medical Center, Phoenix, AZ

‖Clear Lake Regional Medical Center, Webster, TX

Corresponding author: David S. Baskin, M.D.
Department of Neurosurgery
Baylor College of Medicine
[redacted]
Houston, TX 77030

[redacted] (voice)
(fax)
[redacted] (email)

This research was sponsored by Medtronic Sofamor Danek.

ABSTRACT

Study Design: A prospective, randomized, pilot clinical trial was performed comparing recombinant human bone morphogenetic protein (rhBMP-2) with autograft bone for the treatment of human cervical disc disease.

Objective: To examine the safety of using INFUSE Bone Graft (rhBMP-2 applied to an absorbable collagen sponge) compared to autogenous bone graft inside the CORNERSTONE-SR™ fibular allograft in anterior cervical discectomy and interbody fusion. NOTE ALSO IN PLATED PROCEDURES

Summary of Background Data: rhBMP-2 is an osteoinductive protein that induces a reliable fusion in the lumbar spine, but it has not been studied in patients with degenerative cervical disc disease.

METHODS: Thirty-three patients with degenerative cervical disc disease were randomly assigned to investigational or control groups. The investigational group received a fibular allograft (CORNERSTONE-SR™) with an rhBMP-2-laden collagen carrier, inside the graft, with an ATLANTIS™ anterior cervical plate. The control group received a fibular allograft with cancellous iliac crest autograft placed inside of it, with an ATLANTIS™ anterior cervical plate.

Patients underwent plain x-rays at 6 weeks and at 3, 6, 12, and 24 months, and CT scans at 3 and 6 months postoperatively, and completed general health profiles and self-evaluation scales. Adverse events were evaluated for severity, duration, association with the implant, and the need for a second surgical procedure.

Deleted: in

Deleted: (ACS)

Deleted: ACS

RESULTS: All patients had solid fusions at 6, 12 and 24 months after surgery. There were no device related adverse events. At 24 months the investigational patients had significantly better improvement in Neck Disability and Arm Pain than did the controls. **CONCLUSIONS:** This pilot study demonstrates the feasibility of using rhBMP-2 safely and effectively in the cervical spine.

Key words: anterior cervical fusion, bone morphogenetic protein, osteoinduction, radiography, allograft, anterior cervical plating

Key points:

- The fusion rates for all control and investigational groups were 100% at 6, 12 and 24 months postoperative.
- There were no device related adverse events.
- Investigational and control groups both had significant improvement in neck disability and in neck and arm pain following surgery.
- Investigational patients had statistically significant improvement in Neck Disability and Arm Pain compared to controls, although the small sample size precludes concluding that the investigational treatment is superior.
- The use of rhBMP-2 in anterior cervical fusion procedures eliminates the pain, scarring, and morbidity of iliac crest bone harvesting.

Précis

A prospective, randomized, trial compared rhBMP-2 to autograft in anterior cervical fusions. Successful fusion occurred in 100% of the patients. Investigational patients had better results than controls in several outcome measures. Investigational group patients required no iliac crest graft harvest, and therefore experienced no graft site pain or complications.

INTRODUCTION

Anterior cervical discectomy and fusion is an effective and extensively practiced treatment for degenerative cervical disc disease. Smith and Robinson (11), and Cloward (2) first described the technique in the 1950's. Initially, autogenous bone, typically harvested from the iliac crest, was used for the interbody graft. The procedure has developed to include alternatives to autograft; allograft and interbody fusion devices avoid the pain, scarring, and morbidity associated with autograft harvest, yet maintain high fusion rates. Anterior cervical plating has become an accepted component of the procedure, as it has been shown to provide immediate stability, maintain sagittal alignment, and increase the fusion rate (10,12).

Recombinant human bone morphogenetic protein-2 (rhBMP-2) has been shown to initiate osteoinduction and achieve spinal arthrodesis in a non-human primate model (5,9). The application of rhBMP-2 in humans has been explored in a lumbar fusion indication. Human clinical studies have demonstrated that patients treated with rhBMP-2, when soaked onto an absorbable collagen sponge and placed into the central cavity of the LT-CAGE™ interbody fusion device, had consistent and clear osteoinduction (1,7).

The use of rhBMP-2 in an anterior cervical fusion application was previously unexplored. The authors took part in a prospective, randomized, controlled clinical trial in which rhBMP-2 was compared to autograft as an interbody graft filler. A total of 33 patients suffering from 1 or 2-level cervical disc disease were enrolled into the study and have been followed to 2 years postoperatively. Clinical and radiographic

comparisons have been made between the 2 treatments groups at the 6 week, 3 month, 6 month, 1 year and 2 year postoperative intervals.

MATERIALS AND METHODS

Study Design. Between September 1999 and May 2000, 33 patients were enrolled in this prospective, randomized, controlled FDA approved pilot clinical trial. The clinical trial was conducted at 4 investigational centers in the United States. All patients enrolled into the study met the prescribed inclusion/exclusion criteria and signed an informed consent. The patients were randomized into their treatment group on a 1:1 basis. After randomization, neither the surgeon nor the patient was blinded to the treatment. All patients received a standard 1 or 2 level anterior cervical discectomy and the disc spaces were prepared for a Smith-Robinson style interbody allograft (in this study, a CORNERSTONE-SR™ Allograft Ring, Regeneration Technologies Incorporated, Alachua, FL) AND ATLANTIS PLATE. At this point the interbody allografts were prepared according to the patient's treatment randomization (see surgical technique).

Patient Data. Preoperatively, all patients suffered from one or two levels of cervical disc disease producing radiculopathy and/or myelopathy. Preoperative imaging studies demonstrated herniated disc and/or posterior osteophyte formation at the involved level(s). All patients underwent a minimum of 6 weeks of conservative therapy prior to surgery, unless symptoms progressed to require surgery earlier. The investigational and control treatment groups were very similar, and did not significantly differ in any of

the demographic parameters measured. Eighteen patients were enrolled in the investigational group and 15 patients in the control group. Mean age was 51.3 years (investigational) or 47.1 years (control). Mean weight was 169.6 pounds (investigational) or 173.7 pounds (control). Eight of 18 (44%) investigational patients were male, and 7 of 15 (47%) control patients were male. Tobacco was used by 5 of 18 investigational patients and by 7 of 15 control patients.

Clinical and Radiographic Outcome Measurements. Patients were evaluated clinically and radiographically preoperatively, immediately postoperatively, and at 6 weeks, and 3, 6, 12 and 24 months postoperative. The clinical outcome measures were neurological status, the Neck Disability Index, the SF-36, Neck, Arm, and Graft Site pain visual analog scales, and patient satisfaction questionnaires.

Dynamic flexion/extension x-rays were used to determine fusion status at 6 weeks and 3, 6, 12 and 24 months postoperative. CT scans were used at 3 and 6 months postoperatively to further assess fusion status WHAT ABOUT 12 AND 24 MONTHS?. Two independent, blinded radiologists reviewed all x-rays and CT scans. A third independent, blinded radiologist was used to resolve conflicting fusion findings. Fusion was defined as less than 4 degrees difference in angular motion between flexion and extension as seen on lateral flexion extension radiographs, no radiolucency greater than 2 mm in thickness covering more than 50% of the superior or inferior surface of the graft(s) and evidence of bridging trabecular bone seen on radiographs and CT scans.

Clinical and Radiographic Follow-up. The rate of patient return for follow-up was high at all postoperative periods. Three investigational and one control patient were lost to follow-up at 24 months. Of the patients not lost to follow-up, the rate of patient return at 24 months for the investigational group was 86% and for the control group was 85%. The follow-up rate did not drop below 85% at any postoperative interval.

Antibody Assessment. Patient blood samples were collected preoperatively and at 3 months postoperatively to determine titers for antibodies against rhBMP-2 and against the bovine Type 1 collagen in the sponge. A patient was considered to have an authentic elevated immune response if the preoperative sample for a patient was negative (titer < 50) while the postoperative sample was positive (titer ≥ 50), or if the preoperative sample was positive and the postoperative sample was 3-fold higher than the preoperative titer.

Surgical Technique. All patients received the standard ACDF procedure. Patients were placed in the supine position on the operating room table. A transverse incision was made over the cervical spine. An avascular dissection plane was developed between the trachea and esophagus medially and the carotid sheath laterally. After the anterior vertebral column was exposed, the longus colli muscles were elevated, and retraction was achieved via self-retaining retractors placed underneath the longus colli muscles. The appropriate level(s) were identified radiographically. Vertebral body distraction was often applied at this time. A discectomy and/or osteophytectomy was then completed to achieve neural decompression.

The disc space was then prepared for the interbody graft. A parallel cavity was made for the graft by shaping the end plates with a high-speed drill. The extent of endplate and bone removal was left to the discretion of the individual surgeon. Sizing trial tools were used to determine the appropriate graft size to select. For investigational patients, once the appropriate size of allograft was determined, the central cavity of the allograft was then filled with rhBMP-2. The carrier matrix was prepared to a concentration of 1.5 mg/ml rhBMP-2 (InFUSE™ Bone Graft; Medtronic Sofamor Danek, Memphis, TN) INFUSE BONE GRAFT IS RHBMP2 AND ACS NOT JUST THE PROTEIN by reconstituting with 3.2 ml sterile water. Then, 0.4 ml reconstituted rhBMP-2 solution was uniformly distributed on a 1.5 cm x 2.5 cm piece of collagen sponge. The sponge was allowed to soak for 15 minutes and then was placed inside the fibular allograft, which was gently tapped into the prepared disc space for each level fused. Irrigation after implantation was contraindicated. MAYBE WORTHWHILE TO ALSO NOTE OTHER PROTOCOL RESTRICTIONS (E.G., NO GELFOAM, NO ELECTRICAL STIM, NO ADCON-L, ETC)

Deleted: high-speed drill was utilized to create a

For patients in the control group, a small incision was made over the iliac crest, and blunt dissection was performed to expose the crest. A trephine was then used to take a core of cancellous bone, which was then packed into the central cavity of the allograft. The filled allograft was then gently tapped into the prepared disc space. For two level cases, the second disc space and interbody graft were prepared using the same method.

All patients received an appropriately sized anterior cervical plate (ATLANTIS™ Anterior Cervical Plate; Medtronic Sofamor Danek, Memphis, TN) to provide increased

stability to the construct. The plate construct utilized either all fixed angle screws, all variable angle screws, or a hybrid construct using both fixed angle and variable angel screws. The screws were secured by an attached locking mechanism, which was engaged after final screw seating. The appropriate placement of the construct was then confirmed radiographically.

A postoperative regimen that prohibited bone growth stimulators, and recommended against steroids, athletic activities, lifting and bending was recommended. Postoperative bracing requirements were left to the discretion of the individual surgeons.

RESULTS

As there were no differences in preoperative, operative, or outcome variables between the one-level and the two-level patients, their data was combined to form two treatment groups, investigational and control.

Surgery Information. One level arthrodesis was performed on 10 of 18 (56%) investigational patients, and eight of 15 (53%) control patients. The remaining patients received two level arthrodesis. Mean operative time for investigational and control groups was 1.8 hours each. Mean blood loss was 91.4 mL for investigational and 123.3 mL for control patients (N.S.). Mean hospital stay was 1.4 days (investigational) or 1.1 days (control) (N.S.). There were no unanticipated device-related adverse events in either treatment group.

Graft Site REFER TO AS DONOR SITE?

The level of postoperative pain and morbidity associated with the iliac crest graft harvesting was measured using numeric rating scales for pain intensity and duration. At discharge and 6 weeks after surgery, control patients had significantly high levels of pain at the graft site ($p < 0.007$, student's t - test) and complained about the appearance of the graft site. By 12 months after surgery, the patients graft-site pain had resolved ($p < 0.165$) and no patients complained about the graft-site appearance. ALTHOUGH THE PATIENTS DID NOT COMPLAIN ABOUT APPEARANCE DIDN'T SOME STILL EXPERIENCE PAIN AT DONOR SITE? SEEMS LIKE RESIDUAL EFFECTS OF DONOR SITE SHOULD BE NOTED

Antibody Production

No patients produced detectable antibodies to the rhBMP-2. One investigational and one control patient had elevated titers to bovine Type 1 collagen at 3 months. These patients were not positive for antibodies to human Type 1 collagen.

Clinical Outcomes

Neck Disability Index Questionnaire scores. The Neck Disability Index (NDI) Questionnaire measures cervical pain and disability associated with activities of daily living. The NDI questionnaire was administered preoperatively and at each postoperative interval. At all postoperative intervals, both treatment groups demonstrated statistical improvement compared with their preoperative scores (Table 1).

The investigational group demonstrated superior mean improvement than the control group at 24 months ($p < 0.03$), although this group began with slightly worse NDI preoperatively than did controls.

Neurologic Status. Neurologic status of the patients was determined by evaluating motor and sensory function. Values for each of the subsets of objective findings were totaled and expressed as a percentage of the maximum possible score. Measurements were then compared with the patient's preoperative score. Neurologic success was based on demonstrating maintenance or improvement in both subsets. At 24 months after surgery, the overall neurologic success rate for each group was 100% (Table 2).

Neck Pain. Neck pain frequency and intensity were measured using a 20-point numeric rating scale. Adding the numeric rating scores for neck pain frequency and intensity created a composite neck pain score (Table 3). The mean neck pain scores at all postoperative periods were improved from the preoperative mean values for both treatment groups. At 24 months the mean change was 13 points for the Investigational group and 9 points for the control group, which was not statistically significant ($p < 0.055$).

Neck pain success on an individual patient basis was determined by comparing the postoperative score with the preoperative score. Success was based on the patient having at least a 3-point improvement in neck pain score after surgery (Table 3). At 24 months after surgery, the overall neck pain success rate for each group was 100%.

Arm Pain. Arm pain was also assessed using a numeric rating scale for both the frequency and intensity of the pain. Mean arm pain scores improved significantly after surgery in both treatment groups (Table 4). At all postoperative intervals, both

treatment groups demonstrated statistical improvement compared with their preoperative scores (Table 4). Furthermore, the investigational group had superior mean improvement than the control group at 24 months ($p < 0.03$), although the investigational group began with slightly worse Arm Pain preoperatively than did controls.

Arm pain success was defined according to the following algorithm. If a patient had a preoperative pain score of 10 points or more, success was defined as a 3-point improvement on his or her postoperative scores. In those patients who had preoperative arm pain scores of less than 10 points, success was defined as maintenance or improvement in scores when compared with their preoperative condition.

General Health. The SF-36 questionnaire was used to measure the patients' general health status. The SF-36 questionnaire was administered preoperatively and at each postoperative interval. The SF-36 was analyzed according to its physical (PCS) and mental (MCS) components. The investigational group showed similar mean improvement to the control group at all postoperative intervals in both the PCS and MCS (Table 5). At 24 months, the mean improvements in the PCS and MCS scores were 16.7 points and 21.8 points, respectively, for the investigational group. The control group showed a mean improvement of 14.7 points in the PCS and an improvement of 7.2 in the MCS at 24 months postoperative.

SF-36 success was defined as maintenance or improvement in scores when compared to preoperative scores. At 24 months postoperative, the investigational

group success rates for the PCS and MCS were 92% each. The control group success rates for the PCS and MCS were 100% and 75% respectively at the 24-month interval.

Patient Satisfaction. Patient satisfaction was assessed by three questions inquiring whether the patients were satisfied with the results, were helped as much as they thought they would be, and whether they would have the surgery again for the same condition. At the 24-month postoperative interval, greater than 90% of each group responded favorably for each of the three questions.

Radiographic Outcomes. Fusion status of the study patients was evaluated with lateral flexion and extension radiographs and CT scans. Fusion was based on evidence of bridging bone, angular motion stability, and lucent line criteria (see methods for exact criteria). At 6, 12 and 24 months postoperative, 100% of the patients in both the investigational and the control group that were not lost to follow-up were deemed fused (6 months investigational 15/15 = 100%, control 13/13 = 100%, 12 months 14/14 investigational = 100%, 12/12 control = 100%, 24 months 10/10 investigational, 10/10 control).

Two patients in the investigational group and one patient in the control group demonstrated bone formation immediately anterior to segments adjacent to the treated level. This ossification became clearly visible on the 12 month postoperative x-rays (Fig.1). All 3 patients were treated by the same surgeon.

Secondary Surgical Procedures. One patient in the investigational group required surgical intervention at an adjacent segment to the original two-level fusion. The surgery was unrelated to the original procedure. However, to perform the operation the anterior cervical plate was removed. No other subsequent cervical procedures were performed.

DISCUSSION

This pilot study is the first prospective, randomized clinical evaluation of rhBMP-2 for a cervical spine fusion indication. The primary purpose of this pilot study was to assess the feasibility of using rhBMP-2 in an anterior cervical fusion application. Both groups showed significant postoperative improvement in neck disability and in neck and arm pain and both groups had fusion rates of 100%. The investigational group also avoided the pain and morbidity of iliac crest graft harvest. rhBMP-2 treatment was at least equally successful compared to the use of autograft bone. On some measures, rhBMP-2 provided superior improvement to standard autograft bone I WOULD POINT OUT SPECIFIC DATA THAT SHOWED SUPERIORITY OF INFUSE, E.G., NDI AND ARM PAIN WHICH IS IMPRESSIVE GIVEN THE SMALL SAMPLE SIZE, although the small sample size precludes concluding superiority of treatment.

Generally, a 91 – 97% cervical fusion rate can be expected when spinal instrumentation is used (6). However, in the present study, all radiographs beginning at the 6-month follow-up indicated successful fusion. The fusion rate in the present study is likely due to the fusion criteria utilized. Fusion was defined as less than 4 degrees difference in angular motion between flexion and extension, no radiolucency greater

than 2 mm in thickness covering more than 50% of the superior or inferior surface of the graft(s), and evidence of bridging trabecular bone seen on radiographs and CT scans. While some might use more conservative criteria, these criteria were adopted following discussions with the FDA and were applied equally across treatment groups.

In the current study, the Investigational group received rhBMP-2 together with allograft bone. There is a small risk of disease transmission associated with the use of allograft bone (3). In our opinion, this risk is outweighed by the elimination of bone harvesting surgery and its associated morbidity.

Recombinant human bone morphogenetic protein is an osteoinductive growth factor that stimulates stem cells to form bone (13). A number of animal and human studies have been conducted to evaluate the effectiveness of this substance in promoting spinal fusion, and in many cases, the success rate and quality or quantity of the fusion mass has been superior to autograft (see 4, 8 for reviews).

Anterior bone formation in immediately adjacent segments was demonstrated in two investigational and one control patient. As this occurred in both groups, and the same surgeon treated all three patients, the ossification may be technique related. Furthermore, the general incidence of anterior bone formation in immediately adjacent segments is unknown, and has been observed anecdotally by a number of experienced spine surgeons using standard allograft and autograft constructs. The pathophysiology of spondylosis relates to disc degeneration and segmental instability, to which the response is overgrowth of ligament and bone. It may be that in these cases and in others like them, the adjacent disc and/or facets are already degenerated, and that fusion accelerates the spondylitic process, which includes bony growth.

Deleted: . In this study, the investigational group received rhBMP-2 soaked onto an absorbable collagen sponge and placed into the central cavity of an allograft ring. At 6 and 12 months postoperative, the investigational group was determined to have a fusion rate of 100% by two independent blinded radiologists.¶

The presence of blood and surgical trauma may be associated with ectopic bone formation, and are also factors to consider. In this regard, blood may serve as a sink to extract BMP from its carrier. Meticulous hemostasis and use of drains will be important aspects of technique to consider when using rhBMP-2 in all spinal applications, despite the fact that evidence is lacking in this study to implicate rhBMP-2 as the cause of adjacent segment anterior bone overgrowth.

rhBMP-2 has been shown in clinical trials to be safe and effective when used in a lumbar interbody fusion application (1,7). The use of rhBMP-2 is associated with high fusion rates without the need for harvesting bone from the iliac crest, avoiding the pain and morbidity of that procedure. This pilot study demonstrates that the use of rhBMP-2 in an anterior cervical fusion application is sufficiently safe to study its use in a larger clinical trial. Further clinical studies are underway to evaluate the safety and effectiveness of rhBMP-2 for this indication.

WHY ISN'T THERE A CONCLUSIONS SECTION? IT WOULD BE NICE PLACE TO POINT OUT HIGHLIGHTS AND TAKEHOMES

ACKNOWLEDGEMENTS

This research was sponsored by Medtronic Sofamor Danek. The authors thank Newt Metcalf, Missy Taylor and Mark Marchan for the important role they played in the creation of this manuscript.

REFERENCES

1. Boden SD, Zdeblick TA, Sandhu HS, et al. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25:376-81.

2. Cloward RB. The anterior approach for removal of rupture cervical disks. J Neurosurg 1958;15:601-617.

3. Hardin CK. Banked bone. Otolaryngol Clin North Am 1994; 27:911-925.

4. Harvinder S, Sandhu MD. Anterior lumbar interbody fusion with osteoinductive growth factors. Clin Orthop 2000; 2000:56-60.

5. Hecht BP, Fischgrund JS, Herkowitz HN, et al. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999; 24:629-36.

6. Kaiser MG, Haid RW Jr, Subach BR, Barnes B, Rodts GE Jr: Anterior cervical plating enhances arthrodesis after discectomy and fusion with cortical allograft. Neurosurgery 2002; 50:229-236.

7. Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2. A prospective study of clinical and radiographic outcomes. Spine 2001; 26:2751-2756.

8. Ludwig SC, Kowalski JM, Boden SD. Osteoinductive bone graft substitutes. Eur Spine J 2000; 9:S119-125.

9. Martin GJ Jr, Boden SD, Marone MA, et al. Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: important lessons learned regarding dose, carrier, and safety. J Spinal Disord. 1999; 12:179-186.

10. Schulte K, Clark CR, Goel VK. Kinematics of the cervical spine following discectomy and stabilization. Spine 1989; 14:1116-1121.

11. Smith GW, Robinson RA. The treatment of certain cervical spinal disorders by anterior removal of the intervertebral disc and interbody fusion. J Bone Joint Surg 1958; 40:607-624.

12. Spivak JM, Balderston RA. Spinal instrumentation. Curr Opin Rheumatol 1994; 6:187-94.

13. Urist MR. Bone: Formation by autoinduction. Science 1965; 150:893-899.

Figure Legend

Figure 1. Twelve Month Postoperative Lateral X-rays.

Panel A - Investigational Patient #2.

Panel B - Control Patient #6.

Panel C - Investigational Patient #9.

Note the formation of anterior bone in segments immediately adjacent to the fused vertebra in these three patients (white arrows).

TABLE 1 – Neck Disability Index Scores

Period	Variable	Investigational	Control
Preoperative			
	n	18	15
	Mean	61.3	55.4
6 Weeks			
	n	18	15
	Mean	23.9	22.8
Improvement from Preoperative	Mean	37.4	32.6
	P value[1]	<0.001	<0.001
3 Months			
	n	17	15
	Mean	21.3	21.9
Improvement from Preoperative	Mean	39.2	33.5
	P value	<0.001	<0.001
6 Months			
	n	17	13
	Mean	12.9	13.4
Improvement from Preoperative	Mean	47.8	38.8
	P value	<0.001	<0.001
12 Months			
	n	15	14
	Mean	16.3	12.3
Improvement from Preoperative	Mean	45.7	40.8
	P value	<0.001	<0.001
24 Months			
	n	14	12
	Mean	10.1	14.5
*Improvement from Preoperative	Mean	52.7	36.9
	P value	<0.001	<0.001

[1] P values for change from preoperative in each group are from paired T-tests
Patients in both treatment groups experienced significant improvement in neck disability following surgery.
* At 24 months, improvement was superior in the Investigational patients compared to Controls ($p < 0.03$, Student's t-test).

TABLE 2. Neurologic Outcomes

Period	Variable	Investigational n (%)	Control n (%)
6 Weeks			
	Success	17 (94)	15 (100)
	Failure	1 (6)	0 (0)
3 Months			
	Success	18 (100)	15 (100)
	Failure	0 (0)	0 (0)
6 Months			
	Success	15 (88)	13 (100)
	Failure	2 (12)	0 (0)
12 Months			
	Success	15 (100)	13 (93)
	Failure	0 (0)	1 (7)
24 Months			
	Success	14 (100)	12 (100)
	Failure	0 (0)	0 (0)

Patients in both treatment groups maintained or improved in motor function, sensory function and reflexes, indicating successful neurologic outcome.

TABLE 3. Neck Pain

Period	Variable	Investigational	Control
Preoperative	n	18	15
	Mean	16.1	14.3
6 Weeks	n	18	15
	Mean	5.2	6.9
Improvement from Preoperative	Mean	10.9	7.4
	P value[1]	<0.001	<0.001
3 Months	n	17	15
	Mean	6.2	6.7
Improvement from Preoperative	Mean	10.6	7.6
	P value	<0.001	<0.001
6 Months	n	17	13
	Mean	4.6	4.1
Improvement from Preoperative	Mean	11.4	9.6
	P value	<0.001	<0.001
12 Months	n	15	14
	Mean	3.5	5.4
Improvement from Preoperative	Mean	12.1	8.6
	P value	<0.001	<0.001
24 Months	n	14	12
	Mean	2.8	5.3
Improvement from Preoperative	Mean	13.0	9.0
	P value	<0.001	<0.001

[1] P values for change from preoperative in each group are from paired T-test.
Patients in both treatment groups experienced significant improvement in neck pain frequency and intensity. At 24 months the difference between groups in improvement approached statistical significance ($p < 0.055$)

Deleted: <#>Weeks¶ ¶ ¶ ¶ Improvement from Preoperative¶ ¶ ¶ ... [1]
Formatted: Bullets and Numbering

Deleted: <#>Months¶ ¶ ¶ ¶ Improvement from Preoperativ ... [2]
Formatted: Bullets and Numbering

Deleted: <#>Months¶ ¶ ¶ ¶ Improvement from Preoperativ ... [3]
Formatted: Bullets and Numbering

Deleted: <#>Months¶ ¶ ¶ ¶ Improvement from Preoperativ ... [4]
Formatted: Bullets and Numbering

TABLE 4. Arm Pain

Period	Variable	Investigational	Control
Preoperative	n	18	15
	Mean	17.3	11.5
6 Weeks	n	18	15
	Mean	3.4	2.6
Improvement from Preoperative	Mean	13.9	8.9
	P value[1]	<0.001	<0.001
3 Months	n	17	15
	Mean	3.6	2.9
Improvement from Preoperative	Mean	14.1	8.5
	P value[1]	<0.001	<0.001
6 Months	n	17	13
	Mean	2.6	0.8
Improvement from Preoperative	Mean	14.8	10.0
	P value[1]	<0.001	<0.001
12 Months	n	15	14
	Mean	2.9	1.5
Improvement from Preoperative	Mean	14.5	9.7
	P value[1]	<0.001	<0.001
24 Months	n	14	12
	Mean	3.3	1.7
*Improvement from Preoperative	Mean	14.0	8.5
	P value[1]	<0.001	<0.001

[1] P values for change from preoperative in each group are from paired test.
Patients in both treatment groups experienced significant improvement in arm pain frequency and intensity.
* At 24 months, improvement was superior in the Investigational patients compared to Controls ($p < 0.03$, Student's t-test).

Deleted: <#>Weeks¶ ¶ ¶ ¶ Improvement from Preoperative¶ ¶ ¶ ... [5]
Formatted: Bullets and Numbering
Deleted: <#>Months¶ ¶ ¶ ¶ Improvement from Preoperative¶ ¶ ¶ ¶ ... [6]
Formatted: Bullets and Numbering
Deleted: <#> Months¶ ¶ ¶ ¶ Improvement from Preoperative¶ ¶ ¶ ¶ ... [7]
Formatted: Bullets and Numbering
Deleted: <#>Months¶ ¶ ¶ ¶ Improvement from Preoperative¶ ¶ ¶ ¶ ... [8]
Formatted: Bullets and Numbering

TABLE 5. SF-36

Period	Variable	Investigational	Control
Preoperative	n	16	15
PCS	Mean	31.7	32.6
MCS	Mean	32.4	42.5
6 Weeks	n	18	15
PCS	Mean	40.4	39.6
MCS	Mean	51.4	52.6
3 Months	n	16	15
PCS	Mean	44.4	44.6
MCS	Mean	48.4	47.6
6 Months	n	15	12
PCS	Mean	45.6	46.5
MCS	Mean	54.9	54.4
12 Months	n	15	14
PCS	Mean	45.7	48.7
MCS	Mean	54.1	50.4
24 Months	n	14	12
PCS	Mean	48.6	48.7
MCS	Mean	54.6	49.0

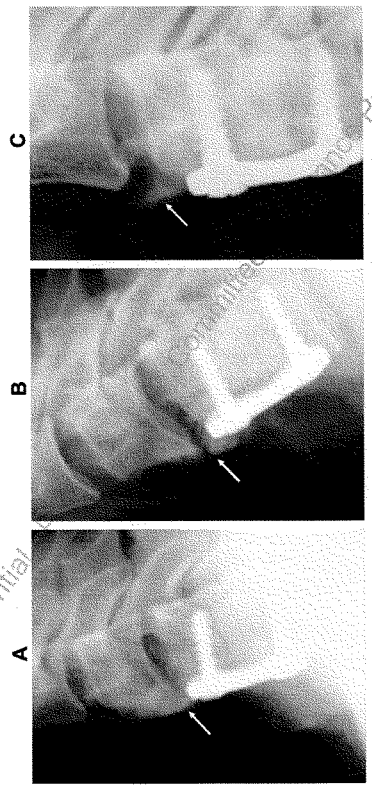
PCS = physical component score. MCS = mental component score
SF-36 is a measure of general physical and mental health. Note that both investigational and control patients improved in physical and mental health following surgery.

Deleted: 6 Weeks¶ - PCS¶ ¶ ¶ - MCS¶ ... [9]

Deleted: 3 Months¶ - PCS¶ ¶ ¶ - MCS¶ ... [10]

Deleted: 6 Months¶ - PCS¶ ¶ ¶ - MCS¶ ... [11]

Deleted: 12 Months¶ - PCS¶ ¶ ¶ - MCS¶ ... [12]



Page 25: [1] Deleted	widmayer	5/17/2002 3:19:00 PM	
Weeks	n	18	15
	Mean	5.2	6.9
Improvement from Preoperative	Mean	10.9	7.4
	P value[1]	<0.001	<0.001
	Success	16/18 (89%)	10/15 (67%)

Page 25: [2] Deleted	widmayer	5/17/2002 3:19:00 PM	
Months	n	17	15
	Mean	6.2	6.7
Improvement from Preoperative	Mean	10.6	7.6
	P value	<0.001	<0.001

Page 25: [3] Deleted	widmayer	5/17/2002 3:19:00 PM	
Months	n	17	13
	Mean	4.6	4.1
Improvement from Preoperative	Mean	11.4	9.6
	P value	<0.001	<0.001

Page 25: [4] Deleted	widmayer	5/17/2002 3:19:00 PM	
Months	n	15	14
	Mean	3.5	5.4
Improvement from Preoperative	Mean	12.1	8.6
	P value	<0.001	<0.001

Page 26: [5] Deleted	widmayer	5/17/2002 3:19:00 PM	
Weeks	n	18	15
	Mean	3.4	2.6
Improvement from Preoperative	Mean	13.9	8.9
	P value[1]	<0.001	<0.001
	Success	16/18 (89%)	15/15 (100%)

Page 26: [6] Deleted	widmayer	5/17/2002 3:19:00 PM

Months	n	17	15
	Mean	3.6	2.90
Improvement from Preoperative	Mean	14.1	8.5
	P value[1]	<0.001	<0.001
	Success	16/17 (94%)	13/15 (87%)

Page 26: [7] Deleted widmayer 5/17/2002 3:19:00 PM

Months	n	17	13
	Mean	2.6	0.8
Improvement from Preoperative	Mean	14.8	10.0
	P value[1]	<0.001	<0.001

Page 26: [8] Deleted widmayer 5/17/2002 3:19:00 PM

Months	n	15	14
	Mean	2.9	1.5
Improvement from Preoperative	Mean	14.5	9.7
	P value[1]	<0.001	<0.001

Page 27: [9] Deleted widmayer 5/17/2002 3:19:00 PM

6 Weeks	n	18	15
PCS	Mean	40.5	39.7
	Success	13/16 (81%)	9/15 (60%)

Page 27: [10] Deleted widmayer 5/17/2002 3:19:00 PM

3 Months	n	16	15
PCS	Mean	44.6	44.7
	Success	14/14 (100%)	12/15 (80%)

Page 27: [11] Deleted widmayer 5/17/2002 3:19:00 PM

6 Months	n	15	12
PCS	Mean	45.8	46.7
	Success	11/13 (85%)	10/12 (83%)

Page 27: [12] Deleted widmayer 5/17/2002 3:19:00 PM

12 Months	n	15	14
PCS	Mean	45.9	48.9
	Success	12/13 (92%)	13/14 (93%)

A Prospective, Randomized, Controlled Cervical Fusion Study using rhBMP-2 with the CORNERSTONE-SR™ Allograft Ring and the ATLANTIS™ Anterior Cervical Plate

David S. Baskin, M.D.*†
Patrick Ryan, M.D.‡
Volker Sonntag, M.D.§
Richard Westmark, M.D.‖
Marsha A. Widmayer, M.A.*

* Departments of Neurosurgery and †Anesthesiology, Baylor College of Medicine, and *Veterans Affairs Medical Center, Houston, TX

‡Jackson Hospital, Montgomery, AL

§Division of Neurological Surgery, Barrow Neurological Institute, and St. Joseph's Hospital and Medical Center, Phoenix, AZ

‖Clear Lake Regional Medical Center, Webster, TX

Corresponding author: David S. Baskin, M.D.
Department of Neurosurgery
Baylor College of Medicine
[redacted]
Houston, TX 77030

[redacted] (voice)
(fax)
[redacted] (email)

This research was sponsored by Medtronic Sofamor Danek.

ABSTRACT

Study Design: A prospective, randomized, pilot clinical trial was performed comparing recombinant human bone morphogenetic protein (rhBMP-2) with autograft bone for the treatment of human cervical disc disease.

Objective: To examine the safety of using rhBMP-2 in an absorbable collagen sponge (ACS) compared to autogenous bone graft inside the CORNERSTONE-SR™ fibular allograft in anterior cervical discectomy and interbody fusion.

Summary of Background Data: rhBMP-2 is an osteoinductive protein that induces a reliable fusion in the lumbar spine, but it has not been studied in patients with degenerative cervical disc disease.

METHODS: Thirty-three patients with degenerative cervical disc disease were randomly assigned to investigational or control groups. The investigational group received a fibular allograft (CORNERSTONE-SR™) with an rhBMP-2-laden carrier ACS inside the graft, with an ATLANTIS™ anterior cervical plate. The control group received a fibular allograft with cancellous iliac crest autograft placed inside of it, with an ATLANTIS™ anterior cervical plate.

Patients underwent plain x-rays at 6 weeks and at 3, 6, 12, and 24 months, and CT scans at 3 and 6 months postoperatively, and completed general health profiles and self-evaluation scales. Adverse events were evaluated for severity, duration, association with the implant, and the need for a second surgical procedure.

RESULTS: All patients had solid fusions at 6, 12 and 24 months after surgery. There were no device related adverse events. At 24 months the investigational patients had significantly better improvement in Neck Disability and Arm Pain than did the controls. **CONCLUSIONS:** This pilot study demonstrates the feasibility of using rhBMP-2 safely and effectively in the cervical spine.

Key words: anterior cervical fusion, bone morphogenetic protein, osteoinduction, radiography, allograft, anterior cervical plating

Key points:

- The fusion rates for all control and investigational groups were 100% at 6, 12 and 24 months postoperative.
- There were no device related adverse events.
- Investigational and control groups both had significant improvement in neck disability and in neck and arm pain following surgery.
- Investigational patients had statistically significant improvement in Neck Disability and Arm Pain compared to controls, although the small sample size precludes concluding that the investigational treatment is superior.
- The use of rhBMP-2 in anterior cervical fusion procedures eliminates the pain, scarring, and morbidity of iliac crest bone harvesting.

Précis

A prospective, randomized, trial compared rhBMP-2 to autograft in anterior cervical fusions. Successful fusion occurred in 100% of the patients. Investigational patients had better results than controls in several outcome measures. Investigational group patients required no iliac crest graft harvest, and therefore experienced no graft site pain or complications.

INTRODUCTION

Anterior cervical discectomy and fusion is an effective and extensively practiced treatment for degenerative cervical disc disease. Smith and Robinson (11), and Cloward (2) first described the technique in the 1950's. Initially, autogenous bone, typically harvested from the iliac crest, was used for the interbody graft. The procedure has developed to include alternatives to autograft; allograft and interbody fusion devices avoid the pain, scarring, and morbidity associated with autograft harvest, yet maintain high fusion rates. Anterior cervical plating has become an accepted component of the procedure, as it has been shown to provide immediate stability, maintain sagittal alignment, and increase the fusion rate (10,12).

Recombinant human bone morphogenetic protein-2 (rhBMP-2) has been shown to initiate osteoinduction and achieve spinal arthrodesis in a non-human primate model (5,9). The application of rhBMP-2 in humans has been explored in a lumbar fusion indication. Human clinical studies have demonstrated that patients treated with rhBMP-2, when soaked onto an absorbable collagen sponge and placed into the central cavity of the LT-CAGE™ interbody fusion device, had consistent and clear osteoinduction (1,7).

The use of rhBMP-2 in an anterior cervical fusion application was previously unexplored. The authors took part in a prospective, randomized, controlled clinical trial in which rhBMP-2 was compared to autograft as an interbody graft filler. A total of 33 patients suffering from 1 or 2-level cervical disc disease were enrolled into the study and have been followed to 2 years postoperatively. Clinical and radiographic

comparisons have been made between the 2 treatments groups at the 6 week, 3 month, 6 month, 1 year and 2 year postoperative intervals.

MATERIALS AND METHODS

Study Design. Between September 1999 and May 2000, 33 patients were enrolled in this prospective, randomized, controlled FDA approved pilot clinical trial. The clinical trial was conducted at 4 investigational centers in the United States. All patients enrolled into the study met the prescribed inclusion/exclusion criteria and signed an informed consent. The patients were randomized into their treatment group on a 1:1 basis. After randomization, neither the surgeon nor the patient was blinded to the treatment. All patients received a standard 1 or 2 level anterior cervical discectomy and the disc spaces were prepared for a Smith-Robinson style interbody allograft (in this study, a CORNERSTONE-SR™ Allograft Ring, Regeneration Technologies Incorporated, Alachua, FL). At this point the interbody allografts were prepared according to the patient's treatment randomization (see surgical technique).

Patient Data. Preoperatively, all patients suffered from one or two levels of cervical disc disease producing radiculopathy and/or myelopathy. Preoperative imaging studies demonstrated herniated disc and/or posterior osteophyte formation at the involved level(s). All patients underwent a minimum of 6 weeks of conservative therapy prior to surgery, unless symptoms progressed to require surgery earlier. The investigational and control treatment groups were very similar, and did not significantly differ in any of the demographic parameters measured. Eighteen patients were enrolled in the

investigational group and 15 patients in the control group. Mean age was 51.3 years (investigational) or 47.1 years (control). Mean weight was 169.6 pounds (investigational) or 173.7 pounds (control). Eight of 18 (44%) investigational patients were male, and 7 of 15 (47%) control patients were male. Tobacco was used by 5 of 18 investigational patients and by 7 of 15 control patients.

Clinical and Radiographic Outcome Measurements. Patients were evaluated clinically and radiographically preoperatively, immediately postoperatively, and at 6 weeks, and 3, 6, 12 and 24 months postoperative. The clinical outcome measures were neurological status, the Neck Disability Index, the SF-36, Neck, Arm, and Graft Site pain visual analog scales, and patient satisfaction questionnaires.

Dynamic flexion/extension x-rays were used to determine fusion status at 6 weeks and 3, 6, 12 and 24 months postoperative. CT scans were used at 3 and 6 months postoperatively to further assess fusion status. Two independent, blinded radiologists reviewed all x-rays and CT scans. A third independent, blinded radiologist was used to resolve conflicting fusion findings. Fusion was defined as less than 4 degrees difference in angular motion between flexion and extension as seen on lateral flexion extension radiographs, no radiolucency greater than 2 mm in thickness covering more than 50% of the superior or inferior surface of the graft(s) and evidence of bridging trabecular bone seen on radiographs and CT scans.

Clinical and Radiographic Follow-up. The rate of patient return for follow-up was high at all postoperative periods. Three investigational and one control patient were lost to

follow-up at 24 months. Of the patients not lost to follow-up, the rate of patient return at 24 months for the investigational group was 86% and for the control group was 85%. The follow-up rate did not drop below 85% at any postoperative interval.

Antibody Assessment. Patient blood samples were collected preoperatively and at 3 months postoperatively to determine titers for antibodies against rhBMP-2 and against the bovine Type 1 collagen in the sponge. A patient was considered to have an authentic elevated immune response if the preoperative sample for a patient was negative (titer < 50) while the postoperative sample was positive (titer ≥ 50), or if the preoperative sample was positive and the postoperative sample was 3-fold higher than the preoperative titer.

Surgical Technique. All patients received the standard ACDF procedure. Patients were placed in the supine position on the operating room table. A transverse incision was made over the cervical spine. An avascular dissection plane was developed between the trachea and esophagus medially and the carotid sheath laterally. After the anterior vertebral column was exposed, the longus colli muscles were elevated, and retraction was achieved via self-retaining retractors placed underneath the longus colli muscles. The appropriate level(s) were identified radiographically. Vertebral body distraction was often applied at this time. A discectomy and/or osteophytectomy was then completed to achieve neural decompression.

The disc space was then prepared for the interbody graft. A parallel cavity was made for the graft by shaping the end plates with a high-speed drill. The extent of

Deleted: high-speed drill was utilized to create a

endplate and bone removal was left to the discretion of the individual surgeon. Sizing trial tools were used to determine the appropriate graft size to select. For investigational patients, once the appropriate size of allograft was determined, the central cavity of the allograft was then filled with rhBMP-2. The carrier matrix was prepared to a concentration of 1.5 mg/ml rhBMP-2 (InFUSE™ Bone Graft; Medtronic Sofamor Danek, Memphis, TN) by reconstituting with 3.2 ml sterile water. Then, 0.4 ml reconstituted rhBMP-2 solution was uniformly distributed on a 1.5 cm x 2.5 cm piece of collagen sponge. The sponge was allowed to soak for 15 minutes and then was placed inside the fibular allograft, which was gently tapped into the prepared disc space for each level fused. Irrigation after implantation was contraindicated.

For patients in the control group, a small incision was made over the iliac crest, and blunt dissection was performed to expose the crest. A trephine was then used to take a core of cancellous bone, which was then packed into the central cavity of the allograft. The filled allograft was then gently tapped into the prepared disc space. For two level cases, the second disc space and interbody graft were prepared using the same method.

All patients received an appropriately sized anterior cervical plate (ATLANTIS™ Anterior Cervical Plate; Medtronic Sofamor Danek, Memphis, TN) to provide increased stability to the construct. The plate construct utilized either all fixed angle screws, all variable angle screws, or a hybrid construct using both fixed angle and variable angel screws. The screws were secured by an attached locking mechanism, which was engaged after final screw seating. The appropriate placement of the construct was then confirmed radiographically.

A postoperative regimen that prohibited bone growth stimulators, and recommended against steroids, athletic activities, lifting and bending was recommended. Postoperative bracing requirements were left to the discretion of the individual surgeons.

RESULTS

As there were no differences in preoperative, operative, or outcome variables between the one-level and the two-level patients, their data was combined to form two treatment groups, investigational and control.

Surgery Information. One level arthrodesis was performed on 10 of 18 (56%) investigational patients, and eight of 15 (53%) control patients. The remaining patients received two level arthrodesis. Mean operative time for investigational and control groups was 1.8 hours each. Mean blood loss was 91.4 mL for investigational and 123.3 mL for control patients (N.S.). Mean hospital stay was 1.4 days (investigational) or 1.1 days (control) (N.S.). There were no unanticipated device-related adverse events in either treatment group.

Graft Site

The level of postoperative pain and morbidity associated with the iliac crest graft harvesting was measured using numeric rating scales for pain intensity and duration. At discharge and 6 weeks after surgery, control patients had significantly high levels of pain at the graft site ($p < 0.007$, student's t - test) and complained about the appearance

of the graft site. By 12 months after surgery, the patients graft-site pain had resolved ($p < 0.165$) and no patients complained about the graft-site appearance.

Antibody Production

No patients produced detectable antibodies to the rhBMP-2. One investigational and one control patient had elevated titers to bovine Type 1 collagen at 3 months. These patients were not positive for antibodies to human Type 1 collagen.

Clinical Outcomes

Neck Disability Index Questionnaire scores. The Neck Disability Index (NDI) Questionnaire measures cervical pain and disability associated with activities of daily living. The NDI questionnaire was administered preoperatively and at each postoperative interval. At all postoperative intervals, both treatment groups demonstrated statistical improvement compared with their preoperative scores (Table 1).

The investigational group demonstrated superior mean improvement than the control group at 24 months ($p < 0.03$), although this group began with slightly worse NDI preoperatively than did controls.

Neurologic Status. Neurologic status of the patients was determined by evaluating motor and sensory function. Values for each of the subsets of objective findings were totaled and expressed as a percentage of the maximum possible score. Measurements were then compared with the patient's preoperative score. Neurologic success was

based on demonstrating maintenance or improvement in both subsets. At 24 months after surgery, the overall neurologic success rate for each group was 100% (Table 2).

Neck Pain. Neck pain frequency and intensity were measured using a 20-point numeric rating scale. Adding the numeric rating scores for neck pain frequency and intensity created a composite neck pain score (Table 3). The mean neck pain scores at all postoperative periods were improved from the preoperative mean values for both treatment groups. At 24 months the mean change was 13 points for the Investigational group and 9 points for the control group, which was not statistically significant ($p < 0.055$).

Neck pain success on an individual patient basis was determined by comparing the postoperative score with the preoperative score. Success was based on the patient having at least a 3-point improvement in neck pain score after surgery (Table 3). At 24 months after surgery, the overall neck pain success rate for each group was 100%.

Arm Pain. Arm pain was also assessed using a numeric rating scale for both the frequency and intensity of the pain. Mean arm pain scores improved significantly after surgery in both treatment groups (Table 4). At all postoperative intervals, both treatment groups demonstrated statistical improvement compared with their preoperative scores (Table 4). Furthermore, the investigational group had superior mean improvement than the control group at 24 months ($p < 0.03$), although the investigational group began with slightly worse Arm Pain preoperatively than did controls.

Arm pain success was defined according to the following algorithm. If a patient had a preoperative pain score of 10 points or more, success was defined as a 3-point improvement on his or her postoperative scores. In those patients who had preoperative arm pain scores of less than 10 points, success was defined as maintenance or improvement in scores when compared with their preoperative condition.

General Health. The SF-36 questionnaire was used to measure the patients' general health status. The SF-36 questionnaire was administered preoperatively and at each postoperative interval. The SF-36 was analyzed according to its physical (PCS) and mental (MCS) components. The investigational group showed similar mean improvement to the control group at all postoperative intervals in both the PCS and MCS (Table 5). At 24 months, the mean improvements in the PCS and MCS scores were 16.7 points and 21.8 points, respectively, for the investigational group. The control group showed a mean improvement of 14.7 points in the PCS and an improvement of 7.2 in the MCS at 24 months postoperative.

SF-36 success was defined as maintenance or improvement in scores when compared to preoperative scores. At 24 months postoperative, the investigational group success rates for the PCS and MCS were 92% each. The control group success rates for the PCS and MCS were 100% and 75% respectively at the 24-month interval.

Patient Satisfaction. Patient satisfaction was assessed by three questions inquiring whether the patients were satisfied with the results, were helped as much as they thought they would be, and whether they would have the surgery again for the same

condition. At the 24-month postoperative interval, greater than 90% of each group responded favorably for each of the three questions.

Radiographic Outcomes. Fusion status of the study patients was evaluated with lateral flexion and extension radiographs and CT scans. Fusion was based on evidence of bridging bone, angular motion stability, and lucent line criteria (see methods for exact criteria). At 6, 12 and 24 months postoperative, 100% of the patients in both the investigational and the control group that were not lost to follow-up were deemed fused (6 months investigational 15/15 = 100%, control 13/13 = 100%, 12 months 14/14 investigational = 100%, 12/12 control = 100%, 24 months 10/10 investigational, 10/10 control).

Two patients in the investigational group and one patient in the control group demonstrated bone formation immediately anterior to segments adjacent to the treated level. This ossification became clearly visible on the 12 month postoperative x-rays (Fig.1). All 3 patients were treated by the same surgeon.

Secondary Surgical Procedures. One patient in the investigational group required surgical intervention at an adjacent segment to the original two-level fusion. The surgery was unrelated to the original procedure. However, to perform the operation the anterior cervical plate was removed. No other subsequent cervical procedures were performed.

DISCUSSION

This pilot study is the first prospective clinical evaluation of rhBMP-2 for a cervical spine fusion indication. The primary purpose of this pilot study was to assess the feasibility of using rhBMP-2 in an anterior cervical fusion application. Both groups showed significant postoperative improvement in neck disability and in neck and arm pain and both groups had fusion rates of 100%. The investigational group also avoided the pain and morbidity of iliac crest graft harvest. rhBMP-2 treatment was at least equally successful compared to the use of autograft bone. On some measures, rhBMP-2 provided superior improvement to standard autograft bone, although the small sample size precludes concluding superiority of treatment.

Generally, a 91 – 97% cervical fusion rate can be expected when spinal instrumentation is used (6). However, in the present study, all radiographs beginning at the 6-month follow-up indicated successful fusion. The fusion rate in the present study is likely due to the fusion criteria utilized. Fusion was defined as less than 4 degrees difference in angular motion between flexion and extension, no radiolucency greater than 2 mm in thickness covering more than 50% of the superior or inferior surface of the graft(s), and evidence of bridging trabecular bone seen on radiographs and CT scans. While some might use more conservative criteria, these criteria were adopted following discussions with the FDA and were applied equally across treatment groups.

In the current study, the Investigational group received rhBMP-2 together with allograft bone. There is a small risk of disease transmission associated with the use of allograft bone (3). In our opinion, this risk is outweighed by the elimination of bone harvesting surgery and its associated morbidity.

Recombinant human bone morphogenetic protein is an osteoinductive growth factor that stimulates stem cells to form bone (13). A number of animal and human studies have been conducted to evaluate the effectiveness of this substance in promoting spinal fusion, and in many cases, the success rate and quality or quantity of the fusion mass has been superior to autograft (see 4, 8 for reviews).

Anterior bone formation in immediately adjacent segments was demonstrated in two investigational and one control patient. As this occurred in both groups, and the same surgeon treated all three patients, the ossification may be technique related. Furthermore, the general incidence of anterior bone formation in immediately adjacent segments is unknown, and has been observed anecdotally by a number of experienced spine surgeons using standard allograft and autograft constructs. The pathophysiology of spondylosis relates to disc degeneration and segmental instability, to which the response is overgrowth of ligament and bone. It may be that in these cases and in others like them, the adjacent disc and/or facets are already degenerated, and that fusion accelerates the spondylitic process, which includes bony growth.

The presence of blood and surgical trauma may be associated with ectopic bone formation, and are also factors to consider. In this regard, blood may serve as a sink to extract BMP from its carrier. Meticulous hemostasis and use of drains will be important aspects of technique to consider when using rhBMP-2 in all spinal applications, despite the fact that evidence is lacking in this study to implicate rhBMP-2 as the cause of adjacent segment anterior bone overgrowth.

rhBMP-2 has been shown in clinical trials to be safe and effective when used in a lumbar interbody fusion application (1,7). The use of rhBMP-2 is associated with high

Deleted: . In this study, the investigational group received rhBMP-2 soaked onto an absorbable collagen sponge and placed into the central cavity of an allograft ring. At 6 and 12 months postoperative, the investigational group was determined to have a fusion rate of 100% by two independent blinded radiologists.¶

fusion rates without the need for harvesting bone from the iliac crest, avoiding the pain and morbidity of that procedure. This pilot study demonstrates that the use of rhBMP-2 in an anterior cervical fusion application is sufficiently safe to study its use in a larger clinical trial. Further clinical studies are underway to evaluate the safety and effectiveness of rhBMP-2 for this indication.

ACKNOWLEDGEMENTS

This research was sponsored by Medtronic Sofamor Danek. The authors thank Newt Metcalf, Missy Taylor and Mark Marchan for the important role they played in the creation of this manuscript.

REFERENCES

1. Boden SD, Zdeblick TA, Sandhu HS, et al. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25:376-81.

2. Cloward RB. The anterior approach for removal of rupture cervical disks. J Neurosurg 1958;15:601-617.

3. Hardin CK. Banked bone. Otolaryngol Clin North Am 1994; 27:911-925.

4. Harvinder S, Sandhu MD. Anterior lumbar interbody fusion with osteoinductive growth factors. Clin Orthop 2000; 2000:56-60.

5. Hecht BP, Fischgrund JS, Herkowitz HN, et al. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999; 24:629-36.

6. Kaiser MG, Haid RW Jr, Subach BR, Barnes B, Rodts GE Jr: Anterior cervical plating enhances arthrodesis after discectomy and fusion with cortical allograft. Neurosurgery 2002; 50:229-236.

7. Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2. A prospective study of clinical and radiographic outcomes. Spine 2001; 26:2751-2756.

8. Ludwig SC, Kowalski JM, Boden SD. Osteoinductive bone graft substitutes. Eur Spine J 2000; 9:S119-125.

9. Martin GJ Jr, Boden SD, Marone MA, et al. Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: important lessons learned regarding dose, carrier, and safety. J Spinal Disord. 1999; 12:179-186.

10. Schulte K, Clark CR, Goel VK. Kinematics of the cervical spine following discectomy and stabilization. Spine 1989; 14:1116-1121.

11. Smith GW, Robinson RA. The treatment of certain cervical spinal disorders by anterior removal of the intervertebral disc and interbody fusion. J Bone Joint Surg 1958; 40:607-624.

12. Spivak JM, Balderston RA. Spinal instrumentation. Curr Opin Rheumatol 1994; 6:187-94.

13. Urist MR. Bone: Formation by autoinduction. Science 1965; 150:893-899.

Figure Legend

Figure 1. Twelve Month Postoperative Lateral X-rays.

Panel A - Investigational Patient #2.

Panel B - Control Patient #6.

Panel C - Investigational Patient #9.

Note the formation of anterior bone in segments immediately adjacent to the fused vertebra in these three patients (white arrows).

TABLE 1 – Neck Disability Index Scores

Period	Variable	Investigational	Control
Preoperative			
	n	18	15
	Mean	61.3	55.4
6 Weeks			
	n	18	15
	Mean	23.9	22.8
Improvement from Preoperative	Mean	37.4	32.6
	P value[1]	<0.001	<0.001
3 Months			
	n	17	15
	Mean	21.3	21.9
Improvement from Preoperative	Mean	39.2	33.5
	P value	<0.001	<0.001
6 Months			
	n	17	13
	Mean	12.9	13.4
Improvement from Preoperative	Mean	47.8	38.8
	P value	<0.001	<0.001
12 Months			
	n	15	14
	Mean	16.3	12.3
Improvement from Preoperative	Mean	45.7	40.8
	P value	<0.001	<0.001
24 Months			
	n	14	12
	Mean	10.1	14.5
*Improvement from Preoperative	Mean	52.7	36.9
	P value	<0.001	<0.001

[1] P values for change from preoperative in each group are from paired T-tests
Patients in both treatment groups experienced significant improvement in neck disability following surgery.
* At 24 months, improvement was superior in the Investigational patients compared to Controls ($p < 0.03$, Student's t-test).

TABLE 2. Neurologic Outcomes

Period	Variable	Investigational n (%)	Control n (%)
6 Weeks			
	Success	17 (94)	15 (100)
	Failure	1 (6)	0 (0)
3 Months			
	Success	18 (100)	15 (100)
	Failure	0 (0)	0 (0)
6 Months			
	Success	15 (88)	13 (100)
	Failure	2 (12)	0 (0)
12 Months			
	Success	15 (100)	13 (93)
	Failure	0 (0)	1 (7)
24 Months			
	Success	14 (100)	12 (100)
	Failure	0 (0)	0 (0)

Patients in both treatment groups maintained or improved in motor function, sensory function and reflexes, indicating successful neurologic outcome.

TABLE 3. Neck Pain

Period	Variable	Investigational	Control
Preoperative	n	18	15
	Mean	16.1	14.3
6 Weeks	n	18	15
	Mean	5.2	6.9
Improvement from Preoperative	Mean	10.9	7.4
	P value[1]	<0.001	<0.001
3 Months	n	17	15
	Mean	6.2	6.7
Improvement from Preoperative	Mean	10.6	7.6
	P value	<0.001	<0.001
6 Months	n	17	13
	Mean	4.6	4.1
Improvement from Preoperative	Mean	11.4	9.6
	P value	<0.001	<0.001
12 Months	n	15	14
	Mean	3.5	5.4
Improvement from Preoperative	Mean	12.1	8.6
	P value	<0.001	<0.001
24 Months	n	14	12
	Mean	2.8	5.3
Improvement from Preoperative	Mean	13.0	9.0
	P value	<0.001	<0.001

[1] P values for change from preoperative in each group are from paired T-test. Patients in both treatment groups experienced significant improvement in neck pain frequency and intensity. At 24 months the difference between groups in improvement approached statistical significance ($p < 0.055$)

Deleted: <#>Weeks¶ ¶ ¶ Improvement from Preoperative¶ ¶ ¶ ... [1]
Formatted: Bullets and Numbering

Deleted: <#>Months¶ ¶ ¶ ¶ Improvement from Preoperativ ... [2]
Formatted: Bullets and Numbering

Deleted: <#>Months¶ ¶ ¶ ¶ Improvement from Preoperativ ... [3]
Formatted: Bullets and Numbering

Deleted: <#>Months¶ ¶ ¶ ¶ Improvement from Preoperativ ... [4]
Formatted: Bullets and Numbering

TABLE 4. Arm Pain

Period	Variable	Investigational	Control
Preoperative	n	18	15
	Mean	17.3	11.5
6 Weeks	n	18	15
	Mean	3.4	2.6
Improvement from Preoperative	Mean	13.9	8.9
	P value[1]	<0.001	<0.001
3 Months	n	17	15
	Mean	3.6	2.9
Improvement from Preoperative	Mean	14.1	8.5
	P value[1]	<0.001	<0.001
6 Months	n	17	13
	Mean	2.6	0.8
Improvement from Preoperative	Mean	14.8	10.0
	P value[1]	<0.001	<0.001
12 Months	n	15	14
	Mean	2.9	1.5
Improvement from Preoperative	Mean	14.5	9.7
	P value[1]	<0.001	<0.001
24 Months	n	14	12
	Mean	3.3	1.7
*Improvement from Preoperative	Mean	14.0	8.5
	P value[1]	<0.001	<0.001

[1] P values for change from preoperative in each group are from paired test.
Patients in both treatment groups experienced significant improvement in arm pain frequency and intensity.
* At 24 months, improvement was superior in the Investigational patients compared to Controls ($p < 0.03$, Student's t-test).

Deleted: <#>Weeks¶ ¶ ¶ Improvement from Preoperative¶ ¶ ¶ ... [5]
Formatted: Bullets and Numbering
Deleted: <#>Months¶ ¶ ¶ ¶ Improvement from Preoperative¶ ¶ ¶ ¶ ... [6]
Formatted: Bullets and Numbering
Deleted: <#> Months¶ ¶ ¶ ¶ Improvement from Preoperative¶ ¶ ¶ ¶ ... [7]
Formatted: Bullets and Numbering
Deleted: <#>Months¶ ¶ ¶ ¶ Improvement from Preoperative¶ ¶ ¶ ¶ ... [8]
Formatted: Bullets and Numbering

TABLE 5. SF-36

Period	Variable	Investigational	Control
Preoperative	n	16	15
PCS	Mean	31.7	32.6
MCS	Mean	32.4	42.5
6 Weeks	n	18	15
PCS	Mean	40.4	39.6
MCS	Mean	51.4	52.6
3 Months	n	16	15
PCS	Mean	44.4	44.6
MCS	Mean	48.4	47.6
6 Months	n	15	12
PCS	Mean	45.6	46.5
MCS	Mean	54.9	54.4
12 Months	n	15	14
PCS	Mean	45.7	48.7
MCS	Mean	54.1	50.4
24 Months	n	14	12
PCS	Mean	48.6	48.7
MCS	Mean	54.6	49.0

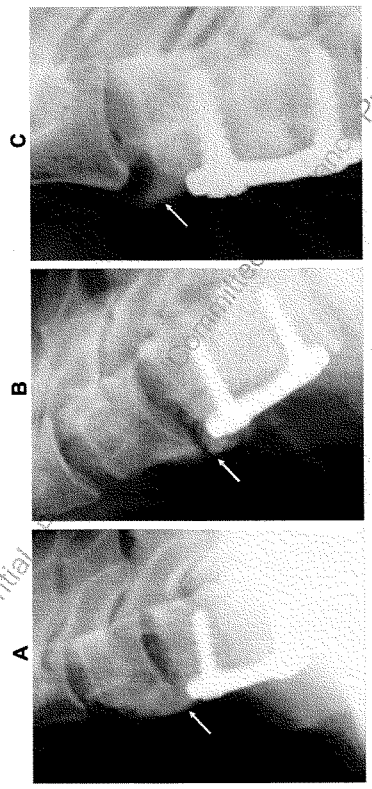
PCS = physical component score. MCS = mental component score
SF-36 is a measure of general physical and mental health. Note that both investigational and control patients improved in physical and mental health following surgery.

Deleted: 6 Weeks¶
. . PCS¶
¶
¶
. . MCS¶ ... [9]

Deleted: 3 Months¶
. . PCS¶
¶
¶
. . MCS¶ ... [10]

Deleted: 6 Months¶
. . PCS¶
¶
¶
. . MCS¶ ... [11]

Deleted: 12 Months¶
. . PCS¶
¶
¶
. . MCS¶ ... [12]



Page 24: [1] Deleted	widmayer	5/17/2002 3:19:00 PM	
Weeks	n	18	15
	Mean	5.2	6.9
Improvement from Preoperative	Mean	10.9	7.4
	P value[1]	<0.001	<0.001
	Success	16/18 (89%)	10/15 (67%)

Page 24: [2] Deleted	widmayer	5/17/2002 3:19:00 PM	
Months	n	17	15
	Mean	6.2	6.7
Improvement from Preoperative	Mean	10.6	7.6
	P value	<0.001	<0.001

Page 24: [3] Deleted	widmayer	5/17/2002 3:19:00 PM	
Months	n	17	13
	Mean	4.6	4.1
Improvement from Preoperative	Mean	11.4	9.6
	P value	<0.001	<0.001

Page 24: [4] Deleted	widmayer	5/17/2002 3:19:00 PM	
Months	n	15	14
	Mean	3.5	5.4
Improvement from Preoperative	Mean	12.1	8.6
	P value	<0.001	<0.001

Page 25: [5] Deleted	widmayer	5/17/2002 3:19:00 PM	
Weeks	n	18	15
	Mean	3.4	2.6
Improvement from Preoperative	Mean	13.9	8.9
	P value[1]	<0.001	<0.001
	Success	16/18 (89%)	15/15 (100%)

Page 25: [6] Deleted	widmayer	5/17/2002 3:19:00 PM

Months	n	17	15
	Mean	3.6	2.90
Improvement from Preoperative	Mean	14.1	8.5
	P value[1]	<0.001	<0.001
	Success	16/17 (94%)	13/15 (87%)

Page 25: [7] Deleted widmayer 5/17/2002 3:19:00 PM

Months	n	17	13
	Mean	2.6	0.8
Improvement from Preoperative	Mean	14.8	10.0
	P value[1]	<0.001	<0.001

Page 25: [8] Deleted widmayer 5/17/2002 3:19:00 PM

Months	n	15	14
	Mean	2.9	1.5
Improvement from Preoperative	Mean	14.5	9.7
	P value[1]	<0.001	<0.001

Page 26: [9] Deleted widmayer 5/17/2002 3:19:00 PM

6 Weeks	n	18	15
PCS	Mean	40.5	39.7
	Success	13/16 (81%)	9/15 (60%)

Page 26: [10] Deleted widmayer 5/17/2002 3:19:00 PM

3 Months	n	16	15
PCS	Mean	44.6	44.7
	Success	14/14 (100%)	12/15 (80%)

Page 26: [11] Deleted widmayer 5/17/2002 3:19:00 PM

6 Months	n	15	12
PCS	Mean	45.8	46.7
	Success	11/13 (85%)	10/12 (83%)

Page 26: [12] Deleted widmayer 5/17/2002 3:19:00 PM

12 Months	n	15	14
PCS	Mean	45.9	48.9
	Success	12/13 (92%)	13/14 (93%)

August 27, 2002

Dr. James N. Weinstein
Editor-in-Chief
Spine
Dartmouth College
[redacted]
Hanover, NH 03755-3863

[redacted]

Dear Dr. Weinstein:

Enclosed is a revised original and three copies of the manuscript, *A Prospective, Randomized, Controlled Cervical Fusion Study using rhBMP-2 with the Cornerstone-SR™ Allograft Ring and the Atlantis™ Anterior Cervical Plate*. Where appropriate, I have made changes in the manuscript to address the reviewers' concerns, and a detailed description of these changes appears below.

Reviewer #1.

1. Reviewer #1 requested further explanation of the 100% fusion rate.

If the same criteria used in many publications were utilized in the present study, the success rate would likely be 91 – 97%, as seen in publications describing clinical practice (see refs). However, the criteria agreed upon by the sponsor and the FDA were different, and resulted in a 100% fusion rate. We have added a paragraph explaining this on page 15.

Reviewer #2.

1. Reviewer #2 pointed out that no trend analyses were done, and that references to trends in the text need to be removed.

We have removed these references. The 2-year follow-up data demonstrate statistically significant differences on two measures, which have been added to the text. However, we have also stated that the small sample size precludes concluding that one treatment is superior to the other.

Reviewer #3.

1. Reviewer #3 requests a 2-year follow-up period for publication in *Spine*.
   We now have 2-year follow-up data, which had been added to the manuscript.

Thank you again for your consideration of this manuscript. I look forward to its publication.

Sincerely,

David S. Baskin, M.D., F.A.C.S.
Corresponding Author
Professor of Neurosurgery
and Anesthesiology

REVIEWERS' COMMENTS

#1

I appreciate the changes the authors have made and believe they have more than accomplished their objective of demonstrating the efficacy of rh BMP-2 fhr at least one one year.

However, I am still unhappy with their explanation of the 100% fusion rate in both groups. Perhaps it reflects my inability to achieve such outstanding results. May I suggest possible explanations, at least as I see them:

1. The four surgeons involved are the best in the country.
   Corollary – they never had a bad result.
2. The four surgeons are very lucky.
3. The patient group was very carefully selected.
4. The numbers in each group are too small to accurately reflect a true non-fusion fusion rate.

Perhaps the authors could chose one or more of the above, unless there are other reasons. I think most people who do cervical spine surgery accept the fact that the anterior approach is good in properly selected patients, even without plating, especially in one level procedures.

The above comments are made, tongue in cheek. I've already said that this is a well done important piece of work. I know it's personal, but I'm unhappy about that 100% fusion rate and hope the authors will indulge me with more explanation.

#2

Spine A0217

The authors have presented the preliminary data relating to a randomized cervical fusion study using rhBMP-2. The manuscript has been revised and the issues are important. The journal is eager to have this preliminary data out for the readership. All the issues have been resolved except for one recurring theme. The authors continue to emphasize a trend in favor of the BMP throughout. Unless there is a critical trend analysis, trends remain non-statistical. Either there is inadequate power or there is "no" difference. I believe the authors should just relate the data and let the readership make their own conclusions. Consequently remove the trend sentence from the abstract, the key points, the precis, page 11 last paragraph, page 12 middle paragraph, page 13 first paragraph, and page 14 middle paragraph. This is an important first start but do not make claims that are not there. It weakens the credibility of the investigation.

#3

Reference: #A0217

The study design and manuscript preparation are outstanding, but I still have a criticism of short follow-up period. The author should read the article regarding the collaboration of SPINE and Journal of Spinal Disorders & Traumatology (see SPINE 2002:27;1253). I recommend that this excellent but premature study should be submitted to JSDT.

From: Beals, Neil
Sent: Thursday, January 2, 2003 08:17:36 AM
To: Wehrly, Peter [ITD Div. Pres.]
CC: Bearcroft, Julie; Charlton, Clark; Martin, Bill
BCC: DeMane, Michael
Subject: RE: PLIF Study Manuscript

Pete,

Based on note below from Bill, it seems that he has already covered this manuscript and its direction with Ken and all that is now needed is data from Bailey. I do not see need for Julie or I to get into this at this point. Please advise if you see things differently. Thanks. Neil

-----Original Message-----
From: Martin, Bill
Sent: Wednesday, January 01, 2003 8:06 AM
To: Beals, Neil; Wehrly, Peter [ITD Div. Pres.]
Cc: Bearcroft, Julie; Charlton, Clark; Martin, Bill; DeMane, Michael; Lipscomb, Bailey
Subject: RE: PLIF Study Manuscript

A word of caution.
I'm pretty sure that on this paper Dr. Burkus just wants us to provide him the data he requested. Dr. Burkus mentioned that his plan for this paper was to do all the work, put Drs Haid, Branch and Alexander's names first, and then he plans to route it to them "as is" for approval. If they don't agree with the data, then they may of course take their name off. Dr. Burkus has done ground work with Charlie and Reg and they have indicated initially that they seem to be fine with this - I don't anticipate any issues between them. Dr. Burkus wanted his name last (and all the neuro's first) so that it would be well accepted by the Neurosurgical community. I know that he has talked in depth with Charlie about what the paper *should*, and equally important, *should not* include.

A couple of additional thoughts:

1. Ken's intent was to purposely NOT include a lot of interpretation/explanation about radiographic observations that don't correlate to the outcomes for concern that it will confuse the issues and again look like an apology (which is part of what he hopes to clear up with this paper).
2. He's stated that the data is good and should stand on its own. His desire is to cleanly report the outcomes.
3. I'm sure that none of us believe the PLIF *technique* is going to have a resurgence from this, but we may want to steer clear of calling it a flawed technique. There are still quite a few surgeons utilizing this technique and we probably don't want to put them in that position. In the past, the way that Haid has approached this is to use verbiage such as "this technique has fallen out of favor, and many surgeons are now choosing to ____". If Reg believes that a statement like this would be necessary to add, he'll have the opportunity to add it when Dr. Burkus routes to him for approval.

Basically, let's provide Dr. Burkus with the information he requested (and I believe he's already working with Bailey on this), and just communicate with him to offer to help in any way he needs to get this done. He does have a plan already and intends to quarterback it.

Thanks,
Bill

-----Original Message-----
From: **Beals, Neil [SMTP:** [redacted]
Sent: Tuesday, December 31, 2002 10:53 AM
To: Wehrly, Peter [ITD Div. Pres.]
Cc: Bearcroft, Julie; Charlton, Clark; Martin, Bill; DeMane, Michael; Lipscomb, Bailey
Subject: RE: PLIF Study Manuscript

Julie and I will be glad to f/u on this.

As we get into this, I think we need to clarify and confirm: 1) the message delivered with this paper, 2) its timing, and 3) balanced input from all authors (Haid, Burkus, Branch/Alexander) with particular attention to positioning this with neuro community.

Ken has done a great job in getting the data into a workable manuscript form (I assume that Bailey will not have problems in filling in gaps Ken has pointed out). In its current form, the paper pretty much reports the data from the study with relatively little interpretation or comment. My recommendation would be to report the data and point out that while this study used a flawed technique that has since been modified (stand alone to instrumented PLIFs) the results, particularly with INFUSE, were quite good. The observation of bone formation should be noted and explanations provided including cage placement, construct stability, tissue disruption, and use of other exogenous materials. I think it would make great sense to include the rationale for the new INFUSE PLIF study in this paper to give these discussions some direction and purpose.

To realize this, I think we need to agree on message (INFUSE works well in PLIF with dated technique and is expected to work more consistently and with greater confidence using revised techniques), timing (get published in peer reviewed journal by year-end and try to think of new message to submit in Feb for presentations at spine meetings in the fall), and well balanced input (this must be balanced between Ken and Charley and Joe and Reg; this may be the toughest challenge and the one for which we will need support from top down (if you agree)).

We'll start cracking on more specific review and proposed revision. In meantime, any thoughts?

Neil

-----Original Message-----
From: Wehrly, Peter [ITD Div. Pres.]
Sent: Monday, December 23, 2002 8:25 AM
To: Beals, Neil; Martin, Bill
Cc: Bearcroft, Julie; Charlton, Clark
Subject: FW: PLIF Study Manuscript

Here is first draft. Neil and Julie, will you champion this?

Pete

> -----Original Message-----
> **From:** Burkus, J. Kenneth
> **Sent:** Saturday, December 21, 2002 11:26 AM
> **To:** DeMane, Michael; Wehrly, Peter
> **Subject:** PLIF Study Manuscript
>
> Mike and Pete,
>
> Here's your Christmas present. I have attached a copy of the PLIF study manuscript. I believe this will make a significant contribution. I also think this should have a high priority to bring to completion.
>
> I have done about all that I can do without further analysis of the PLIF study data.
>
> In the text of the manuscript, you will find numerous areas that are in bold and underlined. I will need further analysis of this data.
>
> The discussion and conclusions and bibliography are lacking but should be relatively easy to fix up.
>
> I have been handicapped in writing this manuscript in that I have not had access to any of the hard numbers involving patient outcomes and x-ray interpretation with this study.
>
> Take the cuffs off.
>
> I am running home to pack and head off to Salt Lake City and catch up with my family. They should be spending their first day on the slopes today.
>
> Thank you for your generosity and support and friendship throughout this past year. I am looking forward to running harder and moving the ball forward this

coming year.

Merry Christmas and best regards to you and your families.

Warm regards,
Ken Burkus

From:	Bearcroft, Julie, PhD
Sent:	Wednesday, June 16, 2004 10:04:33 AM
To:	Treharne, Rick; Beals, Neil; Lipscomb, Bailey; McKay, Bill
CC:	Ma, Guorong; Peckham, Steve, Ph.D.; King, Vanja, Ph.D.; Woodward, Lyndsay; Hood, Tara
Subject:	Combined pilot & pivotal rhBMP-2/TCBD draft manuscript
Attachments:	Bone Dowel BMP superiority revision without tracking changes 061104.doc

Please find attached a revised version of the combined bone dowel data paper. I have made some significant changes to this document (some at the request of Dr Burkus) both in format and content.

For background, Burkus would like to publish this paper first and then one focused on the bone dowel incorporation & fusion patterns separately as well as the effect of biocleanse in a separate paper yet. I think it makes good sense; however, it does add a natural delay in publishing some of the other results.

The highlighted regions are issues that I have not been able to verify and would appreciate your assistance or they are issues that I want to make sure we are all in agreement before going to publication.

I would also like to propose a title change and am open for suggestion. I don't believe this title captures the essence of this paper.

Please review and provide comment.

Additional issues that I would like to propose that we consider include -
1) How much information should we provide relative to adverse events? Lyndsay provided with some of the specifics behind the general numbers in the tables to better understand if there are significant issues here. Most of these are applicable to issues that fall outside of involved level. You will see my not in the attached document but I don't think significant detail on this section is warranted. Thoughts?

2) the effect of biocleanse on these outcomes. Guorong feels very firmly that biocleanse has an influence. This influence is best seen by focusing on the autograft group - divided by with biocleanse and without. I would like to propose that if we move forward with a publication on this topic that we only present the data from these two subsets only (without the rhBMP-2 group where no discernable difference with and without biocleanse can be noted).

3) should we incorporate any discussion related localized resorption zones that may accompany these constructs? I inserted a precursor to the incorporation issue in the discussion because there was a citable reference to talk about it in relationship to other allograft constructs. Am I overlooking a reference for the localized resorption zone?

In the meantime, I will drop a note to Burkus to let him know that I have made some significant changes

and have asked for input from all of you to help make the review process move along more efficiently.

thanks for your help,
julie

The Use of rhBMP-2 with Threaded Allograft Bone Dowels in Stand-Alone Anterior Lumbar Spinal Fusion Surgery

J. Kenneth Burkus, MD *

Harvinder Sandhu, MD #

Matthew Gornet **

Michael Longley +

* Staff Physician, Wilderness Spine Services, The Hughston Clinic, Columbus, Georgia

Professor, Hospital for Special Surgery, Cornel University Medical Center, New York, New York

** Staff Physician, Orthopaedic Center of St. Louis, St. Louis, Missouri

+ Nebraska

Medtronic Sofamor Danek, Memphis, TN, sponsored this study.

Address correspondence and reprint requests to: J.K. Burkus, MD, The Hughston Clinic, PC, [redacted]

ABSTRACT

Background: A non-human primate study of anterior lumbar interbody fusion using non-human allograft dowel in combination with rhBMP-2 delivered on an absorbable collagen (ACS) sponge was compared to similar allograft with autogenous iliac crest bone graft [17]. This study found that using rhBMP-2/ACS had increased the incorporation of the allograft dowels with the host bone. A pilot prospective, randomized clinical trial in humans comparing pairs of threaded allograft cortical bone dowels in stand-alone anterior lumbar interbody fusion having either rhBMP-2/ACS or autogenous bone graft was previously performed which showed increased rates of fusion and improved clinical outcomes in patients treated with rhBMP-2 [6].

Methods: Between 1998 and 2001, a prospective, randomized, multi-centered trial of 131 patients was conducted to determine the safety and efficacy of using rhBMP-2/ACS as an autogenous iliac crest bone graft replacement in anterior lumbar spinal fusion surgery using stand-alone threaded cortical allograft dowels. This study was conducted in two parts: a pilot and pivotal phase. The pilot study utilized a one-to-one randomization ratio of investigational to controls, while the pivotal phase had a two-to-one randomization ratio. Patients were studied pre-operatively, at surgery/discharge, 6 weeks, and 3, 6, 12, and 24 months for clinical and radiographic outcomes using standard clinical instruments including Oswestry Disability Index and SF-36 questionnaires, and numeric rating scales for back, leg and donor site pain. Independent radiographic assessment was conducted at 6, 12 and 24 months using AP and lateral radiographs, flexion/extension radiographs, and thin-slice CT scans.

Deleted: and
Deleted: autograft
Deleted: with allograft dowels treated with rhBMP-2
Deleted: into
Deleted: collagen sponge
Deleted: safety
Deleted: on collagen soaked sponge
Deleted: All p

Results: The use of rhBMP-2/ACS as an iliac crest bone graft replacement provided both immediate surgical advantages and also avoided the long-term morbidity observed with the harvesting procedure. The patients treated with rhBMP-2/ACS had statistically superior outcomes ($p<0.05$) with regard to length of surgery, blood loss, and hospital stay compared to control patients due to the elimination of the second surgery associated with harvesting autograft. Nearly half of the autograft patients reported donor site at the 24-month follow-up. Fusion rates were statistically superior in the rhBMP-2 group compared to the autograft at all time points ($P<0.05$). The need for supplemental surgery over time was reduced with the use of rhBMP-2/ACS as compared to that observed among the autograft patients. Similarly, average Oswestry Disability Index scores, Physical Component Scores (SF-36) low back and leg pain scores, at 6, 12, and 24 months were statistically superior in the rhBMP-2 treated group. No unanticipated adverse effects were identified with the use of rhBMP-2/ACS.

Deleted: and a resorbable collagen sponge

Deleted: and

Deleted: Low back and leg pain visual analog scores,

Deleted: and

Deleted: the

Deleted: of the

Deleted: scores

Deleted: showed

Deleted: outcomes

Deleted: Similarly, fusion rates were statistically superior in the BMP-2 group.

Deleted: and a resorbable collagen sponge.

Conclusions: This study confirms the dramatic findings found in animal studies that rhBMP-2/ACS in conjunction with threaded allograft cortical bone dowels is a safe and effective combination that leads to new bone formation and allograft incorporation in anterior lumbar interbody fusions. In this application, rhBMP-2/ACS is a successful replacement for autogenous bone graft. In combination with threaded allograft cortical bone dowels, the use of rhBMP-2/ACS resulted in higher rates of fusion and improved clinical outcomes in physical function and reduced pain, while eliminating the morbidity associated with graft harvesting.

Level of Evidence: Therapeutic study, Level I-1a (randomized controlled trial [significant difference])

Deleted: added to

Deleted: Adding

Deleted: and bovine collagen sponge to human allograft bone dowels can be

Deleted: The

Deleted: ,

Deleted: and higher rates of fusion

INTRODUCTION

Anterior lumbar interbody fusion (ALIF) is an effective treatment for patients with symptomatic lumbar spondylosis, low-grade spondylolisthesis and radiculopathy. In 1948, Lane and Moore [21] first reported on the treatment of symptomatic degenerative lumbar disc disease by anterior lumbar interbody fusion. Subsequent reports of the treatment of degenerative lumbar conditions by ALIF followed [16]. Over the past decade, a variety of interbody constructs have been proposed for use in this indication which have been reported to exhibit a wide range of clinical success. Some studies have shown a close correlation between fusion and improved clinical outcomes while others have shown that a successful fusion alone does not guarantee an improved clinical outcome [1,10,19,20,22,23,25]. All of these studies have used varying outcome assessment instruments and have relied upon on plain radiographic evidence alone for determination of fusion status.

In clinical attempts to improve the rates of fusion, an evolution in interbody construct design has occurred in the use of stand-alone interbody fusion devices from femoral ring allografts to threaded cortical bone dowels. The use of stand-alone impacted femoral ring allografts has been associated with high rates of pseudarthrosis, graft subsidence and graft extrusion [13,26]. Threaded allograft bone dowels introduced the concept of using precision-machined allograft constructs in interbody fusion to further enhance the stability of the spinal motion segment [8]. Threaded interbody fusion devices are not intradiscal spacers that require additional segmental fixation; in contrast to intradiscal spacers, threaded dowels are designed for use as stand-alone implants. The threaded implants resist expulsion and stabilize the bone–

implant interface. These devices are designed to withstand lumbar compressive loads while maximizing device porosity and to promote load sharing between the allograft and the host bone [3].

There has been a similar evolution in bone grafting techniques in lumbar spinal fusion surgery. The first use of human allograft for an interbody fusion procedure was by Cloward (11,12) in 1952. He added banked human allograft bone as the spacer to the interbody space. Other surgeons (1,13) reported on similar variations of his technique using fresh autogenous bone to fuse the vertebrae together in, around, or through the allograft spacer. Recombinant human bone morphogenetic protein-2 (rhBMP-2) is an osteoinductive protein that, when combined with the proper carrier at an appropriate concentration, has the potential to make autogenous bone grafting unnecessary [28,30]. rhBMP-2 delivered on an absorbable collagen sponge (ACS) carrier has been investigated in preclinical and clinical studies for its application in ALIF procedures with both metal interbody cages and allograft bone dowels [2,18]. A large, pivotal clinical study indicated that the use of rhBMP-2/ACS does provide equivalent clinical and radiographic outcomes to autogenous iliac crest while reducing OR time and intraoperative blood loss [5]. An integrated analysis of three sequential prospective studies showed the use of rhBMP-2/ACS to be superior to autograft in both fusion success and clinical outcomes [4].

The purpose of this study was to assess the clinical and radiographic outcomes resulting from the use of rhBMP-2/ACS as a bone graft replacement when used in combination with the threaded cortical allograft dowels in comparison with autograft control patients. All patients were enrolled in two sequential prospective FDA-approved

Deleted: RhBMP
Deleted: with
Deleted: and collagen sponge
Deleted: autograph
Deleted: rate of
Deleted: is
Deleted: and
Deleted: compare
Deleted: it to

IDE clinical studies to evaluate clinical and radiographic outcomes in a stand-alone ALIF procedure.

Deleted: of this

MATERIALS and METHODS

A prospective, randomized, multi-center FDA-approved IDE study was conducted in two phases sequentially. The pilot phase enrolled 46 patients at 5 clinical sites which were randomized using a one-to-one ratio. In the pivotal phase, 85 patients were enrolled at 13 clinical sites using a two-to-one randomization ratio between the investigational and control groups. The study protocols for both phases were identical. This paper presents the findings from the combined analysis of all patients enrolled in these two phases.

All patients underwent single-level stand-alone ALIF surgery for degenerative disc disease utilizing a pair of threaded cortical bone dowels (MD-II™, Regenerative Tissues, Inc., Alachua, FL). Autogenous iliac crest bone graft was harvested from the control patients. The investigational patients received rhBMP-2/ACS (INFUSE® Bone Graft, Medtronic Sofamor Danek, Memphis, TN) as an alternative to iliac crest bone graft.

A total of 131 patients were enrolled over a three-year period with the first surgery being performed on April 30, 1998, and the last surgery on March 12, 2001. The pilot phase included 24 rhBMP-2 patients and 22 autograft patients. In the pivotal phase, 55 rhBMP-2 patients and 30 autograft patients were enrolled. A total of 79 investigational patients received threaded cortical bone dowels with rhBMP-2/ACS and 52 control patients received bone dowels augmented with morcellized iliac crest autograft. The rhBMP-2 patients did not have a second surgery to harvest iliac crest bone graft while the control patients did.

Deleted: study consisted of

Deleted: that

Deleted: and a pivotal phase that enrolled 85 patients at 13 sites. The study designed consisted of prospective,

Deleted: with patient enrollment in the pilot phase

Deleted: of the investigational rhBMP-2 and collagen sponge in one group and the autograft bone from the iliac crest (the control) in the other

Deleted: was used

Deleted: combination of these two groups (pilot and pivotal) together

Formatted

Deleted: The prospective, randomized, multi-centered clinical trials used allograft bone dowels (MD-II) supplied by the Regeneration Technology, Inc. (Alachua, FL). The studies were conducted in the United States to determine the safety and effectiveness of using this anterior spinal procedure with and without the use of recombinant bone morphogenetic protein 2 and an absorbable collagen carrier. In both phases of this study, a

Deleted: entered

Deleted: study had

Deleted: investigational

Deleted: with bone dowels and autograft

Deleted: study

Deleted: were in the investigational arm

Deleted: in the control arm

Deleted: bone dowel surgeries were performed with the recombinant bone morphogenetic protein

Deleted: 54

Deleted: were implanted

Deleted: in the control

Deleted: investigational

Deleted: arm of the studies

Deleted: arm

Inclusion Criteria

To be entered into the study, the patient had to be over eighteen years of age and have objective measurements of single level degenerative disc disease with up to grade one spondylolisthesis in the lumbar spine. All patients included in the study had disabling low back pain with or without leg pain. These symptoms persisted for a minimum of 6 months and had not resolved with active, supervised treatment that included therapeutic modalities, aerobic conditioning, and nonsteroidal anti-inflammatory agents.

Patients were included in the study if their radiographic findings documented single-level disc disease. (Note – two patients were missing pre-op CT or MRI) All patients enrolled were considered good candidates for a single-level stand-alone anterior lumbar interbody fusion.

Patients were excluded from the study if they had spinal conditions other than single-level symptomatic degenerative disc disease, greater than Grade 1 spondylolisthesis, or a prior anterior spinal fusion procedure at the involved level. Other exclusion criteria included symptomatic disc disease at a level other than the L4-L5 or L5-S1 disc space levels, obesity (more than 40% above ideal body weight), an overt or active local or systemic bacterial infection, or a medical condition that required medication, such as steroids or nonsteroidal anti-inflammatory medications, that could potentially interfere with fusion.

Deleted: , or both
Deleted: had lasted
Deleted: plain
Deleted: , and they had undergone at least one additional confirmatory neuroradiographic study, such as MRI, CT-enhanced myelography, or discography
Deleted: or
Deleted: 0 or
Deleted: were
Deleted: a history of discitis

Patient Demographics

Demographic data were compiled for all patients in the study. Age, weight, sex, workers' compensation, spinal litigation, tobacco use and work status were assessed in all patients (Table 1).

Deleted: There were no statistically significant differences ($P < 0.05$) between the demographic profiles.

Surgical Procedure

The patients underwent an open ALIF procedure using either a transperitoneal or a retroperitoneal approach to the lumbosacral spine. In each patient, a complete anterior discectomy was carried out. An incision was made in the annulus fibrosus, the nucleus pulposus and the cartilaginous endplates were removed under direct visualization. Importantly, the bony endplates were preserved. The disc space was distracted to an anatomic height consistent with adjacent spinal motion segments. Two channels through the vertebral endplates were precisely prepared by sequential reaming through a guide tube centrally placed in the disc space. The endplate channels were tapped and two allograft bone dowels were then inserted into each disc space.

The rhBMP-2 was reconstituted using sterile water and a single dose at a concentration of 1.5 mg/mL was administered. The concentration was the same in all patients. The solution was applied evenly by syringe to appropriately sized (template?) absorbable collagen sponges and the rhBMP-2 was allowed to bind to the sponges for a minimum of 15 minutes prior to further handling or preparation. A single collagen sponge was placed into the central portion of each bone dowel. Two additional (1" x 2" ?) rhBMP-2 bound sponges were placed between the bone dowels. The total dose (8 to 12 mg rhBMP-2) depended on the capacity of the bone dowel (16, 18, or 20 mm) used. No autogenous grafts or local bone reamings were used in the rhBMP-2 group.

Deleted: 30

Deleted: manipulation of the sponges

Deleted: The total dose (8 to 12 mL) depended on the capacity of the bone dowel (16, 18, or 20 mm) used.

Deleted: prepared

Deleted: investigational

The control group received morcellized autogenous iliac crest graft in conjunction with the threaded cortical bone dowels. The iliac grafts were harvested through a separate incision directly over the iliac wing. The inner or outer table of the ilium was exposed subperiostealy and corticocancellous grafts were harvested. A single cortex was preserved in all grafts; no bicortical iliac grafts were obtained. The central opening of the dowels were packed with morcellized autogenous bone graft before their insertion into the disc space. The protocol also allowed for additional bone graft to be packed between and anterior to the dowels per the surgeon's choice.

Deleted: Additional

Deleted: was

All patients were ambulatory immediately after surgery and were instructed to wear an external lumbosacral orthosis for 6 to 12 weeks following surgery. Physical activities were advanced at the discretion of the attending physician.

Radiographic Outcome Measurements

Stability and radiolucent lines were assessed on plain radiographs using anteroposterior, lateral, and flexion-extension views. In addition, thin-slice (1 mm overlapping) computed tomography scans with coronal and sagittal plane reconstructions were utilized to assess bridging bone. Two independent, blinded radiologists interpreted all radiographs and CT scans to critically assess fusion at 6, 12, and 24 months. A third independent radiologist was used to adjudicate conflicting fusion findings.

As in previous interbody spine fusion studies with rhBMP-2/ACS [7], a fusion was considered successful only if all four fusion criteria were achieved: 1) Bridging trabecular bone connecting the two vertebral bodies either through the dowels or around the dowels; 2) No angular motion of 5° or more; 3) No sagittal translation of

more than 3 mm; and 4) No radiolucencies that involved more than half of the interfaces between the dowels and the host vertebral endplates.

Clinical Outcome Measurements

Assessments were completed preoperatively, during the patient's hospitalization, and postoperatively at 6 weeks and 3, 6, 12, and 24 months. Clinical outcomes were measured using well-established instruments: Oswestry Low Back Pain Disability Questionnaire, Short Form 36 (SF-36), work status, and back, leg, and iliac graft site numerical pain questionnaires. The Oswestry Low Back Pain Disability Questionnaire [14], a self-administered instrument, was used to measure the level of pain and disability associated with various daily activities. The Physical Component (PCS) was derived from the SF-36 [24], also a self-administered questionnaire, measured specific health concepts related to physical functioning. Low back, leg, and iliac graft site pain were evaluated using numerical rating scales that identified both pain intensity and duration. Separate, standard 10-point numerical scales were used to quantify the intensity and duration of the painful symptoms. The two scores were then added together to derive a composite score with a maximum of 20 points.

Monitoring for Antibody to rhBMP-2 and Collagen

Patients were tested separately for an antibody response to exposure of rhBMP-2 and bovine collagen pre-operatively and postoperatively beginning at X.

Statistical Analysis

The data from this clinical trial were analyzed using the statistical software package SAS® version 6.12. For continuous variables, *P* values were determined using

Deleted: visual analogue

Deleted: is

Deleted: and

Deleted: of

Deleted: is

Deleted: that measures

Deleted: visual analog

Deleted: pain

Deleted: *Radiographic Outcome Measurements*¶
Radiographs and CT scans were used to evaluate fusion at 6, 12, and 24 months after surgery. Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent radiologist was used to adjudicate conflicting fusion findings.¶
Fusion was defined as bridging bone connecting the adjacent vertebral bodies either through the implants or around the implants, less than 5 degrees of angular motion, less than or equal to 3 mm of translation, and an absence of radiolucent lines around more than 50% of either of the implant surfaces [7]. Stability and radiolucent lines were assessed on plain radiographs using anteroposterior, lateral, and flexion-extension views. Thin-slice (1 mm) computed tomography scans with coronal and sagittal plane reconstructions were evaluated at 6, 12, and 24 months. The presence of continuous trabecular bone formation between the vertebral bodies was assessed using radiographs and computed tomography scans. A fusion was considered successful only if all four criteria were achieved: 1) bridging trabecular bone connecting the two vertebral bodies either through the dowels or around the dowels as evaluated by thin-cut CT scans and radiographs; 2) no angular motion of 5° or more on dynamic plain radiographs; 3) no sagittal translation of more than 3 mm on dynamic plain radiographs; and 4) no radiolucencies that involved more than half of the interfaces between the dowels and the host vertebral endplates.¶

Formatted

Deleted: a

Deleted: from

ANOVA techniques, and for categorical variables, they were derived from Fisher's exact test or chi-square test.

Deleted: are

RESULTS

Patient Demographics

There were no statistically significant differences ($P < 0.05$) between the demographic profiles of the two patient populations. Fifty-two patients with a mean age of 44 years (range 28-68 years) received the control treatment with autograft (Table 1). In this group, there were 19 men (36.5%). The average weight was 173.2 pounds. Seventeen patients (32.7%) had prior lumbar surgery, 17 (32.7%) used tobacco within the past 6 months of surgery, 6 (11.5%) had pending litigation. Twenty-five patients (48.1%) were working prior to surgery and 17 (32.7%) were seeking Worker's Compensation.

Deleted: 43.6

Deleted: 171.3

Seventy-nine patients (32 mates; 40.5%) received the investigational treatment with rhBMP-2/ACS. Their average age was 40 years (range 19-62 years) and their average weight was 172.3 pounds. Twenty-nine patients (36.7%) had prior lumbar surgery, 26 (32.9%) used tobacco within the past 6 months, 7 (8.9%) had pending litigation, and 23 (29.1%) were seeking Worker's Compensation. Forty-seven (59.5%) were working prior to surgery.

Deleted: on a collagen soaked sponge

Deleted: .2

Surgery

The rhBMP-2 group had surgery more commonly at the L4-5 level. In the autograft group, surgery was performed at the L4-L5 level in 14 patients (26.9%) and at the L5-S1 level in 38 patients (73.1%) (Table 2). In the rhBMP-2 group, 23 patients (29.1%) had surgery at the L4-5 level and 56 (70.9%) had surgery at the L5-S1 level. The mean operative time in the rhBMP-2 group was 1.4 hours compared to 1.8 hours in the autograft group ($p<0.001$). The average blood loss was only 87.4cc in the rhBMP-2

Deleted: control

Deleted: investigational

Deleted: investigational

Deleted: treated

Deleted: control

Deleted: The investigational group had surgery more commonly at the L4-5 level.

group as compared to 184.7cc in the autograft group (p<0.001). The average hospital stay was also less in the rhBMP-2 group, 2.9 days versus 3.3 days in the autograft group (p=0.020).

Clinical Follow-up

Patients were followed for a minimum of two years following surgery. One autograft patient died before the 12-month follow-up. Patients undergoing a revision, supplemental fixation or retrieval surgeries were classified as clinical failures. Once a patient was classified as a failure, their clinical data was no longer included in later follow-up periods. Eight autograft patients and two rhBMP-2 patients were classified as failures over the course of the study. Two autograft patients and three rhBMP-2 patients were lost over the course of the study. At 24 months, 42 (81%) control patients and 74 (94%) investigational patients were available for follow-up. Patient return was 93% and 97% for the autograft and rhBMP-2 patients, respectively, at 24 months. (This is more detail than we typically report in accountability – are we all comfortable with this?).

Fusion Assessment Outcomes

At all fusion assessment time points, the rhBMP-2 group exhibited a greater rate of fusion success compared to the autograft patients. At six months following surgery, 95.9% of rhBMP-2 patients had evidence of interbody fusion as compared to 85.1% of autograft patients (p=0.047) (Table 7). At 12 months, 98.6% of rhBMP-2 patients were fused, while the autograft group showed evidence of fusion in 89.4% of patients. At the final two-year radiographic follow-up, 98.5% of patients in the rhBMP-2 group remained fused as compared to 76.1% of patients in the autograft group (p=0.001). All patients

Deleted: control

Deleted: control

Deleted: Outcomes

Deleted: 90

Deleted: or higher

Deleted: (range /// - ///)

Deleted: each follow-up interval

Deleted: No unanticipated adverse events occurred which were related to the use of rhBMP-2 or the collagen sponge carrier.

were deemed to be failures either to radiographic evidence or due to secondary surgeries described below. In the control group, there were no failures of the allograft dowels. Radiographic lucencies developed at the interface of the allograft to the vertebral endplate. There was no migration of the implants.

Oswestry Low Back Disability Questionnaire

Both groups showed sustained improvement in their mean Oswestry scores following surgery at all time points throughout the 24-month follow-up (Table 6). The rhBMP-2 group exhibited significantly better mean Oswestry scores at all time points as compared to the autograft group. Since there was a slight difference, though not a statistical difference, in the preoperative values between the two groups, the average improvement in Oswestry score was calculated at each time interval. At all intervals studied, the rhBMP-2 group showed a greater mean improvement in their Oswestry scores when compared to the autograft group. These differences reached statistical significance at the 3- and 6-month follow-up interval (P=0.021 and P=0.031, respectively).

Physical Component of the SF-36

The physical component score (PCS) was calculated from the SF-36 health survey, where patients evaluated their own condition. At 6 months, the rhBMP-2 group exhibited a mean PCS of 43.4 with an average improvement of 14.3 points from their preoperative status (Table 5). These scores were statistically significantly better than those measured in the autograft group with a mean PCS score of 37.0 (p=0.001) corresponding to a mean improvement of 9.5 points (p=0.017). Both groups continued to improve their PCS scores at 12 and 24 months. The rhBMP-2 group had statistically

Deleted: Low Back Pain¶
Patients in the investigational group (rhBMP-2) had a mean back pain analog score of 7.5 (maximum pain score = 20) and showed an average improvement of more than 8 points at their initial postoperative visit at 3 months (Table 3). At 3 months, the autograft control group had a back pain analog score of 10.2 points and 6-point mean improvement in back pain scores. The difference in mean back pain scores between the investigational and the control group was statically significant at 3 months (p=0.003). Both treatment groups showed continued improvement in back pain scores through the study. The mean analog back pain scores in the investigational BMP-2 group remained significantly improved when compared to the autograft control group (p=0.006 at 6 months; p=0.007 at 12 months; and p=0.032 at 24 months).¶

significantly higher PSC scores when compared to the autograft group at 12 and 24 months (p=0.003 and p=0.015, respectively). At 12 months the mean improvement was greater for the rhBMP-2 group compared to the autograft group (p=0.027).

Back and Leg Pain

Both treatment groups demonstrated significant reductions in average back and leg pain scores at all time points as compared to their preoperative condition (P<0.001). Although reduction in back pain was observed as early as 6 weeks, the rhBMP-2 patients reported a significantly lower average numerical rating back pain score as compared to the autograft patients beginning at 3 months postoperatively and continuing throughout the 24-month follow-up. At three months, the rhBMP-2 group had a mean back pain score of 7.5 (out of a maximum 20 points) and showed an average improvement of more than 8 points from their preoperative visit (Table 3). In comparison, the autograft control group had a back pain score of 10.2 points and a 6.7-point mean improvement from preoperative levels. The difference in mean back pain scores between the rhBMP-2 and the autograft group was statistically significant at 3 months (p=0.003). Both treatment groups maintained this reduction in back pain scores throughout the study. The mean back pain scores in the rhBMP-2 group remained significantly lower when compared to the autograft control group (p=0.006 at 6 months; p=0.007 at 12 months; and p=0.032 at 24 months).

Both groups exhibited a sustained reduction in average numerical rating leg pain scores compared to the preoperative status over the 24-month study; however, the rhBMP-2 group exhibited a statistically significant lower average leg pain score at most of the follow-up time points. At the 6-week follow-up visit, the rhBMP-2 group had a

Formatted

Deleted: initial

Deleted: investigational

mean leg pain score of 6.2 points (out of a maximum 20 points) and average reduction of 6.4 points (Table 4). In comparison, the autograft group had statistically higher mean leg pain score of 8.6 points (p=0.020) corresponding to an average reduction of 5.4 points from the preoperative status. Both groups maintained a reduction in leg pain as compared to their preoperative status; however, the autograft patients reported a slight increase at later follow-up times. The difference in mean leg pain scores was statistically significantly different between the two groups at 6, 12 and 24 months (p=0.043, p=0.011 and p=0.011 respectively).

Return to Work

More patients were working preoperatively in the rhBMP-2 group (59.5%) as compared to the autograft patients (48.1%). By 24 months, more patients from both groups were working as compared to preoperative status. However, the rhBMP-2 group reported improved working status as early as 12 months. Using survivorship analysis, it was determined that the rhBMP-2 patients returned to work at an average of 89 days as compared to 96 days for the autograft patients. This difference was not statistically significant.

Bone Graft Harvest Site Pain

Deleted: analog

Deleted: improvement

Deleted: The

Deleted: a

Deleted: analog

Deleted: and

Deleted: improvement

Deleted: These results at 6 weeks compared favorably statically to the control group (p=0.020).

Deleted: These results remained improved at an average of 6.8 points for the investigational group at last follow-up of 24 months. However, while the autogenous graft group showed initial mean improvement of 5.4 points, the average improvement at 24 months decreased to 4.8 points. The difference in mean leg pain scores remained statistically significant different between the two groups at 6, 12 and 24 months (p=0.043, p=0.011 and p=0.011 respectively).

Deleted: Physical Component of the SF-36¶
General health status on the patients was addressed using the SF-36 short form health survey, where each patient evaluated their own condition. At 6 months in the Physical Component (PCS) of the SF-36, the investigational group showed a mean score of 43.4 with and average improvement of 14.3 points (Table 5). These score were significantly better than the improvement seen in the autograft control group (mean PCS score 37.0 and mean improvement 9.5 points; p<0.001). Both groups continued to show improvements in their PCS scores at 12 and 24 months. The investigational BMP-2 group showed significant improvements in PSC scores when compared to the control group at 12 and 24 months (p=0.003 and p=0.015).

Deleted: Oswestry Low Back Disability Questionnaire¶
. The Oswestry Disability Questionnaire assessed pain associated with activities. Both groups showed improvements in their mean Oswestry scores following surgery and both groups maintained the improvement in Oswestry scores throughout the 24-month follow ... [1]

Deleted: Higher percentages of patients in the investigational group were also able to return to work (Figure //). These patients were also able to return to work earlier th ... [2]

Autograft bone was not harvested from the iliac crest in the rhBMP-2 group of patients and therefore, bone graft harvest site pain was not measured. While the average donor site pain following ALIF surgery was similar to previous reports, the pain was observed to persist at a slightly higher rate of 46.5% of autograft patients for 24 months postoperatively.

Additional Surgery

Patients undergoing a revision, removal, or supplemental fixation were classified as failures. Two (2.5%) patients in the rhBMP-2 group required an additional surgical procedure for supplemental fixation and were classified as failures in the study. Eight (15.4%) patients in the autograft group required an additional surgical procedure for supplemental fixation after their primary surgery.

In the BMP-2 group, /// patient continued to have persistent low back pain at two years postoperatively. The radiographs met the criterion for fusion; however, the attending physician elected to reoperate and supplement the interbody grafts with insertion of posterior pedicle fixation due to slight motion in the facet joints. //// patients in the control group had supplemental posterior fixation inserted from //// months to /// months following their initial surgeries. In each of these cases, the patients complained of persistent low back pain and in some instances referred leg pain.

Adverse Events

Table /// shows the adverse events reported for each treatment group. (To what level do we want to report these? I don't believe we want to report in the same manner

Deleted: investigational

Deleted: and was assumed to be zero

Deleted: ///

Deleted: in the immediate perioperative period

Deleted: : ///

Deleted: control

Deleted: early return to surgery to remove residual disc material. /// patients

Deleted: underwent

Deleted: posterior

Deleted: procedure

Deleted: *Radiographic Outcomes*¶ . At six months following surgery, 95.9% of patients in the investigational BMP-2 group had evidence of interbody fusion as compared to 85.1% of patients in the control group (p=0.047) (Table 7). At 12 months, 98.6% of patients in the investigational group were fused while the control group showed evidence of fusion in 89.4% of patients at one year. At the final two-year radiographic follow-up, 98.5% of patients in the BMP-2 group remained fused as compared to 76.1% of patients in the control group (p=0.001). In the control group, there were no failures of the allograft dowels. Radiographic lucencies developed at the interface of the allograft to the vertebral endplate. There was no migration of the implants. ¶

as we do in IDE studies. I personally think it is appropriate to simply report that they were equivalent in the two groups without the detail.)

Antibody Formation

A total of 49 autograft and 78 rhBMP-2 patients were tested for an elevated antibody response to rhBMP-2 and bovine collagen. Among those tested, no patients from either group developed an elevated antibody response to rhBMP-2. However, four (8.2%) autograft patients and 7 (9.0%) rhBMP-2 patients exhibited an elevated antibody response to bovine collagen.

Deleted: ?? % of patients showed an allergic repose to the bovine collagen; /// % of patients developed an allergic response to rhBMP-2.

DISCUSSION

Prior to the conduction of these clinical studies, a non-human primate (rhesus monkey) study was performed using allograft bone dowels in the lumbar spine (17). In three monkeys, a single smooth allograft bone dowel with rhBMP-2 on an absorbable collagen sponge (ACS) was implanted anteriorly into the disc space of the L7-S1 disc space. At three month following surgery, all three investigational animals showed new bone formation with complete incorporation of the allograft dowels leaving trabecular bone continuous with host bone of both adjacent vertebras. The rapid incorporation of the allograft dowels and intradiscal fusion is, in part, related to the ability of rhBMP to induce direct intramembranous ossification of the collagen carrier [30]. (Do we all believe there is a direct correlation here as this statement is written? I think the issue may address speed of fusion but I'm not sure it explains allograft incorporation.) In contrast, transplanted, transferred autogenous grafts may need to be resorbed or be remodeled before fusing [15]. This feature may partially explain why these animal studies had superior results with rhBMP-2/ACS when compared with autogenous iliac crest bone graft.

The combined date from two clinical trials in humans using threaded cortical bone dowels and rhBMP-2, first in a pilot study (6) and later in a pivotal study, are reported here. The use of rhBMP-2/ACS has been shown to induce new bone formation in single level anterior interbody fusions in humans [2,5,18]. rhBMP-2 used with a threaded tapered titanium cage in ALIF surgery has also been shown to have superior clinical outcomes and radiographic fusion rates when compared to iliac crest bone graft [4]. Superiority over autograft was demonstrated after enrollment of 679 patients in

Deleted: A
Deleted: a bovine
Deleted: into
Deleted: the
Deleted: vertebra
Deleted: containing grafts
Deleted: auto
Deleted: being
Deleted: on a collagen soaked sponge
Deleted: autograft

three sequential prospective studies. By eliminating the need for autograft harvesting, the rhBMP-2 group reported shorter OR times, lower blood loss, and reduced hospital stays. Radiographically, the rhBMP-2 group exhibited higher fusion rates. Clinically, the rhBMP-2 group demonstrated improved results using the Oswestry Disability Questionnaire, SF-36, back and leg pain scales, and return to work. The autograft group reported donor site pain in nearly one-third of patients at 24 months postoperatively. This study clearly demonstrated that rhBMP-2/ACS is an effective replacement for autogenous iliac crest bone graft.

In the present study of 131 patients undergoing stand-alone ALIF with threaded cortical bone dowels, patients treated with rhBMP-2/ACS again exhibited superior outcomes as compared to iliac crest bone graft in many clinical and radiographic outcomes.

As reported above with tapered titanium cages, the elimination of autogenous bone graft harvesting resulted in statistically significant lower operative times, blood loss, and hospital stays ($P \leq 0.020$). Furthermore, by avoiding the harvest procedure, rhBMP-2/ACS eliminated the morbidity reported by the autograft patients. Nearly half of the autograft patients were still reporting donor site pain in this study.

Independent radiographic assessment was conducted at 6, 12 and 24 months using both x-rays and thin-slice CT scans in this study. At all time points, the rhBMP-2 group exhibited statistically higher fusion success as compared to the iliac crest bone graft patients. The greatest difference was seen at 24 months where the rates were 98.5% and 76.1%, respectively ($p<0.001$). This difference is in large part due to a difference in the need for additional surgery to achieve a desired outcome. Only 2

Deleted: only

Deleted: the superiority of

Deleted: over autograft

Deleted: when used with threaded cortical allograft dowels was demonstrated

(2.5%) rhBMP-2 patients required additional spinal surgery as compared to 8 (15.4%) autograft patients.

Although not discussed in detail here, the increased incorporation of the allograft bone dowel with the host's bone when rhBMP-2/ACS is used as an autograft replacement can be seen in some of the serial CT scans. In comparison, the autograft patients did not exhibit this acceleration of incorporation. These observations suggest that there is an interaction between the allograft bone and rhBMP-2 that was not previously observed when used with titanium interbody cages. Although this increased incorporation was noted, it did not negatively affect either the fusion rate or the long-term mechanical stability since these patients did not require supplemental surgery. Interestingly, this incorporation did vary to some extent from patient to patient ranging from complete incorporation to very localized incorporation where there was direct contact with the endplates. Further analysis of the films is needed to better understand the range in response seen and the potential factors that may influence the amount and rate of allograft incorporation.

It is unknown if this incorporation will be seen in different fusion sites or when using constructs with different configurations in combination with rhBMP-2/ACS. Some preliminary results have been presented when rhBMP-2/ACS was used in conjunction with femoral ring allograft in one and two level lumbar fusions in combination with percutaneous posterior instrumentation [**Herman, Jt Sections, 2004**]. When rhBMP-2/ACS was used as an alternative to iliac crest bone graft, the CT scans indicated increased incorporation at the endplates. However, complete incorporation of the femoral ring allograft was not reported within the **one-year** follow-up.

On average, both the autograft and rhBMP-2 groups reported improvement in function and pain as compared to their preoperative status. Clinical improvement was documented as early as 6 weeks in this study. However, the improved fusion rates may have contributed to the better clinical outcomes noted in many of the clinical measures among the rhBMP-2 group, particularly at the longer follow-up time points. At 6, 12 and 24 months in this study, the rhBMP-2/ACS treated patients demonstrated significant improvement over autograft patients in several outcome measurements including: back and leg pain scores, Physical Component Score of the SF-36, and Oswestry Disability index scores. At 24 months, rhBMP-2 patients averaged a 33.4-point improvement in Oswestry pain scores when compared to pre-operative scores. This improvement is the largest reported in any lumbar spinal fusion study.

These data strongly demonstrate that rhBMP-2/ACS can successfully replace harvested iliac bone without the known donor site pain [27,29] and can be used to help incorporate allograft bone dowels in the lumbar spine of humans. Furthermore, these data support the concept that increased fusion rates are associated with improve functional outcomes and decreases in pain scores. The allograft dowels rapid improvement in patient outcome may be, in part, attributed to acceleration of the incorporation of the bone dowel. The allograft bone dowels had a modulus of elasticity similar if not nearly identical to the host bone. Once healing has occurred, their was no distinction between implant and host bone. The stability gained at the involved level as a result of fusion was maintained up to 24 months and appears to contribute to the long-term clinical success associated with the combination of rhBMP-2 and allograft bone dowels.

Deleted: investigational
Deleted: controls
Deleted: visual analog
Deleted: clinical outcomes
Deleted: over
Deleted: 32
Deleted: we have been able to find of
Deleted: show
Deleted: on a collagen sponge
Deleted: These

CONCLUSION

These studies confirm the striking results found in non-human primate studies that rhBMP-2 added to allograft bone is a safe and effective combination in anterior lumbar interbody fusion surgery. The results show that increase in fusion rate was associated with improved functional outcomes and decrease in pain scores, both statistically significant ($p < 0.05$). Although further research is needed, these findings support the use of rhBMP-2 with an absorbable collagen sponge with human allograft dowels for spinal fusion in ALIF applications.

REFERENCES

1. Blumenthal SL, Baker J, Dossett A, Selby DK: The role of anterior lumbar fusion for internal disc disruption. *Spine* 13: 566-569, 1988.

2. Boden SD, Zdeblick TA Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Spine 2000;25:376-381.

3. Boyd, L.M.; Estes, B.T. and Liu M. "Biomechanics of Lumbar Interbody Constructs, *Effect of Design and Materials*." Chirurgie Endoscopique et Mini-invasive du Rachis. Ed. Husson JL, LeHuec JC. Sauramps Médical. Montpelier, France. pp 181-192, 1999.

4. Burkus JK, Heim SE, Gornet MF, Zdeblick TA. Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-CAGE lumbar tapered fusion device. *J Spinal Disord & Techniques* 2003;16:113-22.

5. Burkus JK, Gornet MF, Dickman C, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. *J Spinal Disord Tech* 2002;15:337-49.

6. Burkus JK, Transfeldt EE, Kitchel SH, Watkins RG, Balderston RA. Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2. *Spine* 2002;27:2396-408.

7. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. Neurosurg Focus 2001;10:1-9.

8. Burkus JK: Intervertebral fixation: clinical results with anterior cages. Orthop Clin North Am 2002;33: 349-357.

9. Burkus JK. Threaded Bone Dowels. "Lumbar Interbody Fusion Techniques: Cages, Dowels, and Grafts." Quality Medical Publishing, Inc. 2003:148-168.

10. Chow SP, Leong JCY, Ma A, Yau ACMC: Anterior spinal fusion for deranged lumbar intervertebral disc. *Spine* 5: 452-458, 1980.

11. Cloward RB. The treatment of ruptured lumbar intervertebral disc by vertebral body fusion. III Method of use of banked bone. *Ann Surg* 1952;136:987-91.

12. Cloward RB. Lesions of the intervertebral disks and their treatment by interbody fusion methods. *Clin Orthop* 1963;27:51-77.

13. Dennis S, Watkins R, Landaker S, Dillin W, Springer D. Comparison of disc space heights after anterior lumbar interbody fusion. Spine 1989;14: 876-878.

14. Fairbank JCT and Pynsent PB "The Oswestry Disability Index" *Spine* 25(22): 2940 – 2953, 2000.

15. Goldberg VM, Lance EM. Revascularization and accretion in transplantation. *J Bone Joint SurgAm* 1972;54:807.

16. Harmon PH. Anterior excision and vertebral body fusion operation for intervertebral disc syndromes of the lower lumbar spine. *Clin Orthop* 1963;26:107-27.

17. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. *Spine* 1999;24:629-36.

18. Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2. A prospective study of clinical and radiographic outcomes. Spine 2001;26:2751-6.

19. Kumar A, Kozak JA, Doherty BJ, Dickson JH. Interspace distraction and graft subsidence after anterior lumbar fusion with femoral strut allograft. Spine 1993;18:2393-2400.

20. Kuslich SD, Ulstron CL, Griffith SL, Ahern JW, Dowdle JD "The Bagby and Kuslich method of lumbar interbody fusion: History, techniques, and 2-year follow-up results of a United States prospective, multicenter trial" *Spine* 23(11): 1267 – 1278, 1998.

21. Lane JD, Moore ES. Transperitoneal approach to the intervertebral disc in the lumbar area. *Ann Surg* 1948;127:537-51.

22. Leong JCY, Chun SY, Grange WJ, Fang D: Long-term results of lumbar intervertebral disc prolapse. *Spine* 8: 793-799, 1983.

23. Loguidice VA, Johnson RG, Guyer RD, Stith WJ, Ohnmeiss DD, Hochschuler SH, Rashbaum RF: Anterior lumbar interbody fusion. *Spine* 13:366-369, 1988.

24. McHorney CA, Ware JE Jr., Lu RJF, Sherbourne CD. The MOS 36-Item Short-From Health Survey (SF-36), III: tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994;32:40-66

25. Newman MH, Grinstead GL: Anterior lumbar interbody fusion for internal disc disruption. *Spine* 17: 831-833, 1992.

26. Sasso RC, Kitchel SH, Dawson EG. A prospective, randomized controlled clinical trial of anterior lumbar interbody fusion using a titanium cylindrical threaded fusion device. *Spine* 2004;29:113-22.

27. Sasso, RC, LeHuec JC, Shaffrey C. Iliac crest bone graft donor site pain after anterior lumbar interbody fusion: a prospective patient satisfaction outcome assessment *J Spinal Disord Tech*. In press.

28. Urist MR. Bone formation by autoinduction. *Science* 1965;150:893-99.

29. Vaccaro AR, Kazuhiro C, Heller JG, Patel TC, Thalgott JS, Truumees E, Fischgrund JS, Craig MR, Berta SC, Wang JC. Bone grafting alternatives in spinal surgery. The Spine Journal 2002;2:206-15.

30. Wozney JM. Overview of bone morphogenetic proteins. *Spine* 2002; 27S:2-8.

TABLE 1. Patient demographic data

Demographic Data	rhBMP-2/ACS	Autograft
Number of patients	79	52
Average Age (years)	40.2	43.6
Average Weight (lbs)	172.3	173.2
Sex (male/female)	32/47	19/33
Workers' Compensation (%)	23 (29.1)	17 (32.7)
Spinal litigation (%)	7 (8.9)	6 (11.5)
Tobacco use (%)	26 (32.9)	17(32.7)
Previous surgeries (%)	29 (36.7)	17 (32.7)

Deleted: No.

Deleted: compensation

Table 2. Intraoperative Data

Surgical Data	rhBMP-2/ACS	Autograft	P-Value*
Average Operative time (hr)	1.4	1.8	<0.001
Average Blood loss (mL)	87.4	184.7	<0.001
Surgical Level (%)			0.785
L4-L5	11 (46)	8 (36)	
L5-S1	13 (54)	14 (64)	
Average Hospital stay (days)	2.9	3.3	0.020

*P-values are derived from ANOVA for continuous variables and derived from Fisher's Exact Test for categorical values.

Deleted: rhBMP

Deleted: Levels

Deleted: Table 3: Back pain outcomes Anterior Lumbar Interbody Fusion using threaded cortical bone dowels containing rhBMP-2 and a collagen sponge carrier to iliac crest autograft

Table 3
Summary of Average Back Pain Scores

Period	rhBMP2/ACS	Autograft	P-Value*
Preoperative	15.6	16.8	0.039
6 Weeks	8.1	9.6	0.090
3 Months	7.5	10.2	0.003
6 Months	6.4	9.1	0.006
12 Months	6.4	9.5	0.007
24 Months	7.0	9.7	0.032

*P-values are derived from ANOVA.

Table 4
Summary of Average Leg Pain Scores

Period	RhBMP-2/ACS	Autograft	P-Value*
Preoperative	12.6	14.2	0.094
6 Weeks	6.2	8.6	0.020
3 Months	6.4	8.3	0.065
6 Months	4.9	6.9	0.043
12 Months	5.1	8.0	0.011
24 Months	5.8	9.3	0.011

*P-values are from ANOVA.

Deleted: ¶
¶

Table 5

Physical Component Score derived from SF-36 Health Survey

Period	BMP2	Autograft	P-Value*
Preoperative (Mean)	29.2	27.6	0.184
6 Months (Mean)	43.4	37.0	0.001
12 Months (Mean)	45.3	38.9	0.003
24 Months (Mean)	44.9	39.2	0.015

*P-values are from ANOVA.

TABLE 6

Summary of Oswestry Low Back Pain and Disability Scores

Period		rhBMP-2	ICBG	p-value
Preoperative	Mean	53.7	56.6	0.144
6 weeks	Mean	39.4	47.6	0.008
	Mean improvement	-14.2	-9.0	0.060
3 months	Mean	28.4	38.5	0.001
	Mean improvement	-25.3	-18.5	0.021
6 months	Mean	21.5	30.8	0.003
	Mean improvement	-32.4	-25.6	0.031
12 months	Mean	20.9	29.3	0.018
	Mean improvement	-33.0	-27.0	0.074
24 months	Mean	20.4	28.9	0.037
	Mean improvement	-33.4	-27.0	0.119

p-values are for mean scores are calculated using analysis of variance. P-values for mean improvement are calculated using paired t-test.

Table 7
Summary of Fusion Success Rates

Period	BMP2	Autograft	P-Value*
6 Months	95.9	85.1	0.047
12 Months	98.6	89.4	0.036
24 Months	98.5	76.1	<0.001

*P-values are from Fisher's exact test

Page 18: [1] Deleted Medtronic Employee 6/13/2004 6:41:00 AM

Oswestry Low Back Disability Questionnaire

The Oswestry Disability Questionnaire assessed pain associated with activities. Both groups showed improvements in their mean Oswestry scores following surgery and both groups maintained the improvement in Oswestry scores throughout the 24-month follow-up except for the autograft patients where the improvement dropped slightly at 24 months (Table 6). At all intervals studied, the investigational BMP-2 group showed a greater improvement in their mean Oswestry scores when compared to the autograft control group.

Page 18: [2] Deleted Medtronic Employee 6/13/2004 1:41:00 PM

Higher percentages of patients in the investigational group were also able to return to work (Figure //). These patients were also able to return to work earlier than those in the control group.

From: J. Kenneth Burkus[redacted]
Sent: Saturday, July 3, 2004 11:32:27 AM
To: [redacted] Gornet, Matthew; Carol Binns[redacted]; Carolyn M Capers[redacted]
CC: DeMane, Michael; Miller, David [A-SOF-D]; Wehrly, Peter; Treharne, Rick; Beals, Neil; Martin, Bill; Bearcroft, Julie
Subject: BMP Bone Dowel manuscript

Attachments: Bone Dowel BMP pilot.pivotal studies.doc

Sirs,

I have attached the **first draft** of a manuscript that reports on the combined pilot and pivotal clinical and radiographic data from the Bone Dowel BMP FDA IDE studies.

In short, this manuscript documents the superiority in clinical and radiographic outcomes with the use of rhBMP2 in a study population of only 133 patients.

The manuscript is formatted for submission to *The Journal of Bone and Joint Surgery*.

So, come in off the porch and put down the sparklers, bottle rockets and M-80s. This manuscript will start the real fireworks.

Happy Fourth of July - now get to work read the paper and return it to me as soon as possible with all of your additions/criticisms/changes/additions/deletions.

Best regards,
Ken Burkus

Use of rhBMP-2 in Combination with Structural Cortical Allografts Improves Clinical and Radiographic Outcomes in Anterior Lumbar Spinal Surgery

J. Kenneth Burkus, MD *

Harvinder S. Sandhu, MD #

Matthew F. Gornet, MD **

Michael C. Longley, MD +

* Staff Physician, Wilderness Spine Services, The Hughston Clinic, Columbus, Georgia

Associate Professor, Weill Medical College, Cornel University, New York, New York

** Staff Physician, The Orthopaedic Center of St. Louis, St. Louis, Missouri

+ Staff Physician, Nebraska Spine Center, Omaha, Nebraska

Medtronic Sofamor Danek, Memphis, TN, sponsored this study.

Address correspondence and reprint requests to: J.K. Burkus, MD, The Hughston Clinic, PC, [redacted]

ABSTRACT

Background: A non-human primate study of anterior lumbar interbody fusion using non-human allograft dowel in combination with recombinant human bone morphogenetic protein-2 (rhBMP-2) delivered on an absorbable collagen (ACS) sponge was compared to an allograft dowel with autogenous iliac crest bone graft [17]. This study found that using rhBMP-2/ACS had increased the incorporation of the allograft dowels with the host bone. A pilot prospective, randomized clinical trial in humans comparing pairs of threaded allograft cortical bone dowels in stand-alone anterior lumbar interbody fusion having either rhBMP-2/ACS or autogenous bone graft was previously performed which showed increased rates of fusion and improved clinical outcomes in patients treated with rhBMP-2 [6].

Methods: Between 1998 and 2001, a prospective, randomized, multi-centered trial of 131 patients was conducted to determine the safety and efficacy of using rhBMP-2/ACS as an autogenous iliac crest bone graft replacement in anterior lumbar spinal fusion surgery using stand-alone threaded cortical allograft dowels. This study was conducted in two parts: a pilot and pivotal phase. The pilot study utilized a one-to-one randomization ratio of investigational to controls, while the pivotal phase had a two-to-one randomization ratio. Patients were studied pre-operatively, at surgery/discharge, 6 weeks, and 3, 6, 12, and 24 months for clinical and radiographic outcomes using standard clinical instruments including Oswestry Disability Index and SF-36 questionnaires, and numeric rating scales for back, leg and donor site pain. Independent radiographic assessment was conducted at 6, 12 and 24 months using AP and lateral radiographs, flexion/extension radiographs, and thin-slice (1 mm) CT scans.

Deleted: and
Deleted: autograft
Deleted: with allograft dowels treated with rhBMP-2
Deleted: into
Deleted: collagen sponge
Deleted: safety
Deleted: on collagen soaked sponge
Deleted: All p

Results: The use of rhBMP-2/ACS as an iliac crest bone graft replacement provided both immediate surgical advantages and also avoided the long-term morbidity observed with the bone graft harvesting procedure. The patients treated with rhBMP-2/ACS had statistically superior outcomes ($p<0.05$) with regard to length of surgery, blood loss, and hospital stay compared to control patients due to the elimination of the second surgery associated with harvesting autograft. Nearly half of the autograft patients reported donor site pain at the 24-month follow-up. Fusion rates were statistically superior in the rhBMP-2 group compared to the autograft at all time points ($P<0.05$). The need for supplemental surgery over time was reduced with the use of rhBMP-2/ACS as compared to that observed among the autograft patients. Similarly, average Oswestry Disability Index scores, Physical Component Scores (SF-36) low back and leg pain scores, at 6, 12, and 24 months were statistically superior in the rhBMP-2 treated group. No unanticipated device-related adverse effects were identified with the use of rhBMP-2/ACS.

Deleted: and a resorbable collagen sponge
Deleted: and
Deleted: Low back and leg pain visual analog scores,
Deleted: and
Deleted: the
Deleted: of the
Deleted: scores
Deleted: showed
Deleted: outcomes
Deleted: Similarly, fusion rates were statistically superior in the BMP-2 group.
Deleted: and a resorbable collagen sponge.

Conclusions: This study confirms the dramatic findings found in animal studies that rhBMP-2/ACS in conjunction with threaded allograft cortical bone dowels is a safe and effective combination that leads to new bone formation and allograft incorporation in anterior lumbar interbody fusions. In this application, rhBMP-2/ACS is a successful replacement for autogenous bone graft. In combination with threaded allograft cortical bone dowels, the use of rhBMP-2/ACS resulted in higher rates of fusion and improved clinical outcomes in physical function and reduced pain, while eliminating the morbidity associated with graft harvesting.

Level of Evidence: Therapeutic study, Level I-1a (randomized controlled trial [significant difference])

Deleted: added to

Deleted: Adding

Deleted: the bovine collagen sponge to human allograft bone dowels can be

Deleted: The

Deleted: ,

Deleted: and higher rates of fusion

INTRODUCTION

Anterior lumbar interbody fusion (ALIF) is an effective treatment for patients with symptomatic lumbar spondylosis, low-grade spondylolisthesis and radiculopathy. In 1948, Lane and Moore [21] first reported on the treatment of symptomatic degenerative lumbar disc disease by anterior lumbar interbody fusion. Subsequent reports of the treatment of degenerative lumbar conditions by ALIF followed [16]. Over the past decade, a variety of interbody constructs have been proposed for use in this indication which have been reported to exhibit a wide range of clinical success. Some studies have shown a close correlation between fusion and improved clinical outcomes while others have shown that a successful fusion alone does not guarantee an improved clinical outcome [1,10,19,20,22,23,25]. All of these studies have used varying outcome assessment instruments and have relied upon on plain radiographic evidence alone for determination of fusion status.

In clinical attempts to improve the rates of fusion, an evolution in interbody construct design has occurred in the use of stand-alone interbody fusion devices from femoral ring allografts to threaded cortical bone dowels [9A]. The use of stand-alone impacted femoral ring allografts has been associated with high rates of pseudarthrosis, graft subsidence and graft extrusion [13,26]. Threaded allograft bone dowels introduced the concept of using precision-machined allograft constructs in interbody fusion to further enhance the stability of the spinal motion segment [8]. Threaded interbody fusion devices are not intradiscal spacers that require additional segmental fixation; in contrast to intradiscal spacers, threaded dowels are designed for use as stand-alone implants. The threaded implants resist expulsion and stabilize the bone–

implant interface. These devices are designed to withstand lumbar compressive loads while maximizing device porosity and to promote load sharing between the allograft and the host bone [3].

There has been a similar evolution in bone grafting techniques in lumbar spinal fusion surgery [9A]. The first use of human allograft for an interbody fusion procedure was by Cloward [11,12] in 1952. He added banked human allograft bone as the spacer to the interbody space. Other surgeons [1,13] reported on similar variations of his technique using fresh autogenous bone to fuse the vertebrae together in, around, or through the allograft spacer. Recombinant human bone morphogenetic protein-2 (rhBMP-2) is an osteoinductive protein that, when combined with the proper carrier at an appropriate concentration, has the potential to make autogenous bone grafting unnecessary [28,30]. rhBMP-2 delivered on an absorbable collagen sponge (ACS) carrier has been investigated in preclinical and clinical studies for its application in ALIF procedures with both metal interbody cages and allograft bone dowels [2,18]. A large, pivotal clinical study indicated that the use of rhBMP-2/ACS does provide equivalent clinical and radiographic outcomes to autogenous iliac crest while reducing operating room time and intraoperative blood loss [5]. An integrated analysis of three sequential prospective studies showed the use of rhBMP-2/ACS to be superior to autograft in both fusion success and clinical outcomes [4].

The purpose of this study was to assess the clinical and radiographic outcomes resulting from the use of rhBMP-2/ACS as a bone graft replacement when used in combination with the threaded cortical allograft dowels in comparison with autograft control patients. All patients were enrolled in two sequential prospective FDA-approved

Deleted: RhBMP
Deleted: with
Deleted: and collagen sponge
Deleted: autograph
Deleted: rate of
Deleted: is
Deleted: and
Deleted: compare
Deleted: it to

Deleted: of this

IDE clinical studies to evaluate clinical and radiographic outcomes in a stand-alone ALIF procedure using dual, paired, threaded cortical allograft dowels.

MATERIALS and METHODS

A prospective, randomized, multi-center FDA-approved IDE study was conducted in two phases sequentially. The pilot phase enrolled 46 patients at 5 clinical sites which were randomized using a one-to-one ratio. In the pivotal phase, 85 patients were enrolled at 13 clinical sites using a two-to-one randomization ratio between the investigational and control groups. The study protocols for both phases were identical. This paper presents the findings from the combined analysis of all patients enrolled in these two phases.

All patients underwent single-level stand-alone ALIF surgery for degenerative disc disease utilizing a pair of threaded cortical bone dowels (MD-II™, Regenerative Tissues, Inc., Alachua, FL). In the control group, autogenous iliac crest bone graft was harvested and used in conjunction with the allograft implants. The investigational patients received rhBMP-2/ACS (INFUSE® Bone Graft, Medtronic Sofamor Danek, Memphis, TN) as an alternative to iliac crest bone graft.

A total of 131 patients were enrolled over a three-year period with the first surgery being performed on April 30, 1998, and the last surgery on March 12, 2001. The pilot phase included 24 investigational rhBMP-2 patients and 22 autograft control patients. In the pivotal phase, 55 investigational rhBMP-2 patients and 30 autograft control patients were enrolled. A total of 79 investigational patients received threaded cortical bone dowels with rhBMP-2/ACS and 52 control patients received bone dowels augmented with morcellized iliac crest autograft. The rhBMP-2 patients did not have a second surgery to harvest iliac crest bone graft while the control patients did.

Deleted: study consisted of

Deleted: that

Deleted: and a pivotal phase that enrolled 85 patients at 13 sites. The study designed consisted of prospective,

Deleted: with patient enrollment in the pilot phase

Deleted: of the investigational rhBMP-2 and collagen sponge in one group and the autograft bone from the iliac crest (the control) in the other

Deleted: was used

Deleted: combination of these two groups (pilot and pivotal) together

Formatted

Deleted: The prospective, randomized, multi-centered clinical trials used allograft bone dowels (MD-II) supplied by the Regeneration Technology, Inc (Alachua, FL). The studies were conducted in the United States to determine the safety and effectiveness of using this anterior spinal procedure with and without the use of recombinant bone morphogenetic protein 2 and an absorbable collagen carrier. In both phases of this study, a

Deleted: entered

Deleted: study had

Deleted: investigational

Deleted: with bone dowels and autograft

Deleted: study

Deleted: were in the investigational arm

Deleted: in the control arm

Deleted: bone dowel surgeries were performed with the recombinant bone morphogenetic protein

Deleted: 54

Deleted: were implanted

Deleted: in the control

Deleted: investigational

Deleted: arm of the studies

Deleted: arm

Inclusion Criteria

To be entered into the study, the patient had to be over eighteen years of age and have objective measurements of single level degenerative disc disease with up to Grade-1 spondylolisthesis in the lumbar spine. All patients included in the study had disabling low back pain with or without leg pain. These symptoms persisted for a minimum of 6 months and had not resolved with active, supervised treatment that included therapeutic modalities, aerobic conditioning, and nonsteroidal anti-inflammatory agents.

Patients were included in the study if their radiographic findings documented single-level disc disease and their symptoms correlated with the neuroradiographic findings. All patients enrolled were considered good candidates for a single-level stand-alone anterior lumbar interbody fusion.

Patients were excluded from the study if they had spinal conditions other than single-level symptomatic degenerative disc disease, greater than Grade-1 spondylolisthesis, or a prior anterior spinal fusion procedure at the involved level. Other exclusion criteria included symptomatic disc disease at a level other than the L4-L5 or L5-S1 disc space levels, obesity (more than 40% above ideal body weight), an overt or active local or systemic bacterial infection, or a medical condition that required medication, such as steroids or nonsteroidal anti-inflammatory medications, that could potentially interfere with fusion.

Deleted: , or both
Deleted: had lasted
Deleted: plain
Deleted: , and they had undergone at least one additional confirmatory neuroradiographic study, such as MRI, CT-enhanced myelography, or discography
Deleted: or
Deleted: 0 or
Deleted: were
Deleted: a history of discitis

Patient Demographics

Demographic data were compiled for all patients in the study. Age, weight, sex, workers' compensation, spinal litigation, tobacco use and work status were assessed in all patients (Table 1).

Deleted: There were no statistically significant differences ($P < 0.05$) between the demographic profiles.

Surgical Procedure

The patients underwent an open ALIF procedure using either a transperitoneal or a retroperitoneal approach to the lumbosacral spine. In each patient, a complete anterior discectomy was carried out. A channel discectomy through two, separate anterior annulotomy or a "bulldog" discectomy through single annular opening was completed. In both approaches, an incision was made in the annulus fibrosus, the nucleus pulposus and the cartilaginous endplates were removed under direct visualization. Importantly, the bony endplates were preserved. The disc space was distracted to an anatomic height consistent with adjacent spinal motion segments. Under fluoroscopic guidance, a drill guide tube was centrally placed in the disc space. Two parallel channels were precisely prepared through the adjacent vertebral endplates by sequential reaming through the guide tube. The endplate channels were tapped and two allograft bone dowels were inserted into each disc space.

The rhBMP-2 was reconstituted using sterile water and a single dose at a concentration of 1.5 mg/mL was administered. The concentration was the same in all patients. The solution was applied evenly by syringe to appropriately sized absorbable collagen sponges and the rhBMP-2 was allowed to bind to the sponges for a minimum of 15 minutes prior to further handling or preparation. A single collagen sponge was placed into the central portion of each bone dowel. One additional (1" x 4") rhBMP-2

Deleted: 30

Deleted: manipulation of the sponges

Deleted: The total dose (6 to 12 mL) depended on the capacity of the bone dowel (16, 18, or 20 mm) used.

bound sponge was placed between the bone dowels. The total dose (8.4 to 12 mg rhBMP-2) depended on the capacity of the bone dowel (16, 18, or 20 mm) used (Table 1A). No autogenous grafts or local bone reamings were used in the rhBMP-2 group.

The control group received morcellized autogenous iliac crest graft in conjunction with the threaded cortical bone dowels. The iliac grafts were harvested through a separate incision directly over the iliac wing. The inner or outer table of the ilium was exposed subperiostealy and corticocancellous grafts were harvested. A single iliac cortex was preserved in all graft harvesting procedures; no bicortical iliac grafts were obtained. The central opening of the dowels were packed with morcellized autogenous bone graft before their insertion into the disc space. Additional autogenous grafts were packed between and anterior to the dowels.

All patients were ambulatory soon after surgery and were instructed to wear an external lumbosacral orthosis for approximately 6 weeks following surgery. Physical activities were advanced at the discretion of the attending physician.

Radiographic Outcome Measurements

Stability and radiolucent lines were assessed on plain radiographs using anteroposterior, lateral, and flexion-extension views. In addition, thin-slice (1 mm overlapping) computed tomography scans with coronal and sagittal plane reconstructions were utilized to assess bridging bone and allograft incorporation. Two independent, blinded radiologists interpreted all radiographs and CT scans to critically assess fusion at 6, 12, and 24 months. A third independent radiologist was used to adjudicate conflicting fusion findings.

Deleted: prepared

Deleted: investigational

Deleted: Additional

Deleted: was

As in previous interbody spine fusion studies with rhBMP-2/ACS [7], a fusion was considered successful only if all four fusion criteria were achieved: 1) bridging trabecular bone connecting the two vertebral bodies either through the dowels or around the dowels; 2) no angular motion of 5° or more; 3) no sagittal translation of more than 3 mm; and 4) no radiolucencies that involved more than half of the interfaces between the dowels and the host vertebral endplates.

Clinical Outcome Measurements

Assessments were completed preoperatively, during the patient's hospitalization, and postoperatively at 6 weeks and 3, 6, 12, and 24 months. Clinical outcomes were measured using well-established instruments: Oswestry Low Back Pain Disability Questionnaire, Short Form 36 (SF-36), work status, and back, leg, and iliac graft site numerical pain questionnaires. The Oswestry Low Back Pain Disability Questionnaire [14], a self-administered instrument, was used to measure the level of pain and disability associated with various daily activities. The Physical Component (PCS) was derived from the SF-36 [24], also a self-administered questionnaire, measured specific health concepts related to physical functioning. Low back, leg, and iliac graft site pain were evaluated using numerical rating scales that identified both pain intensity and duration. Separate, standard 10-point visual analogue numerical scales were used to quantify the intensity and duration of the painful symptoms. The two scores were then added together to derive a composite score with a maximum of 20-points.

Monitoring for Antibody to rhBMP-2 and Collagen

Patients were tested separately for an antibody response to exposure of rhBMP-2 and bovine collagen pre-operatively and postoperatively at three months.

Statistical Analysis

The data from this clinical trial were analyzed using the statistical software package SAS® version 6.12. For continuous variables, *P* values were determined using ANOVA techniques, and for categorical variables, they were derived from Fisher's exact test or chi-square test.

Deleted: visual analogue
Deleted: is
Deleted: and
Deleted: of
Deleted: is
Deleted: that measures
Deleted: visual analog
Deleted: pain
Deleted: *Radiographic Outcome Measurements*¶
Radiographs and CT scans were used to evaluate fusion at 6, 12, and 24 months after surgery. Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent radiologist was used to adjudicate conflicting fusion findings.¶
Fusion was defined as bridging bone connecting the adjacent vertebral bodies either through the implants or around the implants, less than 5 degrees of angular motion, less than or equal to 3 mm of translation, and an absence of radiolucent lines around more than 50% of either of the implant surfaces [7]. Stability and radiolucent lines were assessed on plain radiographs using anteroposterior, lateral, and flexion-extension views. Thin-slice (1 mm) computed tomography scans with coronal and sagittal plane reconstructions were evaluated at 6, 12, and 24 months. The presence of continuous trabecular bone formation between the vertebral bodies was assessed using radiographs and computed tomography scans. A fusion was considered successful only if all four criteria were achieved: 1) bridging trabecular bone connecting the two vertebral bodies either through the dowels or around the dowels as evaluated by thin-cut CT scans and radiographs; 2) no angular motion of 5° or more on dynamic plain radiographs; 3) no sagittal translation of more than 3 mm on dynamic plain radiographs; and 4) no radiolucencies that involved more than half of the interfaces between the dowels and the host vertebral endplates.¶
Formatted
Deleted: a
Deleted: from
Deleted: are

RESULTS

Patient Demographics

There were no statistically significant differences ($P < 0.05$) between the demographic profiles of the two patient populations. Fifty-two patients with a mean age of 44 years (range 28-68 years) received the control treatment with autograft (Table 1). In this group, there were 19 men (36.5%). The average weight was 173.2 pounds. Seventeen patients (32.7%) had prior lumbar surgery, 17 (32.7%) used tobacco within the past 6 months of surgery, 6 (11.5%) had pending litigation. Twenty-five patients (48.1%) were working prior to surgery and 17 (32.7%) were seeking Worker's Compensation.

Deleted: 43.6
Deleted: 171.3

Seventy-nine patients (32 males; 40.5%) received the investigational treatment with rhBMP-2/ACS. Their average age was 40 years (range 19-62 years) and their average weight was 172.3 pounds. Twenty-nine patients (36.7%) had prior lumbar surgery, 26 (32.9%) used tobacco within the past 6 months, 7 (8.9%) had pending litigation, and 23 (29.1%) were seeking Worker's Compensation. Forty-seven (59.5%) were working prior to surgery.

Deleted: on a collagen soaked sponge
Deleted: .2

Surgery

The rhBMP-2 group had surgery more commonly at the L4-5 level. In the autograft group, surgery was performed at the L4-L5 level in 14 patients (26.9%) and at the L5-S1 level in 38 patients (73.1%) (Table 2). In the rhBMP-2 group, 23 patients (29.1%) had surgery at the L4-5 level and 56 (70.9%) had surgery at the L5-S1 level. The mean operative time in the rhBMP-2 group was 1.4 hours compared to 1.8 hours in the autograft group ($p<0.001$). The average blood loss was only 87.4cc in the rhBMP-2

Deleted: control
Deleted: investigational

Deleted: investigational
Deleted: treated
Deleted: control
Deleted: The investigational group had surgery more commonly at the L4-5 level.

group as compared to 184.7cc in the autograft group (p<0.001). The average hospital stay was also less in the rhBMP-2 group, 2.9 days versus 3.3 days in the autograft group (p=0.020).

Clinical Follow-up

Patients were followed for a minimum of two years following surgery. One autograft patient died (house fire) before the 12-month follow-up. Patients undergoing a revision, supplemental fixation or retrieval surgeries were classified as clinical failures. Once a patient was classified as a failure, their clinical data was no longer included in later follow-up periods. Eight autograft patients and two rhBMP-2 patients were classified as failures over the course of the study. Two autograft patients and three rhBMP-2 patients were lost over the course of the study. Among those available, patient return was 93% and 97% for the autograft and rhBMP-2 patients, respectively, at 24 months.

Oswestry Low Back Disability Questionnaire

Both groups showed sustained improvement in their mean Oswestry scores following surgery at all time points throughout the 24-month follow-up (Table 6). The rhBMP-2 group exhibited significantly better mean Oswestry scores at all time points as compared to the autograft group. Since there was a slight difference, though not a statistical difference, in the preoperative values between the two groups, the average improvement in Oswestry score was calculated at each time interval. At all intervals studied, the rhBMP-2 group showed a greater mean improvement in their Oswestry scores when compared to the autograft group. These differences reached statistical

Deleted: control

Deleted: control

Deleted: Outcomes

Deleted: 90

Deleted: or higher

Deleted: (range /// - ///)

Deleted: each follow-up interval

Deleted: Low Back Pain¶
Patients in the investigational group (rhBMP-2) had a mean back pain analog score of 7.6 (maximum pain score = 20) and showed an average improvement of more than 8 points at their initial postoperative visit at 3 months (Table 3). At 3 months, the autograft control group had a back pain analog score of 10.2 points and 5-point mean improvement in back pain scores. The difference in mean back pain scores between the investigational and the control group was statically significant at 3 months (p=0.003). Both treatment groups showed continued improvement in back pain scores through the study. The mean analog back pain scores in the investigational BMP-2 group remained significantly improved when compared to the autograft control group (p=0.006 at 6 months; p=0.007 at 12 months; and p=0.032 at 24 months).¶

significance at the 3- and 6-month follow-up interval (P=0.021 and P=0.031, respectively).

Physical Component of the SF-36

The physical component score (PCS) was calculated from the SF-36 health survey, where patients evaluated their own condition. At 6 months, the rhBMP-2 group exhibited a mean PCS of 43.4 with an average improvement of 14.3 points from their preoperative status (Table 5). These scores were statistically significantly better than those measured in the autograft group with a mean PCS score of 37.0 (p=0.001) corresponding to a mean improvement of 9.5 points (p=0.017). Both groups continued to improve their PCS scores at 12 and 24 months. The rhBMP-2 group had statistically significantly higher PSC scores when compared to the autograft group at 12 and 24 months (p=0.003 and p=0.015, respectively). At 12 months the mean improvement was greater for the rhBMP-2 group compared to the autograft group (p=0.027).

Back and Leg Pain

Both treatment groups demonstrated significant reductions in average back and leg pain scores at all time points as compared to their preoperative condition ($P_{\alpha}0.001$). Although reduction in back pain was observed as early as 6 weeks, the rhBMP-2 patients reported a significantly lower average numerical rating back pain score as compared to the autograft patients beginning at 3 months postoperatively and continuing throughout the 24-month follow-up. At three months, the rhBMP-2 group had a mean back pain score of 7.5 (out of a maximum 20 points) and showed an average improvement of more than 8 points from their preoperative visit (Table 3). In comparison, the autograft control group had a back pain score of 10.2 points and a 6.7-

Formatted

point mean improvement from preoperative levels. The difference in mean back pain scores between the rhBMP-2 and the autograft group was statistically significant at 3 months (p=0.003). Both treatment groups maintained this reduction in back pain scores throughout the study. The mean back pain scores in the rhBMP-2 group remained significantly lower when compared to the autograft control group (p=0.006 at 6 months; p=0.007 at 12 months; and p=0.032 at 24 months).

Both groups exhibited a sustained reduction in average numerical rating leg pain scores compared to the preoperative status over the 24-month study; however, the rhBMP-2 group exhibited a statistically significant lower average leg pain score at most of the follow-up time points. At the 6-week follow-up visit, the rhBMP-2 group had a mean leg pain score of 6.2 points (out of a maximum 20 points) and average reduction of 6.4 points (Table 4). In comparison, the autograft group had statistically higher mean leg pain score of 8.6 points (p=0.020) corresponding to an average reduction of 5.4 points from the preoperative status. Both groups maintained a reduction in leg pain as compared to their preoperative status; however, the autograft patients reported a slight increase at later follow-up times. The difference in mean leg pain scores was statistically significantly different between the two groups at 6, 12 and 24 months (p=0.043, p=0.011 and p=0.011 respectively).

Return to Work

More patients were working preoperatively in the rhBMP-2 group (59.5%) as compared to the autograft patients (48.1%). By 24 months, more patients from both groups were working as compared to preoperative status. However, the rhBMP-2 group reported improved working status as early as 12 months. Using survivorship analysis, it

Deleted: initial

Deleted: investigational

Deleted: analog

Deleted: improvement

Deleted: The

Deleted: a

Deleted: analog

Deleted: and

Deleted: improvement

Deleted: These results at 6 weeks compared favorably statically to the control group (p=0.020).

Deleted: These results remained improved at an average of 6.8 points for the investigational group at last follow-up of 24 months. However, while the autogenous graft group showed initial mean improvement of 5.4 points, the average improvement at 24 months decreased to 4.6 points. The difference in mean leg pain scores remained statistically significant different between the two groups at 6, 12 and 24 months (p=0.043, p=0.011 and p=0.011 respectively).

Deleted: Oswestry Low Back Disability Questionnaire¶
. The Oswestry Disability Questionnaire assessed pain associated with activities. Both groups showed improvements in their mean Oswestry scores following surgery and both groups maintained the improvement in Oswestry scores throughout the 24-month follow-up except for the autograft patients where the improvement dropped slightly at 24 months (Table 6). At all intervals studied, the investigational BMP-2 group showed a greater improvement in their mean Oswestry scores when compared to the autograft control group. ¶

Deleted: Higher percentages of patients in the investigational group were also able to return to work (Figure //). These patients were also able to return to work earlier than those in the control group.

was determined that the rhBMP-2 patients returned to work at an average of 89 days as compared to 96 days for the autograft patients. This difference was not statistically significant.

Bone Graft Harvest Site Pain

Autograft bone was not harvested from the iliac crest in the rhBMP-2 group of patients and therefore, bone graft harvest site pain was not measured. While the average donor site pain following ALIF surgery was similar to previous reports, the pain was observed to persist at a slightly higher rate of 46.5% of autograft patients for 24 months postoperatively.

Additional Surgery

Patients undergoing a revision, removal, or supplemental fixation were classified as failures. Two (2.5%) patients in the rhBMP-2 group required an additional surgical procedure for supplemental fixation and were classified as failures in the study. Eight (15.4%) patients in the autograft group required an additional surgical procedure for supplemental fixation after their primary surgery.

Antibody Formation

A total of 49 autograft and 78 rhBMP-2 patients were tested for an elevated antibody response to rhBMP-2 and bovine collagen. Among those tested, no patients from either group developed an elevated antibody response to rhBMP-2. However, four (8.2%) autograft patients and 7 (9.0%) rhBMP-2 patients exhibited an elevated antibody response to bovine collagen.

Deleted: investigational

Deleted: and was assumed to be zero

Deleted: ///

Deleted: in the immediate perioperative period

Deleted: ; ///

Deleted: control

Deleted: early return to surgery to remove residual disc material ///

Deleted: underwent

Deleted: posterior

Deleted: procedure

Deleted: ?? % of patients showed an allergic repose to the bovine collagen; /// % of patients developed an allergic response to rhBMP-2

Fusion Assessment Outcomes

At all fusion assessment time points, the rhBMP-2 group exhibited a greater rate of fusion success compared to the autograft patients. At six months following surgery, 95.9% of rhBMP-2 patients had evidence of interbody fusion as compared to 85.1% of autograft patients (p=0.047) (Table 7). At 12 months, 98.6% of rhBMP-2 patients were fused, while the autograft group showed evidence of fusion in 89.4% of patients. At the final two-year radiographic follow-up, 98.5% of patients in the rhBMP-2 group remained fused as compared to 76.1% of patients in the autograft group (p=0.001).

All patients deemed to be failures were either due to radiographic evidence or due to secondary surgeries described below. In the control group, there were no fractures, migration or extrusion of the allograft implants. Radiographic lucencies developed at the interface of the allograft to the vertebral endplates.

DISCUSSION

Prior to the conduction of these clinical studies, a non-human primate (rhesus monkey) study was performed using allograft bone dowels in the lumbar spine (17). In three rhesus monkeys, a single smooth allograft bone dowel with rhBMP-2 on an absorbable collagen sponge (ACS) was implanted anteriorly into the disc space of the L7-S1 disc space. At three month following surgery, all three investigational animals showed new bone formation with complete incorporation of the allograft dowels leaving trabecular bone continuous with host bone of both adjacent vertebras. In this non-human primate model, the control animals treated with autogenous grafts demonstrated delays in healing of the allograft implants and in new trabecular bone formation. In contrast to the rhBMP-2 soaked sponge, the transplanted autogenous grafts may need to be resorbed or be remodeled before fusing [15]. This feature may partially explain why these animal studies had superior healing patterns with rhBMP-2/ACS when compared with autogenous iliac crest bone graft.

The combined date from two clinical trials in humans using threaded cortical bone dowels and rhBMP-2, first in a pilot study (6) and later in a pivotal study, are reported here. The use of rhBMP-2/ACS has been shown to induce new bone formation in single level anterior interbody fusions in humans [2,5,18]. rhBMP-2 used with a threaded tapered titanium cage in ALIF surgery has also been shown to have superior clinical outcomes and radiographic fusion rates when compared to iliac crest bone graft [4]. Superiority over autograft was demonstrated after enrollment of 679 patients in three sequential prospective studies. By eliminating the need for autograft harvesting, the rhBMP-2 group reported shorter OR times ($p<0.001$), lower blood loss ($p=0.024$),

Deleted: A
Deleted: a bovine
Deleted: into
Deleted: the
Deleted: vertebra
Deleted: containing grafts
Deleted: auto
Deleted: being
Deleted: on a collagen soaked sponge
Deleted: autograft

and reduced hospital stays (p<0.001). Radiographically, the rhBMP-2 group exhibited higher fusion rates. Clinically, the rhBMP-2 group demonstrated improved results using the Oswestry Disability Questionnaire, SF-36, back and leg pain scales, and return to work. The autograft group reported donor site pain in nearly one-third of patients at 24 months postoperatively.

In the present study of only 131 patients undergoing stand-alone ALIF with threaded cortical bone dowels, patients treated with rhBMP-2/ACS again exhibited superior outcomes as compared to iliac crest bone graft in many clinical and radiographic outcomes. Many of the differences observed between the two groups in this study reached statistical significance with a patient population much smaller in number as compared to the titanium cage studies [2,4,5,18].

On average, both the autograft and rhBMP-2 groups reported improvement in function and pain as compared to their preoperative status. Clinical improvement was documented as early as 6 weeks in this study. However, the improved fusion rates may have contributed to the better clinical outcomes noted in many of the clinical measures among the rhBMP-2 group, particularly at the longer follow-up time points. At 6, 12 and 24 months in this study, the rhBMP-2/ACS treated patients demonstrated significant improvement over autograft patients in several outcome measurements including: back and leg pain scores, Physical Component Score of the SF-36, and Oswestry Disability index scores. At 24 months, rhBMP-2 patients averaged a 33.4-point improvement in Oswestry pain scores when compared to pre-operative scores. This improvement is the largest reported in any lumbar spinal fusion study.

Deleted: only
Deleted: the superiority of
Deleted: over autograft
Deleted: when used with threaded cortical allograft dowels was demonstrated
Deleted: investigational
Deleted: controls
Deleted: visual analog
Deleted: clinical outcomes
Deleted: over
Deleted: 32
Deleted: we have been able to find of

Independent radiographic assessment was conducted at 6, 12 and 24 months using both x-rays and thin-slice CT scans. At all time points, the rhBMP-2 group exhibited statistically higher fusion success as compared to the iliac crest bone graft patients. The greatest difference was seen at 24 months where the rates were 98.5% and 76.1%, respectively ($p<0.001$). This difference is in large part due to a difference in the need for additional surgery to achieve a desired outcome. Only 2 (2.5%) rhBMP-2 patients required additional spinal surgery as compared to 8 (15.4%) autograft patients.

Increased incorporation of the allograft bone dowel with the host's bone when rhBMP-2/ACS is used as an autograft replacement can be seen in some of the serial CT scans was seen. In comparison, the autograft patients did not exhibit this acceleration of incorporation. These observations suggest that there is an interaction between the allograft bone and rhBMP-2 that was not previously observed when used with titanium interbody cages. This incorporation did vary from patient to patient ranging from complete incorporation to very localized incorporation where there was direct contact with the endplates. Further analysis of the films is needed to better understand the range in response seen and the potential factors that may influence the amount and rate of allograft incorporation. Similarly, it is unknown if this incorporation will be seen in different fusion sites or when using constructs with different configurations (femoral ring allograft) in combination with rhBMP-2/ACS.

These data strongly demonstrate that rhBMP-2/ACS can successfully replace harvested iliac bone without the known donor site pain [27,29] and can be used to help incorporate allograft bone dowels in the lumbar spine of humans. Furthermore, these data support the concept that increased fusion rates are associated with improved

Deleted: show
Deleted: on a collagen sponge
Deleted: These

functional outcomes and decreases in pain scores. The allograft dowels rapid improvement in patient outcome may be, in part, attributed to acceleration of the incorporation of the bone dowel. The allograft bone dowels had a modulus of elasticity similar if not nearly identical to the host bone. Once healing has occurred, their was no distinction between implant and host bone. The stability gained at the involved level as a result of fusion was maintained up to 24 months and appears to contribute to the long-term clinical success associated with the combination of rhBMP-2 and allograft bone dowels.

CONCLUSION

These studies confirm the striking results found in non-human primate studies that rhBMP-2 added to allograft bone is a safe and effective combination in anterior lumbar interbody fusion surgery. The results show that increase in fusion rate was associated with improved functional outcomes and decrease in pain scores, both statistically significant ($p < 0.05$). Although further research is needed, these findings support the use of rhBMP-2 with an absorbable collagen sponge with human allograft dowels for spinal fusion in ALIF applications.

REFERENCES

1. Blumenthal SL, Baker J, Dossett A, Selby DK: The role of anterior lumbar fusion for internal disc disruption. *Spine* 13: 566-569, 1988.
2. Boden SD, Zdeblick TA Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. *Spine* 2000;25:376-381.
3. Boyd, L.M.; Estes, B.T. and Liu M. "Biomechanics of Lumbar Interbody Constructs, *Effect of Design and Materials*." Chirurgie Endoscopique et Mini-invasive du Rachis. Ed. Husson JL, LeHuec JC. Sauramps Médical. Montpelier, France. pp 181-192, 1999.
4. Burkus JK, Heim SE, Gornet MF, Zdeblick TA. Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-CAGE lumbar tapered fusion device. *J Spinal Disord & Techniques* 2003;16:113-22.
5. Burkus JK, Gornet MF, Dickman C, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. *J Spinal Disord Tech* 2002;15:337-49.
6. Burkus JK, Transfeldt EE, Kitchel SH, Watkins RG, Balderston RA. Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2. *Spine* 2002;27:2396-408.
7. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group -- radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. Neurosurg Focus 2001;10:1-9.

8. Burkus JK: Intervertebral fixation: clinical results with anterior cages. Orthop Clin North Am 2002;33: 349-357.

9. Burkus JK. Threaded Bone Dowels. "Lumbar Interbody Fusion Techniques: Cages, Dowels, and Grafts." Quality Medical Publishing, Inc. 2003:148-168.

9A. Burkus JK. Stand-alone anterior lumbar interbody fusion constructs: effect of interbody design, bone graft and bone morphogenetic protein on clinical and radiographic outcomes. "Advances in Spinal Fusion – Molecular Science, Biomechanics and Clinical Management". Marcel Dekker, Inc. 2003:

10. Chow SP, Leong JCY, Ma A, Yau ACMC: Anterior spinal fusion for deranged lumbar intervertebral disc. *Spine* 5: 452-458, 1980.

11. Cloward RB. The treatment of ruptured lumbar intervertebral disc by vertebral body fusion. III Method of use of banked bone. *Ann Surg* 1952;136:987-91.

12. Cloward RB. Lesions of the intervertebral disks and their treatment by interbody fusion methods. *Clin Orthop* 1963;27:51-77.

13. Dennis S, Watkins R, Landaker S, Dillin W, Springer D. Comparison of disc space heights after anterior lumbar interbody fusion. *Spine* 1989;14: 876-878.

14. Fairbank JCT and Pynsent PB "The Oswestry Disability Index" *Spine* 25(22): 2940 – 2953, 2000.

15. Goldberg VM, Lance EM. Revascularization and accretion in transplantation. *J Bone Joint SurgAm* 1972;54:807.

16. Harmon PH. Anterior excision and vertebral body fusion operation for intervertebral disc syndromes of the lower lumbar spine. *Clin Orthop* 1963;26:107-27.

17. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. *Spine* 1999;24:629-36.

18. Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2. A prospective study of clinical and radiographic outcomes. Spine 2001;26:2751-6.

19. Kumar A, Kozak JA, Doherty BJ, Dickson JH. Interspace distraction and graft subsidence after anterior lumbar fusion with femoral strut allograft. Spine 1993;18:2393-2400.

20. Kuslich SD, Ulstron CL, Griffith SL, Ahern JW, Dowdle JD "The Bagby and Kuslich method of lumbar interbody fusion: History, techniques, and 2-year follow-up results of a United States prospective, multicenter trial" *Spine* 23(11): 1267 – 1278, 1998.

21. Lane JD, Moore ES. Transperitoneal approach to the intervertebral disc in the lumbar area. *Ann Surg* 1948;127:537-51.

22. Leong JCY, Chun SY, Grange WJ, Fang D: Long-term results of lumbar intervertebral disc prolapse. *Spine* 8: 793-799, 1983.

23. Loguidice VA, Johnson RG, Guyer RD, Stith WJ, Ohnmeiss DD, Hochschuler SH, Rashbaum RF: Anterior lumbar interbody fusion. *Spine* 13:366-369, 1988.

24. McHorney CA, Ware JE Jr., Lu RJF, Sherbourne CD. The MOS 36-Item Short-From Health Survey (SF-36), III: tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994;32:40-66

25. Newman MH, Grinstead GL: Anterior lumbar interbody fusion for internal disc disruption. *Spine* 17: 831-833, 1992.

26. Sasso RC, Kitchel SH, Dawson EG. A prospective, randomized controlled clinical trial of anterior lumbar interbody fusion using a titanium cylindrical threaded fusion device. *Spine* 2004;29:113-22.

27. Sasso, RC, LeHuec JC, Shaffrey C. Iliac crest bone graft donor site pain after anterior lumbar interbody fusion: a prospective patient satisfaction outcome assessment *J Spinal Disord Tech*. In press.

28. Urist MR. Bone formation by autoinduction. *Science* 1965;150:893-99.

29. Vaccaro AR, Kazuhiro C, Heller JG, Patel TC, Thalgott JS, Truumees E, Fischgrund JS, Craig MR, Berta SC, Wang JC. Bone grafting alternatives in spinal surgery. *The Spine Journal*.2002;2:206-15.

30. Wozney JM. Overview of bone morphogenetic proteins. *Spine* 2002; 27S:2-8.

TABLE 1. Patient demographic data

Demographic Data	rhBMP-2/ACS	Autograft
Number of patients	79	52
Average Age (years)	40.2	43.6
Average Weight (lbs)	172.3	173.2
Sex (male/female)	32/47	19/33
Workers' Compensation (%)	23 (29.1)	17 (32.7)
Spinal litigation (%)	7 (8.9)	6 (11.5)
Tobacco use (%)	26 (32.9)	17(32.7)
Previous surgeries (%)	29 (36.7)	17 (32.7)

Deleted: No.

Deleted: compensation

Table 1A

Allograft Implant Sizes, Volume and rhBMP-2 Dosage

Dowel Diameter (mm)	Size of rhBMP-2/ACS per Dowel	Size of rhBMP-2/ACS between Dowels	Total rhBMP-2/ACS volume (cc)	Total rhBMP-2 dose (mg)
16	1" x 2"	1" x 4"	5.6	8.4
18	1" x 3"	1" x 4"	6.6	10
20	1" x 4"	1" x 4"	8.0	12

Table 2. Intraoperative Data

Surgical Data	rhBMP-2/ACS	Autograft	P-Value*
Average Operative time (hr)	1.4	1.8	<0.001
Average Blood loss (mL)	87.4	184.7	<0.001
Surgical Level (%)			0.785
L4-L5	11 (46)	8 (36)	
L5-S1	13 (54)	14 (64)	
Average Hospital stay (days)	2.9	3.3	0.020

*P-values are derived from ANOVA for continuous variables and derived from Fisher's Exact Test for categorical values.

Deleted: Table 3: Back pain outcomes[1] Anterior Lumbar Interbody Fusion using threaded cortical bone dowels containing rhBMP-2 and a collagen sponge carrier to iliac crest autograft

Table 3
Summary of Average Back Pain Scores

Period	rhBMP2/ACS	Autograft	P-Value*
Preoperative	15.6	16.8	0.039
6 Weeks	8.1	9.6	0.090
3 Months	7.5	10.2	0.003
6 Months	6.4	9.1	0.006
12 Months	6.4	9.5	0.007
24 Months	7.0	9.7	0.032

*P-values are derived from ANOVA.

Table 4
Summary of Average Leg Pain Scores

Period	RhBMP-2/ACS	Autograft	P-Value*
Preoperative	12.6	14.2	0.094
6 Weeks	6.2	8.6	0.020
3 Months	6.4	8.3	0.065
6 Months	4.9	6.9	0.043
12 Months	5.1	8.0	0.011
24 Months	5.8	9.3	0.011

*P-values are from ANOVA.

Deleted: ¶
¶

Table 5

Physical Component Score derived from SF-36 Health Survey

Period	BMP2	Autograft	P-Value*
Preoperative (Mean)	29.2	27.6	0.184
6 Months (Mean)	43.4	37.0	0.001
12 Months (Mean)	45.3	38.9	0.003
24 Months (Mean)	44.9	39.2	0.015

*P-values are from ANOVA.

TABLE 6

Summary of Oswestry Low Back Pain and Disability Scores

Period		rhBMP-2	ICBG	p-value
Preoperative	Mean	53.7	56.6	0.144
6 weeks	Mean	39.4	47.6	0.008
	Mean improvement	-14.2	-9.0	0.060
3 months	Mean	28.4	38.5	0.001
	Mean improvement	-25.3	-18.5	0.021
6 months	Mean	21.5	30.8	0.003
	Mean improvement	-32.4	-25.8	0.031
12 months	Mean	20.9	29.3	0.018
	Mean improvement	-33.0	-27.0	0.074
24 months	Mean	20.4	28.9	0.037
	Mean improvement	-33.4	-27.0	0.119

p-values are for mean scores are calculated using analysis of variance. P-values for mean improvement are calculated using paired t-test.

Table 7
Summary of Fusion Success Rates

Period	BMP2	Autograft	P-Value*
6 Months	95.9	85.1	0.047
12 Months	98.6	89.4	0.036
24 Months	98.5	76.1	<0.001

*P-values are from Fisher's exact test

From: Treharne, Rick
Sent: Wednesday, December 15, 2004 04:29:48 PM
To: Steve Glassman (E-mail)[redacted]
Subject: Article Reminder

At the meeting we had in Chicago you asked me to send you a reminder to check out the figure descriptions in the draft article you showed me. You wanted to check if the material description was correct or not when it mentioned allograft.

I also checked and the size of the sponges in the small kit. They are 1 inch by 2 inch and there are two in each small kit. There was a reference to a larger size on p. 10 line 21. I don't know what size kit you used or how the volumes were calculated or what figures Bill McKay used to calculate his dosage rates, but you might want to double check that part of the text prior to publication.

Also, on p. 11, line 2 is this sentence: "The relevance, if any, of using a resorbable cage versus an allograft bone dowel (is that right?) is unknown." Although it may be too late at this point, I would suggest deleting the sentence if you can since there is not a resorbable "cage" per se, I know that there are some articles in the literature describing swelling after implantation of large sizes of resorbable implants without rhBMP-2, and I know what Wyeth (Genetics Institute) told me which is that the presence of rhBMP-2 dramatically affects the resorption kinetics of resorbables.

Again it is probably too late, but page 14 line 13 says "The high complication rate is alarming and warrants intense scrutiny." I think what you are trying to say is that the occurrence adverse events (not effects as in the title) in these patients was higher than expected and warrants further investigation.

As we discussed, a table that would help me would be one that shows a breakdown of the complications vs. material type: resorbables, allograft, and metal. Some of the complications reported to us also occurred in the corpectomy cases, so the use of a corpectomy may be the most important factor contributing to the events observed.

If the three allograft cases did not have any adverse events, which is what you say you remember, that makes the conclusion that the higher dose vs. Baskin as the cause somewhat speculative I would think. It was too bad that you did not have any resorbables without rhBMP-2 in the cervical spine since that would have helped answer the question of whether it was the rhBMP-2 or the 135 resorbable cases that caused the events seen. Your observed 7.9% swelling rate is higher than the 1.1 to 5.5% rate range we found in the literature or our clinical trials as described to you in my 9/13/04 email. That makes me wonder about the confounding effect of the presence of the resorbable material.

Anyway, I know you have this about ready to be printed, but I thought I would email you my comments. Let me know if there is anything I can do to help you...Rick

From:	Bearcroft, Julie, PhD
Sent:	Wednesday, November 14, 2007 05:28:05 PM
To:	Ma, Guorong; Norman, Dawn; Kepes, Steven; Peckham, Steve, Ph.D.; Zhu, Youjun
CC:	Beals, Neil; Meyer, Matt; Lanctot, Rodney; McKay, Bill
Subject:	AMPLIFY Manuscript
Attachments:	ManuscriptSept07 Revision (2).doc; AE Table.doc; Second Surgery Table.doc; Table 1.doc

Hello everyone -

I have taken all your collective input and consolidated it into this new manuscript version. Please review and provide commentary no later than Tuesday, November 20.

I have already provided this to Dr Dimar as well since he is anxious to progress this manuscript further. Thus, the need for the short response time. At this stage, he has not shared it with other co-authors since he wanted to incorporate our input prior to distribution.

Thanks,
julie

Julie Bearcroft, PhD
Technical Director, Biologics
Medtronic Spinal and Biologics
Phone: [redacted]
Mobile: [redacted]

Last printed Last printed 4/3/2009 3:29 PM

Deleted: 11/14/2007 2:04 PM

Deleted: 10/24/2007 1:06 PM

A Large-scale, Level 1, Clinical and Radiographic Analysis of an Optimized rhBMP-2 Formulation as an Autograft Replacement in Posterolateral Lumbar Spine Fusion

Formatted: Font: Bold

ABSTRACT

Study Design: Level I therapeutic clinical study.

Objective: To determine the safety and efficacy of using a new recombinant human bone morphogenetic protein-2 formulation with a new compression resistant matrix (rhBMP-2 matrix) as an iliac crest bone graft (ICBG) substitute in patients undergoing posterolateral fusion.

Summary of Background Data: Nonhuman primate studies have demonstrated that rhBMP-2 and an absorbable collagen sponge required additional osteoconductive bulking agents to produce successful posterolateral spine fusion. A new formulation using an optimized rhBMP-2 concentration and a compression resistant carrier developed specifically for posterolateral fusions demonstrated excellent results in nonhuman primates. A small pilot study in humans with an all ceramic carrier demonstrated similar results. Two-year follow-up results from a pivotal, multicenter, prospective, randomized Food and Drug Administration (FDA) Investigational Device Exemption (IDE) study comparing iliac crest bone graft (ICBG) to rhBMP-2 combined with a carrier consisting of bovine collagen and tricalcium/hydroxyapatite to create a compression resistant matrix for single-level posterolateral fusions is reported

Materials and Methods: In this prospective study, 463 patients with symptomatic single-level degenerative disc disease with up to Grade 1 spondylolisthesis were treated with decompression and single-level instrumented posterolateral fusion through an open midline approach. Patients were randomly assigned to either the rhBMP-2 matrix group (239 patients) or the ICBG group (224 patients). Oswestry Disability Index, SF-36, and back and leg pain scores were determined preoperatively and at 1.5, 3, 6, 12 and 24 months postoperatively. Two independent radiologists reviewed radiographs and computed tomography scans taken at 6, 12, and 24 months postoperatively. Fusion was defined as the presence of bilateral, continuous trabeculated bone connecting the transverse processes, translation of less than or equal to 3 mm and angulation of less than 5° on flexion-extension radiographs, and absence of cracking, as evidenced by radiolucent lines through the fusion mass.

Results: No significant differences in demographics existed between the groups. The mean operative time in the rhBMP-2 matrix group (2.5 hours) was less than in the ICBG group (2.9 hours) ($P < 0.001$). Average blood loss in the rhBMP-2 matrix group was 343.1 mL compared

Deleted: feasibility

Deleted: , and a

Deleted: a

Deleted: Currently, a

Deleted: ongoing

Deleted: ongoing

Deleted: ≤

Deleted: ≤

Deleted: <

with 448.6 ml in the ICBG group ($P < 0.001$). Average hospital stay was similar in both groups. No differences existed between the groups in adverse events except cumulative nonunion rate reported by investigators was higher in the ICBG group (8%; 8.0 %,18 patients) than in the rhBMP-2 matrix group (2.5%; 6 patients) ($P = 0.011$). Using fine-cut CT scans with coronal and sagittal reconstructions in addition to standard radiography, at 12 months, 87.5% of patients in the rhBMP-2 matrix group and 82.5% in the ICBG group exhibited fusion success ($P < 0.319$). At 24 months, 95.9% in the rhBMP-2 matrix group were solidly fused compared with 89.3% in the ICBG group ($P < 0.023$). Both groups showed similar improvements in clinical outcomes and reduced pain. At 24 months, 60% of the ICBG group reported persistent donor site pain.

Conclusions: Using rhBMP-2 decreases operative time and blood loss and produces earlier and higher fusion rates than iliac crest bone graft in posterolateral lumbar fusion procedures. Clinical outcomes are similar to those with iliac crest bone graft. Thus, the need for harvesting iliac crest bone is eliminated along with the morbidities associated with the harvest procedure.

Key words: rhBMP-2, posterolateral lumbar fusion, degenerative disc disease

Formatted: Highlight
Deleted: 7.1
Deleted: 18
Deleted: %; 18
Deleted:
Formatted: Highlight
Formatted: Highlight
Deleted: ≤ 0.
Deleted: 042
Formatted: Highlight
Deleted: Based on
Deleted: 86.9
Formatted: Highlight
Formatted: Highlight
Deleted: 71.4
Formatted: Highlight
Formatted: Highlight
Deleted: had evidence of bilateral bridging bone
Formatted: Highlight
Deleted: 001
Formatted: Highlight
Deleted: 93.6
Formatted: Highlight
Formatted: Highlight
Deleted: had bilateral bridging bone
Deleted: 82.6
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Deleted: 4
Deleted:).
Formatted: Highlight
Formatted: Highlight
Comment [sk1]: This number doesn't seem to correspond to the data that I have to compare it to. Based on the 24 month data for Hip Pain, there are 72 pati ... [1]
Deleted: 54
Deleted: %
Deleted: Outcomes
Deleted: ICBG
Deleted: and the morbidities ass ... [2]
Deleted: is

INTRODUCTION

Posterolateral fusion combined with pedicle instrumentation is frequently employed for the treatment of degenerative disease of the lumbosacral spine. Various indications include degenerative disc disease, spondylolisthesis, and instability. The results of instrumented posterolateral fusions in large clinical studies have shown varying rates of fusion and clinical outcomes [1-5]. Traditional sources of grafting material include autograft, obtained locally from the iliac crest or from distal sources, and different types of allograft [2-5].

Previous studies have demonstrated the ability of recombinant human bone morphogenetic protein (rhBMP-2) to achieve a solid fusion [6-8]. Recently prospective randomized human clinical studies demonstrated superior fusion rates and clinical outcomes with rhBMP-2 and a collagen sponge (iNFUSE® Bone Graft, Medtronic Sofamor Danek, Memphis, TN) versus autograft when using either cortical bone dowels or threaded interbody cages in anterior lumbar interbody techniques [9,10]. Nonhuman primate studies have demonstrated that rhBMP-2 delivered on an absorbable collagen sponge required additional osteoconductive bulking agents to produce successful posterolateral spine fusion [11-14]. A new formulation using an optimized rhBMP-2 concentration and a compression resistant carrier developed specifically for posterolateral fusions demonstrated excellent results in nonhuman primates [15]. A small, prospective, randomized, clinical investigation also demonstrated excellent posterolateral fusion results for rhBMP-2 combined with biphasic calcium phosphate as compared to iliac crest autograft [16]. Currently, a prospective randomized Food and Drug Administration (FDA) Investigational Device Exemption (IDE) study is ongoing comparing iliac crest bone graft (ICBG) to rhBMP-2 combined with a compression resistant carrier consisting of bovine collagen and tricalcium/hydroxyapatite (rhBMP-2 matrix) for single-level posterolateral fusions. We report the two-year radiographic results and clinical outcomes using rhBMP-2 matrix or iliac crest bone graft (ICBG) in single-level instrumented posterolateral fusions for lumbosacral degenerative disease.

Deleted: and

Deleted: pilot study on humans

Deleted: similar

Deleted: with

Deleted: versus

Deleted: for posterolateral fusions

Deleted: to create a compression resistant matrix

Deleted: is ongoing

MATERIALS AND METHODS

Four hundred sixty-three patients were treated in this multi-center prospective, randomized, FDA-approved IDE study. Sixty-three spine surgeons performed surgery in the study at 29 investigational sites.

Deleted: enrolled

Deleted: nonblinded,

Deleted: Eighty

Deleted: participated

The indications for surgery were symptomatic, single-level lumbosacral degenerative disease from L2/3 to L5/S1 of at least six months' duration that had not responded to nonoperative care. Clinical symptoms were low back pain with or without radicular leg pain. Additional enrollment criteria were a grade 1 or less spondylolisthesis, no previous fusion, and a minimum pre-operative Oswestry Disability Index score of 30. Exclusion criteria included a previous attempt at fusion at the intended surgical level, significant osteoporosis (less than 2 standard deviations below normal on DEXA bone densitometry scan), autoimmune disease, malignancy, infection, pregnancy, or the inability to harvest graft because of a previous surgical procurement.

All patients were treated with a single-level instrumented fusion using CD Horizon® (Medtronic Sofamor Danek, Memphis, TN USA) pedicle screw and rod instrumentation. Patients were randomly assigned to one of two groups: the control group who received autogenous iliac crest bone graft (ICBG) or the investigational group who received rhBMP-2 matrix (AMPLIFY rhBMP-2 Matrix™, Medtronic Sofamor Danek, Memphis, TN, USA). The dose and concentration of rhBMP-2 used in this study is higher (2.0 mg/cc for a total dose of 40 mg) than that of commercially available rhBMP-2, or INFUSE® Bone Graft (Medtronic Sofamor Danek, Memphis, TN, USA), which is 1.5 mg/cc for a total dose of 12 mg per large kit.

A standard open posterior approach was used for both the ICBG and rhBMP-2 matrix groups. Bone graft from the iliac crest in the ICBG group was obtained in a standard open fashion. Was a separate incision used? The bone graft was morselized and placed in the lateral gutters on the decorticated bony surface of the transverse processes and along the pars interarticularis. As required by the protocol, any local bone graft obtained from the decompression was discarded in both groups.

The rhBMP-2 was reconstituted using sterile water into two 5-mL syringes containing 20 mg of rhBMP-2 each. The matrix measuring 4.7cm in length x 3.8cm in width x 1.1cm in thickness was cut lengthwise with a scalpel into two equal pieces (1.9 cm in width) of 10 cc each using a cutting template. The reconstituted rhBMP-2 from each syringe was then uniformly distributed to each piece of the matrix producing a 2 mg/cc concentration of rhBMP-2 in the matrix. The rhBMP-2 matrices were allowed to stand for a minimum of 5 minutes and were implanted within 60 minutes after preparation. In no instance was the matrix of insufficient length to span the transverse processes in a single-level fusion.

Deleted: and a
Deleted: 1
Deleted: 2
Deleted: ,
Deleted: , 20 mg per side
Formatted: Highlight
Deleted: /

Clinical data were collected preoperatively and postoperatively at 6 weeks, 3 months, 6 months, 12 months, and 24 months. The validated outcome instruments used were the Oswestry Low Back Pain Disability Index (ODI) [17], the Medical Outcomes Study Short Form 36 (SF-36) [18,19], back pain and leg pain scores and, in the ICBG group, graft site pain scores. Patients were asked to rate the frequency and intensity of their pain on a scale of 0 to 10 and the scores were summed to derive a 20-point numerical rating scale. Data on work status, patient satisfaction, and adverse events were also recorded. Results of neurological examinations, which included motor function, sensory function, reflexes, and straight leg raise, were recorded.

Plain radiographs, lateral flexion and extension radiographs, and computed tomography (CT) scans with sagittal and coronal reconstructions were used to evaluate the fusion in both groups at 6, 12, and 24 months after surgery. The CT imaging protocol consisted of 1 millimeter continuous nonoverlapping axial slices that were taken without bone filter. The window and level settings were set to optimize trabecular bone detail (2000/350 on GE Scanners). The field of view was made as small as possible but still encompassed the complete vertebra in between and including the transverse processes.

Fusion success was defined as the presence of bilateral, continuous trabeculated bone connecting the transverse processes, translation of less than or equal to 3 mm and angulation of less than 5° on flexion-extension radiographs, and absence of cracking, as evidenced by radiolucent lines through the fusion mass. The radiographs and computed tomography scans were evaluated by 2 independent radiologists who were blinded to which patient group they were evaluating. A third adjudicate reviewer was used as needed.

The analysis dataset consisted of all patients who were surgically treated. Statistical comparisons were primarily based on the observed and recorded follow-up data. A small number of patients required an additional surgical procedure (removal, revision, or supplemental fixation); their outcomes were recorded as a treatment failure. For other outcome variables, the last observations taken before the additional surgical procedures or interventions were carried forward using the Last Observation Carried Forward technique for all future evaluation periods.

For comparing patients' demographic and preoperative measures, p values for continuous variables were from the analysis of variance, and those for categorical variables were from Fisher's exact test.

Deleted: The rhBMP-2 matrix and ICBG group values were compared using ANOVA for continuous variables and Fisher's exact test for categorical variables for independent samples across each time interval.

Formatted: Justified, Indent: First line: 36 pt, Line spacing: 1.5 lines

For comparing success or event rates, Fisher's exact test was used for assessing the superiority hypothesis. For comparing continuous outcome measurements such as the Oswestry score, analysis of covariance was used, with the preoperative score as the covariate. For assessing the statistical significance of postoperative improvement in outcome scores from preoperative status within each treatment group, a paired t test was used.

One-sided p values were reported for comparing treatment group differences in most clinical outcomes because the study hypotheses defined in the investigational device exemption protocol for those outcomes were one sided, except for surgery data, adverse events, and additional surgical procedures, as well as for days to return to work, for which two-sided p values were reported.

A p value of less than 0.05 was considered to be statistically significant.

RESULTS

Four hundred ten (90%) of expected subjects were available for assessment at 2 years after surgery: 194 in the ICBG group and 216 in the rhBMP-2 matrix group. Seven patients had died due to causes unrelated to surgery during the two-year follow-up. Randomization resulted in a similar distribution of baseline characteristics in the two study groups as shown in Table 1.

The average surgical time for the ICBG patients was 2.9 hours, which was significantly longer ($P < 0.001$) than the 2.5 hours observed in the rhBMP-2 matrix group (Table 2). The average blood loss was 448.6 mL for the ICBG patients, which was significantly greater ($P < 0.001$) than the 343.1 mL blood loss observed with the rhBMP-2 matrix group. The average volume of bone graft obtained from the iliac crest in the ICBG patients was 36mL. There was no statistically significant difference in length of hospital stay between the two groups. No surgeries were abandoned because of technical problems. There were no unanticipated intraoperative complications related to the fusion procedure.

The ODI scores were similar in both groups over all time intervals (Fig. 1) and showed statistically significant improvement when compared with preoperative scores ($P < 0.001$) in both the ICBG and rhBMP-2 matrix groups at all time intervals (Table 3). The SF-36 Physical Component Summary (PCS) scores were similar in both groups at all time intervals (Fig. 2) and showed statistically significant improvement when compared with preoperative scores ($P < 0.001$) in both the ICBG and rhBMP-2 matrix groups (Table 4).

Deleted: All patients were past the 12-month evaluation point, but 24-month follow-up examinations are ongoing.
Deleted: Two hundred eighty-two
Formatted: Highlight
Deleted: 137
Formatted: Highlight
Deleted: 145
Formatted: Highlight
Deleted: 2
Deleted: also
Formatted: Font: Italic

Average back pain scores for the ICBG and rhBMP-2 matrix groups improved significantly from preoperative scores of 15.8 and 15.6 to 7.8 and 7.1 at 24 months, respectively ($P < 0.001$). Both groups showed similar improvements over all time intervals (Fig. 3) with no statistically significant difference in their 24-month average back pain scores ($P = 0.145$). Leg pain scores after surgery in both the ICBG and rhBMP-2 matrix groups improved in a similar manner over all time intervals (Fig. 4). The average improved from 14.0 in both groups, to 6.7 in the ICBG group and 6.2 in the rhBMP-2 matrix group at 24 months ($P < 0.001$). There was no statistically significant difference in 24-month leg pain scores ($P = 0.214$).

Pain resulting from bone harvest in the ICBG group was measured using donor site pain scores. The mean pain score at discharge of 11.3 improved to 7.9 at 6 weeks after surgery and to 6.3 at 3 months postoperatively. There was minimal improvement at subsequent follow-up periods up to 24 months. A large number of patients in the ICBG group (60%) still had persistent donor site pain, with a mean pain score of 5.1, at 24 months after surgery (Fig. 5).

Of the 224 subjects in the ICBG group, 41.1% were working before surgery. At 24 months, 48.4% were able to return to work (Fig. 6). Of the 239 rhBMP-2 matrix group patients, 34.7% were working before surgery. After surgery, 42% of the subjects were working at 24 months.

Using plain radiographs and CT scans, independent radiologists determined fusion according to the IDE protocol-defined analysis, whereby assessment by plain films was considered first. In patients in whom the plain films did not exhibit bridging bone, CT scans were then used to determine the presence of bridging bone. Assessment in this manner showed that statistical differences in fusion success occurred at two time intervals between the two groups. At 6 months, 79.1% of patients in the rhBMP-2 matrix group and 65.3% in the ICBG group achieved fusion success ($P = 0.002$). At 24 months, 95.9% in the rhBMP-2 matrix group had achieved fusion success compared with 89.3% in the ICBG group ($P = 0.014$).

Fine-cut CT scans with sagittal and coronal reconstructions showed that 74.7% of the subjects in the rhBMP-2 matrix group and 56.4% in the ICBG group had evidence of bilateral bridging bone at 6 months ($P < 0.001$). At 12 months, 86.9% of subjects in the rhBMP-2 matrix group and 71.3% in the ICBG group had evidence of bilateral bridging bone ($P < 0.001$). At 24 months, the rate was 94.8% in the rhBMP-2 group compared with 83.8% in the ICBG group ($P = 0.001$) (Fig. 7).

Deleted: Back
Deleted: 8.1
Deleted: 7.1…7. … [3]
Deleted: 8
Deleted: 8
Formatted: Font: Italic
Deleted: Chey
Deleted: 7.4…7.1 … [4]
Formatted: Font: Italic
Deleted: 54…5.0 … [5]
Deleted: 137
Formatted: Highlight
Deleted: Of those
Deleted: 48.5
Deleted: at 24 months…185 … [6]
Formatted: Highlight
Deleted: 40.7
Deleted: returned to work
Deleted: considered…87.5 … [7]
Deleted: 87.4
Deleted: 82.5
Deleted: 93.4
Deleted: at 12 months…199 … [8]
Deleted: 94.9…86.8 … [9]
Deleted: 23
Deleted: 0.074
Formatted: Highlight
Deleted: 4
Formatted … [10]
Deleted: 93.6
Deleted: 82.6
Formatted … [11]
Formatted … [12]
Deleted: 024

A new AE table has been added that corresponds to the IDE submission. Unfortunately, we could not verify the original table included since the categories are not those used in the IDE.

Also a second surgery table has been added as well that you may wish to incorporate.

DISCUSSION

The guiding principle for the surgical treatment of painful or unstable lumbosacral degenerative spinal disease remains the ability to achieve a solid fusion. Although autologous ICBG is the gold standard, the morbidity associated with graft harvest has led surgeons to seek viable alternatives, such as allografts, ceramics, and various types of autologous growth factors [20-24]. These graft substitutes have demonstrated great variability in achieving fusion with the greatest success achieved when used in addition to the iliac crest bone graft and not as an alternative to iliac crest bone graft. Additionally, they present their own unique problems including decreased success of fusion [25], limited availability, and the potential for rejection or immunologic reaction [21, 22].

The development of osteoinductive bone grafting options has resulted in the clinical availability of recombinant human bone morphogenetic protein (rhBMP-2 and rhBMP-7) for spinal fusion [26]. These naturally occurring bone proteins stimulate bone healing via a cascade mechanism that results in the differentiation of primitive mesenchymal cells and preosteoblasts into osteoblasts that promote bone formation and, ultimately, healing [Wozney et al.]. The effectiveness of rhBMP-2 in achieving a solid interbody fusion has been demonstrated in numerous experimental animal studies [6-8]. Subsequently, clinical trials have demonstrated similar fusion rates and clinical outcomes when ICBG was compared with rhBMP-2 combined with a collagen sponge carrier (INFUSE® Bone Graft) and a lordotic threaded interbody cage (LT-CAGE®) [9]. As a result of these findings, the FDA approved the use of rhBMP-2 as an iliac crest bone graft replacement for lumbar interbody fusion in 2002.

A recent randomized human pilot study evaluated a new rhBMP-2 formulation consisting of a 2 mg/cc concentration combined with biphasic calcium phosphate granules versus autograft in achieving a successful posterolateral fusion [16]. The study demonstrated a 40% fusion rate in the autograft group versus a 100% fusion rate with the rhBMP-2 matrix group when evaluated by

Deleted: The most common complication possibly related to the surgery was infection of various types at different sites (Table 5). There was a higher incidence of superficial wound infections in the ICBG group. There was no difference in the incidence of deep wound infections, wound drainage or development of wound hematoma. Sixteen patients in the ICBG group complained of continued pain from the bone graft donor site that required active treatment. One patient developed a donor site infection. No adverse events were observed that could be directly attributable to the use of rhBMP-2 matrix.

Formatted: Highlight

Formatted: Highlight

Formatted: Highlight

Deleted: osteoconductive

Deleted: biologics

Deleted: spine

radiographs and CT scans. ODI and SF-36 outcome measures demonstrated significant but similar improvement in both groups at the end of the study. Although the authors cited several deficiencies—most notably the lack of a 24-month follow-up on all subjects—the study presented evidence of the feasibility of rhBMP-2 in achieving a successful radiographically confirmed fusion in humans.

As part of an ongoing FDA-regulated IDE study, rhBMP-2 is now being evaluated for use in single-level posterolateral fusions combined with pedicle screw and rod instrumentation. We reviewed our two-year clinical outcomes and fusion rates based on CT scans in subjects. We used a specifically designed carrier that combines tricalcium phosphate and hydroxyapatite granules with a collagen matrix. This combination provides significant resistance to compression by the musculature when placed in the lateral gutters while providing a high binding affinity for rhBMP-2 and suitable resorption profile to optimize bone formation. It is also important to emphasize that in this study we used a higher concentration of rhBMP-2 (2.0 mg/cc versus 1.5 mg/cc) than was used in previous clinical studies with an absorbable collagen sponge carrier.

Although local bone graft is rarely discarded in clinical practice, the quality and quantity of local bone grafts are highly variable. In this study, local bone graft was discarded in both groups to allow for a direct comparison of the fusion rates of rhBMP-2 matrix to ICBG without local bone graft as a confounding variable.

Perioperative measures indicated improvements in operative time and blood loss, which were significantly less in the rhBMP-2 matrix group than in the ICBG group. The length of hospital stay was the same for both groups. Because of the nature of adverse event reporting in FDA-regulated trials, most patients experienced an adverse event over the two-year course of the study. There were no statistical differences in adverse events with the exception of iliac crest graft-related complications which occurred in 17 (7.4%) of control patients.

An equally important measure of the success of a fusion procedure, beyond the radiographic evidence of fusion, is how the patient feels and functions after surgery. The use of validated patient-based clinical outcome measures such as the Oswestry Disability Index and the SF-36 provide a self-assessment of the patient's functional improvement rather than the clinician's perception [17]. Most of the improvement in ODI scores and SF-36 PCS occurred within the first three months after surgery, in both groups. This improvement was maintained through the subsequent follow-up periods up to 24 months. The improvement in PCS at 24

Deleted: strongly

Deleted: affinity

Deleted: The incidence of deep wound infections, wound drainage, or development of wound hematoma was similar in both groups. There was a higher incidence of superficial wound infections in the ICBG group possibly because of the need for marked retraction to allow access to the iliac crest through the same incision for bone graft harvest.

Formatted: Highlight

months in both groups was well above the 5.41 point threshold in the literature for clinically significant improvement [27]. The decrease in ODI scores at 24 months in both groups was greater than 25 points, which is also above that necessary to demonstrate treatment efficacy [28, 29].

Most of the improvement in back pain and leg pain scores was noted within the first 6 weeks after surgery, and was maintained throughout the entire follow-up period of 24 months. The 8.4-point average decrease in back pain in the rhBMP-2 matrix group and 8.1-point average decrease in the ICBG group indicates a clinically significant diminution in back pain after surgery. The 7.3-point average decrease in leg pain in the rhBMP-2 matrix group and 6.6-point average decrease in the ICBG group indicates a clinically significant diminution in leg pain after surgery.

The rates of fusion in previously published articles vary widely from 60% to 98%. This may be due to the use of plain radiographs with flexion-extension views which are known to be inaccurate with error rates estimated from 20 to 40% [30-32]. When fusion success was determined using the IDE-protocol-defined criteria, the rhBMP-2 matrix group had significantly higher fusion success rates compared to the ICBG group at 6 and 24 months postoperatively. Using thin-cut CT scans, bilateral bridging bone was reported by the independent blinded radiologists significantly more often in the rhBMP-2 matrix group than in the ICBG group at all 3 time points. At the 24-month follow-up period, there were twice as many patients in the ICBG group with established nonunions. Similarly, there were twice as many non-elective surgical procedures to remove hardware in the ICBG group. In a separate study derived from a subset of this patient population, rhBMP-2 matrix produced a more robust fusion mass than ICBG as judged from CT scans alone [20]. The use of fine-cut CT scans with sagittal and coronal reconstructions may increase the ability to demonstrate the robustness of the fusion and the presence of bilateral confluent bridging bone.

Consider including discussion about Herkowitz observations that short-term follow-up did not result in being able to correlate fusions success with clinical outcomes; however, long-term follow-up did result in a correlation between the two. Perhaps longer-term follow-up will of this series will be able to detect to differences since statistical differences in fusion success was detected.

Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Deleted: smaller differences
Deleted: in
Deleted: than
Deleted: its
Deleted: At the 24-month follow-up period, there were
Formatted: Highlight
Deleted:
Deleted: twice
Deleted: twice
Deleted: as many patients in the ICBG group with established nonunions.

CONCLUSION

This study demonstrates that, for patients with a single-level degenerative disease, an instrumented posterolateral fusion with ICBG and rhBMP-2 matrix provides excellent clinical improvement and exhibits similar clinical outcomes 2 years after surgery. The rhBMP-2 matrix group demonstrated significantly decreased intraoperative blood loss and decreased operative time relative to the ICBG group. The rhBMP-2 matrix demonstrated an improved fusion success rate when compared with the ICBG group at 24 months. There were no significant differences in complications between the two groups with the exception of graft harvesting related complications which were avoided with the use of rhBMP-2 matrix. In conclusion, rhBMP-2 matrix decreases operative time and blood loss with earlier higher fusion rates and similar clinical outcomes as ICBG and can eliminate the need for harvesting iliac crest bone in successful posterolateral lumbar fusion surgery.

Please acknowledge all principle investigators from all sites.

Deleted: than

Formatted: Highlight

A new demographics table has been provided.

Deleted: Table 1: Patient Demographic Data¶ ... [13]

Formatted: Highlight

Table 2. Surgical Data

Variable	rhBMP-2 matrix Group	ICBG Group	P-value
Operative time	2.5	2.9	<0.001
Blood loss	343.1	448.6	<0.001
Hospital stay	4.1	4.0	0.609

Table 3. Mean Improvement from Preoperative Score in Oswestry Disability Index Score at Each Follow-up Interval.

Deleted: Change

Formatted Table

Follow-Up Interval	rhBMP-2 matrix	ICBG	P-value
6 weeks	12.9	13.9	0.530
3 months	22.1	21.2	0.127
6 months	26.0	24.5	0.100
12 months	26.9	25.6	0.119
24 months	26.7	25.5	0.111

Deleted: 580
Deleted: 610
Deleted: 24.4
Formatted: Highlight
Deleted: 382
Formatted: Highlight
Deleted: 25.4
Formatted: Highlight
Deleted: 452
Deleted: 27.2
Deleted: 25.6
Formatted: Highlight
Deleted: 582

Statistically significant improvement from the pre-operative status was noted in both groups at all time intervals ($P<0.001$).

Table 4. Mean Improvement from Preoperative Score in SF-36 Physical Component Summary Score at Each Follow-Up Interval.

Deleted: Change

Formatted Table

Follow-Up Interval	rhBMP-2 matrix/ ICBG	P-value

6 weeks	3.8	4.5	0.733
3 months	9.5	8.8	0.122
6 months	12.9	11.0	0.020
12 months	13.7	11.7	0.020
24 months	13.2	12.3	0.175

Statistically significant improvement from the pre-operative status was noted in both groups at all fi
intervals (P<0.001).

Deleted: 378
Deleted: 465
Deleted: 10.9
Deleted: 073
Deleted: 070
Formatted: Highlight
Deleted: 6
Formatted: Highlight
Formatted: Highlight
Deleted: 12.7
Formatted: Highlight
Formatted: Highlight
Deleted: 8
Formatted: Highlight
Deleted: 990
Formatted: Highlight

13

A new adverse event table has been provided.

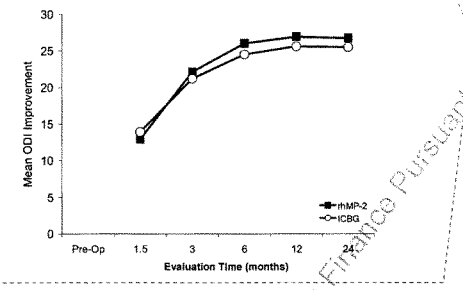


Figure 1. Comparison of mean improvement in Oswestry Disability Index scores in the ICBG and rhBMP-2 matrix groups at each follow-up interval

Comment [sk2]: See attachment for amended Table 5. I have also included a separate table for second surgeries.

Deleted: Table 5. Complications (events during 24-month follow-up period)¶
Complication [14]

Formatted: Highlight

Formatted: Highlight

Deleted: ¶
¶
Page Break

14

Consider including Mean ODI instead of improvement since the chart already provides improvement?

Formatted: Highlight

Deleted: ¶

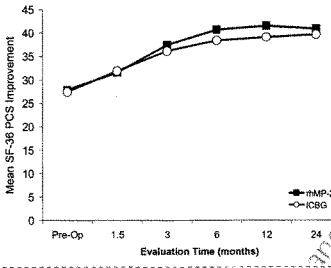
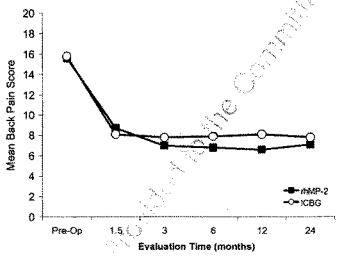


Figure 2. Comparison of SF-36 Physical Component Summary scores in the ICBG and rhBMP-2 matrix groups.

Unable to check numbers used to generate chart. Please ensure they are correct.

Formatted: Highlight



15

Figure 3. Comparison of mean back pain scores in the ICBG and rhBMP-2 matrix groups.

Unable to check numbers used to generate chart. Please ensure they are correct.

Formatted: Highlight

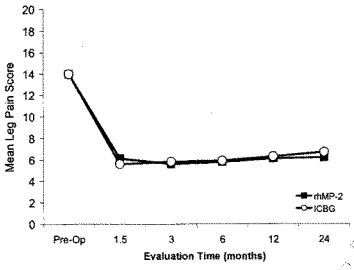


Figure 4. Comparison of mean leg pain scores in the ICBG and rhBMP-2 matrix groups.

Unable to check numbers used to generate chart. Please ensure they are correct.

Formatted: Highlight

Formatted: Body Text 2, Left

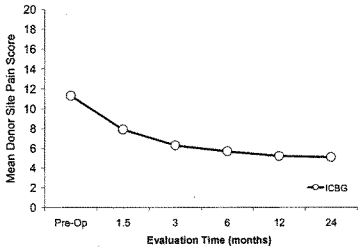
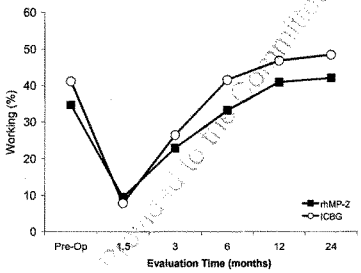


Figure 5. Mean donor site pain scores in the ICBG group.

Unable to check numbers used to generate chart. Please ensure they are correct.

Formatted: Highlight



17

Figure 6. Percentage of subjects working in the ICBG and rhBMP-2 matrix groups.

Unable to check numbers used to generate chart. Please ensure they are correct.

Formatted: Highlight

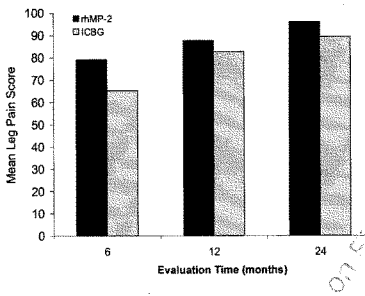


Figure 7. Percentage of subjects with bilateral confluent bridging bone reported by independent radiologists as observed on fine-cut CT scans with reconstructions for the ICBG and rhBMP-2 matrix groups. Differences between groups was statistically significant at all time points.

Y-axis title is wrong

Formatted: Highlight

Unable to check numbers used to generate chart. Please ensure they are correct.

Please insert p values on the chart.

Fusion success table?

Formatted: Highlight

REFERENCES

1. Bono CM, Lee CK. Critical analysis of trends in fusion for degenerative disc disease over the past 20 years: influence of technique on fusion rate and clinical outcome. Spine 2004;29:455-63.

2. An HS, Lynch K, Toth J. Prospective comparison of autograft vs. allograft for adult posterolateral lumbar spine fusion: differences among freeze-dried, frozen, and mixed grafts. J Spinal Disord 1995;8:131-5.

3. Dawson EG, Lotysch M 3rd, Urist MR. Intertransverse process lumbar arthrodesis with autogenous bone graft. Clin Orthop 1981;154:90-6.

4. Dimar J, Glassman S, Burkus JK, Carreon L. A comparison of prospective clincial outcome measures for anterior vs. posterior single-level spine fusion. IMAST Program July 2004

5. Jorgenson SS, Lowe TG, France J, Sabin J. A prospective analysis of autograft versus allograft in posterolateral lumbar fusion in the same patient. A minimum of 1–year follow-up in 144 patients. Spine 1994;19:2048-53.

6. Sandhu HS, Toth JM, Diwan AD, et al. Histological evaluation of the efficacy of rhBMP-2 compared with autograft bone in sheep spinal anterior interbody fusion. Spine 2002;27:567-75.

7. Boden SD, Martin GJ Jr, Horton WC, et al. Laparoscopic anterior spinal arthrodesis with rhBMP-2 in a titanium interbody threaded cage. J Spinal Disord 1998;11:95-101.

8. Hecht BP, Fischgrund JS, Herkowitz HN, et al. The use of recombinant human bone morphogenetic protein-2)rhBMP-2) to promote spinal fusion in a nonjuman primate anterior interbody fusion model. Spine 1999;24:629-36.

9. Burkus JK, Heim SE, Gornet MF, Zdeblick TA: Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-CAGE lumbar tapered fusion device. J Spinal Disord Tech 2003;16:113-22

10. Burkus JK, Sandhu HS, Gornet MF, Longley MC. Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery. J Bone Joint Surg Am. 2005;87:1205-12.

11. Martin JG Jr, Boden SD, Marone MA, Marone MA, Moskovitz PA. Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: important lessons learned regarding dose, carrier, and safety. J Spinal Disord 1999;12:179-86.

12. Barnes B, Boden SD, Louis-Ugbo J, et al. Lower dose of rhBMP-2 achieves spine fusion when combined with an osteoconductive bulking agent in non-human primates. Spine 2005;30:1127-33.

13. Akamaru T, Suh D, Boden SD, et al. Simple carrier matrix modifications can enhance delivery of recombinant human bone morphogenetic protein-2 for posterolateral spine fusion. Spine 2003;28:429-34.

14. Suh DY, Boden SD, Louis-Ugbo J, et al. Delivery of recombinant human bone morphogenetic protein-2 using a compression-resistant matrix in posterolateral spine fusion in the rabbit and in the non-human primate. Spine. 2002;27:353-60.

15. Boden SD, Martin GJ Jr, Morone MA, et al. Posterolateral lumbar intertransverse process spine arthrodesis with recombinant human bone morphogenetic protein 2/hydroxyapatite-tricalcium phosphate after laminectomy in the nonhuman primate. Spine. 1999;24:1179-85.

16. Boden SD, Kang J, Harvinder S, Heller JG. Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial: 2002 Volvo Award in clinical studies. Spine. 2002;27:2662-73.

17. Fairbank JC, Couper J, Davies JB, O'Brien JP. The Oswestry low back pain disability questionnaire. Physiotherapy 1980; 66:271-3.

18. Ware JE Jr, Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;306:473-83.

19. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994;32:40-66.

20. Glassman SD, Dimar JR, Carreon LY, et al. Initial fusion rates with recombinant human bone morphogenetic protein-2/compression resistant matrix and a hydroxyapatite and tricalcium phosphate/collagen carrier in posterolateral spinal fusion. Spine 2005;30;1694-98.

21. Boden SD. Overview of the biology of lumbar spine fusion and principles for selecting a bone graft substitute. Spine 2002;27(16S):S26-S31.

22. Ludwig SC, Kowalski JM and Boden SD. Osteoinductive bone graft substitutes. Eur Spine J 2000; 9(Suppl 1):S119-S125.

23. Lind M, Bunger C. Factors stimulating bone formation. Eur Spine J 2000;9(Suppl 1):S102-S109.

24. Vaccaro AR, Sharon AD, Tuan RS, et al. The use of biologic materials in spinal fusion. Orthopedics 2001;24:191-197.

25. Carreon LY, Glassman SD, Anekstein Y, Puno RM. Platelet gel (AGF) fails to increase fusion rates in instrumented posterolateral fusions. Spine. 2005;30:E243-6.

26. Urist MR: Bone: formation by autoinduction. Science. 1965;150:893-9

27. Ware JE, Kosinski M, Keller SK. SF-36® Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: The Health Institute, 1994.

28. Fairbank JCT, Pynsent PB: The Oswestry Disability Index. Spine 2000;25:2940-53.

29. Walsh TL, Hanscom B, Lurie JD, Weinstein JN. Is a condition-specific instrument for patients with low back pain/leg symptoms really necessary? The responsiveness of the Oswestry Disability index, MODEMS and the SF-36. Spine 2003;28:607-15.

30. Blumenthal SL, Gill K. Can lumbar spine radiographs accurately determine fusion in postoperative patients? Correlation of routine radiographs with a second surgical look at lumbar fusions. Spine. 1993;18:1186-9.

31.Brodsky AE, Kovalsky ES, Kahlil MA. Correlation of radiologic assessment of lumbar spine fusions with surgical exploration. Spine. 1991;16(6 Suppl):S261-5.

32. Kant AP, Daum WJ, Dean SM, Uchida T. Evaluation of lumbar spine fusion. Plain radiographs versus direct surgical exploration and observation. Spine 1995;20:2313-7.

Wozney JM. The bone morphogenetic protein family and osteogenesis [review]. Mol Reprod Dev 1992; 32:160-167

Page 2: [1] Comment [sk1] **kepess1** **10/24/2007 3:19:00 PM**
This number doesn't seem to correspond to the data that I have to compare it to. Based on the 24 month data for Hip Pain, there are 72 patients that reported a score of zero, which corresponds to roughly 32% of the 224 control subjects.

Page 2: [2] Deleted **peckhs1** **10/3/2007 12:47:00 PM**
and the morbidities associated with

Page 7: [3] Deleted **kepess1** **10/24/2007 3:07:00 PM**
7.1

Page 7: [3] Deleted **kepess1** **10/24/2007 3:07:00 PM**
7.

Page 7: [4] Deleted **LeahCarreon** **9/21/2007 10:08:00 AM**
7.4

Page 7: [4] Deleted **LeahCarreon** **9/21/2007 10:08:00 AM**
7.1

Page 7: [5] Deleted **LeahCarreon** **9/21/2007 10:08:00 AM**
54

Page 7: [5] Deleted **LeahCarreon** **9/21/2007 10:09:00 AM**
5.0

Page 7: [6] Deleted **bearcj1** **11/14/2007 1:29:00 PM**
at 24 months

Page 7: [6] Deleted **bearcj1** **11/14/2007 1:30:00 PM**
145

Page 7: [7] Deleted **bearcj1** **11/14/2007 1:31:00 PM**
considereded

Page 7: [7] Deleted **bearcj1** **11/14/2007 1:33:00 PM**
87.5

Page 7: [8] Deleted **bearcj1** **11/14/2007 1:34:00 PM**
at 12 months

Page 7: [8] Deleted **bearcj1** **11/14/2007 1:33:00 PM**
199

Page 7: [9] Deleted **LeahCarreon** **9/21/2007 10:09:00 AM**
94.9

Page 7: [9] Deleted **LeahCarreon** **9/21/2007 10:10:00 AM**
86.8

Table 1. Patient Demographic Data

	rhBMP-2 matrix Group	lCBG Group
Age (years)	53.2	52.3
Sex (% male)	45.2	42.4
Workers' Compensation (%)	11.3	12.5
Smoker (%)	26.4	26.3

Table 5. Complications (events during 24-month follow-up period.)[sk1]

Complication	rhBMP-2 matrix Group	ICBG Group
Wound drainage	5	6
Wound infections	16	23
Wound hematoma	1	0

Epidural hematoma	2	0
Malignancy*	7	2
Anemia	25	32
UTI	5	4
Infection (other sites)	25	19
Infection (total)	46	46
Second surgeries	20	37
Revisions	2	3
Removals	12	26
Supplemental fixations	6	8
Dural tear	14	17
Renal stones	6	6
Pulmonary	14	12
Ileus	8	3
Technical complications	5	5
Malposition	4	2
Displacement/loosening	1	3
Death	3	4
Donor site complaints	0	17
Donor site infection	0	1

*Cancer types in the rhBMP-2 matrix group were follicular, squamous cell, laryngeal, pancreatic, prostate, lung, and basal cell; in the ICBG group, cancer types were non-Hodgkin's lymphoma, and colon.

Table 5. Summary of Numbers (%) of Patients Who Reported Any or Possible† Device-Related Adverse Events

Adverse Event Category	Any Adverse Event					Possible† Device-Related Adverse Event				
	Investigational (n = 239)		Control (n = 224)		p Value *	Investigational (n = 239)		Control (n = 224)		p Value *
	Operative	Up to 24 Months	Operative	Up to 24 Months		Operative	Up to 24 Months	Operative	Up to 24 Months	
Patients who had any adverse events	20 (8.4)	209 (87.4)	20 (8.9)	198(88.4)	0.777	0 (0.0)	21 (8.8)	3 (1.3)	35 (15.6)	0.032
Anatomic/ technical difficulty	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	1.000					
Arthritis/Bursitis	0 (0.0)	22 (9.2)	0 (0.0)	17 (7.6)	0.616	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	0.234
Back and/or leg pain	0 (0.0)	104 (43.5)	0 (0.0)	90 (40.2)	0.510	0 (0.0)	4 (1.7)	0 (0.0)	5 (2.2)	0.745
Cancer 0	0 (0.0)	8 (3.3)	0 (0.0)	2 (0.9)	0.107					
Cardiovascular	2 (0.8)	52 (21.8)	0 (0.0)	54 (24.1)	0.581					
Carpal Tunnel Syndrome	0 (0.0)	9 (3.8)	0 (0.0)	6 (2.7)	0.604					
Death	0 (0.0)	3 (1.3)	0 (0.0)	4 (1.8)	0.717					
Dural Injury	13 (5.4)	14 (5.9)	18 (8.0)	18 (8.0)	0.367	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0.484
Gastrointestinal	0 (0.0)	37 (15.5)	0 (0.0)	33 (14.7)	0.897					
Graft Site Related	0 (0.0)	0 (0.0)	0 (0.0)	17 (7.6)	< 0.001					
Implant Displacement /Loosening	0 (0.0)	1 (0.4)	1 (0.4)	3 (1.3)	0.358	0 (0.0)	1 (0.4)	1 (0.4)	3 (1.3)	0.358
Infection	0 (0.0)	39 (16.3)	0 (0.0)	45 (20.1)	0.335					
Malpositioned Implant	1 (0.4)	5 (2.1)	0 (0.0)	2 (0.9)	0.451	0 (0.0)	4 (1.7)	0 (0.0)	2 (0.9)	0.686
Neurological	0 (0.0)	70 (29.3)	0 (0.0)	60 (26.8)	0.605	0 (0.0)	2 (0.8)	0 (0.0)	1 (0.4)	1.000
Non-Union Failure	0 (0.0)	6 (2.5)	0 (0.0)	18 (8.0)	0.011	0 (0.0)	6 (2.5)	0 (0.0)	18 (8.0)	0.011
Non-Union Outcome Pending	0 (0.0)	5 (2.1)	0 (0.0)	5 (2.2)	1.000	0 (0.0)	5 (2.1)	0 (0.0)	4 (1.8)	1.000
Other	1 (0.4)	70 (29.3)	0 (0.0)	62 (27.7)	0.758					
Other pain	0 (0.0)	29 (12.1)	0 (0.0)	28 (12.5)	1.000					
Respiratory	0 (0.0)	15 (6.3)	0 (0.0)	12 (5.4)	0.697					
Spinal Event	3 (0.7)	17 (7.1)	0 (0.0)	18 (8.0)	0.728					
Trauma	0 (0.0)	67 (28.0)	0 (0.0)	59 (26.3)	0.754					
Urogenital	0 (0.0)	26 (10.9)	0 (0.0)	21 (9.4)	0.646					
Vertebral fracture	3 (1.3)	3 (1.3)	3 (1.3)	5 (2.2)	0.492	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0.484

* p Values were obtained by Fisher's exact test for comparing the rates up to 24 months between the treatment groups.
† Possibly device-related adverse events refer to implant or implant/surgical procedure-related adverse events.
0 Cancer types in the rhBMP-2 matrix group were basal cell carcinoma, lung, lymphoma, ovarian, pancreatic, prostate, squamous cell carcinoma, and vocal cord; in the ICBG group, cancer types were end colon, and lymphoma.

Table ?. Second Surgery Events through 24 Month Follow-Up

Type of Secondary Surgical Procedure	Total Events Through 24 Months		# of Patients Reporting			
	INV	Control	INV N=239		Control N=224	
Revisions	4	4	4	1.7%	4	1.8%
Removals, Non-Elective	10	23	10	4.2%	22	9.8%
Supplemental Fixations	6	9	6	2.5%	9	4.0%

Table 1. Patient Demographics, Preoperative Medical Conditions, and Baseline Clinical Measures

Characteristic	Investigational Group (n = 239)	Control Group (n = 224)	p Value*
Age (years), mean (range)	53.2 (20-81)	52.3 (18-86)	0.408
Height (cm), mean (range)	170.4 (149.9-200.7)	169.7 (147.3-198.1)	0.380
Weight (kg), mean (range)	84.9 (47.2-164.2)	85.5 (44.9-141.5)	0.720
Male (%)	108 (45.2)	95 (42.4)	0.575
White (%)	218 (91.2)	203 (90.6)	0.848
Married (%)	176 (73.9)	155 (69.2)	0.457
College education or higher (%)	151 (63.2)	120 (54.1)	0.136
Workers' compensation (%)	27 (11.3)	28 (12.5)	0.774
Involved in litigation (%)	6 (2.5)	15 (6.7)	0.042
Tobacco use (%)	63 (26.4)	59 (26.3)	1.000
Alcohol use (%)	90 (37.7)	78 (34.8)	0.562
Working before surgery (%)	83 (34.7)	92 (41.1)	0.180
Previous back surgery (%)	73 (30.5)	62 (27.7)	0.540
Total Waddell signs, no. positive (%)	219 (91.6)	209 (93.3)	0.508
Medication use (%)			
Nonnarcotic	154 (64.7)	140 (62.5)	0.630
Weak narcotic	116 (48.5)	116 (51.8)	0.516
Strong narcotic	38 (16.0)	41 (18.4)	0.537
Muscle relaxant	55 (23.1)	55 (24.7)	0.743

*For continuous variables, p values were derived from analysis of variance for categorical variables, they were derived by Fisher's exact test.

From: Ken Burkus[redacted]
Sent: Monday, March 10, 2008 06:28:08 AM
To: Peter Wehrly[redacted]; Beals, Neil
Subject: Confidential

Attachments: Long-term outcomes of BMP-LT CAGE.final.for resubmission.1.doc

Pete and Neil,

I am looking forward to the challenges that the changes with MSD brings. New people - new ideas - new heights.

Importantly with all of the changes, I have to again point out what an outstanding person Brian Hatcher is. Brian has again completed a concise and insightful review and response to the sophisticated reviewers at JBJS. Please see attached his latest contribution. Julie and Brian make a great team. I hope that their tireless efforts are not lost in any of the changes within the Biologics Group.

Respectfully yours,
J. Kenneth Burkus, MD

Long-Term Outcomes of Anterior Lumbar Interbody Fusion Using Interbody Fusion Cages and rhBMP-2

Deleted: 3/9/2008 2/9/2008 2/20/2008

ABSTRACT

Background: Twenty-four month outcomes have been reported in patients with degenerative lumbar disc disease who were treated with stand-alone anterior lumbar interbody fusion using dual tapered interbody fusion cages and recombinant human bone morphogenetic protein-2 (rhBMP-2). This report represents an update of the clinical and radiographic results of this treatment at six years.

Methods: Patients enrolled in two prospective, multi-center FDA-approved investigational device exemption (IDE) studies were followed out to 6 years to determine radiographic and clinical outcomes. A total of 146 patients with single-level degenerative disc disease with up to grade 1 spondylolisthesis were treated with an open or a laparoscopic surgical procedure and completed the 6 year follow-up. The patients received recombinant human bone morphogenetic protein-2 on an absorbable collagen sponge with lumbar fusion cage implants. Outcomes were determined using well-established clinical outcome measurements and radiographic assessments.

Results: At six years, patients treated with rhBMP-2 and stand-alone fusion cages showed high rates of fusion and low rates of additional surgery. Radiographic evidence of fusion was documented in 98.5% of patients, and the second surgery rate between 2 and 6 years was 3.7%. Significant improvements in Oswestry Disability Index scores, SF-36® Health Survey Physical Component Summary scores, and back and leg pain scores were achieved by six weeks in both the open and laparoscopic groups, and were sustained at six years. By six

Deleted: We performed an integrated analysis of the six-year follow-up data from two prospective clinical studies in which 146 patients with single-level degenerative disc disease with up to grade 1 spondylolisthesis were treated with an open or a laparoscopic surgical procedure.

months, a higher percentage of patients were working than were working preoperatively, and this improvement was sustained at six years.

Conclusions: The use of dual tapered threaded fusion cages and rhBMP-2 on an absorbable collagen sponge facilitates and maintains intervertebral spinal fusion, improved clinical outcomes, and reduction of pain after anterior lumbar interbody fusion in patients with degenerative lumbar disc disease.

Level of Evidence: Level II: Prospective Cohort Study

Deleted: 3/9/20082/29/20082/20/2008

Deleted: There was a trend toward greater improvement in Oswestry Disability Index, back pain, and SF-36 Physical Component Summary scores in the laparoscopic group than in the open group.

Deleted: Systematic review of Level I randomized controlled trials.

Deleted: 3/9/20082/29/20082/20/2008

INTRODUCTION

Discogenic low back pain results, in part, from abnormal intersegmental load patterns and movement within a degenerative disc[1]. Clinically painful discs have been shown to display specific patterns of altered stresses in the anulus and vertebral end plates, reflecting abnormal loading[2]. Lumbar interbody fusion can eliminate abnormal stress patterns associated with degenerative disc disease and normalize stress distribution patterns[3,4]. Threaded interbody fusion cages stabilize the spinal motion segment and provide a mechanical environment that optimizes fusion[5]. New bone formation in and around the cages increases the contact area and decreases the magnitude of abnormal load in the fused segment.

Deleted: adjacent vertebrae

Various bone grafts have been used in an effort to enhance bone formation within the interverterbal disc space. Recombinant human bone morphogenetic protein-2 (rhBMP-2) is an osteoinductive growth factor that stimulates pleuripotential cells to form bone. In animal and human studies, rhBMP-2 has been shown to be capable of inducing new bone formation[6,7]. At twenty-four month follow up in randomized clinical trials, the use of rhBMP-2 as an iliac crest bone graft (ICBG) replacement has been shown to increase rates of interbody fusion in patients undergoing anterior lumbar interbody fusion (ALIF), and its use has been associated with decreased pain and improved clinical outcomes[8-10]. When used in combination with the LT-CAGE® Device (Medtronic Sofamor Danek, Memphis, TN), rhBMP-2 caused patients to achieve significantly higher fusion rates than patients treated with ICBG (94.4% vs. 89.4%; p =

0.022)[11]. Additional studies of rhBMP-2 on an absorbable collagen sponge in patients undergoing lumbar interbody fusion have shown similar rates of fusion success[8-10,12-19].

The current study was undertaken to validate the long term safety and efficacy of using stand-alone interbody fusion cages and rhBMP-2/ACS as an iliac crest bone graft replacement. Patients in both the open and laparoscopic IDE trials were prospectively followed in this FDA regulated postapproval study to determine fusion rates and clinical outcomes at 6 years, and to compare them to the outcomes seen at 2 years[9, 10].

MATERIALS AND METHODS

Two prospective, multi-center FDA-approved investigational device exemption (IDE) studies of patients undergoing treatment for single-level lumbar degenerative disc disease were conducted, utilizing a similar fusion technique through two different surgical approaches[9,20]. All patients were entered into these studies between 1997 and 1999 and were treated with INFUSE® Bone Graft and the LT-CAGE® Device (Medtronic Sofamor Danek, Memphis, TN). These studies used the identical inclusion-exclusion criteria; however, the laparoscopic cohort was a nonrandomized, single-arm study whereas the patients in the open study were randomized to receive either recombinant human bone morphogenetic protein on an absorbable collagen sponge (rhBMP-2/ACS) or iliac crest bone graft (ICBG). In this prospective study, patients enrolled in both the open and laparoscopic studies were followed out to 6 years to determine the long term

Deleted: 3/9/20082/29/20082/20/2008

Deleted: Our purpose was to investigate the postapproval long-term clinical and radiographic outcomes in those investigational patients enrolled in the initial FDA trials using stand-alone interbody fusion cages and rhBMP-2 as an iliac crest bone graft replacement. Patients who received rhBMP-2 on an absorbable collagen sponge were followed for a period of six years to determine the long-term efficacy of its use as a replacement to ICBG.¶

Deleted: Our analysis combines data from the patients who were treated with INFUSE® Bone Graft and the LT-CAGE® Device (Medtronic Sofamor Danek, Memphis, TN) in the two FDA IDE trials.

Deleted: 3/9/20082/29/20082/20/2008

radiographic and clinical outcomes. These two studies were conducted to evaluate the efficacy of rhBMP-2/ACS as a replacement to ICBG and to support PMA approval, and were not designed to directly compare the open and laparoscopic surgical approaches. Internal review board (IRB) approval was completed at all study sites, and informed consent was obtained for all patients enrolled in the follow-up studies.

Inclusion-Exclusion Criteria

At the time of surgery, all patients were between the ages of 19 and 70 years and had symptomatic degenerative disc disease at the L4-L5 or L5-S1 levels (Table 1). All had had low back pain for at least six months before their surgery that was recalcitrant to nonoperative treatment modalities, such as physical therapy, bed rest, and anti-inflammatory medications. Patients were included in the study if their plain radiographic findings documented single-level disc disease, and they had undergone at least one additional confirmatory neuroradiographic study, such as MRI, CT-enhanced myelography, or discography. All patients were considered candidates for a single-level stand-alone anterior lumbar interbody fusion (ALIF). Patients were excluded from the study if they had spinal conditions other than single-level symptomatic degenerative disc disease or greater than Grade 1 spondylolisthesis. Other exclusion criteria were symptomatic disc disease at a level other than the L4-L5 or L5-S1, obesity (more than 40% above ideal body weight), or a medical condition that required medication, such as steroids or nonsteroidal anti-inflammatory medications, that could interfere with fusion.

Deleted: 3/9/20082/29/20082/20/2008

Patient Follow-Up

There were 277 total patients enrolled in the open (143 patients) and laparoscopic (134 patients) groups in the initial FDA IDE studies. Of the thirty-one initial sites, twenty-three elected to participate in the long-term follow-up. As a result of second surgery failures and nonparticipating sites, fifty-five patients were excluded from this study leaving a total of 222 patients who were eligible for the FDA IDE postapproval follow-up assessments (109 in the open- and 110 in the laparoscopic-surgery arms). One hundred forty-six patients completed the seventy-two-month follow-up assessments (Table 2). This subgroup of patients was examined to determine the clinical outcome measures and fusion status at each time point from the preoperative examination to the seventy-two month follow-up examination after surgery.

Deleted: eight

Deleted: 19

Comment [h1]: Insert patient accountability table and use this in place of the current Table 2.

Surgical Procedures

Patients underwent an ALIF procedure using either an open[9] or a laparoscopic approach[20]. In the open group, transperitoneal or retroperitoneal approaches to the lumbosacral spine were used; in the laparoscopic group, all approaches were transperitoneal. Patients in both surgical groups had two LT-CAGE Devices implanted anteriorly at either the L4-L5 or L5-S1 lumbar interspace.

RhBMP-2 on the absorbable collagen sponge was used exclusively as an ICBG replacement[9,20]. No autogenous grafts and no local host-bone reamings were used. The rhBMP-2 was reconstituted to a concentration of 1.5 mg/mL and allowed to bind to the collagen sponge for a minimum of fifteen minutes, which

Deleted: using sterile water and applied to the appropriate number of collagen sponges. The rhBMP-2 was

resulted in 95% of the protein being bound to the sponge[21]. The total dose of rhBMP-2 ranged from 4.2 to 8 mg and was determined by matching the volume of the prepared collagen sponge to the internal volume of the fusion cage.

The results from the studies using the two surgical approaches were pooled and analyzed independently to better define the effects of surgical approach in surgical parameters, hospital stay, and the long-term clinical and radiographic outcomes.

Clinical Outcome Measures

Clinical outcome measures, the Oswestry Disability Index (ODI)[22], the MOS 36-item Short-Form health survey (SF-36) questionnaire[23,24], back and leg pain scores, and return-to-work status, were self administered preoperatively and at six weeks, three, six, twelve, twenty-four, forty-eight, and seventy-two months. Back and leg pain scores were determined using a 20-point scale (10 points frequency and 10 points intensity).

Radiographic Assessment

Radiographs (lateral, A/P, and flexion/extension) and thin cut CT scans with sagittal and coronal reconstructions were used to assess the presence of continuous trabecular bone formation between the vertebral bodies and to evaluate fusion[9,10]. Two independent, blinded radiologists interpreted radiographs and CT scans to assess fusion, with a third radiologist available for adjudication. Fusion was defined as bridging bone connecting the adjacent vertebral bodies either through the implants or around the implants, less than 5° of angular motion, less than or equal to 3 mm of translation, and an absence of radiolucent

Deleted: 3/9/2008 2/29/2008 2/20/2008

Deleted: The rhBMP-2-soaked sponges were placed into the central portion of each LT-CAGE Device. No additional rhBMP-2-bound sponges were placed outside of the fusion cages.

Deleted: was assessed using radiographs and computed tomography (CT) scans

Deleted: 3/9/20082/29/20082/20/2008

lines around more than 50% of either implant. Second surgery failures were classified as a failed fusion[9]. Fusion was assessed at six, twelve, twenty-four, forty-eight, and seventy-two months, and was considered successful only if all criteria were achieved.

Additional Surgical Procedures

Secondary surgical procedures performed subsequent to the index operation were classified as revisions, removals, supplemental fixations, or reoperations. Second surgeries that occurred as a result of adjacent level disease, but involved the index level, were classified as second surgery failures. A survivorship analysis was used to determine the percentage of patients who were classified as second surgery failures, taking into account all available patients at each follow-up time point.

Deleted: A revision surgery was defined as any procedure that adjusts or modifies the original implant configuration; a removal was defined as a procedure that removes one or more components of the original implant and replaces it with a different type of implant; supplemental fixation was defined as a procedure in which additional spinal devices not approved as part of the protocol are placed; and reoperation was defined as any surgical procedure at the treated level that does not remove, modify, or add any components, for example, a posterior foraminotomy.

Adverse Events

Adverse events were studied and classified as to their severity and relationship with the implants and with surgical procedures.

Statistical Analysis

For assessing the statistical significance of postoperative improvement in outcome scores from preoperative values within each treatment group, a paired *t* test was used. For statistical comparisons of demographic differences between the open and laparoscopic treatment groups, analysis of variance (ANOVA) was used for continuous variables, and Fisher's exact test was used for categorical data.

Deleted: 3/9/20082/29/20082/20/2008

RESULTS

Patient Follow-Up

One hundred forty-six patients (68 in the laparoscopic group and 78 in the open group) completed the six-year follow-up. The overall follow-up rate was 52.7% (146/277), and the follow-up rate for available patients at six years was 65.8% (146/222). This subset of patients had the demographic characteristics and clinical outcomes prior to 24 months similar to those previously reported for the entire patient population[9,10].

Deleted: 6.7

Deleted: 19

Deleted: A comparison of this subgroup of patients with the entire patient population prior to twenty-four months indicated similar clinical outcomes between the groups, suggesting that this group of patients serves as a representative subset of the

Deleted: two prospective

Deleted: study

Demographic data were compiled for the patients included in the analysis (Table 3). The open and laparoscopic surgical groups were not randomized relative to each other; however, the patients' demographic characteristics and prognostic factors in these 2 groups were similar except for the patient's sex and alcohol use.

Surgical Data

Surgical, hospitalization, and clinical outcomes were analyzed for each surgical technique and the outcomes were combined. The laparoscopic group spent an average of 18 minutes longer under anesthesia and lost an average of 7.3 mL more blood than the open group (Table 4). However, the laparoscopic group left the hospital an average of 1.7 days earlier than the open group.

Clinical Outcomes

Oswestry Disability Scores

ODI scores improved significantly in all groups from the preoperative scores by 6 weeks, and these improvements were maintained out to 6 years

(p<0.001, Table 5 and Figure 1). For the open group, ODI scores improved an average of 32.8 points and 27.7 points at 48 and 72 months, respectively, from a preoperative score of 53.8. For the laparoscopic group, ODI scores improved an average of 34.4 points and 34.3 points at 48 and 72 months, respectively, from a preoperative score of 49.6. These improvements were similar to those seen at 24 months (31.0 points and 32.6 points for the open and laparoscopic groups, respectively).

Back Pain

Back pain scores improved significantly in all groups from the preoperative scores by 6 weeks, and these improvements were maintained out to 6 years (p<0.001, Table 5). For the open group, back pain scores improved an average of 7.7 points and 6.9 points at 48 and 72 months, respectively, from a preoperative score of 15.3. For the laparoscopic group, back pain scores improved an average of 10.6 points and 10.2 points at 48 and 72 months, respectively, from a preoperative score of 15.6. These improvements were similar to those seen at 24 months (8.7 points and 10.1 points for the open and laparoscopic groups, respectively).

Leg Pain

Leg pain scores improved significantly in all groups from the preoperative scores by 6 weeks, and these improvements were maintained out to 6 years (p<0.001, Table 5). For the open group, leg pain scores improved an average of 7.0 points and 6.8 points at 48 and 72 months, respectively, from a preoperative score of 13.4. For the laparoscopic group, leg pain scores improved an average

Deleted: 3/9/20082:29:20082:20:2008

Deleted: The Oswestry Disability Index (ODI) Questionnaire measures the level of pain and disability associated with various activities. ODI scores improved significantly from preoperative values by six weeks, and these improvements were maintained at six years (p < 0.001). For the combined group, ODI scores improved an average of 33.8 points and 31.0 points at forty-eight and seventy-two months, respectively, from a preoperative score of 52.0. These improvements were similar to those observed at twenty-four months (31.7 points). There was a trend towards slightly greater improvements in ODI scores in the laparoscopic group when compared with those in the open group at seventy-two months (Fig. 1).

Deleted: Back pain scores improved significantly from preoperative values by six weeks, and these improvements were maintained at six years (p < 0.001). For the combined group, back pain scores improved an average of 9.3 points and 8.6 points at forty-eight and seventy-two months, respectively. These improvements were similar to those observed at twenty-four months (9.3 points). There was a trend towards slightly greater improvements in back pain scores in the laparoscopic group when compared with the open group at forty-eight and seventy-two months (Fig. 2).

Deleted: 3/9/2008 2:29:20 PM

of 5.8 points and 6.6 points at 48 and 72 months, respectively, from a preoperative score of 9.6. These improvements were similar to those seen at 24 months (7.3 points and 5.2 points for the open and laparoscopic groups, respectively).

SF-36

SF-36 PCS scores improved significantly in all groups from the preoperative scores by 6 weeks, and these improvements were maintained out to 6 years ($p<0.001$, Table 5). For the open group, SF-36 PCS scores improved an average of 15.3 points and 12.4 points at 48 and 72 months, respectively, from a preoperative score of 27.1. For the laparoscopic group, SF-36 PCS scores improved an average of 19.1 points and 17.8 points at 48 and 72 months, respectively, from a preoperative score of 28.7. These improvements were similar to those seen at 24 months (16.3 points and 17.5 points for the open and laparoscopic groups, respectively).

For both the open and laparoscopic groups, all SF-36 outcomes except for general health perception and role emotional improved significantly from the preoperative values at 72 months ($p<0.001$, Table 6). All outcomes in the laparoscopic group were maintained between 24 and 72 months ($p>0.05$), however certain outcomes in the open group declined slightly between 24 and 72 months ($p<0.05$, Table 5).

Deleted: Leg pain scores improved significantly from preoperative values by six weeks, and these improvements were maintained at six years ($p < 0.001$). For the combined group, leg pain scores improved an average of 6.4 points and 6.7 points at forty-eight and seventy-two months, respectively. These improvements were similar to those observed at twenty-four months (6.4 points). The improvement from the preoperative score at seventy-two months was similar in the laparoscopic and open groups (Fig. 3).¶

Deleted: The SF-36 measures specific health concepts related to physical functioning, social functioning, and health perceptions. For the combined group, Physical Component Summary (PCS) scores improved an average of 17.3 points and 15.1 points at forty-eight and seventy-two months, respectively. These improvements were similar to those observed at 24 months (16.1 points). There was a trend towards slightly greater improvement in SF-36 PCS scores in the laparoscopic group than in the open group at forty-eight and seventy-two months (Fig. 4).

Radiographic Outcomes

At seventy-two months, 130 (89.0%, 130/146) patients had complete radiographic follow-up examinations (Fig. 2 A-D). At forty-eight and seventy-two

Deleted: 5

Deleted: 1/9/20082/29/20082/20/2008

Deleted: 8

months, 97.9% (92/94) and 98.5% (128/130) of patients had radiographic evidence of fusion (Fig. 3). The high rates of fusion seen at these later time points were similar to the rates of arthrodesis seen at six, twelve, and twenty-four months. Fusion rates were similar between the open and laparoscopic groups.

Second Surgery Failures

There were a total of twenty-five second surgery failures over the six-year follow-up period: sixteen in the open group and nine in the laparoscopic group. There were twenty-three supplemental fixations, one removal, and one revision. Reasons for second surgeries (implant positioning, migration or loosening, nonunion, suspected nonunion, subsidence, stenosis, radiculopathy, adjacent segment degeneration, and post laminectomy syndrome) were reported by the enrolling surgeon. Second surgery failures occurred between five days and sixty-two months after surgery.

Deleted: pending nonunions

Adjusting for the patients available at each follow-up interval by a time-to-event analysis, the overall second surgery failure rate was 10.4% (13.7% in the open group and 7.1% in the laparoscopic group) (Fig. 4). Eighteen of the twenty-five second surgeries occurred before 2 years, and the second surgery failure rate during this time period was 6.7% for the combined group (6.4% open and 7.1% laparoscopic)[8,19]. The remaining 7 second surgeries occurred between two and six years, and the rate of second surgery failure for the combined group during this time was 3.7% (7.3% open and 0% laparoscopic). All 7 failures were supplemental fixations, and investigators reported suspected nonunion (n=2), back pain (n=2), stenosis (n=2) and post laminectomy syndrome (n=1) as the

Deleted: 7

Deleted: 3/9/2008 2/29/2008 2/20/2008

causes for reoperation. Three of the second surgeries involved only the index level, and the remaining 4 included both the index and adjacent level.

Return-to-Work Status

At forty-eight and seventy-two months, more patients were working than were working before surgery (69.2%;72/104 and 68.1%; 94/138 at forty-eight and seventy-two months, respectively, compared with 52.1% preoperatively). The percentage of patients working at the later time points was similar to that at twenty-four months (70.3%) (Fig. 5). By six months, approximately 90% of the patients who were working preoperatively had returned to work, and this was maintained though the seventy-two-month time point.

Deleted: 8

Adverse Events

Relevant adverse events included anatomical/technical difficulty, malpositioned implants, implant displacement/loosening, and subsidence (Table 7). All AE's within these categories occurred prior to 2 years. Anatomical/technical difficulty was observed to only occur in the laparoscopic surgical group, and all 9 events occurred during the operative period. Seven of these events resulted in a conversion to open or posterior surgery. Subsidence occurred in a total of 7 patients (6 open and 1 lap), with all events occurring within the first 6 months. Of the 24 patients with AE's listed in Table 7, 7 patients had a second surgical procedure.

Deleted: No unanticipated adverse events related to the use of rhBMP-2/ACS occurred during the course of the study. Because the ICBG control group was not followed during the twenty-four- and seventy-two-month time frame, no analysis of adverse events between the investigational and control group could be completed.

DISCUSSION

Results from prospective studies of the LT-CAGE Device have shown a trend towards more rapid fusion with INFUSE Bone Graft and improved clinical

Deleted: 1/9/20082/29/20082/20/2008

outcomes when compared with patients who received autograft ICBG[11]. These improved outcomes are related, in part, to the successful combination of the surgical approach, the advanced cage designs, the avoidance of bone graft harvesting morbidity, and the high rate of successful interbody fusion. This study represents the longest follow-up, to date, of patients undergoing spine fusion with INFUSE Bone Graft[9-20]. In patients with six years of follow-up, observed radiographic fusion rates were high, rates of second surgery were low, and improvements in clinical outcomes were maintained.

Other studies have reported the long-term radiographic and clinical results of lumbar interbody fusion[25-30]. Kuslich et al. reported four-year results from a study enrolling 947 patients who received Bagby and Kuslich (BAK) cages and ICBG[29]. However, only 20.7% (196/947) of patients completed the four-year follow-up,. Fusion success allowed for up to 7° of angulation on flexion-extension films, and did not include CT scans. At four years, the authors reported an overall fusion success of 98% and a repeat surgery rate of 8.7%. Pain scores were maintained out to four years.

Deleted: which included both anterior (n = 122) and posterior (n = 74) approaches and single-level (n = 116) and two-level (n = 80) fusions

Deleted: no thin cut

Deleted: with reconstructed images were obtained to assess fusion

In a similar study, investigators evaluated clinical and radiographic outcomes following ALIF with stand-alone BAK cages implanted by a single author[28]. Patients underwent single-level (n = 40) or two-level (n = 6) ALIF with BAK cages and autograft, allograft, or a combination of both. Thirty-three of forty-six patients (71.7%) reached a mean follow-up of fifty-five months (range, thirty-six to sixty-five months). The authors reported an overall nonunion rate of 30%

Deleted: 3/9/20082/29/20082/20/2008

and a revision rate of 22%. Mean ODI score at final follow-up was 41, with only 42% of patients having an ODI less than or equal to 40.

Brantigan and co-workers also investigated the long-term results of instrumented posterior lumbar interbody fusion (PLIF) [26]. The initial study enrolled 110 patients with degenerative disc disease at six centers. Thirty-three patients selected from two centers completed the ten-year follow-up (30%). Radiographic evidence of fusion, as defined by bridging bone and the absence of radiolucencies was reported in 96.7% of the patients at ten years. At two years, elective removal of pedicle screws indicated that 90% (104/115) of the examined levels were fused. Clinical outcomes were determined using a twenty-point Prolo scale. Preoperatively, 76% of patients had a rating of good or fair. At ten years, 87.8% (29/33) of patients had a rating of excellent, good or fair and achieved clinical success. In our study, 79% (109/138) of patients treated with INFUSE Bone Graft had an ODI improvement of greater than fifteen points at six years.

Deleted: The fusion rates and improvement in ODI scores at four and six years in patients treated with INFUSE Bone Graft and the LT CAGE Device indicate an improvement relative to this published report.

Deleted: A clinical success was defined as a patient with an excellent, good, or fair outcome and a minimum of a three-point improvement.

Martin et al. compared reoperation rates from the early '90s with those of the late '90s in a study involving approximately 25,000 patients undergoing primary lumbar surgery[31]. For patients whose primary procedure was a fusion (19.1%), these authors found a general overall reoperation rate of 14% at four years, and for patients whose primary diagnosis was herniated disc or degenerative disc disease (90.9%), the reoperation rate was approximately 15%. For patients treated with INFUSE Bone Graft and the LT CAGE Device, the secondary surgery failure rate of 9% at four years and 10% at six years compares favorably with overall failure rates cited for the 1990s.

An observation in the current study was that patients treated by the laparoscopic surgical technique trended to have shortened hospital stay, better Oswestry Low Back Pain Disability Questionnaire scores, improved scores on the SF-36 Health Survey, reduced low back pain, and fewer reoperations when compared with the group treated with open surgery at 6 years ($p>0.05$). There are potential benefits of the laparoscopic surgical approach, such as less muscle damage and tissue retraction, shorter hospital stay, and a quicker return to normal activities, that may have accounted for or contributed to this trend. This study was not designed to compare the open and laparoscopic surgical approaches, however, and there are likely a number of confounding factors that may have contributed to this observation. Patients in the open and laparoscopic surgery groups were not randomized to each other and were enrolled in 2 separate studies. There were preoperative differences in patient's demographics, including sex and alcohol use. Additionally, more patients in the open group had substantial changes in their ODI scores between twenty-four and seventy-two months, which may have contributed bias (eighteen patients in the open group had an ODI increase of 20 points or more, compared with only one patient in the laparoscopic group). Review of case report forms for patients in the open group revealed the occurrence of falls, motor vehicle accidents, adjacent level disease, and a high percentage of patients with a BMI of greater than twenty-five, which may have contributed to the slight differences in clinical outcomes. Importantly, the mean improvement scores for both groups in Oswestry pain scores, PCS scores, and back and leg pain scores were

Deleted: 3/9/20082/29/20082/20/2008

Deleted: Patients treated by the laparoscopic surgical technique in the current study trended to have shortened hospital stay, better Oswestry Low Back Pain Disability Questionnaire scores, improved scores on the SF-36 Health Survey, reduced low back pain, and fewer reoperations when compared with the group treated with open surgery. There are potential benefits of the laparoscopic surgical approach, such as less muscle damage and tissue retraction, shorter hospital stay, and a quicker return to normal activities, that may have accounted for or contributed to this trend. Preoperative differences in patient demographics, including sex and alcohol use, also may have contributed, in part, to these differences. Additionally, more patients in the open group had substantial changes in their ODI scores between twenty-four and seventy-two months, which may have contributed bias (eighteen patients in the open group had an ODI increase of 20 points or more, compared with only one patient in the laparoscopic group). Review of case report forms for patients in the open group revealed the occurrence of falls, motor vehicle accidents, adjacent level disease, and a high percentage of patients with a BMI of greater than twenty-five, which may have contributed to the slight differences in clinical outcomes. Finally, the lack of randomization between the open and laparoscopic groups makes it difficult to draw definitive conclusions as to the etiology or clinical significance of this difference. Importantly, the mean improvement scores for both groups in Oswestry pain scores, PCS scores, and back and leg pain scores were significantly improved from preoperative measurements and were maintained between the twenty-four- and seventy-two-month follow-up period.

Comment [h2]: Should we include a comment along the lines of "Whether or not the difference in these outcomes between the open and laparoscopic groups is of clinical significance is a point of debate, as the minimally important clinical difference reported in the literature is variable (refs)." Otherwise, we can specifically address the reviewers comment on this point in the cover letter.

 Deleted: 3/9/2008 2/29/2008 2/20/2008

significantly improved from preoperative measurements and were maintained between the twenty-four- and seventy-two-month follow-up period. Whether or not the difference in these outcomes between the open and laparoscopic groups is of clinical significance is a point of debate, as the minimally important clinical difference reported in the literature is variable [22].

A comparison of three outcome parameters, fusion status, operative time, and hospital stay, show an improvement in care for treatment of degenerative disc disease in the lumbar spine with an advancement in therapy options[5]. Additionally, twenty-four month data comparing INFUSE Bone Graft with ICBG has shown superior rates of fusion and clinical outcomes in patients treated with rhBMP-2[11]. The improvement in functional outcomes is maintained at six years after treatment with rhBMP-2 and is also reflected in the high rates of employment in both the open and laparoscopic groups. In particular, the high rate of segmental arthrodesis may serve to provide long-term maintenance of these significant improvements in clinical outcomes[32].

The use of rhBMP-2 on an absorbable collagen-soaked sponge is an effective method of facilitating anterior intervertebral spinal fusion using a stand-alone interbody fusion device. In this long-term study, treatment with INFUSE Bone Graft and threaded titanium cages was shown to lead to high rates of fusion that were maintained at six years after surgery, and significant improvements in clinical outcome measures were maintained. These results further support the use of rhBMP-2 as a replacement for autograft in lumbar interbody fusion.

REFERENCES

1. Adams MA, Roughley PJ. What is intervertebral disc degeneration, and what causes it? Spine. 2006;31:2151-61.

2. Videman T, Nurminen M. The occurrence of anular tears and their relation to lifetime back pain history: a cadaveric study using barium sulfate discography. Spine. 2004;29:2668-76.

3. Kumar N, Judith MR, Kumar A, Mishra V, Robert MC. Analysis of stress distribution in lumbar interbody fusion. Spine. 2005;30:1731-5.

4. Palm WJ 4th, Rosenberg WS, Keaveny TM. Load transfer mechanisms in cylindrical interbody cage constructs. Spine. 2002;27:2101-7.

5. Burkus JK. Stand-alone anterior lumbar interbody fusion constructs: effect of interbody design, bone graft and bone morphogenetic protein on clinical and radiographic outcomes. In: Lewandrowski K, Yaszemski MJ, White AA, Trantolo DJ, Wise, DL, eds. *Advances in Spinal Fusion: Clinical Applications of Basic Science, Molecular Biology, Biomechanics, and Engineering.* New York, NY: Marcel Dekker; 2003:69-84.

6. Boden SD, Martin GJ Jr, Horton WC, Truss TL, Sandhu HS. Laparoscopic anterior spinal arthrodesis with rhBMP-2 in a titanium interbody threaded cage. J Spinal Disord. 1998;11:95-101.

7. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine. 1999;24:629-36.

8. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine. 2000;25:376-81.

9. Burkus JK, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. J Spinal Disord Tech. 2002;15:337-49.

10. Burkus JK, Sandhu HS, Gornet MF, Longley MC. Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery. J Bone Joint Surg Am. 2005;87:1205-12.

11. Burkus JK, Heim SE, Gornet MF, Zdeblick TA. Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-CAGE lumbar tapered fusion device. J Spinal Disord Tech. 2003;16:113-22.

12. Anand N, Hamilton JF, Perri B, Miraliakbar H, Goldstein T. Cantilever TLIF with structural allograft and RhBMP2 for correction and maintenance of segmental sagittal lordosis: long-term clinical, radiographic, and functional outcome. Spine. 2006;31:E748-53.

13. Kuklo TR, Rosner MK, Polly DW Jr. Computerized tomography evaluation of a resorbable implant after transforaminal lumbar interbody fusion. Neurosurg Focus. 2004;16:E10.

14. Lanman TH, Hopkins TJ. Lumbar interbody fusion after treatment with recombinant human bone morphogenetic protein-2 added to poly(L-lactide-co-D,L-lactide) bioresorbable implants. Neurosurg Focus. 2004;16:E9.

15. Mummaneni PV, Pan J, Haid RW, Rodts GE. Contribution of recombinant human bone morphogenetic protein-2 to the rapid creation of interbody fusion when used in transforaminal lumbar interbody fusion: a preliminary report. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2004. J Neurosurg Spine. 2004;1:19-23.

16. Potter BK, Freedman BA, Verwiebe EG, Hall JM, Polly DW Jr, Kuklo TR. Transforaminal lumbar interbody fusion: clinical and radiographic results and complications in 100 consecutive patients. J Spinal Disord Tech. 2005;18:337-46.

17. Schwender JD, Holly LT, Rouben DP, Foley KT. Minimally invasive transforaminal lumbar interbody fusion (TLIF): technical feasibility and initial results. J Spinal Disord Tech. 2005;18 SuppIS1-6.

18. Slosar PJ, Josey R, Reynolds J. Accelerating lumbar fusions by combining rhBMP-2 with allograft bone: a prospective analysis of interbody fusion rates and clinical outcomes. Spine J. 2007;7:301-7.

19. Villavicencio AT, Burneikiene S, Nelson EL, Bulsara KR, Favors M, Thramann J. Safety of transforaminal lumbar interbody fusion and intervertebral recombinant human bone morphogenetic protein-2. J Neurosurg Spine. 2005;3:436-43.

20. Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2: a prospective study of clinical and radiographic outcomes. Spine. 2001;26:2751-6.

21. Hsu HP, Zanella JM, Peckham SM, Spector M. Comparing ectopic bone growth induced by rhBMP-2 on an absorbable collagen sponge in rat and rabbit models. J Orthop Res. 2006;24:1660-9.

22. Fairbank JC, Couper J, Davies JB, O'Brien JP, The Oswestry low back pain disability questionnaire. Physiotherapy. 1980;66:271-3.

23. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994; 32:40-66.

24. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473-83.

25. Bagby G. The Bagby and Kuslich (BAK) method of lumbar interbody fusion. Spine. 1999;24:1857.

26. Brantigan JW, Neidre A, Toohey JS. The Lumbar I/F Cage for posterior lumbar interbody fusion with the variable screw placement system: 10-year results of a Food and Drug Administration clinical trial. Spine J. 2004; 4:681-8.

27. Brantigan JW, Steffee AD, Lewis ML, Quinn LM, Persenaire JM. Lumbar interbody fusion using the Brantigan I/F cage for posterior lumbar interbody fusion and the variable pedicle screw placement system: two-year results from a Food and Drug Administration investigational device exemption clinical trial. Spine. 2000;25:1437-46.

28. Button G, Gupta M, Barrett C, Cammack P, Benson D. Three- to six-year follow-up of stand-alone BAK cages implanted by a single surgeon. Spine J. 2005;5:155-60.

29. Kuslich SD, Danielson G, Dowdle JD, Sherman J, Fredrickson B, Yuan H, Griffith SL. Four-year follow-up results of lumbar spine arthrodesis using the Bagby and Kuslich lumbar fusion cage. Spine. 2000;25:2656-62.

30. Kuslich SD, Ulstrom CL, Griffith SL, Ahern JW, Dowdle JD. The Bagby and Kuslich method of lumbar interbody fusion. History, techniques, and 2-year follow-up results of a United States prospective, multicenter trial. Spine. 1998;23:1267-78; discussion 1279.

31. Martin BI, Mirza SK, Comstock BA, Gray DT, Kreuter W, Deyo RA. Are lumbar spine reoperation rates falling with greater use of fusion surgery and new surgical technology? Spine. 2007;32:2119-26.

32. Kornblum MB, Fischgrund JS, Herkowitz HN, Abraham DA, Berkower DL, Ditkoff JS. Degenerative lumbar spondylolisthesis with spinal stenosis: a prospective long-term study comparing fusion and pseudarthrosis. Spine. 2004;29:726-33; discussion 733-4.

Deleted: 3/9/20082/29/20082/20/2008

LEGEND OF FIGURES

Figure 1: Comparison of improvement in Oswestry Disability Index scores.

Figure 2: A, Preoperative lateral radiograph in a study patient shows disc space narrowing at L5-S1, posterior radial osteophyte formation and retrolisthesis of L5 on S1 The L4-L5 disc has a normal height, physiologic segmental lordosis, and no radial osteophytes.

B, At six weeks after surgery, the lateral radiograph shows in this patient shows placement of the dual paired interbody fusion cages in the L5-S1 disc space. Physiologic disc space height and normal sagittal contours have been restored at L5-S1.

C, At seventy-two months, this lateral radiograph shows new bone formation spanning the L5-S1 disc space anterior to the cages. There has been no subsidence of the cages. Disc space height and sagittal contours have been maintained from those seen on earlier radiographic studies. The L4-L5 disc shows no radiographic evidence of adjacent segment degeneration.

D, At seventy-two months after surgery, this sagittal computed tomography scan shows continuous trabecular bone formation through the interbody fusion cage spanning the L5-S1 interspace.

Figure 3: Comparison of radiographic fusion success.

Figure 4: Comparison of second surgery failures.

Figure 5: Comparison of return-to-work status.

Deleted: Figure 2: Comparison of improvement in back pain scores.¶ Figure 3: Comparison of improvement in leg pain scores.¶ Figure 4: Comparison of improvement in SF-36 Physical Component Summary scores.¶

Deleted: 5

Deleted: 6

Deleted: 7

Deleted: 8

From: Neil Beals
Sent: Monday, April 8, 2002 04:10:02 PM
To: Julie Bearcroft
Subject: FW: FW: Oswestry Success

Attachments: T_OSW2_15PCT.DOC; T_OSW2_15PCT.DOC

-----Original Message-----
From: Bailey Lipscomb
Sent: Thursday, December 20, 2001 9:18 AM
To: Neil Beals
Subject: FW: FW: Oswestry Success

Here is your answer, ASAP.
Bailey

-----Original Message-----
From: Guorong Ma
Sent: Thursday, December 20, 2001 9:16 AM
To: Bailey Lipscomb
Subject: RE: FW: Oswestry Success

InFUSE/LT Inv. Open, Inv. Lap, & Control

LT-CAGE Lap

> -----Original Message-----
> **From:** Bailey Lipscomb
> **Sent:** Thursday, December 20, 2001 8:15 AM
> **To:** Guorong Ma
> **Subject:** FW: FW: Oswestry Success
>
> -----Original Message-----
> **From:** Neil Beals
> **Sent:** Thursday, December 20, 2001 7:34 AM
> **To:** Bailey Lipscomb
> **Subject:** RE: FW: Oswestry Success

I need this info for InFUSE LT lap and autograft LT lap ASAP; I will be sending these data to technical writing firm to assist in preparation of manuscript for Zdeblick; also need this for InFUSE open LT ASAP for its manuscript submission (this is our biggest priority from pub standpoint) which should be landmark paper in the lit

-----Original Message-----
From: Bailey Lipscomb
Sent: Wednesday, December 19, 2001 2:48 PM
To: Neil Beals
Subject: RE: FW: Oswestry Success

When do you need it. I think that we have already done this for the Burkus et al. paper.

Bailey

-----Original Message-----
From: Neil Beals
Sent: Wednesday, December 19, 2001 9:04 AM
To: Bailey Lipscomb
Cc: Pete Wehrly; Jon Serbousek
Subject: FW: FW: Oswestry Success

Bailey,

Ken and Tom have recommended that we use 15% Oswestry score reduction as success measurement rather 15 points - this will be used in manuscript for publication. Can you recommend how we should best accommodate this request? I think we will need to do this for all future manuscripts and we may need to also rethink other FDA-assigned success criteria which may require revised statistical analysis. I know this is above and beyond PMA sub but it does have significant importance. Please advise me of how we can handle this request.

Neil

-----Original Message-----
From: Dr. Thomas Zdeblick [SMTP[redacted]
Sent: Tuesday, December 18, 2001 7:41 AM
To: Neil Beals
Subject: Re: FW: Oswestry Success

For consistency, we should use the 15% figure. TAZ

InFUSE(TM) Bone Graft/LT-CAGE(TM) Device Open and Lap Studies

Summary of Success* Rates of Oswestry Low Back Pain Measures
[Number (%) of Patients]

Variable	Open Inv. (N=143)	Control (N=136)	Lap Inv. (N=134)
6 Weeks			
Success	70 (50.0)	79 (60.3)	79 (62.2)
Failure	70 (50.0)	52 (39.7)	48 (37.8)
3 Months			
Success	106 (75.2)	101 (75.4)	103 (81.1)
Failure	35 (24.8)	33 (24.6)	24 (18.9)
6 Months			
Success	111 (81.6)	109 (83.2)	99 (82.5)
Failure	25 (18.4)	22 (16.8)	21 (17.5)
12 Months			
Success	110 (84.6)	107 (85.6)	104 (91.2)
Failure	20 (15.4)	18 (14.4)	10 (8.8)
24 Months			
Success	103 (84.4)	89 (82.4)	86 (92.5)
Failure	19 (15.6)	19 (17.6)	7 (7.5)

Program (Date): T_OSW2_15PCT (20DEC01) (08:50) (PAGE 1 OF 1)

* Success: 100*(Pre Score - Post Score)/Pre Score => 15.

InFUSE(TM) Bone Graft/LT-CAGE(TM) Device Open and Lap Studies

Summary of Success* Rates of Oswestry Low Back Pain Measures
[Number (%) of Patients]

Variable	Open Inv. (N=143)	Control (N=136)	Lap Inv. (N=134)
6 Weeks			
Success	70 (50.0)	79 (60.3)	79 (62.2)
Failure	70 (50.0)	52 (39.7)	48 (37.8)
3 Months			
Success	106 (75.2)	101 (75.4)	103 (81.1)
Failure	35 (24.8)	33 (24.6)	24 (18.9)
6 Months			
Success	111 (81.6)	109 (83.2)	99 (82.5)
Failure	25 (18.4)	22 (16.8)	21 (17.5)
12 Months			
Success	110 (84.6)	107 (85.6)	104 (91.2)
Failure	20 (15.4)	18 (14.4)	10 (8.8)
24 Months			
Success	103 (84.4)	89 (82.4)	86 (92.5)
Failure	19 (15.6)	19 (17.6)	7 (7.5)

Program (Date): T_OSW2_15PCT (20DEC01) (08:50)PAGE 1 OF 1]

* Success: 100*(Pre Score - Post Score)/Pre Score => 15.

From: Burkus, J. Kenneth
Sent: Saturday, December 21, 2002 11:30:39 AM
To: Martin, Bill; Beals, Neil; Bearcroft, Julie; Treharne, Rick
Subject: PLIF Study

Attachments: PLIF BMP paper.1.doc

Dear Sirs and Ma'am,

Merry Christmas. I am rushing off to Salt Lake City.

I have completed about as much as I can on the PLIF manuscript without further data analysis.

I have attached the manuscript. Within the text you will find bolded areas which require further data analysis.

I hope that you will agree with me that this project should be high on the priority list.

Let me know how I can help. I look forward to your insights, comments and input.

I hope that you and your families have a Merry Christmas.

Warm regards,
Ken Burkus

A Prospective, Randomized Posterior Lumbar Interbody Fusion Study using rhBMP-2 with Cylindrical Interbody Cages

Regis Haid, MD[‡]

Joseph Alexander MD [†]

Charlie Branch MD*

J. Kenneth Burkus MD[§]

[‡] Professor, Department of Neurosurgery, Emory University, Atlanta, Georgia

[†] Assistant professor, Department of Neurosurgery

* Chairman, Department of Neurosurgery,

[§] Simple Country Spine Surgeon at The Hughston Clinic, Columbus, Georgia

Address correspondence and reprint requests to J.K. Burkus, MD, The Hughston Clinic, [redacted]

ABSTRACT

Study Design. In a multi-center, prospective, randomized, nonblinded, 2-year study, 67 patients who underwent a single-level posterior lumbar interbody fusion with two paired cylindrical threaded titanium fusion devices were randomized into two groups: one received autogenous iliac crest bone graft, the other, recombinant human bone morphogenetic protein-2 (rhBMP-2) on a collagen sponge carrier.

Objectives. The objective of the study was to determine the clinical and radiographic outcomes in patients treated for single-level degenerative lumbar disc disease with a posterior interbody fusion using stand-alone cylindrical threaded titanium fusion cages with autogenous bone graft or rhBMP-2 and an absorbable collagen sponge carrier.

Summary of Background Data. In a large series of human patients undergoing anterior lumbar interbody fusion with a tapered titanium fusion cage, rhBMP-2 has been shown to promote osteoinduction and fusion and to decrease operative time and blood loss.

Methods. In this prospective nonblinded study, 67 patients were randomly divided into 2 groups that underwent interbody fusion using two cylindrical threaded fusion cages: the investigational group (34 patients) that received rhBMP-2 on an absorbable collagen sponge and a control group (33 patients) that received autogenous iliac crest bone graft. Assessment of a patient's clinical outcome was based on low back and leg pain questionnaires, Short Form SF36 questionnaires, Oswestry Low Back Pain Disability scores and work status. Plain radiographs and computed tomographic scans were used to evaluate fusion at 6,12 and 24 months postoperatively.

Results. Mean operative time (2.6 hours) and blood loss (322.8 mL) was less in the investigational rhBMP-2 group than in the autograft control group (3.0 hours and 372.7 mL). At 24 months, the investigational group's fusion rate of 92.3% was higher than the control's at 77.8%. At all postoperative intervals, the mean Oswestry, back pain and leg pain scores and both the mental and physical components of the SF36 improved in both treatment groups compared with the preoperative scores. **In the control group, ?? adverse events related to harvesting of the iliac crest graft occurred in ?? patients (??%), and, at 24 months after surgery, ??% patients still reported graft site discomfort and ??% were bothered by the appearance of graft site.**

Conclusions. The investigational group had shorter operative times and less blood loss. At 24 months, this group had a fusion rate that was more than 14 percentage points greater than the control group. All clinical outcome measurements that were studied showed greater improvement in the investigational (rhBMP-2) patients. Overall results show that the use of rhBMP-2 can eliminate the need for harvesting iliac crest graft for successful posterior lumbar interbody fusions.

Key words: posterior lumbar interbody fusion, bone morphogenetic protein, osteoinduction, radiography, interbody fusion cages

Key points:

- At 24 months, the average rate of fusion for patients treated with rhBMP-2 was more than 14 percentage points higher (92.3% vs. 77.8%) than for patients treated with autograft. **??<u>This difference was statistically significant??</u>**
- The average operative time was 2.6 hours for patients treated with rhBMP-2 compared with 3.0 hours in the autograft group. **??<u>This difference was statistically significant??</u>**
- Blood loss was less for patients treated with rhBMP-2 than for patients who underwent iliac crest bone graft harvesting.
- At all postoperative assessment intervals, patients in both treatment groups showed improvement in Oswestry disability scores, in back and leg pain outcomes and in both the PCS and MCS scores of the SF36.
- The use of rhBMP-2 in posterior lumbar interbody fusion procedures eliminates the complications of iliac crest bone harvesting including postoperative pain and scarring.

Précis

In a 2-year prospective randomized study of 67 patients, the investigational group that received rhBMP-2 with paired cylindrical cage devices had a higher rate of fusion, reduced operative times, and decreased blood loss when compared with the control group that received autogenous bone graft. Clinical outcomes showed greater improvement in the rhBMP-2 group at 3, 6, 12 and 24 months. The rhBMP-2 group avoided the complications that can arise from an iliac crest bone harvesting procedure.

INTRODUCTION

Posterior lumbar interbody fusion (PLIF) is an effective treatment for patients with symptomatic degenerative disc disease, spondylolithesis and other painful discogenic syndromes. Fusion of the degenerative and unstable lumbar spinal motion segment can give significant relief from this disabling and often progressive condition. PLIF limits the extent of posterolateral soft tissue exposure, muscle stripping, and injury. With this technique, the surgeon uses the traditional posterior approach to the lumbar spine; however, dissection is limited laterally to the facet joints. Through this approach, direct neural decompression can be completed, disc space height and sagittal balance can be restored, and intervertebral grafts can be placed in a biomechanically advantageous position.

Lumbar spine stabilization procedures that limit the extent of posterior spinal muscles exposure have some significant advantages. With PLIF surgical techniques, the fusion bed is within the disc space and it eliminates the exposure of the transverse processes. The PLIF approach to the lumbosacral spine enables the surgeon to re-establish the normal anatomic alignment and relationships of the spinal motion segment while avoiding excessive injury to the posterior paravertebral muscles.

Cloward presented his technique for this demanding procedure in 1953. In his surgical technique, he described using a wide laminectomy and facetectomies that would allow for the placement of large structural bone grafts in the denuded and meticulously prepared disc space. Later, Lin modified this intervertebral grafting technique of structural grafts. This modified PLIF technique involves filling the disc space with cancellous bone strips. It allows for preservation of a portion the posterior

elements and avoids the complication of insertion of large structural grafts. Additional modifications of the bone graft technique and bone graft materials have been made. Kutlich and Ray introduced the idea of using threaded interbody fusion cages inserted through a PLIF approach as means of stabilizing the lumbar motion segment, increasing rates of fusion and improving clinical outcomes.

Recombinant human bone morphogenetic protein 2 (rhBMP-2) applied to an absorbable collagen sponge carrier has been shown to promote osteoinduction and fusion in the lumbar spine. In a large series of patients who underwent stand-alone anterior lumbar interbody fusion with fusion cages, rhBMP-2 was shown to enhance rates of fusion, reduce surgical time and improve clinical outcomes. To further evaluate this method of bone graft replacement, we evaluated the clinical and radiographic outcomes at 24 months of 67 patients who underwent a single level PLIF. We compared the outcomes in the investigational patients (rhBMP-2) with those in the control patients (autogenous bone).

MATERIALS AND METHODS

Study Design. **Between 19?? and 19??,** 67 patients completed surgery in this prospective, randomized, nonblinded, FDA approved study at 14 investigational sites. All patients underwent a single-level posterior lumbar fusion with two paired INTERFIX™ devices (Medtronic Sofamor Danek, Memphis, TN). The interbody fusion cages were used as stand-alone construct in the disc space. Patients were randomly assigned in a 1:1 manner to one of two groups: the investigational group received rhBMP-2 on an absorbable collagen sponge carrier and the control group received autogenous iliac crest bone graft. InFUSE Bone Graft™ (Medtronic Sofamor Danek, Memphis, TN) is the trademarked name for recombinant human bone morphogenetic protein-2 applied to an absorbable collagen sponge.

Patient Data. Preoperatively, all patients had symptomatic, single-level degenerative lumbar disc disease and symptoms of disabling low back or leg pain, or both, of at least 6 months' duration that had not responded to nonoperative treatments. The two treatment groups were similar demographically (Table). **There were ?? statistically significant differences (??P < 0.05) for any of the variables.** The rhBMP-2 group consisted of 34 patients and the control group consisted of 33 patients. The average age at surgery was 46.3 years for the rhBMP-2 group and 46.1 years for the control group. In the rhBMP-2 group, 18 patients (52.9%) had used tobacco within 6 months before surgery compared with 15 patients (45.5%) in the control group. The percentage of patients with pending litigation was 8.8% and 3.0% in the rhBMP-2 and control groups, respectively. The percentage of patients seeking worker's compensation was 23.5% in the rhBMP-2 group and 27.3.6% in the control group.

Clinical and Radiographic Outcome Measurements. Patient assessments were completed preoperatively, during hospitalization, and postoperatively at 6 weeks and at 3, 6, 12, and 24 months. Clinical outcomes were assessed using back, leg, and graft site pain questionnaires, short form SF36, Oswestry Low Back Pain Disability scores, and work status. Back and leg symptoms were assessed separately on a visual analog scale. Back and leg pain intensity and the duration of these symptoms were assessed using a 20-point numeric rating scale. Both intensity of pain and duration of pain were given a ten-point visual analog rating scale. Adding the numeric rating scores for pain intensity and pain duration allowed examiners to derive a composite back and leg pain score.

Radiographs and computed tomography (CT) scans were used to evaluate fusion at 6, 12, and 24 months after surgery. Plain radiographs including standing lateral and flexion-extension lateral were obtained at each interval. Thin-cut1-mm CT scans were taken at 6, 12 and 24 months. Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent, blinded radiologist was used to adjudicate conflicting fusion findings. **There was ?? agreement between the radiologists reviewing the studies. At 6, 12, and 24 months after surgery, agreement between the independent reviewers was ??%.**

Fusion was defined as an absence of radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation less than 5° on flexion-extension radiographs, and continuous trabecular bone growth connecting the vertebral bodies. Patients who had secondary surgeries because of persistent low back symptoms and clinically suspected nonunions were considered as having failed fusions

and were classified as failures in all fusion calculations, regardless of their independent radiological assessment.

Clinical and Radiographic Follow-up. **The rate of patient return for follow-up was ?? at all postoperative periods. At 12 months, the rate of patient return for both treatment groups was ?? %. At 24 months, the follow-up rate for the investigational group was ??% and the control group rate was ??%.**

Surgical Technique.

An open posterior interbody fusion procedures was carried out in each patient. Preoperatively, the patients disc space was templated to determine the appropriate intraoperative disc space distraction and cage size. Plain radiographs are assessed to determine normal disc space height of the adjacent spinal motion segments. Axial CT scan or MR images are used to establish the anterior-posterior dimension of the disc space to ensure proper cage sizing.

The patient was placed in the prone position on padded bolsters that support the chest and pelvis and suspend the abdomen. Care is taken to ensure that the pelvis is extended to ensure that lumbar lordosis was preserved. The operating room table accommodated plain radiographs or fluoroscopy.

A complete laminectomy with facetectomies or extensive bilateral laminotomies and facetectomies with preservation of the mid-line elements was performed in each case. The lateral borders of the disc were exposed along with the traversing and exiting nerve roots. Bilateral annulotomies were made and a complete discectomy was carried through these annular windows. The annulotomies are placed lateral to the dural tube. The midportion of the lateral annular window was centered adjacent to the medial wall of pedicle. The anterior

and lateral walls of the annulus were preserved; the entire nucleus is removed. Cartilaginous end plates were resected using curettes.

Reduction of sagittal and frontal plane deformities was achieved through disc space height restoration and annular tensioning. Inserting progressively larger dilators into the collapsed disc restored disc space height and the normal sagittal contours of the spine.

The vertebral end plates were prepared with reamers that uniformly cut a channel through the adjacent bony end plates. Great care is taken to visualize and gently retract both the traversing and exiting nerve roots. These soft tissue elements were protected by a tubular reamer guide, which was impacted into the disc space prior to reaming. Care was taken to ensure that the endplate cuts are made parallel and equally into each end plates.

The INTERFIX cages were packed with either the rhBMP-2 soaked sponges or morcellized autograft prior to insertion. The cages were sequentially inserted in the disc space and away from any soft tissue or neural elements. The cages were not routinely recessed within the disc space. The majority of the cages were left flush to the posterior cortical wall of the vertebral bodies. Their position was assessed intraoperatively with plain radiographs or fluoroscopy.

Iliac crest bone graft harvesting

The control group received morcellized autogenous iliac crest graft placed within the cages. The bone graft was harvested from the outer table of the iliac wing. The graft was morcellized using a rongeur and was tightly packed into the cages before their insertion.

rhBMP-2 preparation

The rhBMP-2 used was reconstituted using sterile water and was used as a single dose of 1.5 mg/mL in all study patients. The 1.5 mg rhBMP-2/mL solution was

applied to a bovine collagen sponge and allowed to bind to the sponge for 15 minutes. **The dosage of rhBMP-2 varied by patient depending on cage size, with the total dose ranging from ?? mg to ?? mg.** The rhBMP-2 soaked sponge was then placed in the hollow central portion of the INTERFIX device before its insertion into the prepared disc space. No additional sponges were placed outside of the devices. No autogenous grafts were used in the investigational group.

Postoperatively, patients were placed in a soft lumbar corset. Activities were advanced by the treating physician. Isometric strengthening and exercise program were started at six weeks postoperatively.

Statistical Methods

??The data from this clinical trial were analyzed using the statistical software package SAS® version 6.12. For continuous variables, *P* values are from ANOVA, and for categorical variables, they are from Fisher's exact test or chi-square test.??

RESULTS

Surgery

The mean operative time in the investigational rhBMP-2 group (2.6 hours) was less than in the control group (3.0 hours) (Table). The average blood loss in the rhBMP-2 group was 322.8 ml as compared with 372.7 ml in the control group. The average hospital stay was less in the investigational group (3.4 days for the investigational group vs. 5.2 days for the control group). There were no unanticipated device-related adverse events in either treatment group.

Complications

Vascular events.

?? patients developed deep venous thrombosis and were treated with anticoagulation medications.

Iliac crest graft site. **In the control group, adverse events related to harvesting of the iliac crest graft were identified in ?? patients (??%). These events included ?? infections and ?? hematomas. ?? required an additional surgery**. There were no graft site adverse events in the investigational group since the use of rhBMP-2 precluded the need to harvest bone graft.

The level of postoperative pain and morbidity associated with the iliac crest graft harvesting was measured using numeric rating scales for pain intensity and duration (Table). After surgery, all of the control patients experienced hip donor site pain. **The highest levels of pain were noted immediately after surgery with a mean score of ?? points out of 20 points. The percentage of patients experiencing pain decreased over time; however, at 24 months after surgery, nearly ??one-third?? of the control patients (??%) still experienced pain . At two years, the graft site pain scores averaged ?? points.**

Antibody Testing

Antibody results. **Antibodies to rhBMP-2 were evaluated ??preoperatively and ?? months postoperatively using enzyme-linked immunosorbent assays (ELISAs). The results were similar between the investigational and control groups (??% and ??%, respectively). ??There appeared to be no negative clinical consequence to positive antibody test results ??.**

Clinical Outcomes

Oswestry Disability Questionnaire scores. The Oswestry Low Back Pain Disability Questionnaire measured pain associated with activities. The Oswestry Questionnaire was administered preoperatively as well as at each postoperative visit. At all postoperative visits, both treatment groups demonstrated statistical improvements as compared with the preoperative scores that were maintained through two years (Table). At all postoperative time intervals after the first 6-week follow-up period, the investigational group showed improvement over the control group in the mean overall Oswestry scores. **At last follow-up at 24 months, the mean improvements in the Oswestry scores were ?? points in the investigational group and ?? points in the controls (Figure ??). In the rhBMP-2 group, ??% of patients showed an improvement of at least 15% in their disability scores at 12 months after surgery as compared with ??% of patients in the control group. At 24 months, the ??% of the investigational group was improved and compared favorably with ??% improved in the control group.**

Back Pain. The mean back pain scores at all postoperative periods were improved from the preoperative mean values for both treatment groups. The mean improvements in back pain scores at all five postoperative intervals studied were greater for the investigational group than for the control autograft group (Figure). **At 24 month the average improvement in back pain in the investigation group was almost twice that of the control group (?? point improvement vs. ?? point improvement). Statistics??**

Leg Pain. Leg pain was assessed in a similar manner using a numeric rating scale for both the intensity and duration of painful symptoms. Mean leg pain scores improved significantly after surgery in each group (Table). However, at each study interval average leg pain scores were less in the investigational group when compared to the control group. Similarly, the investigational group also showed higher average improvement scores at each interval studied. **At 24 months, the average improvement in leg pain was ?? points in the investigational group compared to ?? points in the control group. Statistics??**

Short Form SF36. At all postoperative intervals studied the investigational group showed greater improvement in both the physical and mental components of the short form SF36 when compared to the controls (Figures).

Work Status. Many factors affect a patient's work status, such as the nature of the work performed and ability of the work place to accommodate work restrictions. Prior to surgery, in the investigational group only 22%?? were gainfully employed while over 40% of the control patients were employed (Table). **For patients who were working before surgery, the median return to work time was ?? days in the investigational group and ?? days in the control group**. At last follow-up, more people in the investigational treatment group were working than were working before their surgery. At 2 years following surgery in the investigational group, 14 patients were employed while only 8 were employed before surgery. The percentage of people working in the control group remained unchanged at the 24-month follow-up. In the control group, 14 were working before surgery and 14 were working at two years after surgery.

Patient Satisfaction. **At 12 and 24 months after surgery, the results were ?? in each treatment group. At 24 months, ??% of the investigational patients and ??% of the controls were satisfied with their surgical outcomes. In the investigational group, ??% said they would undergo surgery again compared with ??% of the control patients who would undergo surgery again. In the investigational group, ??% believed that they were helped as much as they had expected to be from the surgery; ??% of the control group felt they had been.**

Radiographic Outcomes

Cage placement

Cage placement was assessed on both plain radiographs and thin-cut CT scan. The CT scans were found to more accurately reflect the position of the cage in relation

to the spinal canal posteriorly and neuroforamina laterally. There were no differences between the two patient groups regarding cage placement (Figure). Only 6% of patients in each group (2/34 investigational group; 2/33 control group) showed cages that were countersunk 3mm or more from the posterior margin of the vertebral body. Approximately one-third of patients in each group had cages that extended into the spinal canal on postoperative CT studies (11/34 investigational group; 10/33 control group). The remainder of the cages were placed either flush to the posterior cortex of the vertebral bodies or were recessed by only 2mm or less.

Sagittal plane balance

Preoperatively, ?? patients had a grade 1 spondylolithesis . Nearly one third of patients (19/67; 28%) postoperatively had some sagittal plane imbalance following surgery. At the last follow-up, 6 patients had some residual spondylolithesis from failure to fully reduce the deformity at the time of surgery and two patients developed spondylolithesis postoperatively. Eleven patients had residual retrolithesis following surgery.

Intradiscal bone formation

Fusion status of the study patients was evaluated on plain radiographs and CT scans. At six months after surgery, 93.1% of patients in both the investigational and control groups had evidence of fusion (Table). At 12 months, in the investigational group the fusion rate dropped to 85.2% while the control group maintained a fusion rate of 92%. This is decrease in fusion rate was, in part, related to poor follow-up in the investigational group at the 12-month time frame. **?? patients were recorded as non-union because they failed to return fro radiographs during this time interval**. In the

control group, 30 patients (92%) showed evidence of fusion at one year. However, at 24 months, the investigational group had a 92.3% fusion rate, which was more than 14 percentage points higher than that of the control group (77.8%).

Bone formation outside of the disc space

The thin cut 1.0 mm CT scans were able to identify new bone formation adjacent to the interbody fusion cages. New bone formation extending outside of the disc space and into the spinal canal or neuroforamina was found in 28 patients. Five patients (15%) in the control group had new formation in the spinal canal while 23 patients (68%) in the investigational group had bone formation outside of the disc space.

Sagittal plane balance. In the control group, one of the 5 patients (20%) with bone in the spinal canal had a residual unreduced spondylolithesis following surgery. New bone formation was identified in the canal posterior to the unreduced superior vertebra. In the control group, new bone formation was identified in four patients extending into the spinal canal in patients with normal segmental sagittal plane balance.

In the investigational group, 10 of the 23 patients (43%) with bone in the spinal canal had some residual postoperative sagittal plane imbalance. Five patients (5/23; 22%) had spondylolithesis and 5 (5/23;22%) had retrolithesis. In each of these cases, new bone formation occurred posterior to the unreduced vertebral body. Thirteen patients had a normal segmental sagittal plane balance and new bone formation in the spinal canal.

Cage placement.

In the investigational group cage placement was strongly associated with the development of bone in the spinal canal. In the investigational group 39% of patients

with cages placed at the margin or within 2mm of the margin of the posterior vertebral cortex developed some bone in the spinal canal. Twelve percent of patients in the control group with cages placed within 2mm of the vertebral margins developed bone in the spinal canal.

Secondary Surgical Procedures

In the investigational group, ?? patients (??%) had a second surgery and ?? patients (??%) in the control group had second surgeries. ?? investigational patients underwent supplemental fixation for presumed pseudarthrosis, ?? underwent supplemental fixation after posterior decompression for persistent radicular symptoms after the initial surgery.

In the control group, ?? patients underwent supplemental posterior fixation for a presumed pseudarthrosis and ?? underwent supplemental posterior fixation for persistent discogenic pain.

DISCUSSION

Threaded cylindrical cages represent a new, distinct class of segmental spinal fixation devices. These devices were not designed as spacers that require segmental stabilization; rather, they were designed as stand-alone Intervertebral devices that function as an "instrumented PLIF." Threaded interbody devices are biomechanically different from interbody spacers. Biomechanical studies have shown that cage size is of some significance in stand-alone cage fusions; however, stand-alone cages do not significantly increase spinal stiffness in studies using human cadavers. Larger cages improve stiffness in rotation and lateral bending. Reduction of motion in flexion is not significantly improved with larger cages. Larger cages require more extensive facet joint resection or complete facetectomy, which further destabilizes the spinal motion segment. A cylindrical device increases in its medial-lateral dimension equal to its increase in height, which necessitates greater mobilization and retraction of the neural elements.

Initial clinical studies reported high rates of fusion and clinical success in certain centers. These results have not been widely reproduced. Authors of clinical and radiographic studies on stand-alone interbody implants without supplemental fixation have reported fusion rates between 83% and 100%. Hacker (20) compared two groups of patients treated for disabling back pain; one group was treated with a stand-alone PLIF using BAK implants, and the other group was treated with combined anteroposterior fusion. He found equal patient satisfaction between the two groups. Ray (48) presented a prospective series of 236 patients treated with stand-alone interbody fusion and reported a 96% fusion rate at two years after surgery. These fusion criteria

did correlate with improved clinical outcomes. In this study group, only 65% had good to excellent clinical outcomes on the Prolo scale and 14% had a poor result.

This study is a prospective clinical evaluations of a stand-alone PLIF procedure. The randomized patient groups had no statistically significant differences in the variables assessed. **Clinical and radiographic follow-up exceeded ??% at all intervals.** The use of recombinant human bone morphogenetic protein has been shown to accelerate fusion in both animal models and in human clinical trials. Improved clinical outcomes with the use of rhBMP-2 with stand-alone interbody cages have also been established in clinical trials.

This study shows that bone formation in the spinal canal may occur following PLIF procedures with cylindrical interbody fusion cages. Bone formation in the spinal canal occurred in both the control group and investigational group. Bone formation in the spinal canal appears to be a multi-factorial event. Bone formation in the spinal canal is largely dependent upon cage placement and Sagittal balance of the instrumented vertebral motion segment. Patients with residual Sagittal plane imbalance form bone behind the unreduced vertebral segment. This may be the result of lifting of a periosteal flap along the posterior cortex of the listhesed vertebral body. Cages placed that were not recessed within the confines of the disc space margins were also associated with bone formation in the spinal canal.

RhBMP-2 on an absorbable collagen sponge has been shown to induce bone formation in the Intervertebral disc space. Prior studies have shown that this montage will routinely produce a fusion zone extending 3mm around the cage. It is not surprising

that bone may extend into the spinal canal when cages containing rhBMP-2 are not recessed 3mm or more within the confines of the disc space.

The PLIF procedure using threaded cylindrical fusion cages disrupts a wide channel, which includes the posterior margin of the disc, the posterior longitudinal ligament and annular structures. This injury can result in adjacent bone formation, which can extend into the spinal canal. This new bone formation is best visualized on CT scan. Both the control group and investigational group exhibited bone formation outside of the disc space following this procedure.

Bone formation in the spinal canal had no discernable influence on patient outcomes. Bone formation in the spinal canal following the PLIF procedure with stand-alone cylindrical interbody fusion cages appears to be a radiographic finding alone with no associated clinical sequalae.

REFERENCES

. Boden SD, Schimandle JH, Hutton WC. 1995 Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 1995;20:2633-44.

. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25:376-81.

. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. Neurosurg Focus 2001;10:1-9.

. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999;24:629-36.

. Sandhu HS, Kanim LEA, Toth JM, et al. Experimental spinal fusion with recombinant human bone morphogenetic protein-2 without decortication of osseous elements. Spine 1997;22:1171-80.

. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995; 20:1326-37.

. Urist MR. Bone: Formation by autoinduction. Science 1965;150:893-9.

TABLE 1.

Patient Demographics

	INFUSE Bone Graft	Iliac Crest Autograft
Age (yr.)	46.3	46.1
Weight (lbs.)	180.5	172.8
Sex (% males)	55.0	45.5
Worker's Compensation (%)	23.5	27.3
Spinal Litigation (%)	8.8	3.0
Tobacco Use (%)	52.9	45.5
Previous Surgery (%)	35.3	39.4

From: Burkus, J. Kenneth
Sent: Saturday, February 1, 2003 06:13:31 PM
To: Wehrly, Peter; Beals, Neil; Martin, Bill; Bearcroft, Julie
Subject: PLIF revision manuscript

Attachments: PLIF BMP paper.5.doc

Sirs and Ma'am:

I have attached a first revision of the PLIF manuscript.

I have reviewed Reg Haid's comments and I have incorporated all of them in this revision.

Please make all of your final comments directly on the manuscript.

I will review them with you on Friday at AAOS.

Best regards,
Ken Burkus

A Prospective, Randomized Posterior Lumbar Interbody Fusion Study Using rhBMP-2 with Cylindrical Interbody Cages

Regis Haid, MD[‡]

Charlie Branch MD*

Joseph Alexander MD [†]

J. Kenneth Burkus MD[§]

[‡] Professor, Department of Neurosurgery, Emory University, Atlanta, Georgia

* Chairman, Department of Neurosurgery, Bowman Gray, School of Medicine, Winston-Salem, North Carolina

[†] Assistant professor, Department of Neurosurgery, Bowman Gray, School of Medicine, Winston-Salem, North Carolina

[§] Spine Surgeon at The Hughston Clinic, Columbus, Georgia

Address correspondence and reprint requests to J.K. Burkus, MD, The Hughston Clinic, [redacted]

ABSTRACT

Study Design. In a multi-center, prospective, randomized, non-blinded, 2-year study, 67 patients who underwent a single-level posterior lumbar interbody fusion with two paired cylindrical threaded titanium fusion devices were randomized into two groups: one received recombinant human bone morphogenetic protein-2 (rhBMP-2) on a collagen sponge carrier, the other autogenous iliac crest bone graft.

Objectives. The objective of the study was to determine the clinical and radiographic outcomes in patients treated for single-level degenerative lumbar disc disease with a posterior interbody fusion using stand-alone cylindrical threaded titanium fusion cages with autogenous bone graft or rhBMP-2 and an absorbable collagen sponge carrier.

Summary of Background Data. In a large series of human patients undergoing open anterior lumbar interbody fusion with a tapered titanium fusion cage, rhBMP-2 on a bovine collagen sponge has been shown to decrease operative time and blood loss, to promote osteoinduction and fusion, and to be a safe and effective substitute for iliac crest harvesting.

Methods. In this prospective non-blinded study, 67 patients were randomized into 2 groups that underwent interbody fusion using two cylindrical threaded fusion cages: the investigational group (34 patients) that received rhBMP-2 on an absorbable collagen sponge and a control group (33 patients) that received autogenous iliac crest bone graft. Assessment of a patient's clinical outcome was based on low back and leg pain numerical rating scales, Short Form SF36 questionnaire, Oswestry Low Back Pain Disability questionnaire, and work status. Plain radiographs and computed tomographic scans were used to evaluate fusion at 6,12 and 24 months postoperatively.

Results. The mean operative time and blood loss for the investigational rhBMP-2 group was 2.6 hours and 322.8 mL, respectively. For the autograft control group these values were 3.0 hours and 372.7 mL. Although not statistically different, at 24 months, the investigational group's fusion rate of 92.3% was higher than the control's at 77.8%. At all postoperative intervals, the mean Oswestry, back pain and leg pain scores and physical components of the SF36 improved in both treatment groups compared with the preoperative scores. A statistically significant difference in the change in back pain was found at 24 months for the investigational group. In the control group, two adverse events related to harvesting of the iliac crest graft occurred in two patients (6.1%), and, at 24 months after surgery, 3.0% of the patients still reported graft site discomfort.

Conclusions. Although not statistically different, on average the investigational group had shorter operative times and less blood loss. At 24 months, this group had a fusion rate that was more than 14 percentage points greater than the control group. All clinical outcome measurements that were studied showed, on average, greater improvement in the investigational (rhBMP-2) patients with a statistically significant improvement in back pain. Overall results show that the use of rhBMP-2 can eliminate the need for harvesting iliac crest graft and a positive trend for being an equivalent or better replacement for autograft for use in successful posterior lumbar interbody fusions. Further studies of the use of rhBMP-2 in PLIF cage procedures are needed.

Key words: posterior lumbar interbody fusion, bone morphogenetic protein, osteoinduction, radiography, interbody fusion cages

Key points:

- At 24 months, the average rate of fusion for patients treated with rhBMP-2 was more than 14 percentage points higher (92.3% vs. 77.8%) than for patients treated with autograft. This difference, while large and promising, was not statistically different (p=0.250).
- The average operative time was 2.6 hours for patients treated with rhBMP-2 compared with 3.0 hours in the autograft group. Although not statistically different, the change was nearly so (p=0.065).
- Blood loss tended to be less for patients treated with rhBMP-2 than for patients who underwent iliac crest bone graft harvesting.
- At all postoperative assessment intervals, patients in both treatment groups showed improvement in Oswestry disability scores, in back and leg pain outcomes and in the PCS scores of the SF36.
- The use of rhBMP-2 in posterior lumbar interbody fusion procedures eliminates the complications of iliac crest bone harvesting including postoperative pain.
- Future studies of the use of rhBMP-2 in PLIF cages are needed.

Précis

In a 2-year prospective randomized study of 67 patients, the investigational group that received rhBMP-2 paired with cylindrical cage devices tended to have a higher rate of fusion, reduced operative times, and decreased blood loss when compared with the control group that received the same cylindrical cage device filled with autogenous bone graft. Clinical outcomes trended towards greater improvement in the rhBMP-2 group at 3, 6, 12 and 24 months. At 2-years, the rhBMP-2 group had statistically less back pain. The rhBMP-2 group avoided the complications that can arise from an iliac crest bone harvesting procedure.

INTRODUCTION

Posterior lumbar interbody fusion (PLIF) is an effective treatment for patients with symptomatic degenerative disc disease, spondylolithesis and other painful discogenic syndromes. Fusion of the degenerative and unstable lumbar spinal motion segment can give significant relief from this disabling and often progressive condition. PLIF limits the extent of posterolateral soft tissue exposure, muscle stripping, and injury. With this technique, the surgeon uses the traditional posterior approach to the lumbar spine; however, dissection is limited laterally to the facet joints. Through this approach, direct neural decompression can be completed, disc space height and sagittal balance can be restored, and intervertebral grafts can be placed in a biomechanically advantageous position.

Lumbar spine stabilization procedures that limit the extent of posterior spinal muscles exposure have some significant advantages. With PLIF surgical techniques, the fusion bed is within the disc space and it eliminates the exposure of the transverse processes. The PLIF approach to the lumbosacral spine enables the surgeon to re-establish the normal anatomic alignment and relationships of the spinal motion segment while avoiding excessive injury to the posterior paravertebral muscles.

Cloward [8] presented his technique for this innovative procedure in 1953. In his surgical technique, he described using a wide laminectomy and facetectomies that would allow for the placement of large structural bone grafts in the denuded and meticulously prepared disc space. Later, Lin [15] modified this intervertebral grafting technique of structural grafts. This modified PLIF technique involves filling the disc space with cancellous bone strips, allowing for preservation of a portion the posterior

elements and avoiding the complication of insertion of large structural grafts. Additional modifications of the bone graft technique and bone graft materials have been made. Kuslich [14] and Ray [19] introduced the idea of using threaded interbody fusion cages inserted through a PLIF approach as a means of stabilizing the lumbar motion segment, increasing rates of fusion and improving clinical outcomes.

Recombinant human bone morphogenetic protein 2 (rhBMP-2) [21] applied to an absorbable collagen sponge carrier has been shown to promote osteoinduction and fusion in the lumbar spine [1,2,13,20]. In a large series of patients who underwent stand-alone anterior lumbar interbody fusion with fusion cages, rhBMP-2 was shown to enhance rates of fusion, reduce surgical time and improve clinical outcomes [4,5] To further evaluate this method of bone graft replacement, we evaluated the clinical and radiographic outcomes at 24 months of 67 patients who underwent a single level PLIF. We compared the outcomes in the investigational patients (rhBMP-2) with those in the control patients (autogenous bone).

MATERIALS AND METHODS

Study Design. Between March 1999 and December 1999, 67 patients with degenerative disc disease completed surgery in this prospective, randomized, non-blinded, FDA approved study at 14 investigational sites. All patients underwent a single-level posterior lumbar fusion with two paired INTER FIX™ devices (Medtronic Sofamor Danek, Memphis, TN). The interbody fusion cages were used as stand-alone construct in the disc space from L2 to S1, with the majority being L4-L5. Patients were randomly assigned in a 1:1 manner to one of two groups: the investigational group received rhBMP-2 on an absorbable collagen sponge carrier and the control group received autogenous iliac crest bone graft taken from a posterior approach. INFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, TN) is the trademarked name for recombinant human bone morphogenetic protein-2 applied to an absorbable collagen sponge.

Patient Data. Preoperatively, all patients had symptomatic, single-level degenerative lumbar disc disease and symptoms of disabling low back or leg pain, or both, of at least 6 months duration that had not responded to non-operative treatments. The two treatment groups were similar demographically (Table 1). No statistically significant differences ($p < 0.05$) were found for any of the pre-operative variables. The rhBMP-2 group consisted of 34 patients and the control group consisted of 33 patients. The average age at surgery was 46.3 years for the rhBMP-2 group and 46.1 years for the control group. In the rhBMP-2 group, 18 patients (52.9%) had used tobacco within 6 months before surgery compared with 15 patients (45.5%) in the control group. The percentage of patients with pending litigation was 8.8% and 3.0% in the rhBMP-2 and

control groups, respectively. The percentage of patients seeking worker's compensation was 23.5% in the rhBMP-2 group and 27.3.6% in the control group.

Clinical and Radiographic Outcome Measurements. Patient assessments were completed preoperatively, during hospitalization, and postoperatively at 6 weeks and at 3, 6, 12, and 24 months. Clinical outcomes were assessed using back, leg, and graft site pain questionnaires, short form SF36, Oswestry Low Back Pain Disability questionnaire, and work status. Back and leg symptoms were assessed separately on a visual analog scale. Both intensity of pain and duration of pain in back and leg symptoms were measured on a ten-point numerical rating scale. Adding the numeric rating scores for pain intensity and pain duration allowed examiners to derive a composite back and leg pain score—i.e., ranging from 0 (no pain) to 20 (maximum pain).

Radiographs and computed tomography (CT) scans were used to evaluate fusion at 6, 12, and 24 months after surgery [6]. Plain radiographs including standing lateral and flexion-extension lateral were obtained at each interval. Thin-cut 1-mm CT scans were taken at 6, 12 and 24 months. Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent, blinded radiologist was used to adjudicate conflicting fusion findings. Fusion was defined as an absence of radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation less than 5° on flexion-extension radiographs, and continuous bone growth connecting the vertebral bodies [6]. Patients who had secondary surgeries because of persistent low back symptoms and clinically suspected non-unions were

considered as having failed fusions and were classified as failures in all fusion calculations, regardless of their independent radiological assessment.

Clinical and Radiographic Follow-up. The rate of patient return for follow-up was at least 89.6% at all postoperative periods. At 12 months, the rate of patient return for both treatment groups was at least 90 %. At 24 months, the follow-up rate for the investigational group was 89.6% and the control group rate was 100%.

Surgical Technique.

An open posterior interbody fusion procedure was carried out in each patient. Preoperatively, the patients disc space was templated to determine the appropriate intraoperative disc space distraction and cage size. Plain radiographs were reassessed to determine normal disc space height of the adjacent spinal motion segments. Axial CT scan or MR images were used to establish the anterior-posterior dimension of the disc space to ensure proper cage sizing.

The patient was placed in the prone position on padded bolsters that support the chest and pelvis and suspend the abdomen. Care was taken to extend the pelvis to ensure that lumbar lordosis was preserved. The operating room table accommodated plain radiographs or fluoroscopy.

A complete laminectomy with facetectomies or extensive bilateral laminotomies and facetectomies with preservation of the mid-line elements was performed in each case. The lateral borders of the disc were exposed along with the traversing and exiting nerve roots. Bilateral annulotomies were made and a complete discectomy was carried through these annular windows. The annulotomies were placed lateral to the dural tube. The midportion of the lateral annular window was centered adjacent to the medial wall

of pedicle. The anterior and lateral walls of the annulus were preserved; the entire nucleus was removed. Cartilaginous end plates were resected using curettes.

Reduction of sagittal and frontal plane deformities was achieved through disc space height restoration and annular tensioning. Inserting progressively larger dilators into the collapsed disc restored disc space height and the normal sagittal contours of the spine.

The vertebral end plates were prepared with reamers that uniformly cut a channel through the adjacent bony end plates. Great care was taken to visualize and gently retract both the traversing and exiting nerve roots. These soft tissue elements were protected by a tubular reamer guide, which was impacted into the disc space prior to reaming. Care was taken to ensure that the endplate cuts were made parallel and equally into each end plate.

The INTER FIX^{TM} cages were packed with either the rhBMP-2 soaked sponges or morsecellized autograft prior to insertion. The cages were sequentially inserted in the disc space and away from any soft tissue or neural elements. The cages were not routinely recessed within the disc space. The majority of the cages were left flush to the posterior cortical wall of the vertebral bodies. Their position was assessed intraoperatively with plain radiographs or fluoroscopy.

Iliac crest bone graft harvesting

The control group received autogenous iliac crest graft placed within the cages. The bone graft was harvested from the outer table of the iliac wing. The graft was morscellized using a rongeur and was tightly packed into the cages before their insertion.

rhBMP-2 preparation

The rhBMP-2 was reconstituted using sterile water and was used as a single dose of 1.5 mg/mL in all study patients. The 1.5 mg rhBMP-2/mL solution was applied to a bovine collagen sponge and allowed to bind to the sponge for 15 minutes. The dosage of rhBMP-2 varied by patient depending on cage size, with the total dose ranging from 4.0 mg to 8.0 mg. The rhBMP-2 soaked sponge was then placed in the hollow central portion of the INTER FIX™ device before its insertion into the prepared disc space. No additional sponges were placed outside of the devices. No autogenous grafts were used in the investigational group.

Postoperatively, patients were placed in a soft lumbar corset. The treating physician decided when the patient would advance in activities. Isometric strengthening and exercise program were started at six weeks postoperatively.

Statistical Methods

The data from this clinical trial were analyzed using the statistical software package SAS® version 6.12. For comparisons between the groups for continuous variables, *p*-values are from ANOVA, and for categorical variables, they are from Fisher's exact test or chi-square test. For changes (improvements) from the preoperative within each group, the p-values are from the paired t-test.

RESULTS

Surgery

The mean operative time in the investigational rhBMP-2 group (2.6 hours) was less than in the control group (3.0 hours) (Table 2). The average blood loss in the

rhBMP-2 group was 322.8 ml as compared to 372.7 ml in the control group. The average hospital stay was less in the investigational group (3.4 days for the investigational group vs. 5.2 days for the control group). None of these differences between treatment groups was statistically significant, although the time of surgery approached significance (p=0.065). No unanticipated device-related adverse events occurred in either treatment group.

Complications

Vascular events.

One control patient developed deep venous thrombosis and was treated with anticoagulation medications.

Iliac crest graft site. In the control group, adverse events related to harvesting of the iliac crest graft were identified in two patients (6.1%). These events included one case of pain and one hematoma. Neither of these patients required additional surgery. Obviously, no graft site adverse events occurred in the investigational group since the use of rhBMP-2 precluded the need to harvest bone graft.

The level of postoperative pain and morbidity associated with the iliac crest graft harvesting was measured using numeric rating scales for pain intensity and duration (Figure 1). After surgery, all of the control patients experienced hip donor site pain. The highest levels of pain were noted immediately after surgery with a mean score of 11.6 points out of 20 points. The percentage of patients experiencing pain decreased over time; however, at 24 months after surgery, 60% of the control patients still experienced pain (i.e., had scores greater than 0). At two years, the graft site pain scores averaged

5.5 points out of 20 and 13.3% of the patients still felt that the appearance of the graft site bothered them some and 3.0% of the patients still reported graft site discomfort.

Antibody Testing

Antibody results. Antibodies to rhBMP-2, bovine Type I collagen, and human Type I collagen were evaluated preoperatively and 3 months postoperatively using enzyme-linked immunosorbent assays (ELISAs). None of the patients in either group tested positive for antibodies to rhBMP-2 or human Type I collagen. The incidence of bovine Type I collagen antibody formation in the investigational group was 13.3% whereas the incidence in the control group was 35.7%. No negative clinical consequence to the positive collagen antibody test results was evident.

Clinical Outcomes

Oswestry Disability Questionnaire scores. The Oswestry Low Back Pain Disability Questionnaire measured pain associated with activities. The Oswestry Questionnaire was administered preoperatively as well as at each postoperative visit. At all postoperative visits, both treatment groups demonstrated highly significant improvements as compared with the preoperative scores (Figure 2). At all postoperative time intervals after the first 6-week follow-up period, the investigational group showed greater improvements over the control group in the mean overall Oswestry scores. At last follow-up at 24 months, the mean improvements in the Oswestry scores were 29.6 points in the investigational group and 24.9 points in the controls (Figure 2). In the rhBMP-2 group, 69% of patients showed an improvement of

at least 15 points in their disability scores at 12 months after surgery as compared with 55.6% of patients in the control group. At 24 months, the 76.0% of the investigational group was improved and compared favorably with 64.3% improved in the control group. (Table 3)

Back Pain. The mean back pain scores at all postoperative periods were improved from the preoperative mean values for both treatment groups. The mean improvements in back pain scores at all five postoperative intervals studied were greater for the investigational group than for the control autograft group (Figure 4). At 24 months, the average improvement in back pain in the investigational group was almost twice that of the control group (9 point improvement vs. 4.5 point improvement). This difference was highly significant with a p-value of 0.009.

Leg Pain. Leg pain was assessed in a similar manner using a 20-point numeric rating scale that reflects both the intensity and duration of painful symptoms. Mean leg pain scores improved significantly after surgery in each group (Figure 5). At each study interval average leg pain scores were less (better) in the investigational group when compared to the control group. Similarly, the investigational group also showed higher average improvement scores at each interval studied. At 24 months, the average improvement in leg pain was 7.7 points in the investigational group compared to 6.5 points in the control group. This difference was not statistically significant.

Short Form SF36. At all postoperative intervals studied the investigational group showed greater improvement in the physical component of the short form SF36 when compared to the controls (Figure 6).

Neurological Status. Preoperatively and at all five post-operative time points, the motor, sensory, reflexes, and straight leg raise measurements were essentially the same for both treatment groups and showed no statistical differences. At 24 months, using the protocol criteria for determining overall neurological success, which represents a combination of the four neurological measurements, both groups had 100% success. Table 3 contains the change from pre-operative results at 24 months for the motor, sensory, reflex, and straight leg raise measurements.

Work Status. Many factors affect a patient's work status, such as the nature of the work performed and ability of the work place to accommodate work restrictions. Prior to surgery, in the investigational group only 26.5% were gainfully employed while over 45.5% of the control patients were employed (Table 3). For patients who were working before surgery, the median return to work time was 43 days in the investigational group and 137 days in the control group. Although striking, this difference was not statistically significant. At last follow-up, more people in the investigational treatment group were working than were working before their surgery. At 2 years following surgery in the investigational group, 12 patients were employed while only 9 were employed before surgery. In the control group, 15 were working before surgery and 14 were working at two years after surgery. In other words, the percent of the investigational patients working went from 26.5% before surgery to 35.3% at two years, while in the control group the rate went from 45.5% to 42.4%. Although none of these changes are statistically significant, the trend is promising and may be reflective of the statistically significant difference of lower back pain in the investigational patients.

Patient Satisfaction. At 12 and 24 months after surgery, the results were similar in each treatment group. At 24 months, 72.4% of the investigational patients and 80.0% of the control patients were satisfied (answering definitely true or mostly true) with their surgical outcomes. In the investigational group, 69.0% said they would undergo surgery again (answering definitely true or mostly true) compared with 83.3% of the control patients who would undergo surgery again. In the investigational group, 72.4% believed that they were helped as much as they had expected to be from the surgery; 70.0% of the control group felt they had been. None of these subjective differences was statistically significant.

Radiographic Outcomes

Cage placement

Cage placement was assessed on both plain radiographs and thin-cut CT scan. The CT scans were found to reflect more accurately the position of the cage in relation to the spinal canal posteriorly and neuroforamina laterally. No differences between the two patient groups regarding cage placement were detected. Only 6% of patients in each group (2/34 investigational group; 2/33 control group) showed cages that were countersunk 3mm or more from the posterior margin of the vertebral body. Approximately one-third of patients in each group had cages that extended into the spinal canal on postoperative CT studies (11/34 investigational group; 10/33 control group). The remainder of the cages were placed either flush to the posterior cortex of the vertebral bodies or were recessed by only 2mm or less.

Sagittal Plane Balance

Nearly one third of patients (19/67; 28%) postoperatively had some sagittal plane imbalance following surgery. At the last follow-up, 6 patients had some residual spondylolithesis from failure to fully reduce the deformity at the time of surgery (up to Grade I spondylolisthesis was allowed) and two patients developed spondylolithesis postoperatively. Eleven patients had residual retrolithesis following surgery.

Intradiscal bone formation

Fusion status of the study patients was evaluated on plain radiographs and CT scans. At six months after surgery, 93.1% of patients in both the investigational and control groups had evidence of fusion. At 12 months, in the investigational group the fusion rate dropped to 85.2% while the control group maintained a fusion rate of 92%. This decrease in fusion rate may have, in part, been related to poor follow-up in the investigational group at the 12-month time frame. (Seven investigational and 8 control patients were recorded as non-union because they failed to obtain radiographs during this time period.) At 24 months, the investigational group had a 92.3% fusion rate, which was more than 14 percentage points higher than that of the control group (77.8%). While this difference was not statistically significant, it does show a positive trend in favor of the investigational group.

Bone formation outside of the disc space

The thin cut 1.0 mm CT scans were able to identify new bone formation adjacent to the interbody fusion cages. New bone formation extending outside of the disc space and into the spinal canal or neuroforamina was found in 28 patients (23 investigational and 5 controls).

Sagittal plane balance.

In the control group, one of the 5 patients (20%) with bone in the spinal canal had a residual unreduced spondylolithesis following surgery. New bone formation was identified in the canal posterior to the unreduced superior vertebra under the posterior longitudinal ligament and annulus. In the control group, new bone formation was identified in four patients extending into the spinal canal in patients with normal segmental sagittal plane balance.

In the investigational group, 10 of the 23 patients (43%) with bone in the spinal canal had some residual postoperative sagittal plane imbalance. Five patients (5/23; 22%) had spondylolithesis and 5 (5/23;22%) had retrolithesis. In each of these cases, new bone formation occurred posterior to the unreduced vertebral body, under the posterior longitudinal ligament lifted off the unreduced vertebral body. Thirteen patients in the investigational group (13/34; 38%) had a normal postoperative segmental sagittal plane balance and new bone formation in the spinal canal.

Cage placement.

In the investigational group cage placement was strongly associated with the development of bone in the spinal canal. In the investigational group 39% of patients with cages placed at the margin or within 2mm of the margin of the posterior vertebral cortex developed some bone in the spinal canal. Twelve percent of patients in the control group with cages placed within 2mm of the vertebral margins developed bone in the spinal canal. No patients in either group that had the cages recessed by 3mm or more developed bone in spinal canal.

Secondary Surgical Procedures

In the investigational group, 7 of 34 (20.6%) had some type of secondary spinal surgery. Three of 34 (8.8%) had second surgery at the same site of the initial PLIF surgery. Two investigational patients received supplemental fixation for presumed pseudarthrosis; one patient underwent surgical site exploration for a presumed infection. Four patients (4/34;11.8%) had second spinal surgeries unrelated to the PLIF procedure.

In the control group, 6 of 33 (18.2%) had some type of secondary spinal surgery. Three of 33 (9.1%) had surgery at the same level of the initial PLIF procedure; all three of these patients received supplemental fixation for presumed pseudarthrosis. Three additional patient in the control group (3/33;9.1%) had second spinal surgeries, unrelated to the initial PLIF procedure.

DISCUSSION

Threaded cylindrical cages represent a new, distinct class of segmental spinal fixation devices. These devices were not designed as spacers that require segmental stabilization; rather, they were designed as stand-alone intervertebral devices that function as an "instrumented PLIF." Threaded interbody devices are biomechanically different from interbody spacers. Biomechanical studies have shown that cage size has some significance in stand-alone cage fusions; however, stand-alone cages do not significantly increase spinal stiffness in studies using human cadavers [3,9,11,12,16,18]. This finding largely explains the current trend clinically to utilize posterior segmental fixation in PLIF constructs.

Larger cages improve stiffness in rotation and lateral bending in a lumbar spinal motion segment; however, reduction of motion in flexion is not significantly improved with larger cages [12,16]. Larger cages require more extensive facet joint resection or complete facetectomy, which further destabilizes the spinal motion segment. A cylindrical device increases in its medial-lateral dimension equal to its increase in height, which necessitates greater mobilization and retraction of the neural elements. Retraction and mobilization of the neural element during cylindrical cage insertion has been associated with permanent neurologic injury [A,B]. The current trend in PLIF surgery is limit neural element retraction through the use of a transforaminal surgical approach or through the used of impacted interbody spacers.

Initial clinical studies reported high rates of fusion and clinical success in certain centers. These results have not been widely reproduced. Authors of clinical and radiographic studies on stand-alone interbody implants without supplemental fixation

have reported fusion rates between 83% and 100% [14,19]. Hacker [10] compared two groups of patients treated for disabling back pain; one group was treated with a stand-alone PLIF using BAK implants, and the other group was treated with combined anteroposterior fusion. He found equal patient satisfaction between the two groups. Ray [19] presented a prospective series of 236 patients treated with stand-alone interbody fusion and reported a 96% fusion rate at two years after surgery. These fusion criteria did correlate with improved clinical outcomes. In this study group, only 65% had good to excellent clinical outcomes on the Prolo scale and 14% had a poor result.

However, performing PLIF procedures or any other type of spinal fusion with autograft from the iliac crest comes with a price in pain for the patient. Figure 1 shows that the iliac crest graft site pain in this study was found to be similar to that measured in the same way for a larger study of the LT-CAGE Device [4] with two exceptions. First, in this study the pain at 24 months was 5.5 on a scale of 20, while in the anterior LT-CAGE study, the value was 1.8. Second, in this posterior INTER FIX study, 60% of the patients had some pain at 24 months, while in the LT-CAGE study 32% did. Although these were two different studies using different surgeons, different numbers of cases (30 vs.118), and different sizes of cages (the INTER FIX cage is cylindrical and the LT-CAGE version is a smaller volume tapered design), these results are consistent with a review of other studies that showed that a posterior approach to the iliac crest is more painful for the patients [17]. The pain associated with the posterior bone graft harvest may be secondary in part the extensive stripping of the gluteus musculature, more extensive bone graft harvesting techniques or injury to the sacroiliac joint. For whatever reason, the measured iliac crest graft site pain scores in this study imply that, from the

patients' point of view, the need for an autograft replacement in PLIF cylindrical cage procedures is greater than in ALIF tapered cage procedures.

This study shows that extra bone formation in the spinal canal may occur following PLIF procedures with cylindrical interbody fusion cages regardless of the source of the bone graft since bone formation in the spinal canal occurred in both the control and investigational groups. Bone formation in the spinal canal appears to be a multi-factorial event. Bone formation in the spinal canal is largely dependent upon cage placement and sagittal balance of the instrumented vertebral motion segment. Patients with residual sagittal plane imbalance form bone behind the unreduced vertebral segment. This may be the result of lifting of a periosteal flap along the posterior cortex of the listhesed vertebral body. Cages placed that were not recessed within the confines of the disc space margins were also associated with bone formation in the spinal canal. Thin cut CT scans were essential is determining postoperative cage placement and new bone formation.

rhBMP-2 on an absorbable collagen sponge has been shown to induce bone formation in the intervertebral disc space [2,4,5,13]. Prior studies have shown that this montage in this milieu will routinely produce a fusion zone extending 3mm around the cage [7]. It is not surprising that bone may extend into the spinal canal when cages containing rhBMP-2 are not recessed 3mm or more within the confines of the disc space.

The PLIF procedure using threaded cylindrical fusion cages disrupts a wide channel, which includes the posterior margin of the disc, the posterior longitudinal ligament and annular structures. This injury can result in adjacent bone formation,

which can extend into the spinal canal. This new bone formation is best visualized on CT scan. Both the control group and investigational group exhibited bone formation outside of the disc space following this procedure.

Although not desirable, Bone formation in the spinal canal had no discernable influence on patient outcomes. Bone formation in the spinal canal following the PLIF procedure with stand-alone cylindrical interbody fusion cages appears to be a radiographic finding alone with no associated clinical sequalae.

This study, because of its small size, amounted to a pilot study of the ability of a bone morphogenetic protein to replace autograft in a stand-alone PLIF cage procedure. Even though the number of patients was small, a statistically significant improvement in back pain in the rhBMP-2 investigational patients was found. Although the other findings were not statistically different, if just the surgical and clinical outcome data at two years are examined (Tables 2 & 3), all of the outcomes measured (except for two out of three of the subject patient satisfaction questions) favored the investigational group. These finding imply that a larger study would have shown statistical equivalence or improvement in all clinically important outcomes. Predicting such a result can be based not only upon the data in the pilot study presented here, but also upon the large-scale human clinical spinal trials of rhBMP-2 already conducted. The same protein studied here, used in the same concentration inside metal cages for the same lumbar indication but from a different approach (anterior), has been shown in a 679 patient analysis to be superior to autograft [5]. The direction of implantation of a cage should not affect the ability of INFUSE Bone Graft contained inside to form bone.

In conclusion, this detailed, independent review of the results, which represent the first use of osteoinductive proteins in a PLIF procedure, are encouraging. These findings along with other studies for other indications imply that future larger PLIF studies with rhBMP-2 are needed. Current studies are assessing the use of rhBMP-2 with a TLIF techniques. Additional PLIF studies are evaluating placement of the BMP-soaked adjacent to the anterior annulus away from the posterior annulotmy sites. In future studies using modified surgical techniques, such as using more recessed cages to allow for extra posterior bone formation, adding steps to minimize bleeding and surgical variables, using narrower, non-cylindrical cages that would be easier to put in and cause less tissue destruction, and/or adding secondary instrumentation may be beneficial. Further, possibly modifying patient selection, such as entering patients with less vertebral slip, may also help minimize the confounding variables. All of these changes may produce more convincing evidence that INFUSE Bone Graft can also be used as a substitute for autograft in PLIF cage procedures.

ACKNOWLEDGEMENTS

Special thanks to the following doctors who were principal or co-prinicipal clinical investigators at the 14 sites for this study. These surgeons in alphabetical order are Drs. C. William Bacon, Steven Barnes, Charles Branch, Randall Dryer, Paul Geibel, Fred Geisler, Scott Graham, Peter Holiday, Timothy Holt, Zenko Hrynkiw, Dennis Maiman, David Masel, Bruce Mathern, Christopher Meyer, Phillip Tibbs, and Frank Tomecek. The work of the Clinical Research Department at Medtronic Sofamor Danek in collecting the clinical data and performing the statistical analyses is acknowledged.

REFERENCES

A. Barnes B, Rodts GE, McLaughlin MR, Haid RW Jr. Threaded cortical bone dowels for lumbar interbody fusion: over 1-year mean follow up in 28 patients. J Neurosurg 2002; 95(1 Suppl):1-4.

B. Barnes B, Rodts GE, Haid RW Jr, Subach BR, McLaughlin MR. Allograft implants for posterior lumbar interbody fusion: results comparing cylindrical dowels and impacted wedges. Neurosurgery 2002;51(5):1191-1198.

1. Boden SD, Schimandle JH, Hutton WC. 1995 Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 1995;20:2633-44.

2. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25:376-81.

3. Brodke DS, Dick JC, Kunz DN, McCabe R, Zbeblick TA: Posterior lumbar interbody fusion: a biomechanical comparison, including a new threaded cage. Spine 1997;22:26-31.

4. Burkus JK, Gornet MF, Dickman C, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. J Spinal Disord 2002; 337-349.

5. Burkus JK, Heim SE, Gornet MF, Zdeblick TA. Is INFUSE™ Bone Graft Superior to Autograft Bone? An Integrated Analysis of Clinical Trials Using the LT-CAGE™ Lumbar Tapered Fusion Device. J Spinal Disord 2003 in press

6. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. Neurosurg Focus 2001;10:1-9.

7. Burkus JK, Dorchak JD, Sanders DL, Radiographic assessment of interbody fusion using recombinant human bone morphogenetic protein type 2. Spine 2003 28 in press.

8. Cloward RB: The treatment of ruptured intervertebral discs by vertebral body fusion. I. Indications, operative technique, after care. J Neursurg 1953;10:154-168

9. Dimar JR, Wang M, Beck DJ, Glassman SD, Voor MJ: Posterior lumbar interbody cages do not augment segmental biomechanical stability. Paper presented at: Scoliosis Research Society; September 22-25, 1999; San Diego, CA

10. Hacker RJ: Comparison of interbody fusion approaches for disabling low back pain. Spine 1997;22:660-665

11. Hasegawa K, Ikeda M, Washio T, Hara T: An experimental study of porcine lumbar segmental stiffness by the distraction-compression principle using a threaded interbody cage. J Spinal Disorders 2000;13:247-252.

12. Kettler A, Wilke HJ, Dietl R, Krammer M, Lumenta C, Claes L: Stabilizing effect of posterior lumbar interbody fusion cages before and after cyclic loading. J Neurosurg 2000;92:87-92

13. Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2. A prospective study of clinical and radiographic outcomes. Spine 2001;26:2751-6.

14. Kuslich SD, Ulstrom CL, Griffith SL, Ahern JW, Dowdle JD: The Bagby and Kuslich method of lumbar interbody fusion. History, techniques, and 2-year follow-up results of a United States prospective, multicenter trial. Spine 1998;23:1267-1278.

15. Lin PM, Cautilli RA, Joyce MF: Posterior lumbar interbody fusion. Clin Orthop 1983;180:154-168.

16. Lund T, Oxland TR, Jost B, Cripton P, Grassmann S, Etter C, Nolte LP: Interbody cage stabilization in the lumbar spine: biomechanical evaluation of cage design, posterior instrumentation and bone density. J Bone Joint Surg Br 1998;80:351-359.

17. Polly DW, Kuklo TR. Bone graft donor site pain. Paper presented at: Scoliosis Research Society; September 19-21, 2002; Seattle, WA

18. Rapoff AJ, Ghanayem AJ, Zdeblick TA: Biomechanical comparison of posterior lumbar interbody fusion cages. Spine 1997;22:2375-2379

19. Ray CD: Threaded titanium cages for lumbar interbody fusions. Spine 1997;22:667-679.

20. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995; 20:1326-37.

21. Urist MR. Bone: Formation by autoinduction. Science 1965;150:893-9.

Table 1

Patient Demographic Information

Variable	Investigational (n=34)	Control (n=33)	p-value *
Age (years) [mean (range)]	46.3 (25.8 – 66.1)	46.1 (28.5 – 70.9)	0.928
Weight (lb) [mean ± s.d.]	180.5 ± 38.4	172.8 ± 35.7	0.400
Gender [n (%)]			
Male	17 (50)	15 (45.5)	0.808
Female	17 (50)	18 (54.5)	
Worker's compensation [n (%)]	8 (23.5)	9 (27.3)	0.784
Spinal litigation [n (%)]	3 (8.8)	1 (3.0)	0.614
Tobacco used [n (%)]	18 (52.9)	15(45.5)	0.628
Alcohol use [n (%)]	15 (44.1)	9 (27.3)	0.204
Preoperative work status [n (%) working]	9 (26.5)	15 (45.5)	0.131
Previous back surgery [n (%)]	12 (35.3)	13 (39.4)	0.803

- For continuous variables, p-values are from ANOVA and for categorical variables, they are from Fisher's exact.

Table 2

Surgical Parameters

	Investigational	Control
Mean operative time	2.6 hours	3.0 hours
Average blood loss	322.8 ml	372.7 ml
Average hospital stay	3.4 days	5.2 days

Table 3

24 Month Clinical Outcome Parameters

	Investigational	Control
Improvement Points in Oswestry Score	29.6	24.9
% Patients with ≥15 point Oswestry Improvement	69%	55.6%
% Patients with Oswestry Improvement	76.0%	64.3%
Back Pain Improvement from Pre-Op (Points)	9*	4.5
Leg Pain Average Improvement from Pre-Op (Points)	7.7	6.5
Motor change from Pre-Op	4.5	2.8
Sensory Change from Pre-Op	8.0	2.8
Reflex change from Pre-Op	7.0	5.4
Straight Leg Raise change from Pre-Op	48.0	39.3
Net Change in % patients working	+8.8%	-3.1%
Median return to work time	43 days	137 days
Fusion rate	97.3%	77.8%

*statistically different

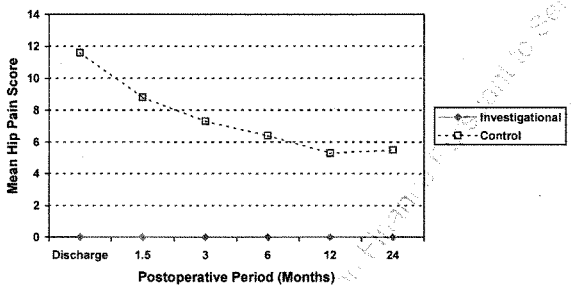


Figure 1. **Mean hip pain scores over the time**

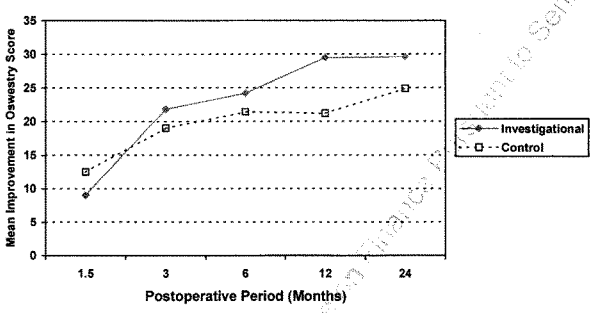


Figure 2. **Mean improvement in Oswestry scores over the time**

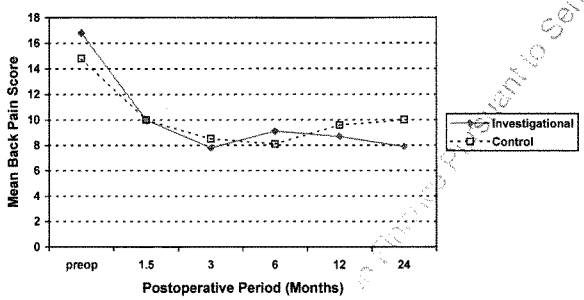


Figure 3. **Mean back pain scores over the time**

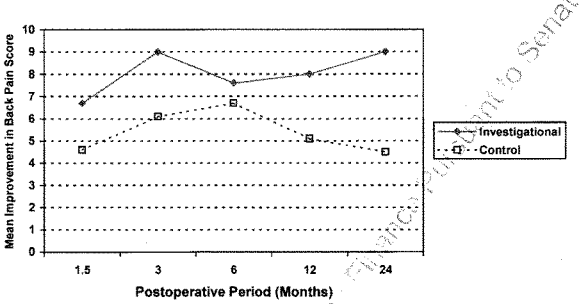


Figure 4. **Mean improvement in back pain scores over the time**

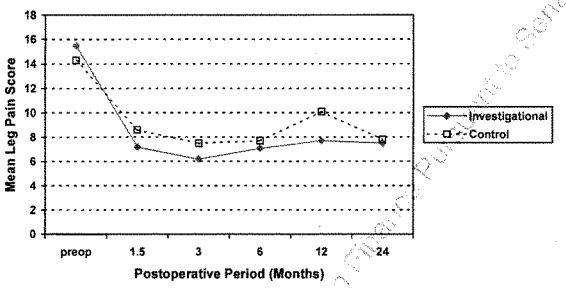


Figure 5. **Mean leg pain scores over the time**

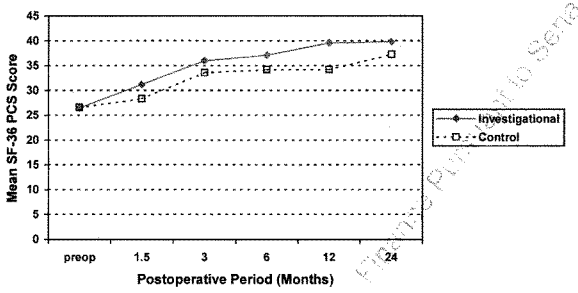


Figure 6. **Mean SF-36 PCS scores over the time**

From: Bearcroft, Julie
Sent: Friday, March 7, 2003 05:04:09 PM
To: Burkus, J. Kenneth
Subject: PLIF manuscript

Attachments: PLIF BMP paper.5.doc

Dr Burkus -
Hope you enjoyed your week in the Caymans. I am looking forward to my time in Hawaii beginning next week. Things have been just crazy since AAOS and I am definitely overdue for a break.

Per your request, I have reviewed the attached manuscript and provided some comments. I hope it helps. I apologize for my delay in getting back to you and I hope that it did not create an inconvenience. I've added some language as you requested referencing the safety studies and the altered surgical protocol in the newly approved IDE study. If you want to discuss any of the proposed changes I have noted, feel free to contact me. But I have to warn you, Tuesday I will be on my way to the white sands...

julie

A Prospective, Randomized Posterior Lumbar Interbody Fusion Study Using rhBMP-2 with Cylindrical Interbody Cages

Regis Haid, MD[‡]

Charlie Branch MD*

Joseph Alexander MD [†]

J. Kenneth Burkus MD[§]

[‡] Professor, Department of Neurosurgery, Emory University, Atlanta, Georgia

* Chairman, Department of Neurosurgery, Bowman Gray, School of Medicine, Winston-Salem, North Carolina

[†] Assistant professor, Department of Neurosurgery, Bowman Gray, School of Medicine, Winston-Salem, North Carolina

[§] Spine Surgeon at The Hughston Clinic, Columbus, Georgia

Address correspondence and reprint requests to J.K. Burkus, MD, The Hughston Clinic, [redacted]

ABSTRACT

Study Design. In a multi-center, prospective, randomized, non-blinded, 2-year study, 67 patients who underwent a single-level posterior lumbar interbody fusion with two paired cylindrical threaded titanium fusion devices were randomized into two groups: one received recombinant human bone morphogenetic protein-2 (rhBMP-2) on a collagen sponge carrier, the other autogenous iliac crest bone graft.

Objectives. The objective of the study was to determine the clinical and radiographic outcomes in patients treated for single-level degenerative lumbar disc disease with a posterior interbody fusion using stand-alone cylindrical threaded titanium fusion cages with autogenous bone graft or rhBMP-2 and an absorbable collagen sponge carrier.

Summary of Background Data. In a large series of human patients undergoing open anterior lumbar interbody fusion with a tapered titanium fusion cage, rhBMP-2 on a bovine collagen sponge has been shown to decrease operative time and blood loss, to promote osteoinduction and fusion, and to be a safe and effective substitute for iliac crest harvesting.

Methods. In this prospective non-blinded study, 67 patients were randomized into 2 groups that underwent interbody fusion using two cylindrical threaded fusion cages: the investigational group (34 patients) that received rhBMP-2 on an absorbable collagen sponge and a control group (33 patients) that received autogenous iliac crest bone graft. Assessment of a patient's clinical outcome was based on low back and leg pain numerical rating scales, SF-36 questionnaire, Oswestry Low Back Pain Disability questionnaire, and work status. Plain radiographs and computed tomographic scans were used to evaluate fusion at 6,12 and 24 months postoperatively.

Deleted: Short Form

Results. The mean operative time and blood loss for the investigational rhBMP-2 group was 2.6 hours and 322.8 mL, respectively. For the autograft control group, these values were 3.0 hours and 372.7 mL. Although not statistically different, at 24 months, the investigational group's fusion rate of 92.3% was higher than the control's at 77.8%. At all postoperative intervals, the mean Oswestry, back pain and leg pain scores and physical components of the SF-36 improved in both treatment groups compared with the preoperative scores. A statistically significant difference in the change in back pain was found at 24 months for the investigational group. In the control group, two adverse events related to harvesting of the iliac crest graft occurred in two patients (6.1%), and, at 24 months after surgery, 60% of the patients still reported graft site discomfort.

Deleted: SF36

Deleted: 3.0

Conclusions. Although not statistically different, on average the investigational group had shorter operative times and less blood loss. At 24 months, this group had a fusion rate that was more than 14 percentage points greater than the control group. All clinical outcome measurements that were studied showed, on average, greater improvement in the investigational (rhBMP-2) patients with a statistically significant improvement in back pain. Overall, results show that the use of rhBMP-2 can eliminate the need for harvesting iliac crest graft and a positive trend for being an equivalent or better replacement for autograft for use in successful posterior lumbar interbody fusions. Further studies of the use of rhBMP-2 in PLIF cage procedures are needed.

Key words: posterior lumbar interbody fusion, bone morphogenetic protein, osteoinduction, radiography, interbody fusion cages

Key points:

- At 24 months, the average rate of fusion for patients treated with rhBMP-2 was more than 14 percentage points higher (92.3% vs. 77.8%) than for patients treated with autograft. This difference, while large and promising, was not statistically different (p=0.250).
- The average operative time was 2.6 hours for patients treated with rhBMP-2 compared with 3.0 hours in the autograft group. This finding was not statistically significant (p=0.065).
- Blood loss tended to be less for patients treated with rhBMP-2 than for patients who underwent iliac crest bone graft harvesting.
- At all postoperative assessment intervals, patients in both treatment groups showed improvement in Oswestry disability scores, in back and leg pain outcomes and in the PCS scores of the SF-36.
- The use of rhBMP-2 in posterior lumbar interbody fusion procedures eliminates the complications of iliac crest bone harvesting including postoperative pain.
- Future studies of the use of rhBMP-2 in PLIF cages are needed.

Deleted: Although not statistically different, the change was nearly so

Deleted: SF36

Précis

In a 2-year prospective randomized study of 67 patients, the investigational group that received rhBMP-2 paired with cylindrical cage devices tended to have a higher rate of fusion, reduced operative times, and decreased blood loss when compared with the control group that received the same cylindrical cage device filled with autogenous bone graft. Clinical outcomes trended towards greater improvement in the rhBMP-2 group at 3, 6, 12 and 24 months. At 2-years, the rhBMP-2 group had statistically less back pain. The rhBMP-2 group avoided the complications that can arise from an iliac crest bone harvesting procedure.

INTRODUCTION

Posterior lumbar interbody fusion (PLIF) is an effective treatment for patients with symptomatic degenerative disc disease, spondylolithesis and other painful discogenic syndromes. Fusion of the degenerative and unstable lumbar spinal motion segment can give significant relief from this disabling and often progressive condition. PLIF limits the extent of posterolateral soft tissue exposure, muscle stripping, and injury. With this technique, the surgeon uses the traditional posterior approach to the lumbar spine; however, dissection is limited laterally to the facet joints. Through this approach, direct neural decompression can be completed, disc space height and sagittal balance can be restored, and intervertebral grafts can be placed in a biomechanically advantageous position.

Lumbar spine stabilization procedures that limit the extent of posterior spinal muscles exposure have some significant advantages. With PLIF surgical techniques, the fusion bed is within the disc space and it eliminates the exposure of the transverse processes. The PLIF approach to the lumbosacral spine enables the surgeon to re-establish the normal anatomic alignment and relationships of the spinal motion segment while avoiding excessive injury to the posterior paravertebral muscles.

Cloward [8] presented his technique for this innovative procedure in 1953. In his surgical technique, he described using a wide laminectomy and facetectomies that would allow for the placement of large structural bone grafts in the denuded and meticulously prepared disc space. Later, Lin [15] modified this intervertebral grafting technique of structural grafts. This modified PLIF technique involves filling the disc space with cancellous bone strips, allowing for preservation of a portion the posterior

elements and avoiding the complication of insertion of large structural grafts. Additional modifications of the bone graft technique and bone graft materials have been made. Kuslich [14] and Ray [19] introduced the idea of using threaded interbody fusion cages inserted through a PLIF approach as a means of stabilizing the lumbar motion segment, increasing rates of fusion and improving clinical outcomes.

Recombinant human bone morphogenetic protein 2 (rhBMP-2) [21] applied to an absorbable collagen sponge carrier has been shown to promote osteoinduction and fusion in the lumbar spine [1,2,13,20]. In a large series of patients who underwent stand-alone anterior lumbar interbody fusion with fusion cages, rhBMP-2 was shown to enhance rates of fusion, reduce surgical time and improve clinical outcomes [4,5]. To further evaluate this method of bone graft replacement, we evaluated the clinical and radiographic outcomes through 24 months of 67 patients who underwent a single level PLIF. We compared the outcomes in the investigational patients (rhBMP-2) with those in the control patients (autogenous bone).

Deleted: at

MATERIALS AND METHODS

Study Design. Between March 1999 and December 1999, 67 patients with degenerative disc disease completed surgery in this prospective, randomized, non-blinded, FDA approved study at 14 investigational sites. All patients underwent a single-level posterior lumbar fusion with two paired INTER FIX™ devices (Medtronic Sofamor Danek, Memphis, TN). The interbody fusion cages were used as a stand-alone construct in the disc space from L2 to S1, with the majority being L4-L5. Patients were randomly assigned in a 1:1 manner to one of two groups: the investigational group received rhBMP-2 on an absorbable collagen sponge carrier at a concentration of 1.5 mg/mL and the control group received autogenous iliac crest bone graft taken from a posterior approach. INFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, TN) is the trademarked name for recombinant human bone morphogenetic protein-2 applied to an absorbable collagen sponge.

Patient Data. Preoperatively, all patients had symptomatic, single-level degenerative lumbar disc disease and symptoms of disabling low back or leg pain, or both, of at least 6 months duration that had not responded to non-operative treatments. The two treatment groups were similar demographically (Table 1). No statistically significant differences ($p < 0.05$) were found for any of the pre-operative variables. The rhBMP-2 group consisted of 34 patients and the control group consisted of 33 patients. The average age at surgery was 46.3 years for the rhBMP-2 group and 46.1 years for the control group. In the rhBMP-2 group, 18 patients (52.9%) had used tobacco within 6 months before surgery compared with 15 patients (45.5%) in the control group. The percentage of patients with pending litigation was 8.8% and 3.0% in the rhBMP-2 and

control groups, respectively. The percentage of patients seeking worker's compensation was 23.5% in the rhBMP-2 group and 27.3% in the control group.

Clinical and Radiographic Outcome Measurements. Patient assessments were completed preoperatively, during hospitalization, and postoperatively at 6 weeks and at 3, 6, 12, and 24 months. Clinical outcomes were assessed using back, leg, and graft site pain questionnaires, SF-36, Oswestry Low Back Pain Disability questionnaire, and work status. Back and leg symptoms were assessed separately on a visual analog scale. Both intensity of pain and duration of pain in back and leg symptoms were measured on a ten-point numerical rating scale. Adding the numeric rating scores for pain intensity and pain duration allowed examiners to derive a composite back and leg pain score—i.e., ranging from 0 (no pain) to 20 (maximum pain).

Radiographs and computed tomography (CT) scans were used to evaluate fusion at 6, 12, and 24 months after surgery [6]. Plain radiographs including standing lateral and flexion-extension lateral were obtained at each interval. Thin-cut 1-mm CT scans were taken at 6, 12 and 24 months. Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent, blinded radiologist was used to adjudicate conflicting fusion findings. Fusion was defined as an absence of radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation less than 5° on flexion-extension radiographs, and continuous bone growth connecting the vertebral bodies [6]. Patients who had secondary surgeries because of persistent low back symptoms and clinically suspected non-unions were considered as having failed fusions and were classified as failures in all fusion calculations, regardless of their independent radiological assessment.

Deleted: 6

Deleted: short form SF36

Clinical and Radiographic Follow-up. The rate of patient return for follow-up was at least 89.6% at all postoperative periods. At 12 months, the rate of patient return for both treatment groups was at least 90 %. At 24 months, the follow-up rate for the investigational group was 89.6% and the control group rate was 100%.

Surgical Technique.

An open posterior interbody fusion procedure was carried out in each patient. Preoperatively, the patients disc space was templated to determine the appropriate intraoperative disc space distraction and cage size. Plain radiographs were reassessed to determine normal disc space height of the adjacent spinal motion segments. Axial CT scan or MR images were used to establish the anterior-posterior dimension of the disc space to ensure proper cage sizing.

The patient was placed in the prone position on padded bolsters that support the chest and pelvis and suspend the abdomen. Care was taken to extend the pelvis to ensure that lumbar lordosis was preserved. The operating room table accommodated plain radiographs or fluoroscopy.

A complete laminectomy with facetectomies or extensive bilateral laminotomies and facetectomies with preservation of the mid-line elements was performed in each case. The lateral borders of the disc were exposed along with the traversing and exiting nerve roots. Bilateral annulotomies were made and a complete discectomy was carried through these annular windows. The annulotomies were placed lateral to the dural tube. The midportion of the lateral annular window was centered adjacent to the medial wall of pedicle. The anterior and lateral walls of the annulus were preserved; the entire nucleus was removed. Cartilaginous end plates were resected using curettes.

Reduction of sagittal and frontal plane deformities was achieved through disc space height restoration and annular tensioning. Inserting progressively larger dilators into the collapsed disc restored disc space height and the normal sagittal contours of the spine.

The vertebral end plates were prepared with reamers that uniformly cut a channel through the adjacent bony end plates. Great care was taken to visualize and gently retract both the traversing and exiting nerve roots. These soft tissue elements were protected by a tubular reamer guide, which was impacted into the disc space prior to reaming. Care was taken to ensure that the endplate cuts were made parallel and equally into each end plate.

The INTER FIX™ cages were packed with either the rhBMP-2 soaked sponges or morsecellized autograft prior to insertion. The cages were sequentially inserted in the disc space and away from any soft tissue or neural elements. The cages were not routinely recessed within the disc space. The majority of the cages were left flush to the posterior cortical wall of the vertebral bodies. Their position was assessed intraoperatively with plain radiographs or fluoroscopy.

Iliac crest bone graft harvesting

The control group received autogenous iliac crest graft placed within the cages. The bone graft was harvested from the outer table of the iliac wing. The graft was morscellized using a rongeur and was tightly packed into the cages before their insertion.

rhBMP-2 preparation

The rhBMP-2 was reconstituted using sterile water and was used as a single dose of 1.5 mg/mL in all study patients. The 1.5 mg rhBMP-2/mL solution was applied to a bovine collagen sponge and allowed to bind to the sponge for 15 minutes. The dosage of rhBMP-2 varied by patient depending on cage size, with the total dose ranging from 4.0 mg to 8.0 mg. The rhBMP-2 soaked sponge was then placed in the hollow central portion of the INTER FIX™ device before its insertion into the prepared disc space. No additional sponges were placed outside of the devices. No autogenous grafts were used in the investigational group.

Postoperatively, patients were placed in a soft lumbar corset. The treating physician decided when the patient would advance in activities. Isometric strengthening and exercise program were started at six weeks postoperatively.

Statistical Methods

The data from this clinical trial were analyzed using the statistical software package SAS® version 6.12. For comparisons between the groups for continuous variables, *p*-values were calculated using ANOVA techniques, and for categorical variables the Fisher's exact test or chi-square test were used. For changes (improvements) from the preoperative within each group, the p-values were calculated using a paired t-test.

Deleted: are
Deleted: from
Deleted: they are from
Deleted:
Deleted: are from the

RESULTS

Surgery

The mean operative time in the investigational rhBMP-2 group (2.6 hours) was less than in the control group (3.0 hours) (Table 2). The average blood loss in the rhBMP-2 group was 322.8 ml as compared to 372.7 ml in the control group. The

average hospital stay was less in the investigational group (3.4 days for the investigational group vs. 5.2 days for the control group). None of these differences between treatment groups was statistically significant, although the time of surgery approached significance (p=0.065). No unanticipated device-related adverse events occurred intraoperatively in either treatment group.

Complications

Vascular events.

One control patient developed deep venous thrombosis and was treated with anticoagulation medications.

Iliac crest graft site. In the control group, adverse events related to harvesting of the iliac crest graft were identified in two patients (6.1%). These events included one case of pain and one hematoma. Neither of these patients required additional surgery. Obviously, no graft site adverse events occurred in the investigational group since the use of rhBMP-2 precluded the need to harvest bone graft.

The level of postoperative pain and morbidity associated with the iliac crest graft harvesting was measured using numeric rating scales for pain intensity and duration (Figure 1). After surgery, all of the control patients experienced hip donor site pain. The highest levels of pain were noted immediately after surgery with a mean score of 11.6 points out of 20 points. The percentage of patients experiencing pain decreased over time; however, at 24 months after surgery, 60% of the control patients still experienced pain (i.e., had scores greater than 0). At two years, the graft site pain scores averaged 5.5 points out of 20 and 13.3% of the patients still felt that the appearance of the graft site bothered them some and 60% of the patients still reported graft site discomfort.

Deleted: 3.0

Antibody Testing

Antibody results. Antibodies to rhBMP-2, bovine Type I collagen, and human Type I collagen were evaluated preoperatively and 3 months postoperatively using enzyme-linked immunosorbent assays (ELISAs). None of the patients in either group tested positive for antibodies to rhBMP-2 or human Type I collagen. The incidence of bovine Type I collagen antibody formation in the investigational group was 13.3% whereas the incidence in the control group was 35.7%. No negative clinical consequence to the positive collagen antibody test results was evident.

Clinical Outcomes

Oswestry Disability Questionnaire scores. The Oswestry Low Back Pain Disability Questionnaire measured pain associated with activities. The Oswestry Questionnaire was administered preoperatively as well as at each postoperative visit. At all postoperative visits, both treatment groups demonstrated highly significant improvements as compared with the preoperative scores (Figure 2). At all postoperative time intervals after the first 6-week follow-up period, the investigational group showed greater improvements over the control group in the mean overall Oswestry scores. At last follow-up at 24 months, the mean improvements in the Oswestry scores were 29.6 points in the investigational group and 24.9 points in the controls (Figure 2). In the rhBMP-2 group, 69% of patients showed an improvement of at least 15 points in their disability scores at 12 months after surgery as compared with 55.6% of patients in the

Deleted:

control group. At 24 months, the 76.0% of the investigational group was improved and compared favorably with 64.3% improved in the control group. (Table 3)

Back Pain. The mean back pain scores at all postoperative periods were improved from the preoperative mean values for both treatment groups. The mean improvements in back pain scores at all five postoperative intervals studied were greater for the investigational group than for the control autograft group (Figure 4). At 24 months, the average improvement in back pain in the investigational group was almost twice that of the control group (9 point improvement vs. 4.5 point improvement). This difference was highly statistically significant ($p = 0.009$).

Deleted: with a
Deleted: -value of

Leg Pain. Leg pain was assessed in a similar manner using a 20-point numeric rating scale that reflects both the intensity and duration of painful symptoms. Mean leg pain scores improved significantly after surgery in each group (Figure 5). At each study interval, average leg pain scores were less (better) in the investigational group when compared to the control group. Similarly, the investigational group also showed higher average improvement scores at each interval studied. At 24 months, the average improvement in leg pain was 7.7 points in the investigational group compared to 6.5 points in the control group. This difference was not statistically significant.

Medical Outcomes Study 36-Item Short Form Health Survey (SF-36). At all postoperative intervals studied the investigational group showed greater improvement in the physical component of the SF-36 when compared to the controls (Figure 6).

Deleted: SF36
Deleted: short form SF36

Neurological Status. Preoperatively and at all five post-operative time points, the motor, sensory, reflexes, and straight leg raise measurements were essentially the same for both treatment groups and showed no statistical differences. At 24 months,

using the protocol criteria for determining overall neurological success, which represents a combination of the four neurological measurements, both groups had 100% success. Table 3 contains the average change from pre-operative results at 24 months for the motor, sensory, reflex, and straight leg raise measurements.

Work Status. Many factors affect a patient's work status, such as the nature of the work performed and ability of the work place to accommodate work restrictions. Prior to surgery, in the investigational group only 26.5% were gainfully employed while over 45.5% of the control patients were employed (Table 3). For patients who were working before surgery, the median return to work time was 43 days in the investigational group and 137 days in the control group. Although striking, this difference was not statistically significant. At last follow-up, more people in the investigational treatment group were working than were working before their surgery. At 2 years following surgery in the investigational group, 12 patients were employed while only 9 were employed before surgery. In the control group, 15 were working before surgery and 14 were working at two years after surgery. In other words, the percent of the investigational patients working increased from 26.5% before surgery to 35.3% at two years, while over the same time period, the percentage working in the control group decreased from 45.5% to 42.4%. Although none of these changes are statistically significant, the trend is promising and may be reflective of the statistically significant difference of lower back pain in the investigational patients.

Deleted: went

Deleted: in

Deleted: the rate went

Patient Satisfaction. At 12 and 24 months after surgery, the results were similar in each treatment group. At 24 months, 72.4% of the investigational patients and 80.0% of the control patients were satisfied (answering definitely true or mostly true) with their

surgical outcomes. In the investigational group, 69.0% said they would undergo surgery again (answering definitely true or mostly true) compared with 83.3% of the control patients who would undergo surgery again. In the investigational group, 72.4% believed that they were helped as much as they had expected to be from the surgery; 70.0% of the control group felt they had been. None of these subjective differences was statistically significant.

Radiographic Outcomes

Cage placement

Cage placement was assessed utilizing both plain radiographs and thin-cut CT scans. The CT scans were found to reflect more accurately the position of the cage in relation to the spinal canal posteriorly and neuroforamina laterally. No differences between the two patient groups regarding cage placement were detected. Only 6% of patients in each group (2/34 investigational group; 2/33 control group) showed cages that were countersunk 3mm or more relative to the posterior margin of the vertebral body. The posterior margin of the superior vertebra was used as the point of reference to determine the relative position of the cages in patients presenting spondylolisthesis. Approximately one-third of patients in each group had cages that extended into the spinal canal on postoperative CT studies (11/34 investigational group; 10/33 control group). The remainder of the cages were placed either flush to the posterior cortex of the vertebral bodies or were recessed by only 2mm or less.

Deleted: on

Deleted: from

Sagittal Plane Balance

Nearly one third of patients (19/67; 28%) postoperatively had some sagittal plane imbalance following surgery. At the last follow-up, 6 patients had some residual

spondylolithesis from failure to fully reduce the deformity at the time of surgery (up to Grade I spondylolisthesis was allowed) and two patients developed spondylolithesis postoperatively. Eleven patients had residual retrolithesis following surgery.

Intradiscal bone formation

Fusion status of the study patients was evaluated on plain radiographs and CT scans. At six months after surgery, 93.1% of patients in both the investigational and control groups had evidence of fusion. At 12 months, in the investigational group the fusion rate dropped to 85.2% while the control group maintained a fusion rate of 92%. This decrease in fusion rate may have, in part, been related to poor follow-up in the investigational group at the 12-month time frame. (Seven investigational and 8 control patients were recorded as non-union because they failed to obtain radiographs during this time period.) At 24 months, the investigational group had a 92.3% fusion rate, which was more than 14 percentage points higher than that of the control group (77.8%). While this difference was not statistically significant, it does show a positive trend in favor of the investigational group.

Bone formation outside of the disc space

The thin cut 1.0 mm CT scans were able to identify new bone formation adjacent to the interbody fusion cages. New bone formation extending outside of the disc space and into the spinal canal or neuroforamina was found in 28 patients (23 investigational and 5 controls).

Sagittal plane balance.

In the control group, one of the 5 patients (20%) with bone in the spinal canal had a residual unreduced spondylolithesis following surgery. New bone formation was

identified in the canal posterior to the unreduced superior vertebra under the posterior longitudinal ligament and annulus. In the control group, new bone formation was identified in four patients extending into the spinal canal in patients with normal segmental sagittal plane balance. Wording? There were no grade III patients in this group.

In the investigational group, 10 of the 23 patients (43%) with bone in the spinal canal had some residual postoperative sagittal plane imbalance. Five patients (5/23; 22%) had spondylolithesis and 5 (5/23; 22%) had retrolithesis. In each of these cases, new bone formation occurred posterior to the unreduced vertebral body, under the posterior longitudinal ligament lifted off the unreduced vertebral body. Thirteen patients in the investigational group (13/34; 38%) had a normal postoperative segmental sagittal plane balance and new bone formation in the spinal canal.

Cage placement.

In the investigational group, cage placement was strongly associated with the potential for development of new bone formation in the spinal canal. In the investigational group, 39% of patients with cages placed at the margin or within 2mm of the margin of the posterior vertebral cortex developed some bone in the spinal canal. Twelve percent of patients in the control group with cages placed within 2mm of the vertebral margins developed bone in the spinal canal. No patients in either group that had the cages recessed by 3mm or more developed bone in spinal canal. (Add some commentary on the appearance of this bone – its shape, potential to cause stenosis or nerve impingement?)

Secondary Surgical Procedures

In the investigational group, 7 of 34 (20.6%) had some type of secondary spinal surgery. Three of 34 (8.8%) had second surgery at the same site of the initial PLIF surgery. Two investigational patients received supplemental fixation for presumed pseudarthrosis; one patient underwent surgical site exploration for a presumed infection. Four patients (4/34;11.8%) had second spinal surgeries unrelated to the PLIF procedure.

In the control group, 6 of 33 (18.2%) had some type of secondary spinal surgery. Three of 33 (9.1%) had surgery at the same level of the initial PLIF procedure; all three of these patients received supplemental fixation for presumed pseudarthrosis. Three additional patients in the control group (3/33;9.1%) had second spinal surgeries, unrelated to the initial PLIF procedure.

DISCUSSION

Threaded cylindrical cages represent a new, distinct class of segmental spinal fixation devices. These devices were not designed as spacers that require additional posterior segmental stabilization; rather, they were designed as stand-alone intervertebral devices that function as an "instrumented PLIF." Threaded interbody devices are biomechanically different from interbody spacers. Biomechanical studies have shown that cage size has some significance in stand-alone cage fusions; however, stand-alone cages do not significantly increase spinal stiffness in studies using human cadavers [3,9,11,12,16,18]. This finding largely explains the current trend clinically to utilize posterior segmental fixation in PLIF constructs.

Larger cages improve stiffness in rotation and lateral bending in a lumbar spinal motion segment; however, reduction of motion in flexion is not significantly improved with larger cages [12,16]. Larger cages require more extensive facet joint resection or complete facetectomy, which further destabilizes the spinal motion segment. A cylindrical device increases in its medial-lateral dimension equal to its increase in height, which necessitates greater mobilization and retraction of the neural elements. Retraction and mobilization of the neural element during cylindrical cage insertion has been associated with permanent neurologic injury [A,B]. The current trend in PLIF surgery is to limit neural element retraction through the use of a transforaminal surgical approach or through the used of impacted interbody spacers.

Initial clinical studies reported high rates of fusion and clinical success in certain centers. These results have not been widely reproduced. Authors of clinical and radiographic studies on stand-alone interbody implants without supplemental fixation

have reported fusion rates between 83% and 100% [14,19] (when iliac crest bone graft is used?). Hacker [10] compared two groups of patients treated for disabling back pain; one group was treated with a stand-alone PLIF using BAK implants, and the other group was treated with combined anteroposterior fusion. He found equal patient satisfaction between the two groups. Ray [19] presented a prospective series of 236 patients treated with stand-alone interbody fusion and reported a 96% fusion rate at two years after surgery. These fusion criteria did correlate with improved clinical outcomes. In this study group, only 65% had good to excellent clinical outcomes on the Prolo scale and 14% had a poor result.

However, performing PLIF procedures or any other type of spinal fusion with autograft from the iliac crest comes with a price in pain for the patient. Figure 1 shows that the iliac crest graft site pain in this study was found to be similar to that measured in the same way for a larger study of the LT-CAGE Device [4] with two exceptions. First, in this study, the average pain score at 24 months was 5.5 on a scale of 20, while in the anterior LT-CAGE study, the value was 1.8. Second, in this posterior INTER FIX study, 60% of the patients had some pain at 24 months, while in the LT-CAGE study 32% did. Although these were two different studies using different surgeons, different numbers of cases (30 vs.118), and different sizes of cages (the INTER FIX cage is cylindrical and the LT-CAGE version is a smaller volume tapered design), these results are consistent with a review of other studies that showed that a posterior approach to the iliac crest is more painful for the patients [17]. The pain associated with the posterior bone graft harvest may be secondary, in part, to the extensive stripping of the gluteus musculature, more extensive bone graft harvesting techniques or injury to the sacroiliac joint. For

whatever reason, the measured iliac crest graft site pain scores in this study imply that, from the patients' point of view, the need for an autograft replacement in PLIF cylindrical cage procedures is greater than in ALIF tapered cage procedures.

This study shows that extra bone formation in the spinal canal may occur following PLIF procedures with cylindrical interbody fusion cages regardless of the source of the bone graft, since bone formation in the spinal canal occurred in both the control and investigational groups. Bone formation in the spinal canal appears to be a multi-factorial event. Bone formation in the spinal canal is largely dependent upon cage placement and sagittal balance of the instrumented vertebral motion segment. Patients with residual sagittal plane imbalance form bone behind the unreduced vertebral segment. This may be the result of lifting a periosteal flap along the posterior cortex of the listhesed vertebral body. Cages placed that were not recessed within the confines of the disc space margins were also associated with bone formation in the spinal canal. Thin cut CT scans were essential is determining postoperative cage placement and new bone formation. Cage placement based on plain radiographs alone were difficult to interpret accurately particularly if patient positioning is not ideal relative to the film.

Deleted: of

rhBMP-2 on an absorbable collagen sponge has been shown to induce bone formation in the intervertebral disc space [2,4,5,13]. Prior interbody fusion studies have shown that this montage in this milieu will routinely produce a fusion zone extending 3mm around the cage [7] without extending beyond the intradiscal space. It is not surprising that bone formation may extend into the spinal canal when cages containing rhBMP-2 are not recessed 3mm or more within the confines of the disc space.

Although radiographic evidence of posterior bone formation was observed, There was no evidence of bone formation extending into the dura in these patients. Histological results from a preclinical safety study where rhBMP-2 soaked on collagen sponge was applied directly to the dura with and without a dural puncture in a canine model revealed complete fusion without stimulating bone formation within the dural membrane. The normal convexity to the lamina had returned via remodeling which was thought, in part, to be due to the pulsatile nature of the dura. (Meyer *et al.*)

The PLIF procedure using threaded cylindrical fusion cages disrupts a wide channel, which includes the posterior margin of the disc, the posterior longitudinal ligament and annular structures. This injury can stimulate adjacent bone formation, which can extend into the spinal canal. This new bone formation is best visualized on CT scan. Both the control group and investigational group exhibited bone formation outside of the disc space following this procedure.

Although not desirable, bone formation in the spinal canal had no discernable influence on patient outcomes. Bone formation in the spinal canal following the PLIF procedure with stand-alone cylindrical interbody fusion cages appears to be a radiographic finding alone with no associated clinical sequalae.

Even though the number of patients was small, a statistically significant improvement in back pain in the rhBMP-2 investigational patients was found. Although the other clinical findings were not statistically different between the two groups, if just the surgical and clinical outcome data at two years are examined (Tables 2 & 3), all of the outcomes measured (except for two out of three of the subject patient satisfaction questions) favored the investigational group. These findings imply that a larger study

Formatted

Deleted: result in

Deleted: Bone

Deleted: This study, because of its small size, amounted to a pilot study of the ability of a bone morphogenetic protein to replace autograft in a stand-alone PLIF cage procedure.

would have shown statistical equivalence or improvement in all clinically important outcomes. Predicting such a result can be based not only upon the data in the pilot study presented here, but also upon the large-scale human clinical spinal trials of rhBMP-2 already conducted. The same protein studied here, used in the same concentration inside metal cages for the same lumbar indication but from a different approach (anterior), has been shown in a 679 patient analysis to be superior to autograft [5] (in which clinical measures?). The direction of implantation of a cage should not affect the ability of INFUSE Bone Graft contained inside to form bone.

Based upon these results, an alternative surgical technique for future clinical use of rhBMP-2 in a PLIF procedure should be considered to potentially minimize the risk of posterior bone formation. Substituting the cylindrical threaded cages with impacted cages should minimize the potential surgical trauma to the soft and neural tissues during retraction and end plate preparation. Furthermore, careful surgical technique to ensure that the cages are properly countersunk coupled with anterior placement of the rhBMP-2 soaked sponges may help to reduce the risk of posterior bone formation. Furthermore, adding posterior instrumentation should provide greater mechanical stability, particularly in patients exhibiting spondylolisthesis or retrolisthesis.

In conclusion, this detailed, independent review of the results, which represent the first use of osteoinductive proteins in a PLIF procedure, are encouraging. These findings along with other studies for other indications imply that future larger PLIF studies with rhBMP-2 are needed. Current studies are assessing the use of rhBMP-2 with a TLIF techniques. Additional PLIF studies are evaluating placement of the BMP-soaked adjacent to the anterior annulus away from the posterior annulotmy sites. In

future studies using modified surgical techniques, such as using more recessed cages to allow for extra posterior bone formation, adding steps to minimize bleeding and surgical variables, using narrower, non-cylindrical cages that would be easier to put in and cause less tissue destruction, and/or adding secondary instrumentation may be beneficial. Further, possibly modifying patient selection, such as entering patients with less vertebral slip, may also help minimize the confounding variables. All of these changes may produce more convincing evidence that INFUSE Bone Graft can also be used as a substitute for autograft in PLIF cage procedures.

ACKNOWLEDGEMENTS

Special thanks to the following doctors who were principal or co-prinicipal clinical investigators at the 14 sites for this study. These surgeons in alphabetical order are Drs. C. William Bacon, Steven Barnes, Charles Branch, Randall Dryer, Paul Geibel, Fred Geisler, Scott Graham, Peter Holiday, Timothy Holt, Zenko Hrynkiw, Dennis Maiman, David Masel, Bruce Mathem, Christopher Meyer, Phillip Tibbs, and Frank Tomecek. The work of the Clinical Research Department at Medtronic Sofamor Danek in collecting the clinical data and performing the statistical analyses is acknowledged.

REFERENCES

A. Barnes B, Rodts GE, McLaughlin MR, Haid RW Jr. Threaded cortical bone dowels for lumbar interbody fusion: over 1-year mean follow up in 28 patients. J Neurosurg 2002; 95(1 Suppl):1-4.

B. Barnes B, Rodts GE, Haid RW Jr, Subach BR, McLaughlin MR. Allograft implants for posterior lumbar interbody fusion: results comparing cylindrical dowels and impacted wedges. Neurosurgery 2002;51(5):1191-1198.

1. Boden SD, Schimandle JH, Hutton WC. 1995 Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 1995;20:2633-44.

2. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25:376-81.

3. Brodke DS, Dick JC, Kunz DN, McCabe R, Zbeblick TA: Posterior lumbar interbody fusion: a biomechanical comparison, including a new threaded cage. Spine 1997;22:26-31.

4. Burkus JK, Gornet MF, Dickman C, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. J Spinal Disord 2002; 337-349.

5. Burkus JK, Heim SE, Gornet MF, Zdeblick TA. Is INFUSE™ Bone Graft Superior to Autograft Bone? An Integrated Analysis of Clinical Trials Using the LT-CAGE™ Lumbar Tapered Fusion Device. J Spinal Disord 2003 in press

6. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. Neurosurg Focus 2001;10:1-9.

7. Burkus JK, Dorchak JD, Sanders DL, Radiographic assessment of interbody fusion using recombinant human bone morphogenetic protein type 2. Spine 2003 28 in press.

8. Cloward RB: The treatment of ruptured intervertebral discs by vertebral body fusion. I. Indications, operative technique, after care. J Neursurg 1953;10:154-168

9. Dimar JR, Wang M, Beck DJ, Glassman SD, Voor MJ: Posterior lumbar interbody cages do not augment segmental biomechanical stability. Paper presented at: Scoliosis Research Society; September 22-25, 1999; San Diego, CA

10. Hacker RJ: Comparison of interbody fusion approaches for disabling low back pain. Spine 1997;22:660-665

11. Hasegawa K, Ikeda M, Washio T, Hara T: An experimental study of porcine lumbar segmental stiffness by the distraction-compression principle using a threaded interbody cage. J Spinal Disorders 2000;13:247-252.

12. Kettler A, Wilke HJ, Dietl R, Krammer M, Lumenta C, Claes L: Stabilizing effect of posterior lumbar interbody fusion cages before and after cyclic loading. J Neurosurg 2000;92:87-92

13. Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2. A prospective study of clinical and radiographic outcomes. Spine 2001;26:2751-6.

14. Kuslich SD, Ulstrom CL, Griffith SL, Ahern JW, Dowdle JD: The Bagby and Kuslich method of lumbar interbody fusion. History, techniques, and 2-year follow-up results of a United States prospective, multicenter trial. Spine 1998;23:1267-1278.

15. Lin PM, Cautilli RA, Joyce MF: Posterior lumbar interbody fusion. Clin Orthop 1983;180:154-168.

16. Lund T, Oxland TR, Jost B, Cripton P, Grassmann S, Etter C, Nolte LP: Interbody cage stabilization in the lumbar spine: biomechanical evaluation of cage design, posterior instrumentation and bone density. J Bone Joint Surg Br 1998;80:351-359.

17. Polly DW, Kuklo TR. Bone graft donor site pain. Paper presented at: Scoliosis Research Society; September 19-21, 2002; Seattle, WA

18. Rapoff AJ, Ghanayem AJ, Zdeblick TA: Biomechanical comparison of posterior lumbar interbody fusion cages. Spine 1997;22:2375-2379

19. Ray CD: Threaded titanium cages for lumbar interbody fusions. Spine 1997;22:667-679.

20. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995; 20:1326-37.

21. Urist MR. Bone: Formation by autoinduction. Science 1965;150:893-9.

Table 1

Patient Demographic Information

Variable	Investigational (n=34)	Control (n=33)	p-value *
Age (years) [mean (range)]	46.3 (25.8 – 66.1)	46.1 (28.5 – 70.9)	0.928
Weight (lb) [mean ± s.d.]	180.5 ± 38.4	172.8 ± 35.7	0.400
Gender [n (%)]			
Male	17 (50)	15 (45.5)	0.808
Female	17 (50)	18 (54.5)	
Worker's compensation [n (%)]	8 (23.5)	9 (27.3)	0.784
Spinal litigation [n (%)]	3 (8.8)	1 (3.0)	0.614
Tobacco used [n (%)]	18 (52.9)	15(45.5)	0.628
Alcohol use [n (%)]	15 (44.1)	9 (27.3)	0.204
Preoperative work status [n (%) working]	9 (26.5)	15 (45.5)	0.131
Previous back surgery [n (%)]	12 (35.3)	13 (39.4)	0.803

- For continuous variables, p-values are from ANOVA and for categorical variables, they are from Fisher's exact.

Table 2

Surgical Parameters

	Investigational	Control
Mean operative time	2.6 hours	3.0 hours
Average blood loss	322.8 ml	372.7 ml
Average hospital stay	3.4 days	5.2 days

Table 3

24 Month Clinical Outcome Parameters

	Investigational	Control
Improvement Points in Oswestry Score	29.6	24.9
% Patients with ≥15 point Oswestry Improvement	69%	55.6%
% Patients with Oswestry Improvement	76.0%	64.3%
Back Pain Improvement from Pre-Op (Points)	9*	4.5
Leg Pain Average Improvement from Pre-Op (Points)	7.7	6.5
Motor change from Pre-Op	4.5	2.8
Sensory Change from Pre-Op	8.0	2.8
Reflex change from Pre-Op	7.0	5.4
Straight Leg Raise change from Pre-Op	48.0	39.3
Net Change in % patients working	+8.8%	-3.1%
Median return to work time	43 days	137 days
Fusion rate	97.3%	77.8%

*statistically different

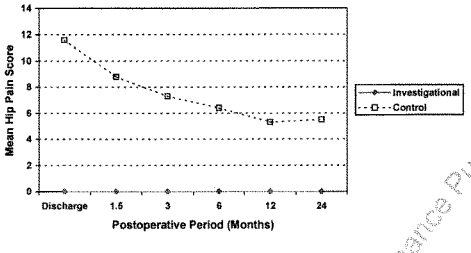


Figure 1. **Mean hip pain scores over the time**

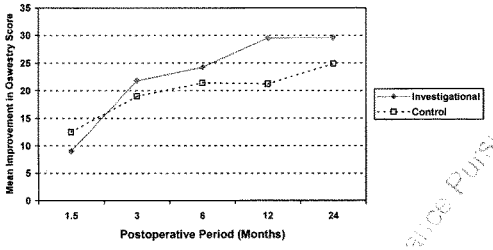


Figure 2. **Mean improvement in Oswestry scores over the time**

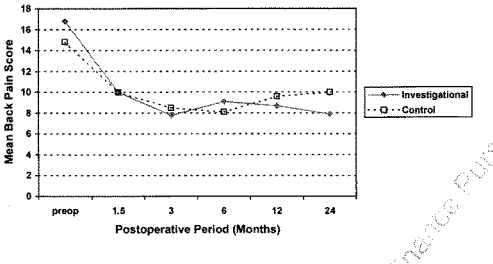


Figure 3. **Mean back pain scores over the time**

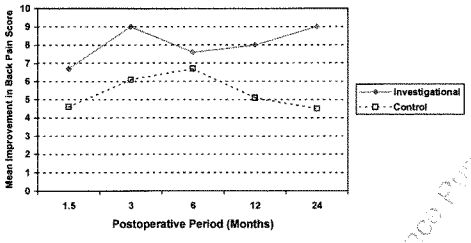


Figure 4. **Mean improvement in back pain scores over the time.**

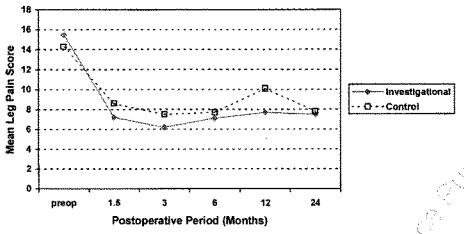


Figure 5. **Mean leg pain scores over the time**

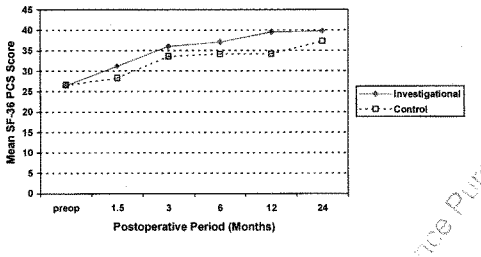


Figure 6. **Mean SF-36 PCS scores over the time**

From: Treharne, Rick
Sent: Wednesday, May 28, 2003 03:48:45 PM
To: Joe, Jennifer
CC: English, Judy; Bearcroft, Julie
Subject: PLIF paper response

Attachments: Spine Journal Manuscript.doc

Please review this draft letter to The Spine Journal. I told Dr. Burkus I would get him something by tonight to look at...Thanks...Rick

June 2, 2003

Tom G. Mayer, M.D.
Editor-in-Chief
The Spine Journal
[redacted]
LaGrange, IL 60525

RE: MS 30023

Dear Dr. Mayer:

We have revised our manuscript, entitled "Posterior Lumbar Interbody Fusion Using rhBMP-2 with Cylindrical Interbody Cages". Enclosed are three copies. We believe we have addressed all the reviewers' comments with this revised manuscript. This paper presents data that will not be researched again for perhaps years to come. We believe this paper addresses an important issue and needs to be presented to the spinal community as soon as possible.

To demonstrate how we addressed the reviewer's comments, in the following in bold type are the reviewer's comments with our response in regular type:

This study should not be published in its current form. As noted by both Reviewer A and B, there is very little statistical significance differentiating the two groups, but the authors and/or company sponsoring this study have attempted to use any possible positive trend to promote this technique. Unless the authors can discuss the results of this study in an unbiased manner, which they have been unable to do in its present form, this data should not be published.

We believe we have discussed the results in an unbiased, objective manner and are not quite sure what the specific problem is here, nor do we believe we are trying to promote this technique. We believe the data speaks for itself and the readers can make up their own mind as to whether to use this technique. In our mind, we believe the article warns potential users about performing it. There will be more comments on this subject later in our response.

This is a very important study, but there are some problems with the study's execution and with the data as it is presented. First, why was this "2-year study" stopped after 9 months?

Our paper did not say that the study was stopped after 9 months. It said that all the patients were entered in a 9 month period. As the discussion says the size of this study represents in essence a pilot study. We assumed The Spine Journal would want 2 year

follow-up. Nevertheless, we have added a footnote to the text to explain why more patients were not entered into the study.

The authors state that larger numbers might have helped show greater differences between the two groups, so the question remains, why stop at 67 patients after 9 months (other rhBMP-2 studies included over 300 patients)?

Performing large-scale studies is very expensive and not all studies need to be large scale. What is the reviewer suggesting is the proper alternative here? To not publish this data? We believe this information is important and should be shared with the spinal community. As was mentioned, the added footnote addresses this reviewer's comment.

Also, the authors cannot talk about "greater differences" and "better outcomes" in the results unless the differences are statistically significant.

We did a search of the manuscript and cannot find the phrase "greater differences" or "better outcomes" in the text. So we do not know how to address this issue. The manuscript had the phrase "although not statistically significant" six times in the text.

They analyzed statistically almost every conceivable outcome variable, except for the one finding strongly against rhBMP-2 -- that is, a higher rate of new bone growth in the spinal canal! This is the greatest fear that surgeons have regarding BMP's -- uncontrolled new bone formation. It happened in 23/34 BMP patients,

versus 5/33 bone graft patients. They did not do a statistical analysis of this, but I ran a Fisher's exact 2-tailed test for this data....and P<0.0001, the most significant of all differences found in this study, yet the authors did not even run this analysis! This is very troubling, and raises the issues of commercial support of such a study leading to a biased reporting of results. I ask the authors to explain this point, and include and emphasize its importance prior to acceptance for publication.

As we understand this comment the reviewer is in essence saying that we have statistically analyzed too many outcomes parameters and then asks us to do one more. We believe the point about bone formation is obvious, but we have added the statistical analysis he has asked for in the revised manuscript.

We are not quite sure what the reviewer is saying about "commercial support" since any human study of recombinant proteins will be very expensive and require some type of commercial support in order to be performed. The reviewer seems to think that this paper is advocating the use of rhBMP-2 in PLIF procedures. Readers of this paper, once published, will see that such use, which is not FDA approved and may never be, can have unexpected radiographic findings, and surgeons will hesitate performing surgeries in the same manner as used in the study without further study or without modifying their technique. Without any publications of any kind on this subject, surgeons may have a false sense of security that rhBMP-2 can be used in PLIF procedures just as in ALIF cages.

As was mentioned, we do not believe our independent review of these results encourages or discourages the procedure in either the investigational or control groups. Rather we just report the facts that until this paper gets published are only known about with rhBMP and PLIF cages through hearsay and rumor. Although we do not come out and say it (because we felt such comments would be inappropriate in a scientific publicaton) the use of stand alone cylindrical cages in PLIF procedures seems to have gone into disfavor in the US. We believe the net effect to the reader on the use of rhBMP inside a PLIF cage will be discouragement (which ironically will not be favorable to the to the industrial community) as will the reader for the use of stand alone cylindrical PLIF cages with autograft.

Nevertheless, we have added the statistical analysis the reviewer has requested to the revised text in the results section.

They also need to specify how many patients with ectopic bone had new or persistent leg pain, not just overall average leg pain scores.

We did not ever use the term "ectopic" in the original paper. In the re-write we added the term "unexpected". We have expanded our discussion on the bone formation outside the disc space to be more descriptive and added a discussion of recurrent leg pain.

Page 16, Patient Satisfaction: Please give patient satisfaction data in tabular form, as it is given for all of the other clinical outcomes.

A table has been added per this reviewer's request.

Page 18, end 1st paragraph: "Positive trend" usually refers to a P value between 0.05 and 0.10. If this is not true, then this term "positive trend" probably should not be used.

We have eliminated the term "positive trend" from the revised text.

Page 18, 2nd paragraph: Regarding bone formation outside of the disc space, it is surprising that 23 of 34 investigational patients versus 5 of 33 control patients had this problem. This appeared to me to be a statistically significant difference and in fact by Fisher's Exact Test the difference was highly significant with a P value of less than 0.0001. Why is this not stated in the text? A statistical analysis and description of these results, both in tabular format and in the text of the Results and Discussion is necessary.

This analysis was added to the text. We also found a small error in the calculations and have corrected it in the revised text.

Page 19, 1st paragraph: Did any patients who had new bone formation have residual leg pain or new leg pain? The results describe overall average scores for leg pain, but we do not know specifically how many of the patients in each group still had leg pain or developed leg pain following surgery. This is important as this might suggest that there was a clinical impact to the new bone formation.

The revised manuscript addresses this issue. There was no correlation.

Page 19, 3rd & 4th paragraph: What are spine surgery failures? Does this mean pseudoarthrosis? Does this mean the patients had recurrent or residual leg pain?

Second surgery spine failures are defined as patients who have had a revision, removal, or supplemental fixation. These cases could include pseudarthrosis and included 3 controls and 2 investigational. One additional investigational patient had recurrent leg pain. We added text about the recurrent leg pain.

Page 21, middle of 2nd paragraph: It is again confusing that 60% of patients had some pain in the bone graft site and yet only one patient is mentioned in the Abstract and Results section as having pain on follow-up.

A 20 point scale was used to quantify hip donor site pain. At 2 years, 60% of the patients had a score of 1 or greater. This is different from a reported complication of graft site discomfort. To make the paper more clear, we will eliminate the graft site discomfort reference from the text.

Page 22, 2nd paragraph: Here there should be a discussion regarding the greater likelihood of bone formation in the canal with rhBMP-2. Please discuss whether this new bone formation may have caused leg pain in any of the patients.

The revised manuscript addresses this point.

Page 23, 2nd paragraph: I would agree with this point of the discussion if there truly were no patients with post op leg pain and bone in the canal, whether or not the two were related.

The revised manuscript addresses this point.

Page 23, 3rd paragraph: The authors cannot state that "all the outcomes measured favored the investigational group", unless these differences were statistically significant. Since they were not, this statement is not accurate.

We have revised the text to tone down this sentence and add the phrases "on average" and "although not statistically different".

General Comments:

This is described as a two-year study yet it seems that small numbers of patients were enrolled and only over a short nine-month period. Why is this? Was the study ended prematurely? If so, this should be stated at least in the body of the paper.

The revised manuscript addresses this point.

Page 3, end of 3rd paragraph: 3.0% of patients reporting graft site discomfort is one patient and should be stated as such instead of with percentage.

As was mentioned, the revised manuscript addresses this point.

Page 5, Introduction, 1st paragraph: references are needed regarding the clinical results of PLIF, as well as clinical results for DDD, spondylolisthesis, etc.

References were added to the revised text.

Page 5, Introduction: How is sagittal balance restored in the setting of stand-alone PLIF? Please reference the biomechanical studies which demonstrate this.

References were added to the text.

Page 5, 2nd paragraph: Can the authors reference papers describing the restoration of normal anatomic alignment with PLIF?

We added several references to this paragraph, although none may specifically address the reviewer's question..

Page 12, Complications: Were there are dural tears? Were there any neuropraxic injuries, i.e. patients with postoperative weakness or postoperative numbness? These should also be cited under Complications.

Three investigational (8.8%) and 2 controls (6.1%) had dural tears. As far as neurological complications, in the investigational patients 16 events occurred in 14 patients, while in the control 18 events occurred in 14 patients. We have added these figures to the revised text.

Page 12, 2nd paragraph: It is confusing that the authors describe one patient having graft site discomfort two years out from surgery yet they in the same paragraph state that 60% of patients who had a graft harvested had pain. They state that at two years the graft site pain scores averaged 5.5 points out of 20, yet

they stated only one patient had graft site discomfort. Please explain these apparently confusing results.

This issue has been addressed in the revised text.

Page 13: Please discuss why there might have been such a high percentage of antibody formation to bovine type I collagen in the control group. Was this related to the use of gel foam?

GELFOAM sponge was used in 15 of the 34 (44%) investigational patients. Of these 15, 2 developed antibody formations to bovine collagen. GELFOAM sponge was also used in 20 of 33 (61%) of the controls. Of these 20, 7 had antibody formation to the bovine collagen. This result was added to the text.

Page 14 & 15: Throughout the Clinical Outcomes section the authors cannot describe "greater improvements", and "better" scores when there is no signficant difference. For example, in the 1st paragraph of page 14 the 4th sentence should read "after the first six week follow-up the investigational group showed no significant differences over the control group in the mean overall Oswestry scores". This can then be followed by giving the actual scores that were obtained for each group. The reader can then interpret the difference in numbers as they wish, but

the fact that it is not statistically significant needs to be stated rather than stating that there were greater improvements when these differences were not statistically significant. The same is true for the results under Back Pain, Leg Pain, and Short Form SF-36.

We believe the revised paper addresses this issue.

Reviewer A

This manuscript is not worthy of publication in its current form. There are many issues which I will develop to this end, but the most significant is that the conclusions do not support the data contained therein. I will outline the concepts for the authors. First, none of the differences, in the end, are statistically significant, yet the authors take the liberty to interject statements that there are "trends that the investigational group showed better results" when there is no evidence for this. Whenever the control group has a similar positive trend, no mention of this is made (which is appropriate, but not consistent).

The revised manuscript addresses this point, as was previously mentioned.

The manuscript is full of biased statements that are a reflection of the data evaluators - the company that markets the product. No mention is made in the discussion, or methods section about the introduction of bias (which is well

documented in the scientific literature, I refer the authors to this months AMA News as one of many articles) which may occur when the data is collated, collected and analyzed by industry personnel. While this cannot be proven, it must at least be discussed and the potential for bias stated. We do not have disclosures of the authors or the surgeons in the multiple centers who participated, and this should have been clearly identified.

To eliminate bias, only one of the co-authors was a clinical investigator. Since this is a clinical IDE study sponsored by a company, only the company would have all the data in its database—data which is reviewed by FDA auditors.

Was this IRB approved at all centers? If not, why? Was consent obtained in all patients prior to inclusion into the study? All questions which should be answered via the methods section.

Of course since this study was an IDE study, IRB approval and informed consent was obtained. Text was added to the revised manuscript to state this.

There is no data given for the economic impact of the use of this product (does the cost to the insurance company or patient justify it's use at this point?) Yes, OR time is greater if a bone graft is taken, and blood loss slightly higher, but patient satisfaction was actually higher (although not statistically significant) in the control patients. This fact is very important, but glossed over and not discussed, as it should be.

An economic analysis is beyond the scope of this study and would require much more data than can be presented here. Besides, this product is not FDA approved and any economic analysis would be purely academic.

The methods section is grossly lacking. There is no control for diagnosis. What were the entry criteria? This is really a consecutive series of cases using a specific product versus autograft. The authors state that degenerative disc disease was the diagnosis in all cases, yet in the results section discuss spondylolisthesis, spondylolysis as well as degenerative disc disease, but no data is given as to the breakdown of the two groups. Did all of the investigational patients have spondylolisthesis or visa versa? This may impact the results.

The revised manuscript makes the indications section more clear and says that spondylolisthesis patients could be entered into the study.

The definition of fusion is not clearly defined and the lucency of the implant data needs to be better delineated and quantified. The concept that reoperations, if felt to be *clinically* failed fusions, were so documented is not logical, and not *scientifically* based.

The definitions used were the same as given by the FDA. We did not change the definitions.

The postoperative recovery of patients was not controlled and very well in such a small group affected the outcome. For example, if all patients in the control group

were ambulated earlier than the investigational group a higher pseudo rate may have an effect.

The study protocol allowed the surgeons to decide the post-op recovery. [NOTE: Is this true?]

This group of patients overall had a very high rate of reoperation, and is very concerning, and bears further discussion. This rate is much higher than the literature would suggest. The author's statements about the effects of isolated PLIF procedures decreasing biomechanical stability of the motion segment is in fact true, and when the facet joints are compromised instability results. This operation is not recommended unless posterior stability is provided by supplemental instrumentation and is likely why the failure/reoperation rate was so high. The exceedingly high reoperation rate needs to be clearly discussed. Based upon these results, the authors should recommend abandonment of the procedure.

We believe the revised manuscript and its closing sentence addresses this point.

IF the shortcomings and bias of this manuscript are clearly incorporated it may have benefit to the readership. As it stands it is an advertisement for a specific product without significant scientific merit.

The purpose of the paper was not to evaluate the viability of using stand-alone cylindrical PLIF cages. Instead, its purpose was to investigate the feasibility of using rhBMP-2 to replace autograft in a PLIF procedure. We feel that our comments in the discussion is appropriate—more research is needed, and if performed should be carried out making the

changes in the protocol described. We do not believe the revised or original paper is an advertisement for a specific product. In general though, the data show reasons to be encouraged and cautioned about in the use of rhBMP-2 in PLIF procedures. Encouraged because the need is so great and the preliminary data are trending favorably, but cautionary in nature because of the occurrence of posterior bone formation.

We have modified the revised manuscript to include some language advising the reader that this use is not FDA approved and its use is not recommended by the method described. If the reader decides to use BMP in this manner anyway, extreme caution should be taken (like countersinking the cages) and the patients carefully followed.

Please let us know if you need us to clarify anything else in this manuscript, for we feel that the changes made now make this paper acceptable for publication.

Thank you.

Sincerely,

Ken Burkus, M.D.

From:	Treharne, Rick
Sent:	Wednesday, May 28, 2003 06:54:08 PM
To:	Burkus, J. Kenneth
CC:	Bearcroft, Julie
Subject:	PLIF paper
Attachments:	PLIF BMP paper.submited 5.28.03 JJ.doc; Posterior Lumbar Interbody Fusion-Revised.doc; Spine Journal Manuscript.doc

I said I wanted to get you a reply by today for the response to the PLIF paper since I am leaving town tomorrow. Attached on the left is a marked up copy for your review. The copy in the middle is a cleaned up version. I understand that Julie is still triple checking some of the data and she may have a few more changes. If so, she will get them to you.

The document on the right is a draft letter to The Spine Journal replying to address the reviewers' comments.

Two questions though: it appeared that the references were in random order rather than by order of appearance or alphabetical. I added two more and added them to the end. Which way is right? Maybe Carol Binns can put them in the order of appearance or we can reorder them if you know which way they go. Also, I noticed that Reference 10, one of your articles, does not have a volume number. Please add that if you have it. (A new Table 4 was added in response to one of the reviewer's comments, by the way.) Also, look for a note in the draft letter response. There is one clinical question about post-op treatment. If you do not know the answer, Charlie Branch will. I took a guess as to the correct response.

Thanks for letting me help out with this. This was fun...Rick

Posterior Lumbar Interbody Fusion Using rhBMP-2 with Cylindrical Interbody Cages

Regis W. Haid, Jr., MD*

Charles L. Branch, Jr., MD†

Joseph T. Alexander, MD‡

J. Kenneth Burkus, MD§

*Professor, Department of Neurosurgery, Emory University School of Medicine, Atlanta, Georgia

†Professor and Chair, Department of Neurosurgery, Wake Forest School of Medicine, Winston-Salem, North Carolina

‡Assistant Professor, Department of Neurosurgery, Wake Forest School of Medicine, Winston-Salem, North Carolina

§Spine Surgeon, The Hughston Clinic, Columbus, Georgia

Address correspondence and reprint requests to J.K. Burkus, MD, The Hughston Clinic, [redacted]

Deleted: 05/28/200305/28/200302/2002 003

ABSTRACT

Background context: In a large series of human patients undergoing open anterior lumbar interbody fusion with a tapered titanium fusion cage, rhBMP-2 on a bovine collagen sponge has been shown to decrease operative time and blood loss, to promote osteoinduction and fusion, and to be a safe and effective substitute for iliac crest harvesting.

Purpose: The purpose of the study was to determine the clinical and radiographic outcomes in patients treated for single-level degenerative lumbar disc disease with a posterior interbody fusion using stand-alone cylindrical threaded titanium fusion cages with either autogenous bone graft or rhBMP-2 and an absorbable collagen sponge carrier.

Study design/setting: In a, prospective, randomized, nonblinded, 2-year study at 14 investigational sites, 67 patients underwent posterior lumbar interbody fusion using two paired cylindrical threaded titanium fusion devices. Patients were randomly assigned to one of two groups: one received recombinant human bone morphogenetic protein-2 (rhBMP-2) on a collagen sponge carrier, the other autogenous iliac crest bone graft.

Patient sample: Between March 1999 and December 1999, 67 patients with symptomatic, single-level degenerative lumbar disc disease of at least 6 months duration underwent a single-level posterior lumbar interbody fusion.

Outcome measures: Clinical outcomes were measured using low back and leg pain numerical rating scales, the Short Form 36, Oswestry Low Back Pain Disability Questionnaire, and work status. Plain radiographs and computed tomographic scans were used to evaluate fusion at 6,12 and 24 months after surgery. For comparisons between the groups for continuous variables, *P*-values are from ANOVA, and for categorical variables, they are from Fisher's exact tests or chi-

Deleted: 05/28/2003|05/28/2003|02/2/2003

square tests. For changes (improvements) from the preoperative within each group, the *P* values are from paired *t* tests.

Methods: In this prospective nonblinded study, 67 patients were randomized into 2 groups that underwent interbody fusion using two cylindrical threaded fusion cages: the investigational group (34 patients) who received rhBMP-2 on an absorbable collagen sponge and a control group (33 patients) who received autogenous iliac crest bone graft.

Results: The mean operative time and blood loss for the investigational rhBMP-2 group was 2.6 hours and 322.8 mL, respectively. For the autograft control group, these values were 3.0 hours and 372.7 mL. Although not statistically different, at 24 months, the investigational group's fusion rate of 92.3% was higher than the control's at 77.8%. At all postoperative intervals, the mean Oswestry, back and leg pain scores, and physical components of the SF-36 improved in both treatment groups compared with preoperative scores. A statistically significant difference in the change in back pain was found at 24 months for the investigational group. In the control group, two adverse events related to harvesting of the iliac crest graft occurred in two patients (6.1%),

Deleted: %), and, at 24 months after surgery, 3.0% of the patients still reported graft site discomfort.

Conclusions: Although not statistically different, the investigational group had shorter average operative times and less blood loss. At 24 months, this group had a fusion rate that was more than 14 percentage points greater than the control group. All clinical outcome measurements that were studied showed, on average, greater improvement in the investigational (rhBMP-2) patients with a statistically significant improvement in back pain. Overall results show that the use of rhBMP-2 can eliminate the need for harvesting iliac crest graft and may be an equivalent or better replacement for autograft for use in successful posterior lumbar interbody fusions. Further studies of the use of rhBMP-2 in PLIF cage procedures are needed.

Deleted: a positive trend for being

Deleted: 05/28/200305/28/200302/28/2003

Key words: posterior lumbar interbody fusion, bone morphogenetic protein, osteoinduction, radiography, interbody fusion cages

Deleted: 05/28/200305/28/200302/2003

INTRODUCTION

Posterior lumbar interbody fusion (PLIF) is an effective treatment for patients with symptomatic degenerative disc disease, spondylolisthesis, and other painful discogenic syndromes. Fusion of the degenerative and unstable lumbar spinal motion segment can give significant relief from this disabling and often progressive condition.[1–4] PLIF limits the extent of posterolateral soft tissue exposure, muscle stripping, and injury. With this technique, the surgeon uses the traditional posterior approach to the lumbar spine; however, dissection is limited laterally to the facet joints. Through this approach, direct neural decompression can be completed, disc space height and sagittal balance can be restored, and intervertebral grafts can be placed in a biomechanically advantageous position.

Lumbar spine stabilization procedures that limit the extent of posterior spinal muscle exposure have some significant advantages. With PLIF surgical techniques, the fusion bed is within the disc space, which eliminates the exposure of the transverse processes. The PLIF approach to the lumbosacral spine enables the surgeon to re-establish the normal anatomic alignment and the relationships of the spinal motion segment while avoiding excessive injury to the posterior paravertebral muscles.[2-4, 13, 24]

Cloward [1] presented his technique for this innovative procedure in 1953. In his surgical technique, he described using a wide laminectomy and facetectomies that would allow for the placement of large structural bone grafts in the denuded and meticulously prepared disc space. Later, Lin and associates [2] modified this intervertebral grafting technique of structural grafts.

Deleted: 05/28/200305/28/200302/28/2003

This modified PLIF technique involves filling the disc space with cancellous bone strips, allowing for preservation of a portion of the posterior elements and avoiding the complication of insertion of large structural grafts. Additional modifications of the bone graft technique and bone graft materials have been made. Kuslich et al. [3] and Ray [4] introduced the idea of using threaded interbody fusion cages inserted through a PLIF approach as a means of stabilizing the lumbar motion segment, increasing rates of fusion and improving clinical outcomes.

Recombinant human bone morphogenetic protein type 2 (rhBMP-2) [5] applied to an absorbable collagen sponge carrier has been shown to promote osteoinduction and fusion in the lumbar spine [6-9]. In a large series of patients who underwent stand-alone anterior lumbar interbody fusion with fusion cages, rhBMP-2 was shown to enhance rates of fusion, reduce surgical time, and improve clinical outcomes [10,11] To further evaluate this method of bone graft replacement, we evaluated the clinical and radiographic outcomes at 24 months of 67 patients who underwent a single level PLIF. We compared the outcomes in the investigational patients (rhBMP-2) with those in the control patients (autogenous bone).

MATERIALS AND METHODS

Study Design. Between March 1999 and December 1999, 67 patients* with degenerative disc disease underwent surgery in this prospective, randomized, non-blinded, FDA-approved study at 14 investigational sites. All sites had local Investigational Review Board approval and the

* Although the study was originally planned to enter hundreds of patients, some preliminary CT-scans at 6 months of early patients revealed bone resorption to the PLIF cages. Out an abundance of caution, enrollment was suspended. By the time it was determined that the radiographic finding did not affect clinical outcome, the use of stand alone PLIF cages had gone out of favor and the study was not restarted.

Deleted: 05/28/200305/28/200302/20/2003

patients entered into the study gave their informed consent. All patients underwent a single-level posterior lumbar interbody fusion with two paired INTER FIX™ devices (Medtronic Sofamor Danek, Memphis, TN). The interbody fusion cages were used as stand-alone construct in the disc space from L2 to S1, with the majority being L4-L5. Patients were randomly assigned in a 1:1 manner to one of two groups: the investigational group who received rhBMP-2 on an absorbable collagen sponge carrier and the control group who received autogenous iliac crest bone graft taken from the posterior approach. INFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, TN) is the trademarked name for recombinant human bone morphogenetic protein type 2 applied to an absorbable collagen sponge.

Patient Data. Preoperatively, all patients had symptomatic, single-level degenerative lumbar disc disease and symptoms of disabling low back or leg pain, or both, of at least 6-months duration that had not responded to nonoperative treatment. Patients could also have up to Grade I spondylolisthesis. The investigational, or rhBMP-2, group comprised 34 patients, and the control group comprised 33 patients. The two treatment groups were similar demographically (Table 1). No statistically significant differences ($P < 0.05$) were found for any of the preoperative variables.

Clinical and Radiographic Outcome Measurements. Patient assessments were completed preoperatively, during hospitalization, and postoperatively at 6 weeks and at 3, 6, 12, and 24 months. Clinical outcomes were assessed using back, leg, and graft-site pain questionnaires, Short Form (SF-36), Oswestry Low Back Pain Disability Questionnaire, and work status. Back and leg symptoms were assessed separately on a visual analog scale. The intensity of pain and

the duration of pain in back and leg symptoms were measured on a ten-point numeric rating scale. Adding the numeric rating scores for pain intensity and pain duration allowed examiners to derive a composite back and leg pain score, which ranged from 0 (no pain) to 20 (maximum pain).

Radiographs and computed tomography (CT) scans were used to evaluate fusion at 6, 12, and 24 months after surgery [12]. Standing lateral and flexion-extension lateral radiographic views were obtained at each follow-up interval. Thin-cut 1-mm CT scans were taken at 6, 12 and 24 months. Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent, blinded radiologist was used to adjudicate conflicting fusion findings. Fusion was defined as an absence of radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation of less than 5° on flexion-extension radiographs, and continuous bone growth connecting the vertebral bodies. Patients who had secondary surgeries because of persistent low back symptoms and clinically suspected nonunions were considered as having failed fusions and were classified as failures in all fusion calculations, regardless of their independent radiologic assessment.

Clinical and Radiographic Follow-up. The rate of patient return for follow-up was at least 89.6% at all postoperative periods. At 12 months, the rate of patient return for both treatment groups was at least 90%. At 24 months, the follow-up rate for the investigational group was 89.6% and the control group's rate was 100%.

Surgical Technique

Deleted: 05/28/200305/28/200302/2003

An open posterior interbody fusion procedure was carried out in each patient. Preoperatively, the patient's disc space was templated to determine the appropriate intraoperative disc space distraction and cage size. Plain radiographs were reassessed to determine normal disc space height of the adjacent spinal motion segments. Axial CT scans or MR images were used to establish the anterior-posterior dimension of the disc space to ensure proper cage sizing.

The patient was placed in the prone position on padded bolsters that support the chest and pelvis and suspend the abdomen. Care was taken to extend the pelvis to ensure that lumbar lordosis was preserved. The operating room table accommodated plain radiographs or fluoroscopy.

We performed a complete laminectomy with facetectomies or extensive bilateral laminotomies and facetectomies with preservation of the midline elements in each patient. The lateral borders of the disc were exposed along with the traversing and exiting nerve roots. Bilateral annulotomies were made and a complete discectomy was carried through these annular windows. The annulotomies were placed lateral to the dural tube. The midportion of the lateral annular window was centered adjacent to the medial wall of the pedicle. The anterior and lateral walls of the annulus were preserved; the entire nucleus was removed. Cartilaginous end plates were resected using curettes.

Reduction of sagittal and frontal plane deformities was achieved through disc space height restoration and annular tensioning. Inserting progressively larger dilators into the collapsed disc restored disc space height and the normal sagittal contours of the spine.

Deleted: 05/28/200305/28/200302/20/2003

The vertebral end plates were prepared with reamers that uniformly cut a channel through the adjacent bony end plates. Great care was taken to visualize and gently retract both the traversing and exiting nerve roots. A tubular reamer guide that was impacted into the disc space protected these soft tissue elements before reaming. Care was taken to ensure that the end plate cuts were made parallel and equally into each end plate.

The INTER FIX™ cages were packed with either the rhBMP-2 soaked sponges or morcellized autograft before they were inserted. The cages were inserted sequentially in the disc space and away from any soft tissue or neural elements. The cages were not routinely recessed within the disc space. The majority of the cages were left flush to the posterior cortical wall of the vertebral bodies. Their position was assessed intraoperatively with plain radiographs or fluoroscopy.

Iliac crest bone graft harvesting. The control group received autogenous iliac crest graft placed within the cages. The bone graft was harvested from the outer table of the iliac wing. The graft was morcellized using a rongeur and was tightly packed into the cages before their insertion.

RhBMP-2 preparation. The rhBMP-2 was reconstituted using sterile water and was used as a single dose of 1.5 mg/mL in all study patients. The 1.5 mg rhBMP-2/mL solution was applied to a bovine collagen sponge and allowed to bind to the sponge for 15 minutes. The dose of rhBMP-2 varied by patient depending on cage size, with the total dose ranging from 4.0 mg to 8.0 mg. The rhBMP-2 soaked sponge was then placed in the hollow central portion of the INTER FIX™

Deleted: 05/28/200305/28/200302/28/2003

device before its insertion into the prepared disc space. No additional sponges were placed outside of the devices. No autogenous grafts were used in the investigational group.

Postoperatively, patients were placed in a soft lumbar corset. The treating physician decided when the patient would advance in activities. Isometric strengthening and exercise programs were started at six weeks after surgery.

Statistical Methods

The data from this clinical trial were analyzed using the statistical software package SAS® version 6.12. For comparisons between the groups for continuous variables, *P*-values are from ANOVA, and for categorical variables, they are from Fisher's exact tests or chi-square tests. For changes (improvements) from the preoperative within each group, the *P*-values are from paired t-tests.

RESULTS

Surgery

The mean operative time, average blood loss, and average hospital stay were less for the investigational group than for the control group (Table 2). None of these differences between treatment groups was statistically significant, although the time of surgery approached

Deleted: 05/28/200305/28/200302/10/2003

Deleted: 0

significance ($P = .065$). No unanticipated device-related adverse events occurred in either treatment group.

Complications

Vascular events. One control patient developed deep venous thrombosis and was treated with anticoagulation medications.

Neurological events. Three investigational (8.8%) and 2 controls (6.1%) had dural tears. As for neurological complications: in the investigational patients 16 events occurred in 14 patients; while in the control 18 events occurred in 14 patients.

Formatted

Iliac crest graft site. In the control group, adverse events related to harvesting of the iliac crest graft were identified in two patients (6.1%). These events included one case of pain and one hematoma. Neither of these patients required additional surgery. Obviously, no graft site adverse events occurred in the investigational group since the use of rhBMP-2 precluded the need to harvest bone graft.

The level of postoperative pain and morbidity associated with the iliac crest graft harvesting was measured using numeric rating scales for pain intensity and duration (Figure 1). After surgery, all of the control patients experienced hip donor site pain. The highest levels of pain were noted immediately after surgery with a mean score of 11.6 points out of 20 points. The percentage of patients experiencing pain decreased over time; however, at 24 months after surgery, 60% of the control patients still experienced pain (i.e., had scores greater than 0). At two years, the graft site

Deleted: 05/28/200305/28/200302/20/2003

pain scores averaged 5.5 points out of 20 and 13.3% of the patients still felt that the appearance of the graft site bothered them some. ,

Deleted: and 3.0% of the patients still reported graft site discomfort.

Antibody Testing

Antibody results. Antibodies to rhBMP-2, bovine Type I collagen, and human Type I collagen were evaluated preoperatively and 3 months postoperatively using enzyme-linked immunosorbent assays (ELISAs). None of the patients in either group tested positive for antibodies to rhBMP-2 or human Type I collagen. Authentic (>3 times baseline) bovine Type I collagen antibody formation occurred in 3 investigational and 5 control patients. GELFOAM sponge was used in 15 of the 34 (44%) investigational patients. Of these 15, 2 developed antibody formations to bovine collagen. GELFOAM sponge was also used in 20 of 33 (61%) of the controls. Of these 20, 7 had antibody formation to the bovine collagen. Of the 3 investigational patients that had elevated antibodies, only one had GELFOAM sponge used. Of the 5 control patients who had bovine collagen antibodies, only 2 had GELFOAM sponge used. Thus, there is no obvious correlation between GELFOAM sponge use and antibody formation. No negative clinical consequence to the positive bovine collagen antibody test results was evident in any of the patients; and the fact that the bovine antibody response occurred as often in the investigational group as the control shows that the bovine collagen sponge used to deliver the rhBMP-2 is not the cause of the antibody reaction. A similar result was found when the same carrier and dose of rhBMP-2 were used inside cages implanted anteriorly [7, 10].

Deleted: The incidence of

Deleted: in the investigational group

Deleted: was 13.3% whereas the incidence in the control group was 35.7%. No negative clinical consequence to the positive collagen antibody test results was evident.

Formatted

Deleted: 05/28/200305/28/200302/20/2003

Clinical Outcomes

Oswestry Disability Questionnaire scores. The Oswestry Low Back Pain Disability Questionnaire measured pain associated with activities. The Oswestry Questionnaire was administered preoperatively as well as at each postoperative visit. At all postoperative visits, both treatment groups demonstrated highly significant improvements as compared with the preoperative scores (Figure 2). At all postoperative time intervals after the first 6-week follow-up period, the investigational group showed greater improvements over the control group in the mean overall Oswestry scores. At last follow-up at 24 months, the mean improvements in the Oswestry scores were 29.6 points in the investigational group and 24.9 points in the controls (Figure 2). In the investigational group, 69% of patients showed an improvement of at least 15 points in their disability scores at 12 months after surgery as compared with 55.6% of patients in the control group. At 24 months, the 76.0% of the investigational group was improved and compared favorably with 64.3% improved in the control group (Table 3).

Back Pain. The mean back pain scores at all postoperative periods were improved from the preoperative mean values for both treatment groups. The mean improvements in back pain scores at all five postoperative intervals studied were greater for the investigational group than for the control autograft group (Figure 4). At 24 months, the average improvement in back pain in the investigational group was almost twice that of the control group (9 point improvement vs. 4.5 point improvement). This difference was highly significant with a *P* value of.009.

Deleted: 0

Deleted: 05/28/200305/28/200302/20/2003

Leg Pain. Leg pain was assessed in a similar manner using a 20-point numeric rating scale that reflects both the intensity and duration of painful symptoms. Mean leg pain scores improved significantly after surgery in each group (Figure 5). At each study interval, average leg pain scores were less (better) in the investigational group when compared with the control group. Similarly, the investigational group also showed higher average improvement scores at each interval studied. At 24 months, the average improvement in leg pain was 7.7 points in the investigational group compared to 6.5 points in the control group. This difference was not statistically significant.

Short Form SF-36. At all postoperative follow-up intervals, the investigational group showed greater improvement in the physical component of the short form SF-36 when compared with the controls (Figure 6).

Neurological Status. Preoperatively and at all five postoperative time points, the motor, sensory, reflexes, and straight-leg-raise measurements were essentially the same for both treatment groups and showed no statistical differences. At 24 months, using the protocol criteria for determining overall neurological success, which represents a combination of the 4 neurological measurements, both groups had 100% success. Table 3 contains the change from preoperative results at 24 months for the motor, sensory, reflex, and straight-leg-raise measurements.

Work Status. Many factors affect a patient's work status, such as the nature of the work performed and ability of the work place to accommodate work restrictions. Before surgery, only 26.5% of the investigational group was employed while more than 45.5% of the control patients

Deleted: 05/28/200305/28/200302/20/2003

were employed (Table 3). For patients who were working before surgery, the median return-to-work interval was 43 days in the investigational group and 137 days in the control group. Although marked, this difference was not statistically significant. At last follow-up, more people in the investigational treatment group were working than were working before their surgery. At 2 years after surgery, 12 patients in the investigational group were employed while only 9 were employed before surgery. In the control group, 15 were working before surgery and 14 were working at 2 years after surgery. In other words, the percent of the investigational patients working went from 26.5% before surgery to 35.3% at two years, while in the control group the rate went from 45.5% to 42.4%. Although none of these changes are statistically significant, the trend is promising and may be reflective of the statistically significant difference of lower back pain in the investigational patients.

Patient Satisfaction. At 12 and 24 months after surgery, the results were similar in each treatment group (Table 4). At 24 months, 72.4% of the investigational patients and 80.0% of the control patients were satisfied (answering definitely true or mostly true) with their surgical outcomes. In the investigational group, 69.0% said they would undergo surgery again (answering definitely true or mostly true) compared with 83.3% of the control patients who would undergo surgery again. In the investigational group, 72.4% believed that they were helped as much as they had expected to be from the surgery; 70.0% of the control group felt they had been. None of these subjective differences was statistically significant.

Radiographic Outcomes

Deleted: 05/28/200305/28/200302/20/2003

Cage placement. Cage placement was assessed on both plain radiographs and thin-cut CT scan. The CT scans were found to reflect more accurately the position of the cage in relation to the spinal canal posteriorly and neuroforamina laterally. No differences between the two patient groups regarding cage placement were detected. Only 6% of patients in each group (2/34 in the investigational group; 2/33 in the control group) showed cages that were countersunk 3 mm or more from the posterior margin of the vertebral body. Approximately one-third of patients in each group had cages that extended into the spinal canal on postoperative CT studies (11/34 in the investigational group; 10/33 in the control group). The remainder of the cages were placed either flush to the posterior cortex of the vertebral bodies or were recessed by only 2 mm or less.

Sagittal Plane Balance. Nearly one-third of the patients (19/67; 28%) had some sagittal plane imbalance after surgery. At their last follow-up, 6 patients had some residual spondylolithesis from failure to fully reduce the deformity at the time of surgery (up to Grade I spondylolisthesis was allowed) and 2 patients developed spondylolithesis after surgery. Eleven patients had residual retrolithesis after surgery.

Intradiscal bone formation

Fusion status of the study patients was evaluated on plain radiographs and CT scans. At 6 months after surgery, 93.1% of patients in both the investigational and control groups had evidence of fusion. At 12 months, the fusion rate in the investigational group dropped to 85.2% while the control group maintained a fusion rate of 92%. This decrease in fusion rate in the investigational group at 12 months appears to be artificially low because 7 patients who were

Deleted: 05/28/200305/28/200302/28/2003

evaluated at 24 months could not be evaluated at 12 months because of the unavailability of reconstructed CT views or poor quality films.) At 24 months, the investigational group had a 92.3% fusion rate, which was more than 14 percentage points higher than that of the control group (77.8%). While this difference was not statistically significant, it does show a positive trend in favor of the investigational group.

Bone formation outside the disc space

The thin cut 1.0 mm CT scans and plain radiographs were used by multiple reviewers to examine for new bone formation adjacent to the interbody fusion cages in 32 of 34 investigational patients and 31 of 33 controls. (The 4 missing cases were either not available because they were not taken or were too poor a quality to read.). New bone formation extending outside the disc space and into the spinal canal or neuroforamina was found in 28 patients (24 investigational and 4 control group patients). According to the Fisher's Exact Test, this difference is statistically significant (P<.0001). Despite the statistical difference, this unexpected posterior bone formation was not correlated to a recurrence or increase in leg pain from the pre-op state. In 10 (29%) investigational and 12 (36%) control patients, the leg pain at some point in the follow-up increased at least one point (on a 20 point scale) over the pre-op value. Interestingly, 7 of the 22 control patients with increased leg pain had absolutely no bone formation posteriorly. This last finding implies that posterior cage bone formation is not the only possible explanation of recurrent leg pain.

Deleted: identify

Deleted: 23

Deleted: 5

Deleted: 10/34;

Deleted: 12/33;

Sagittal plane balance. In the control group, 2 of the 4 patients (50%) with bone in the spinal canal had a residual unreduced spondylolithesis after surgery. New bone formation was identified in the canal posterior to the unreduced superior vertebra under the posterior longitudinal ligament and annulus. In two (2/4; 50%) patients with normal segmental sagittal plane balance in the control group, new bone formation was identified extending into the spinal canal.

In the investigational group, 12 of the 24 patients (50%) with bone in the spinal canal had some residual postoperative sagittal plane imbalance. Six patients (6/24, 25%) had spondylolithesis and 6 (6/24, 25%) had retrolithesis. In each of these patients, new bone formation occurred posterior to the unreduced vertebral body under the posterior longitudinal ligament lifted off the unreduced vertebral body. Twelve patients in the investigational group (12/32; 38%) had a normal postoperative segmental sagittal plane balance and new bone formation in the spinal canal.

Cage placement. In the investigational group, cage placement was strongly associated with the development of bone in the spinal canal. In the investigational group, 39% of patients with cages placed at the margin or within 2 mm of the margin of the posterior vertebral cortex developed some bone in the spinal canal. Twelve percent of patients in the control group whose cages were placed within 2 mm of the vertebral margins developed bone in the spinal canal. No patient in either group whose cage had been recessed by 3 mm or more developed bone in the spinal canal.

Deleted: 05/28/200305/28/200302/20/2003
Deleted: 1
Deleted: 5
Deleted: 25
Deleted: 0
Deleted: four
Deleted: 10
Deleted: 23
Deleted: 43
Deleted: Five
Deleted: 5/23
Deleted: 22
Deleted: 5
Deleted: 5/23
Deleted: 22
Deleted: Thirteen
Deleted: 13/34

Secondary Surgical Procedures

In the investigational group, 7 of 34 (20.6%) had some type of secondary surgical procedure. Three (8.8%) had second spinal surgery failures; 3 (8.8%) had second spinal surgeries, but not failures; and 1 (2.9%) had an unrelated second surgery (i.e., breast surgery). Of the 3 secondary surgery failures, 2 patients received supplemental fixation for presumed pseudarthrosis.

In the control group, 9 of 33 (27.3%) patients had some type of secondary surgical procedure; 3 (9.1%) had second spinal surgery failures; 3 (9.1%) had second spinal surgeries but not failures; and 3 (9.1%) had an unrelated secondary surgery (i.e., carpal tunnel, knee, coronary artery bypass graft surgery). Of the 3 secondary surgery failures, 3 control patients received supplemental fixation for presumed pseudarthrosis.

DISCUSSION

Threaded cylindrical cages represent a new, distinct class of segmental spinal fixation devices. These devices were not designed as spacers that require segmental stabilization; rather, they were designed as stand-alone intervertebral devices that function as an "instrumented PLIF." Threaded interbody devices are biomechanically different from interbody spacers. Biomechanical studies have shown that cage size has some significance in stand-alone cage fusions; however, stand-alone cages do not significantly increase spinal stiffness in studies using human cadavers [13-18]. This finding largely explains the current clinical trend toward using posterior segmental fixation in PLIF constructs.

Deleted: 05/28/200305/28/200302/20/2003

Larger cages improve stiffness in rotation and lateral bending in a lumbar spinal motion segment; however, reduction of motion in flexion is not significantly improved with larger cages [16,17]. Larger cages require more extensive facet joint resection or complete facetectomy, which further destabilizes the spinal motion segment. A cylindrical device increases in its medial-lateral dimension equal to its increase in height, which necessitates greater mobilization and retraction of the neural elements. Retraction and mobilization of the neural element during cylindrical cage insertion has been associated with permanent neurologic injury [19,20]. The current trend in PLIF surgery is to limit neural element retraction through the use of a transforaminal surgical approach or through the use of impacted underbody spacers.

Initial clinical studies reported high rates of fusion and clinical success in certain centers. These results have not been widely reproduced. Authors of clinical and radiographic studies on stand-alone interbody implants without supplemental fixation have reported fusion rates between 83% and 100% [3,4]. Hacker [21] compared two groups of patients treated for disabling back pain; one group was treated with a stand-alone PLIF using BAK implants, and the other group was treated with combined anteroposterior fusion. He found equal patient satisfaction between the two groups. Ray [4] presented a prospective series of 236 patients treated with stand-alone interbody fusion and reported a 96% fusion rate at 2 years after surgery. These fusion criteria did correlate with improved clinical outcomes. In this study group, only 65% had good-to-excellent clinical outcomes on the Prolo scale, and 14% had a poor result.

Deleted: 05/28/200305/28/200303/28/2003

However, PLIF procedures or any other type of spinal fusion procedure that uses autograft from the iliac crest come with a price in pain for the patient. Figure 1 shows that the iliac crest graft site pain in this study was found to be similar to that measured in the same way for a larger study of the LT-CAGE device [10] with two exceptions. First, in this study, the pain at 24 months was 5.5 on a scale of 20, while in the anterior fusion LT-CAGE study, the value was 1.8. Second, in this posterior INTER FIX study, 60% of the patients had some pain at 24 months, while in the LT-CAGE study 32% had. Although these were two separate studies using different surgeons, different numbers of patients (30 versus 118), and different sizes of cages (the INTER FIX cage is cylindrical and the LT-CAGE version is a smaller volume tapered design), these results are consistent with a review of other studies that showed that a posterior approach to the iliac crest is more painful for the patients [22]. The pain associated with the posterior bone graft harvest may be secondary, in part, to the extensive stripping of the gluteus musculature, more extensive bone graft harvesting techniques, or injury to the sacroiliac joint. For whatever reason, the measured iliac crest graft site pain scores in this study suggest that, from the patient's point of view, the need for an autograft replacement in PLIF cylindrical cage procedures is greater than in ALIF tapered cage procedures.

We found that, regardless of the source of the bone graft, extra bone formation in the spinal canal can occur after PLIF procedures with cylindrical interbody fusion cages because it occurred in both study groups (Fig. 7). Bone formation in the spinal canal appears to be a multifactorial event. It appears to be largely dependent on cage placement and sagittal balance of the instrumented vertebral motion segment. Patients with residual sagittal plane imbalance form bone behind the unreduced vertebral segment. This may be the result of lifting of a periosteal

Deleted: 05/28/200305/28/200302/20/2003

flap along the posterior cortex of the listhesed vertebral body (Fig. 8). Cages that were not recessed within the confines of the disc space margins were also associated with bone formation in the spinal canal (Fig. 9). Thin-cut CT scans were essential to determine cage placement and new bone formation postoperatively.

RhBMP-2 on an absorbable collagen sponge has been shown to induce bone formation in the intervertebral disc space [7,8,10,11]. A recent study has shown that this montage in this milieu routinely produces a fusion zone extending 3 mm around the cage [23]. It is not surprising that bone may extend into the spinal canal when cages containing rhBMP-2 are not recessed 3 mm or more within the confines of the disc space.

The PLIF procedure using threaded cylindrical fusion cages disrupts a wide channel, which includes the posterior margin of the disc, the posterior longitudinal ligament, and annular structures. This injury can result in adjacent bone formation, which can extend into the spinal canal. This new bone formation is best visualized on CT scan. Both the control group and investigational group exhibited bone formation outside of the disc space after this procedure.

Although not desirable, bone formation in the spinal canal does not appear to have a discernable effect on patient outcomes. Therefore, bone formation in the spinal canal after the PLIF procedure with stand-alone cylindrical interbody fusion cages appears to be primarily just a radiographic finding that is not associated with any clinical outcome. This human study seems to confirm the safety results in a canine study using rhBMP-2 on a bovine collagen sponge [25]. In that laminectomy study, the sponge was placed directly on an exposed dura. Even though bone

Deleted: 05/28/200303/28/200302/26/2003

formed, no negative outcomes were found. In both the canine and now the human study, the de novo rhBMP-induced bone formed slowly and passively, not compressing neural structures.

Because of its small size, this study should be considered a pilot study of the ability of a bone morphogenetic protein to replace autograft in a stand-alone PLIF cage procedure. Even though the number of patients was small, we found a statistically significant improvement in back pain in the rhBMP-2 investigational patients. Although the other differences were not statistically significant, assessment of just the surgical and clinical outcome data at two years (Tables 2 and 3) and the averages of all of the outcomes measured (except for 2 of the 3 subjective patient satisfaction questions) favored the investigational group. These findings suggest that a larger study would show statistical equivalence or improvement in all clinically important outcomes. Predicting such a result can be based not only on the data in the pilot study presented here but also on the large-scale human clinical trials of spinal surgery and rhBMP-2 already conducted. In a recent 679-patient analysis, the same protein used in the same concentration inside metal cages for the same lumbar indication but from an anterior approach was shown to be superior to autograft [11]. The direction of implantation of a cage should not affect the ability of rhBMP-2 contained inside to form bone.

In conclusion, this detailed, independent review of the results, which represents the first use of osteoinductive proteins in a PLIF procedure, are encouraging. These findings along with other studies for other indications suggest that larger PLIF studies with rhBMP-2 are needed. Currently, studies are being conducted to assess the use of rhBMP-2 in transforaminal lumbar interbody fusion procedures. Additional PLIF studies are being done to evaluate placement of the

Deleted: 05/28/200305/28/200302/20/2003

BMP-soaked sponge adjacent to the anterior annulus and away from the posterior annulotomy sites. In future studies using modified surgical techniques, such as using more recessed cages to allow for extra posterior bone formation, adding steps to minimize bleeding and surgical variables, using narrower, noncylindrical cages that would be easier to put in and cause less tissue destruction, or adding secondary instrumentation may be beneficial. Modifying patient selection, such as entering patients with less vertebral slip, could also help minimize the confounding variables. All of these changes may produce more convincing evidence that INFUSE™ Bone Graft can also be used as a substitute for autograft in PLIF cage procedures.

Until those future studies are completed, the readers should be advised that at this writing the use described in this article are not FDA approved and use with rhBMP-2 as described is not recommended by the stand alone method described. If the reader decides to use rhBMP-2 in this manner anyway, extreme caution should be taken (like countersinking the cages) and the patients should be carefully followed.

Formatted
Formatted
Formatted
Formatted
Formatted
Formatted

Deleted: 05/28/200305/28/200302/20/2003

ACKNOWLEDGMENTS

Special thanks to the following doctors who were principal or co-principal clinical investigators at the 14 sites for this study. These surgeons in alphabetical order are Drs.C. William Bacon, Steven Barnes, Charles Branch, Randall Dryer, Paul Geibel, Fred Geisler, Scott Graham, Peter Holiday, Timothy Holt, Zenko Hrynkiw, Dennis Maiman, David Masel, Bruce Mathem, Christopher Meyer, Phillip Tibbs, and Frank Tomecek. The work of the Clinical Research Department at Medtronic Sofamor Danek in collecting the clinical data and performing the statistical analyses is acknowledged. D. Lynn Sanders, CCRC was instrumental in sorting and organizing radiographic data for analysis.

Deleted: ¶ Page Break REFERENCES

REFERENCES

1. Cloward RB. The treatment of ruptured intervertebral discs by vertebral body fusion. I. Indications, operative technique, after care. *J Neurosurg* 1953;10:154-168

2. Lin PM, Cautilli RA, Joyce MF. Posterior lumbar interbody fusion. *Clin Orthop* 1983;180:154-168.

3. Kuslich SD, Ulstrom CL, Griffith SL, Ahern JW, Dowdle JD. The Bagby and Kuslich method of lumbar interbody fusion. History, techniques, and 2-year follow-up results of a United States prospective, multicenter trial. *Spine* 1998;23:1267-1268.

4. Ray CD. Threaded titanium cages for lumbar interbody fusions. Spine 1997;22:667-679.

Deleted: 03/28/200305/28/200302/2003

5. Urist MR. Bone: Formation by autoinduction. *Science* 1965;150:893-899.

6. Boden SD, Schimandle JH, Hutton WC. 1995 Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. *Spine* 1995;20:2633-2644.

7. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. *Spine* 2000;25:376-381.

8. Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2. A prospective study of clinical and radiographic outcomes. *Spine* 2001;26:2751-2756.

9. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. *Spine* 1995; 20:1326-1337.

10. Burkus JK, Gornet MF, Dickman C, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. *J Spinal Disord Tech* 2002; 337-349.

11. Burkus JK, Heim SE, Gornet MF, Zdeblick TA. Is INFUSE™ Bone Graft Superior to Autograft Bone? An Integrated Analysis of Clinical Trials Using the LT-CAGE™ Lumbar Tapered Fusion Device. *J Spinal Disord Tech* 2003; 16:113-122.

Deleted: in press

12. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. *Neurosurg Focus* 2001;10:1-9.

13. Brodke DS, Dick JC, Kunz DN, McCabe R, Zbeblick TA. Posterior lumbar interbody fusion: a biomechanical comparison, including a new threaded cage. *Spine* 1997;22:26-31.

14. Dimar JR, Wang M, Beck DJ, Glassman SD, Voor MJ: Posterior lumbar interbody cages do not augment segmental biomechanical stability. *Am J Orthop* 2001;30:636-639

15. Hasegawa K, Ikeda M, Washio T, Hara T: An experimental study of porcine lumbar segmental stiffness by the distraction-compression principle using a threaded interbody cage. *J Spinal Disord* 2000;13:247-252.

16. Kettler A, Wilke HJ, Dietl R, Krammer M, Lumenta C, Claes L: Stabilizing effect of posterior lumbar interbody fusion cages before and after cyclic loading. *J Neurosurg* 2000;92:87-92

17. Lund T, Oxland TR, Jost B, Cripton P, Grassmann S, Etter C, Nolte LP. Interbody cage stabilisation in the lumbar spine: biomechanical evaluation of cage design, posterior instrumentation and bone density. *J Bone Joint Surg Br* 1998;80:351-359.

18. Rapoff AJ, Ghanayem AJ, Zdeblick TA: Biomechanical comparison of posterior lumbar interbody fusion cages. *Spine* 1997;22:2375-2379.

19. Barnes B, Rodts GE, McLaughlin MR, Haid RW Jr. Threaded cortical bone dowels for lumbar interbody fusion: Over 1-year mean follow-up in 28 patients. *J Neurosurg* 2002;95(1 Suppl):1-4.

20. Barnes B, Rodts GE, Haid RW Jr, Subach BR, McLaughlin MR. Allograft implants for posterior lumbar interbody fusion: results comparing cylindrical dowels and impacted wedges. *Neurosurgery* 2002;51:1191-1198.

21. Hacker RJ: Comparison of interbody fusion approaches for disabling low back pain. *Spine* 1997;22:660-665

22. Polly DW, Kuklo TR. Bone graft donor site pain [Abstract]. In Program and abstracts of 39th Annual Meeting of the Scoliosis Research Society; September 18-21,2002; Seattle, WA; p. 178.

Deleted: 05/28/200305/28/200302/20/2003

23. Burkus JK, Dorchak JD, Sanders DL. Radiographic assessment of interbody fusion using recombinant human bone morphogenetic protein type 2. *Spine* 2003; 28:372-377.

24. Palm WJ, Rosenberg WS, Keaveny TM: Load transfer mechanisms in cylindrical interbody cage constructs. *Spine* 2002;27:2101-7.

25. Meyer RA, Gruber HE, Howard BA, et al. Safety of recombinant human bone morphogenetic protein-2 after spinal laminectomy in the dog. *Spine* 1999;24:747-54.

Deleted: in press

Formatted

Table 1. Patient Demographic Information.

Variable	Investigational (n=34)	Control (n=33)	*P* value *
Age (years) [mean (range)]	46.3 (25.8 – 66.1)	46.1 (28.5 – 70.9)	,928
Weight (lb) [mean ± SD]	180.5 ± 38.4	172.8 ± 35.7	,400
Sex [n (%)]			
Male	17 (50)	15 (45.5)	,808
Female	17 (50)	18 (54.5)	
Workers' compensation [n (%)	8 (23.5)	9 (27.3)	,784
Spinal litigation [n (%)]	3 (8.8)	1 (3.0)	,614
Tobacco used [n (%)]	18 (52.9)	15(45.5)	,628
Alcohol use [n (%)]	15 (44.1)	9 (27.3)	,204
Preoperative work status [n (%) working]	9 (26.5)	15 (45.5)	,131
Previous back surgery [n (%)]	12 (35.3)	13 (39.4)	,803

For continuous variables, *P* values are from ANOVA, and for categorical variables, they are from Fisher's exact test.

Deleted: 05/28/200305/28/200302/20/2003

Deleted: 0

Deleted: 0

Deleted: 0

Deleted: 0

Deleted: 0

Deleted: 0

Deleted: 0

Deleted: 0

Table 2. Surgical Parameters.

Variable	Investigational group	Control group
Mean operative time	2.6 hours	3.0 hours
Average blood loss	322.8 ml	372.7 ml
Average hospital stay	3.4 days	5.2 days

Table 3. 24-Month Clinical Outcome Parameters

	Investigational	Control
Improvement Points in Oswestry Score	29.6	24.9
% Patients with ≥15 point Oswestry Improvement	69%	55.6%
% Patients with Oswestry Improvement	76.0%	64.3%
Back Pain Improvement from preop (Points)	9*	4.5
Leg Pain Average Improvement from preop (Points)	7.7	6.5
Motor change from preop	4.5	2.8
Sensory Change from preop	8.0	2.8
Reflex change from preop	7.0	5.4
Straight leg raise change from preop	48.0	39.3
Net change in % patients working	+8.8%	-3.1%
Median return to work time	43 days	137 days
Fusion rate	97.3%	77.8%

*Statistically significant difference ($P < .05$)

Deleted: 05/28/200305/28/200302/20/2003

Table 4. Summary of Patient Satisfaction with Results of Surgery at 24 Months
[Number (%) of Patients]

Variable	Investigational	Control	P-value*	Deleted: p
I was satisfied with the results of my surgery.				
Definitely True	15 (51.7)	16 (53.3)	.388	Deleted: 0
Mostly True	6 (20.7)	8 (26.7)		
Do not Know	3 (10.3)	5 (16.7)		
Mostly False	3 (10.3)	0 (0.0)		
Definitely False	2 (6.9)	1 (3.3)		
I was helped as much as I thought I would be by my surgery.				
Definitely True	13 (44.8)	16 (53.3)	.159	Deleted: 0
Mostly True	8 (27.6)	5 (16.7)		
Do not Know	3 (10.3)	8 (26.7)		
Mostly False	3 (10.3)	0 (0.0)		
Definitely False	2 (6.9)	1 (3.3)		
All things considered I would have the surgery again for the same condition.				
Definitely True	18 (62.1)	16 (53.3)	.196	Deleted: 0
Mostly True	2 (6.9)	9 (30.0)		
Do not Know	5 (17.2)	2 (6.7)		
Mostly False	1 (3.4)	1 (3.3)		
Definitely False	3 (10.3)	2 (6.7)		

Deleted: p

*P-values are from the Chi-square test.

Deleted: 05/28/200305/28/200302/20/2003

LEGEND OF FIGURES

Figure 1. Mean hip pain scores.

Figure 2. Mean improvement in Oswestry scores.

Figure 3. Mean back pain scores.

Figure 4. Mean improvement in back pain scores.

Figure 5. Mean leg pain scores.

Figure 6. Mean SF-36 PCS scores.

Figure 7. **A**. Lateral radiograph of the L3-L4 interspace three months after a PLIF procedure using autogenous iliac bone graft. The disc space height has been restored anatomically and the cages are recessed by 3 mm within the disc space. There is no bone posterior to the cages. **B**. Lateral radiograph at 24 months after the PLIF with autograft shows loss of disc space height, subsidence of the implants through the vertebral endplates and new bone formation posterior to the cages (arrows). The posterior bone formation extends into the spinal canal. **C**. Sagittal CT scan reconstruction across the L3-L4 interspace at 20 months after the PLIF using autograft confirms that there is new bone formation posterior to the implants that extend into the spinal canal (arrows). **D**. Axial CT scan across the L3-L4 interspace at 24 months after surgery shows new bone formation (arrow) extending into the spinal canal.

Figure 8. Schematic illustration of an unreduced spondylolisthesis treated by a stand-alone PLIF technique. There is elevation of the posterior longitudinal ligament with a triangular subperiosteal zone behind the unreduced superior vertebral body (shaded area). This zone commonly filled in with bone following the PLIF procedure in both the BMP and autograft treated patients.

Figure 9. **A**. Preoperative lateral radiograph shows significant disc space narrowing and radial osteophyte formation. **B**. Lateral radiograph at three months after a PLIF using rhBMP-2 on a collagen sponge carrier shows that the disc space height has been restored both anteriorly and posteriorly (arrows). The cages are recessed by less than 3 mm. **C**. Lateral radiograph at 24 months after surgery shows loss of disc space height, implant subsidence, and bone formation extending into the spinal canal (arrows). **D**. Sagittal reconstructed CT scan shows new bone formation posterior to the cages and extending into the spinal canal (arrows). **E**. Axial CT scan at 24 months after surgery shows asymmetric cage placement (arrow) within the disc space. There is also new asymmetric bone growth. There is more bone behind the more prominent centrally placed cage.

Posterior Lumbar Interbody Fusion Using rhBMP-2 with Cylindrical Interbody Cages

Regis W. Haid, Jr., MD*

Charles L. Branch, Jr., MD†

Joseph T. Alexander, MD‡

J. Kenneth Burkus, MD§

*Professor, Department of Neurosurgery, Emory University School of Medicine, Atlanta, Georgia

†Professor and Chair, Department of Neurosurgery, Wake Forest School of Medicine, Winston-Salem, North Carolina

‡Assistant Professor, Department of Neurosurgery, Wake Forest School of Medicine, Winston-Salem, North Carolina

§Spine Surgeon, The Hughston Clinic, Columbus, Georgia

Address correspondence and reprint requests to J.K. Burkus, MD, The Hughston Clinic, [redacted]

ABSTRACT

Background context: In a large series of human patients undergoing open anterior lumbar interbody fusion with a tapered titanium fusion cage, rhBMP-2 on a bovine collagen sponge has been shown to decrease operative time and blood loss, to promote osteoinduction and fusion, and to be a safe and effective substitute for iliac crest harvesting.

Purpose: The purpose of the study was to determine the clinical and radiographic outcomes in patients treated for single-level degenerative lumbar disc disease with a posterior interbody fusion using stand-alone cylindrical threaded titanium fusion cages with either autogenous bone graft or rhBMP-2 and an absorbable collagen sponge carrier.

Study design/setting: In a, prospective, randomized, nonblinded, 2-year study at 14 investigational sites, 67 patients underwent posterior lumbar interbody fusion using two paired cylindrical threaded titanium fusion devices. Patients were randomly assigned to one of two groups: one received recombinant human bone morphogenetic protein-2 (rhBMP-2) on a collagen sponge carrier, the other autogenous iliac crest bone graft.

Patient sample: Between March 1999 and December 1999, 67 patients with symptomatic, single-level degenerative lumbar disc disease of at least 6 months duration underwent a single-level posterior lumbar interbody fusion.

Outcome measures: Clinical outcomes were measured using low back and leg pain numerical rating scales, the Short Form 36, Oswestry Low Back Pain Disability Questionnaire, and work status. Plain radiographs and computed tomographic scans were used to evaluate fusion at 6,12 and 24 months after surgery. For comparisons between the groups for continuous variables, *P*-values are from ANOVA, and for categorical variables, they are from Fisher's exact tests or chi-

square tests. For changes (improvements) from the preoperative within each group, the *P* values are from paired *t* tests.

Methods: In this prospective nonblinded study, 67 patients were randomized into 2 groups that underwent interbody fusion using two cylindrical threaded fusion cages: the investigational group (34 patients) who received rhBMP-2 on an absorbable collagen sponge and a control group (33 patients) who received autogenous iliac crest bone graft.

Results: The mean operative time and blood loss for the investigational rhBMP-2 group was 2.6 hours and 322.8 mL, respectively. For the autograft control group, these values were 3.0 hours and 372.7 mL. Although not statistically different, at 24 months, the investigational group's fusion rate of 92.3% was higher than the control's at 77.8%. At all postoperative intervals, the mean Oswestry, back and leg pain scores, and physical components of the SF-36 improved in both treatment groups compared with preoperative scores. A statistically significant difference in the change in back pain was found at 24 months for the investigational group. In the control group, two adverse events related to harvesting of the iliac crest graft occurred in two patients (6.1%).

Conclusions: Although not statistically different, the investigational group had shorter average operative times and less blood loss. At 24 months, this group had a fusion rate that was more than 14 percentage points greater than the control group. All clinical outcome measurements that were studied showed, on average, greater improvement in the investigational (rhBMP-2) patients with a statistically significant improvement in back pain. Overall results show that the use of rhBMP-2 can eliminate the need for harvesting iliac crest graft and may be an equivalent or better replacement for autograft for use in successful posterior lumbar interbody fusions. Further studies of the use of rhBMP-2 in PLIF cage procedures are needed.

Key words: posterior lumbar interbody fusion, bone morphogenetic protein, osteoinduction, radiography, interbody fusion cages

INTRODUCTION

Posterior lumbar interbody fusion (PLIF) is an effective treatment for patients with symptomatic degenerative disc disease, spondylolisthesis, and other painful discogenic syndromes. Fusion of the degenerative and unstable lumbar spinal motion segment can give significant relief from this disabling and often progressive condition.[1-4] PLIF limits the extent of posterolateral soft tissue exposure, muscle stripping, and injury. With this technique, the surgeon uses the traditional posterior approach to the lumbar spine; however, dissection is limited laterally to the facet joints. Through this approach, direct neural decompression can be completed, disc space height and sagittal balance can be restored, and intervertebral grafts can be placed in a biomechanically advantageous position.

Lumbar spine stabilization procedures that limit the extent of posterior spinal muscle exposure have some significant advantages. With PLIF surgical techniques, the fusion bed is within the disc space, which eliminates the exposure of the transverse processes. The PLIF approach to the lumbosacral spine enables the surgeon to re-establish the normal anatomic alignment and the relationships of the spinal motion segment while avoiding excessive injury to the posterior paravertebral muscles.[2-4, 13, 24]

Cloward [1] presented his technique for this innovative procedure in 1953. In his surgical technique, he described using a wide laminectomy and facetectomies that would allow for the placement of large structural bone grafts in the denuded and meticulously prepared disc space. Later, Lin and associates [2] modified this intervertebral grafting technique of structural grafts.

This modified PLIF technique involves filling the disc space with cancellous bone strips, allowing for preservation of a portion of the posterior elements and avoiding the complication of insertion of large structural grafts. Additional modifications of the bone graft technique and bone graft materials have been made. Kuslich et al. [3] and Ray [4] introduced the idea of using threaded interbody fusion cages inserted through a PLIF approach as a means of stabilizing the lumbar motion segment, increasing rates of fusion and improving clinical outcomes.

Recombinant human bone morphogenetic protein type 2 (rhBMP-2) [5] applied to an absorbable collagen sponge carrier has been shown to promote osteoinduction and fusion in the lumbar spine [6-9]. In a large series of patients who underwent stand-alone anterior lumbar interbody fusion with fusion cages, rhBMP-2 was shown to enhance rates of fusion, reduce surgical time, and improve clinical outcomes [10,11] To further evaluate this method of bone graft replacement, we evaluated the clinical and radiographic outcomes at 24 months of 67 patients who underwent a single level PLIF. We compared the outcomes in the investigational patients (rhBMP-2) with those in the control patients (autogenous bone).

MATERIALS AND METHODS

Study Design. Between March 1999 and December 1999, 67 patients* with degenerative disc disease underwent surgery in this prospective, randomized, non-blinded, FDA-approved study at 14 investigational sites. All sites had local Investigational Review Board approval and the

* Although the study was originally planned to enter hundreds of patients, some preliminary CT-scans at 6 months of early patients revealed bone postrior to the PLIF cages. Out an abundance of caution, enrollment was suspended. By the time it was determined that the radiographic finding did not affect clinical outcome, the use of stand alone PLIF cages had gone out of favor and the study was not restarted.

patients entered into the study gave their informed consent. All patients underwent a single-level posterior lumbar interbody fusion with two paired INTER FIX™ devices (Medtronic Sofamor Danek, Memphis, TN). The interbody fusion cages were used as stand-alone construct in the disc space from L2 to S1, with the majority being L4-L5. Patients were randomly assigned in a 1:1 manner to one of two groups: the investigational group who received rhBMP-2 on an absorbable collagen sponge carrier and the control group who received autogenous iliac crest bone graft taken from the posterior approach. INFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, TN) is the trademarked name for recombinant human bone morphogenetic protein type 2 applied to an absorbable collagen sponge.

Patient Data. Preoperatively, all patients had symptomatic, single-level degenerative lumbar disc disease and symptoms of disabling low back or leg pain, or both, of at least 6-months duration that had not responded to nonoperative treatment. Patients could also have up to Grade I spondylolisthesis. The investigational, or rhBMP-2, group comprised 34 patients, and the control group comprised 33 patients. The two treatment groups were similar demographically (Table 1). No statistically significant differences ($P < 0.05$) were found for any of the preoperative variables.

Clinical and Radiographic Outcome Measurements. Patient assessments were completed preoperatively, during hospitalization, and postoperatively at 6 weeks and at 3, 6, 12, and 24 months. Clinical outcomes were assessed using back, leg, and graft-site pain questionnaires, Short Form (SF-36), Oswestry Low Back Pain Disability Questionnaire, and work status. Back and leg symptoms were assessed separately on a visual analog scale. The intensity of pain and

the duration of pain in back and leg symptoms were measured on a ten-point numeric rating scale. Adding the numeric rating scores for pain intensity and pain duration allowed examiners to derive a composite back and leg pain score, which ranged from 0 (no pain) to 20 (maximum pain).

Radiographs and computed tomography (CT) scans were used to evaluate fusion at 6, 12, and 24 months after surgery [12]. Standing lateral and flexion-extension lateral radiographic views were obtained at each follow-up interval. Thin-cut 1-mm CT scans were taken at 6, 12 and 24 months. Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent, blinded radiologist was used to adjudicate conflicting fusion findings. Fusion was defined as an absence of radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation of less than 5° on flexion-extension radiographs, and continuous bone growth connecting the vertebral bodies. Patients who had secondary surgeries because of persistent low back symptoms and clinically suspected nonunions were considered as having failed fusions and were classified as failures in all fusion calculations, regardless of their independent radiologic assessment.

Clinical and Radiographic Follow-up. The rate of patient return for follow-up was at least 89.6% at all postoperative periods. At 12 months, the rate of patient return for both treatment groups was at least 90%. At 24 months, the follow-up rate for the investigational group was 89.6% and the control group's rate was 100%.

Surgical Technique

An open posterior interbody fusion procedure was carried out in each patient. Preoperatively, the patient's disc space was templated to determine the appropriate intraoperative disc space distraction and cage size. Plain radiographs were reassessed to determine normal disc space height of the adjacent spinal motion segments. Axial CT scans or MR images were used to establish the anterior-posterior dimension of the disc space to ensure proper cage sizing.

The patient was placed in the prone position on padded bolsters that support the chest and pelvis and suspend the abdomen. Care was taken to extend the pelvis to ensure that lumbar lordosis was preserved. The operating room table accommodated plain radiographs or fluoroscopy.

We performed a complete laminectomy with facetectomies or extensive bilateral laminotomies and facetectomies with preservation of the midline elements in each patient. The lateral borders of the disc were exposed along with the traversing and exiting nerve roots. Bilateral annulotomies were made and a complete discectomy was carried through these annular windows. The annulotomies were placed lateral to the dural tube. The midportion of the lateral annular window was centered adjacent to the medial wall of the pedicle. The anterior and lateral walls of the annulus were preserved; the entire nucleus was removed. Cartilaginous end plates were resected using curettes.

Reduction of sagittal and frontal plane deformities was achieved through disc space height restoration and annular tensioning. Inserting progressively larger dilators into the collapsed disc restored disc space height and the normal sagittal contours of the spine.

The vertebral end plates were prepared with reamers that uniformly cut a channel through the adjacent bony end plates. Great care was taken to visualize and gently retract both the traversing and exiting nerve roots. A tubular reamer guide that was impacted into the disc space protected these soft tissue elements before reaming. Care was taken to ensure that the end plate cuts were made parallel and equally into each end plate.

The INTER FIX™ cages were packed with either the rhBMP-2 soaked sponges or morcellized autograft before they were inserted. The cages were inserted sequentially in the disc space and away from any soft tissue or neural elements. The cages were not routinely recessed within the disc space. The majority of the cages were left flush to the posterior cortical wall of the vertebral bodies. Their position was assessed intraoperatively with plain radiographs or fluoroscopy.

Iliac crest bone graft harvesting. The control group received autogenous iliac crest graft placed within the cages. The bone graft was harvested from the outer table of the iliac wing. The graft was morcellized using a rongeur and was tightly packed into the cages before their insertion.

RhBMP-2 preparation. The rhBMP-2 was reconstituted using sterile water and was used as a single dose of 1.5 mg/mL in all study patients. The 1.5 mg rhBMP-2/mL solution was applied to a bovine collagen sponge and allowed to bind to the sponge for 15 minutes. The dose of rhBMP-2 varied by patient depending on cage size, with the total dose ranging from 4.0 mg to 8.0 mg. The rhBMP-2 soaked sponge was then placed in the hollow central portion of the INTER FIX™

device before its insertion into the prepared disc space. No additional sponges were placed outside of the devices. No autogenous grafts were used in the investigational group.

Postoperatively, patients were placed in a soft lumbar corset. The treating physician decided when the patient would advance in activities. Isometric strengthening and exercise programs were started at six weeks after surgery.

Statistical Methods

The data from this clinical trial were analyzed using the statistical software package SAS® version 6.12. For comparisons between the groups for continuous variables, *P*-values are from ANOVA, and for categorical variables, they are from Fisher's exact tests or chi-square tests. For changes (improvements) from the preoperative within each group, the *P*-values are from paired t-tests.

RESULTS

Surgery

The mean operative time, average blood loss, and average hospital stay were less for the investigational group than for the control group (Table 2). None of these differences between treatment groups was statistically significant, although the time of surgery approached

significance (P = .065). No unanticipated device-related adverse events occurred in either treatment group.

Complications

Vascular events. One control patient developed deep venous thrombosis and was treated with anticoagulation medications.

Neurological events. Three investigational (8.8%) and 2 controls (6.1%) had dural tears. In regard to neurological complications: in the investigational patients 16 events occurred in 14 patients, while in the control 18 events occurred in 14 patients.

Iliac crest graft site. In the control group, adverse events related to harvesting of the iliac crest graft were identified in two patients (6.1%). These events included one case of pain and one hematoma. Neither of these patients required additional surgery. Obviously, no graft site adverse events occurred in the investigational group since the use of rhBMP-2 precluded the need to harvest bone graft.

The level of postoperative pain and morbidity associated with the iliac crest graft harvesting was measured using numeric rating scales for pain intensity and duration (Figure 1). After surgery, all of the control patients experienced hip donor site pain. The highest levels of pain were noted immediately after surgery with a mean score of 11.6 points out of 20 points. The percentage of patients experiencing pain decreased over time; however, at 24 months after surgery, 60% of the control patients still experienced pain (i.e., had scores greater than 0). At two years, the graft site

pain scores averaged 5.5 points out of 20 and 13.3% of the patients still felt that the appearance of the graft site bothered them some.

Antibody Testing

Antibody results. Antibodies to rhBMP-2, bovine Type I collagen, and human Type I collagen were evaluated preoperatively and 3 months postoperatively using enzyme-linked immunosorbent assays (ELISAs). None of the patients in either group tested positive for antibodies to rhBMP-2 or human Type I collagen. Authentic (>3 times baseline) bovine Type I collagen antibody formation occurred in 3 investigational and 5 control patients. GELFOAM sponge was used in 15 of the 34 (44%) investigational patients. Of these 15, 2 developed antibody formations to bovine collagen. GELFOAM sponge was also used in 20 of 33 (61%) of the controls. Of these 20, 7 had antibody formation to the bovine collagen. Of the 3 investigational patients that had elevated antibodies, only one had GELFOAM sponge used. Of the 5 control patients who had bovine collagen antibodies, only 2 had GELFOAM sponge used. Thus, there is no obvious correlation between GELFOAM sponge use and antibody formation. No negative clinical consequence to the positive bovine collagen antibody test results was evident in any of the patients; and the fact that the bovine antibody response occurred as often in the investigational group as the control shows that the bovine collagen sponge used to deliver the rhBMP-2 is not the cause of the antibody reaction. A similar result was found when the same carrier and dose of rhBMP-2 were used inside cages implanted anteriorly [7, 10].

Clinical Outcomes

Oswestry Disability Questionnaire scores. The Oswestry Low Back Pain Disability Questionnaire measured pain associated with activities. The Oswestry Questionnaire was administered preoperatively as well as at each postoperative visit. At all postoperative visits, both treatment groups demonstrated highly significant improvements as compared with the preoperative scores (Figure 2). At all postoperative time intervals after the first 6-week follow-up period, the investigational group showed greater improvements over the control group in the mean overall Oswestry scores. At last follow-up at 24 months, the mean improvements in the Oswestry scores were 29.6 points in the investigational group and 24.9 points in the controls (Figure 2). In the investigational group, 69% of patients showed an improvement of at least 15 points in their disability scores at 12 months after surgery as compared with 55.6% of patients in the control group. At 24 months, the 76.0% of the investigational group was improved and compared favorably with 64.3% improved in the control group (Table 3).

Back Pain. The mean back pain scores at all postoperative periods were improved from the preoperative mean values for both treatment groups. The mean improvements in back pain scores at all five postoperative intervals studied were greater for the investigational group than for the control autograft group (Figure 4). At 24 months, the average improvement in back pain in the investigational group was almost twice that of the control group (9 point improvement vs. 4.5 point improvement). This difference was highly significant with a *P* value of .009.

Leg Pain. Leg pain was assessed in a similar manner using a 20-point numeric rating scale that reflects both the intensity and duration of painful symptoms. Mean leg pain scores improved significantly after surgery in each group (Figure 5). At each study interval, average leg pain scores were less (better) in the investigational group when compared with the control group. Similarly, the investigational group also showed higher average improvement scores at each interval studied. At 24 months, the average improvement in leg pain was 7.7 points in the investigational group compared to 6.5 points in the control group. This difference was not statistically significant.

Short Form SF-36. At all postoperative follow-up intervals, the investigational group showed greater improvement in the physical component of the short form SF-36 when compared with the controls (Figure 6).

Neurological Status. Preoperatively and at all five postoperative time points, the motor, sensory, reflexes, and straight-leg-raise measurements were essentially the same for both treatment groups and showed no statistical differences. At 24 months, using the protocol criteria for determining overall neurological success, which represents a combination of the 4 neurological measurements, both groups had 100% success. Table 3 contains the change from preoperative results at 24 months for the motor, sensory, reflex, and straight-leg-raise measurements.

Work Status. Many factors affect a patient's work status, such as the nature of the work performed and ability of the work place to accommodate work restrictions. Before surgery, only 26.5% of the investigational group was employed while more than 45.5% of the control patients

were employed (Table 3). For patients who were working before surgery, the median return-to-work interval was 43 days in the investigational group and 137 days in the control group. Although marked, this difference was not statistically significant. At last follow-up, more people in the investigational treatment group were working than were working before their surgery. At 2 years after surgery, 12 patients in the investigational group were employed while only 9 were employed before surgery. In the control group, 15 were working before surgery and 14 were working at 2 years after surgery. In other words, the percent of the investigational patients working went from 26.5% before surgery to 35.3% at two years, while in the control group the rate went from 45.5% to 42.4%. Although none of these changes are statistically significant, the trend is promising and may be reflective of the statistically significant difference of lower back pain in the investigational patients.

Patient Satisfaction. At 12 and 24 months after surgery, the results were similar in each treatment group (Table 4). At 24 months, 72.4% of the investigational patients and 80.0% of the control patients were satisfied (answering definitely true or mostly true) with their surgical outcomes. In the investigational group, 69.0% said they would undergo surgery again (answering definitely true or mostly true) compared with 83.3% of the control patients who would undergo surgery again. In the investigational group, 72.4% believed that they were helped as much as they had expected to be from the surgery; 70.0% of the control group felt they had been. None of these subjective differences was statistically significant.

Radiographic Outcomes

Cage placement. Cage placement was assessed on both plain radiographs and thin-cut CT scan. The CT scans were found to reflect more accurately the position of the cage in relation to the spinal canal posteriorly and neuroforamina laterally. No differences between the two patient groups regarding cage placement were detected. Only 6% of patients in each group (2/34 in the investigational group; 2/33 in the control group) showed cages that were countersunk 3 mm or more from the posterior margin of the vertebral body. Approximately one-third of patients in each group had cages that extended into the spinal canal on postoperative CT studies (11/34 in the investigational group; 10/33 in the control group). The remainder of the cages were placed either flush to the posterior cortex of the vertebral bodies or were recessed by only 2 mm or less.

Sagittal Plane Balance. Nearly one-third of the patients (19/67; 28%) had some sagittal plane imbalance after surgery. At their last follow-up, 6 patients had some residual spondylolithesis from failure to fully reduce the deformity at the time of surgery (up to Grade I spondylolisthesis was allowed) and 2 patients developed spondylolithesis after surgery. Eleven patients had residual retrolithesis after surgery.

Intradiscal bone formation

Fusion status of the study patients was evaluated on plain radiographs and CT scans. At 6 months after surgery, 93.1% of patients in both the investigational and control groups had evidence of fusion. At 12 months, the fusion rate in the investigational group dropped to 85.2% while the control group maintained a fusion rate of 92%. This decrease in fusion rate in the investigational group at 12 months appears to be artificially low because 7 patients who were

evaluated at 24 months could not be evaluated at 12 months because of the unavailability of reconstructed CT views or poor quality films.) At 24 months, the investigational group had a 92.3% fusion rate, which was more than 14 percentage points higher than that of the control group (77.8%). While this difference was not statistically significant, it does show a positive trend in favor of the investigational group.

Bone formation outside the disc space

The thin cut 1.0 mm CT scans and plain radiographs were used by multiple reviewers to examine for new bone formation adjacent to the interbody fusion cages in 32 of 34 investigational patients and 31 of 33 controls. (The 4 missing cases were either not available because they were not taken or were too poor a quality to read.). New bone formation extending outside the disc space and into the spinal canal or neuroforamina was found in 28 patients (24 investigational and 4 control group patients). According to the Fisher's Exact Test, this difference is statistically significant (P<.0001). Despite the statistical difference, this unexpected posterior bone formation was not correlated to a recurrence or increase in leg pain from the pre-op state. In 10 (29%) investigational and 12 (36%) control patients, the leg pain at some point in the follow-up increased at least one point (on a 20 point scale) over the pre-op value. Interestingly, 7 of the 22 control patients with increased leg pain had absolutely no bone formation posteriorly. This last finding implies that posterior cage bone formation is not the only possible explanation of recurrent leg pain.

Sagittal plane balance. In the control group, 2 of the 4 patients (50%) with bone in the spinal canal had a residual unreduced spondylolithesis after surgery. New bone formation was identified in the canal posterior to the unreduced superior vertebra under the posterior longitudinal ligament and annulus. In two (2/4; 50%) patients with normal segmental sagittal plane balance in the control group, new bone formation was identified extending into the spinal canal.

In the investigational group, 12 of the 24 patients (50%) with bone in the spinal canal had some residual postoperative sagittal plane imbalance. Six patients (6/24, 25%) had spondylolithesis and 6 (6/24, 25%) had retrolithesis. In each of these patients, new bone formation occurred posterior to the unreduced vertebral body under the posterior longitudinal ligament lifted off the unreduced vertebral body. Twelve patients in the investigational group (12/32; 38%) had a normal postoperative segmental sagittal plane balance and new bone formation in the spinal canal.

Cage placement. In the investigational group, cage placement was strongly associated with the development of bone in the spinal canal. In the investigational group, 39% of patients with cages placed at the margin or within 2 mm of the margin of the posterior vertebral cortex developed some bone in the spinal canal. Twelve percent of patients in the control group whose cages were placed within 2 mm of the vertebral margins developed bone in the spinal canal. No patient in either group whose cage had been recessed by 3 mm or more developed bone in the spinal canal.

Secondary Surgical Procedures

In the investigational group, 7 of 34 (20.6%) had some type of secondary surgical procedure. Three (8.8%) had second spinal surgery failures; 3 (8.8%) had second spinal surgeries, but not failures; and 1 (2.9%) had an unrelated second surgery (i.e., breast surgery). Of the 3 secondary surgery failures, 2 patients received supplemental fixation for presumed pseudarthrosis.

In the control group, 9 of 33 (27.3%) patients had some type of secondary surgical procedure; 3 (9.1%) had second spinal surgery failures; 3 (9.1%) had second spinal surgeries but not failures; and 3 (9.1%) had an unrelated secondary surgery (i.e., carpal tunnel, knee, coronary artery bypass graft surgery). Of the 3 secondary surgery failures, 3 control patients received supplemental fixation for presumed pseudarthrosis.

DISCUSSION

Threaded cylindrical cages represent a new, distinct class of segmental spinal fixation devices. These devices were not designed as spacers that require segmental stabilization; rather, they were designed as stand-alone intervertebral devices that function as an "instrumented PLIF." Threaded interbody devices are biomechanically different from interbody spacers. Biomechanical studies have shown that cage size has some significance in stand-alone cage fusions; however, stand-alone cages do not significantly increase spinal stiffness in studies using human cadavers [13-18]. This finding largely explains the current clinical trend toward using posterior segmental fixation in PLIF constructs.

Larger cages improve stiffness in rotation and lateral bending in a lumbar spinal motion segment; however, reduction of motion in flexion is not significantly improved with larger cages [16,17]. Larger cages require more extensive facet joint resection or complete facetectomy, which further destabilizes the spinal motion segment. A cylindrical device increases in its medial-lateral dimension equal to its increase in height, which necessitates greater mobilization and retraction of the neural elements. Retraction and mobilization of the neural element during cylindrical cage insertion has been associated with permanent neurologic injury [19,20]. The current trend in PLIF surgery is to limit neural element retraction through the use of a transforaminal surgical approach or through the use of impacted underbody spacers.

Initial clinical studies reported high rates of fusion and clinical success in certain centers. These results have not been widely reproduced. Authors of clinical and radiographic studies on stand-alone interbody implants without supplemental fixation have reported fusion rates between 83% and 100% [3,4]. Hacker [21] compared two groups of patients treated for disabling back pain; one group was treated with a stand-alone PLIF using BAK implants, and the other group was treated with combined anteroposterior fusion. He found equal patient satisfaction between the two groups. Ray [4] presented a prospective series of 236 patients treated with stand-alone interbody fusion and reported a 96% fusion rate at 2 years after surgery. These fusion criteria did correlate with improved clinical outcomes. In this study group, only 65% had good-to-excellent clinical outcomes on the Prolo scale, and 14% had a poor result.

However, PLIF procedures or any other type of spinal fusion procedure that uses autograft from the iliac crest come with a price in pain for the patient. Figure 1 shows that the iliac crest graft site pain in this study was found to be similar to that measured in the same way for a larger study of the LT-CAGE device [10] with two exceptions. First, in this study, the pain at 24 months was 5.5 on a scale of 20, while in the anterior fusion LT-CAGE study, the value was 1.8. Second, in this posterior INTER FIX study, 60% of the patients had some pain at 24 months, while in the LT-CAGE study 32% had. Although these were two separate studies using different surgeons, different numbers of patients (30 versus 118), and different sizes of cages (the INTER FIX cage is cylindrical and the LT-CAGE version is a smaller volume tapered design), these results are consistent with a review of other studies that showed that a posterior approach to the iliac crest is more painful for the patients [22]. The pain associated with the posterior bone graft harvest may be secondary, in part, to the extensive stripping of the gluteus musculature, more extensive bone graft harvesting techniques, or injury to the sacroiliac joint. For whatever reason, the measured iliac crest graft site pain scores in this study suggest that, from the patient's point of view, the need for an autograft replacement in PLIF cylindrical cage procedures is greater than in ALIF tapered cage procedures.

We found that, regardless of the source of the bone graft, extra bone formation in the spinal canal can occur after PLIF procedures with cylindrical interbody fusion cages because it occurred in both study groups (Fig. 7). Bone formation in the spinal canal appears to be a multifactorial event. It appears to be largely dependent on cage placement and sagittal balance of the instrumented vertebral motion segment. Patients with residual sagittal plane imbalance form bone behind the unreduced vertebral segment. This may be the result of lifting of a periosteal

flap along the posterior cortex of the listhesed vertebral body (Fig. 8). Cages that were not recessed within the confines of the disc space margins were also associated with bone formation in the spinal canal (Fig. 9). Thin-cut CT scans were essential to determine cage placement and new bone formation postoperatively.

RhBMP-2 on an absorbable collagen sponge has been shown to induce bone formation in the intervertebral disc space [7,8,10,11]. A recent study has shown that this montage in this milieu routinely produces a fusion zone extending 3 mm around the cage [23]. It is not surprising that bone may extend into the spinal canal when cages containing rhBMP-2 are not recessed 3 mm or more within the confines of the disc space.

The PLIF procedure using threaded cylindrical fusion cages disrupts a wide channel, which includes the posterior margin of the disc, the posterior longitudinal ligament, and annular structures. This injury can result in adjacent bone formation, which can extend into the spinal canal. This new bone formation is best visualized on CT scan. Both the control group and investigational group exhibited bone formation outside of the disc space after this procedure.

Although not desirable, bone formation in the spinal canal does not appear to have a discernable effect on patient outcomes. Therefore, bone formation in the spinal canal after the PLIF procedure with stand-alone cylindrical interbody fusion cages appears to be primarily just a radiographic finding that is not associated with any clinical outcome. This human study seems to confirm the safety results in a canine study using rhBMP-2 on a bovine collagen sponge [25]. In that laminectomy study, the sponge was placed directly on an exposed dura. Even though bone

formed, no negative outcomes were found. In both the canine and now the human study, the de novo rhBMP-formed bone occurred slowly and passively, not compressing neural structures.

Because of its small size, this study should be considered a pilot study of the ability of a bone morphogenetic protein to replace autograft in a stand-alone PLIF cage procedure. Even though the number of patients was small, we found a statistically significant improvement in back pain in the rhBMP-2 investigational patients. Although the other differences were not statistically significant, assessment of just the surgical and clinical outcome data at two years (Tables 2 and 3) and the averages of all of the outcomes measured (except for 2 of the 3 subjective patient satisfaction questions) favored the investigational group. These findings suggest that a larger study would show statistical equivalence or improvement in all clinically important outcomes. Predicting such a result can be based not only on the data in the pilot study presented here but also on the large-scale human clinical trials of spinal surgery and rhBMP-2 already conducted. In a recent 679-patient analysis, the same protein used in the same concentration inside metal cages for the same lumbar indication but from an anterior approach was shown to be superior to autograft [11]. The direction of implantation of a cage should not affect the ability of rhBMP-2 contained inside to form bone.

In conclusion, this detailed, independent review of the results, which represents the first use of osteoinductive proteins in a PLIF procedure, are encouraging. These findings along with other studies for other indications suggest that larger PLIF studies with rhBMP-2 are needed. Currently, studies are being conducted to assess the use of rhBMP-2 in transforaminal lumbar interbody fusion procedures. Additional PLIF studies are being done to evaluate placement of the

BMP-soaked sponge adjacent to the anterior annulus and away from the posterior annulotomy sites. In future studies using modified surgical techniques, such as using more recessed cages to allow for extra posterior bone formation, adding steps to minimize bleeding and surgical variables, using narrower, noncylindrical cages that would be easier to put in and cause less tissue destruction, or adding secondary instrumentation may be beneficial. Modifying patient selection, such as entering patients with less vertebral slip, could also help minimize the confounding variables. All of these changes may produce more convincing evidence that INFUSE™ Bone Graft can also be used as a substitute for autograft in PLIF cage procedures.

Until those future studies are completed, the readers should be advised that at this writing the use described in this article are not FDA approved and use with rhBMP-2 as described is not recommended by the stand alone method described. If the reader decides to use rhBMP-2 in this manner anyway, extreme caution should be taken (like countersinking the cages) and the patients should be carefully followed.

ACKNOWLEDGMENTS

Special thanks to the following doctors who were principal or co-principal clinical investigators at the 14 sites for this study. These surgeons in alphabetical order are Drs.C. William Bacon, Steven Barnes, Charles Branch, Randall Dryer, Paul Geibel, Fred Geisler, Scott Graham, Peter Holiday, Timothy Holt, Zenko Hrynkiw, Dennis Maiman, David Masel, Bruce Mathern, Christopher Meyer, Phillip Tibbs, and Frank Tomecek. The work of the Clinical Research Department at Medtronic Sofamor Danek in collecting the clinical data and performing the statistical analyses is acknowledged. D. Lynn Sanders, CCRC was instrumental in sorting and organizing radiographic data for analysis.

REFERENCES

1. Cloward RB. The treatment of ruptured intervertebral discs by vertebral body fusion. I. Indications, operative technique, after care. *J Neurosurg* 1953;10:154-168

2. Lin PM, Cautilli RA, Joyce MF. Posterior lumbar interbody fusion. *Clin Orthop* 1983;180:154-168.

3. Kuslich SD, Ulstrom CL, Griffith SL, Ahern JW, Dowdle JD. The Bagby and Kuslich method of lumbar interbody fusion. History, techniques, and 2-year follow-up results of a United States prospective, multicenter trial. *Spine* 1998;23:1267-1268.

4. Ray CD. Threaded titanium cages for lumbar interbody fusions. Spine 1997;22:667-679.

5. Urist MR. Bone: Formation by autoinduction. *Science* 1965;150:893-899.

6. Boden SD, Schimandle JH, Hutton WC. 1995 Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. *Spine* 1995;20:2633-2644.

7. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. *Spine* 2000;25:376-381.

8. Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2. A prospective study of clinical and radiographic outcomes. *Spine* 2001;26:2751-2756.

9. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. *Spine* 1995; 20:1326-1337.

10. Burkus JK, Gornet MF, Dickman C, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. *J Spinal Disord Tech* 2002; 337-349.

11. Burkus JK, Heim SE, Gornet MF, Zdeblick TA. Is INFUSE™ Bone Graft Superior to Autograft Bone? An Integrated Analysis of Clinical Trials Using the LT-CAGE™ Lumbar Tapered Fusion Device. *J Spinal Disord Tech* 2003; 16:113-122.

12. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. *Neurosurg Focus* 2001;10:1-9.

13. Brodke DS, Dick JC, Kunz DN, McCabe R, Zbeblick TA. Posterior lumbar interbody fusion: a biomechanical comparison, including a new threaded cage. *Spine* 1997;22:26-31.

14. Dimar JR, Wang M, Beck DJ, Glassman SD, Voor MJ: Posterior lumbar interbody cages do not augment segmental biomechanical stability. *Am J Orthop* 2001;30:636-639

15. Hasegawa K, Ikeda M, Washio T, Hara T: An experimental study of porcine lumbar segmental stiffness by the distraction-compression principle using a threaded interbody cage. *J Spinal Disord* 2000;13:247-252.

16. Kettler A, Wilke HJ, Dietl R, Krammer M, Lumenta C, Claes L: Stabilizing effect of posterior lumbar interbody fusion cages before and after cyclic loading. *J Neurosurg* 2000;92:87-92

17. Lund T, Oxland TR, Jost B, Cripton P, Grassmann S, Etter C, Nolte LP. Interbody cage stabilisation in the lumbar spine: biomechanical evaluation of cage design, posterior instrumentation and bone density. *J Bone Joint Surg Br* 1998;80:351-359.

18. Rapoff AJ, Ghanayem AJ, Zdeblick TA: Biomechanical comparison of posterior lumbar interbody fusion cages. *Spine* 1997;22:2375-2379.

19. Barnes B, Rodts GE, McLaughlin MR, Haid RW Jr. Threaded cortical bone dowels for lumbar interbody fusion: Over 1-year mean follow-up in 28 patients. *J Neurosurg* 2002;95(1 Suppl):1-4.

20. Barnes B, Rodts GE, Haid RW Jr, Subach BR, McLaughlin MR. Allograft implants for posterior lumbar interbody fusion: results comparing cylindrical dowels and impacted wedges. *Neurosurgery* 2002;51:1191-1198.

21. Hacker RJ: Comparison of interbody fusion approaches for disabling low back pain. *Spine* 1997;22:660-665

22. Polly DW, Kuklo TR. Bone graft donor site pain [Abstract]. In Program and abstracts of 39th Annual Meeting of the Scoliosis Research Society; September 18-21,2002; Seattle, WA; p. 178.

23. Burkus JK, Dorchak JD, Sanders DL. Radiographic assessment of interbody fusion using recombinant human bone morphogenetic protein type 2. *Spine* 2003; 28:372-377..

24. Palm WJ, Rosenberg WS, Keaveny TM: Load transfer mechanisms in cylindrical interbody cage constructs. *Spine* 2002;27:2101-7.

25. Meyer RA, Gruber HE, Howard BA, et al. Safety of recombinant human bone morphogenetic protein-2 after spinal laminectomy in the dog. *Spine* 1999;24:747-54.

Table 1. Patient Demographic Information.

Variable	Investigational (n=34)	Control (n=33)	*P* value *
Age (years) [mean (range)]	46.3 (25.8 – 66.1)	46.1 (28.5 – 70.9)	.928
Weight (lb) [mean ± SD]	180.5 ± 38.4	172.8 ± 35.7	.400
Sex [n (%)]			
Male	17 (50)	15 (45.5)	.808
Female	17 (50)	18 (54.5)	
Workers' compensation [n (%)	8 (23.5)	9 (27.3)	.784
Spinal litigation [n (%)]	3 (8.8)	1 (3.0)	.614
Tobacco used [n (%)]	18 (52.9)	15(45.5)	.628
Alcohol use [n (%)]	15 (44.1)	9 (27.3)	.204
Preoperative work status [n (%) working]	9 (26.5)	15 (45.5)	.131
Previous back surgery [n (%)]	12 (35.3)	13 (39.4)	.803

For continuous variables, *P* values are from ANOVA, and for categorical variables, they are from Fisher's exact test.

Table 2. Surgical Parameters.

Variable	Investigational group	Control group
Mean operative time	2.6 hours	3.0 hours
Average blood loss	322.8 ml	372.7 ml
Average hospital stay	3.4 days	5.2 days

Table 3. 24-Month Clinical Outcome Parameters

	Investigational	Control
Improvement Points in Oswestry Score	29.6	24.9
% Patients with ≥15 point Oswestry Improvement	69%	55.6%
% Patients with Oswestry Improvement	76.0%	64.3%
Back Pain Improvement from preop (Points)	9*	4.5
Leg Pain Average Improvement from preop (Points)	7.7	6.5
Motor change from preop	4.5	2.8
Sensory Change from preop	8.0	2.8
Reflex change from preop	7.0	5.4
Straight leg raise change from preop	48.0	39.3
Net change in % patients working	+8.8%	-3.1%
Median return to work time	43 days	137 days
Fusion rate	97.3%	77.8%

*Statistically significant difference ($P < .05$)

Table 4. Summary of Patient Satisfaction with Results of Surgery at 24 Months
[Number (%) of Patients]

Variable	Investigational	Control	P value*
I was satisfied with the results of my surgery.			
Definitely True	15 (51.7)	16 (53.3)	.388
Mostly True	6 (20.7)	8 (26.7)	
Do not Know	3 (10.3)	5 (16.7)	
Mostly False	3 (10.3)	0 (0.0)	
Definitely False	2 (6.9)	1 (3.3)	
I was helped as much as I thought I would be by my surgery.			
Definitely True	13 (44.8)	16 (53.3)	.159
Mostly True	8 (27.6)	5 (16.7)	
Do not Know	3 (10.3)	8 (26.7)	
Mostly False	3 (10.3)	0 (0.0)	
Definitely False	2 (6.9)	1 (3.3)	
All things considered I would have the surgery again for the same condition.			
Definitely True	18 (62.1)	16 (53.3)	.196
Mostly True	2 (6.9)	9 (30.0)	
Do not Know	5 (17.2)	2 (6.7)	
Mostly False	1 (3.4)	1 (3.3)	
Definitely False	3 (10.3)	2 (6.7)	

*P values are from the Chi-square test.

LEGEND OF FIGURES

Figure 1. Mean hip pain scores.

Figure 2. Mean improvement in Oswestry scores.

Figure 3. Mean back pain scores.

Figure 4. Mean improvement in back pain scores.

Figure 5. Mean leg pain scores.

Figure 6. Mean SF-36 PCS scores.

Figure 7. **A**. Lateral radiograph of the L3-L4 interspace three months after a PLIF procedure using autogenous iliac bone graft. The disc space height has been restored anatomically and the cages are recessed by 3 mm within the disc space. There is no bone posterior to the cages. **B**. Lateral radiograph at 24 months after the PLIF with autograft shows loss of disc space height, subsidence of the implants through the vertebral endplates and new bone formation posterior to the cages (arrows). The posterior bone formation extends into the spinal canal. **C**. Sagittal CT scan reconstruction across the L3-L4 interspace at 20 months after the PLIF using autograft confirms that there is new bone formation posterior to the implants that extend into the spinal canal (arrows). **D**. Axial CT scan across the L3-L4 interspace at 24 months after surgery shows new bone formation (arrow) extending into the spinal canal.

Figure 8. Schematic illustration of an unreduced spondylolisthesis treated by a stand-alone PLIF technique. There is elevation of the posterior longitudinal ligament with a triangular subperiosteal zone behind the unreduced superior vertebral body (shaded area). This zone commonly filled in with bone following the PLIF procedure in both the BMP and autograft treated patients.

Figure 9. **A**. Preoperative lateral radiograph shows significant disc space narrowing and radial osteophyte formation. **B**. Lateral radiograph at three months after a PLIF using rhBMP-2 on a collagen sponge carrier shows that the disc space height has been restored both anteriorly and posteriorly (arrows). The cages are recessed by less than 3 mm. **C**. Lateral radiograph at 24 months after surgery shows loss of disc space height, implant subsidence, and bone formation extending into the spinal canal (arrows). **D.** Sagittal reconstructed CT scan shows new bone formation posterior to the cages and extending into the spinal canal (arrows). **E**. Axial CT scan at 24 months after surgery shows asymmetric cage placement (arrow) within the disc space. There is also new asymmetric bone growth. There is more bone behind the more prominent centrally placed cage.

June 2, 2003

Tom G. Mayer, M.D.
Editor-in-Chief
The Spine Journal
[redacted]
LaGrange, IL 60525

RE: MS 30023

Dear Dr. Mayer:

We have revised our manuscript, entitled "Posterior Lumbar Interbody Fusion Using rhBMP-2 with Cylindrical Interbody Cages". Enclosed are three copies. We believe we have addressed all the reviewers' comments with this revised manuscript. This paper presents data that will not be researched again for perhaps years to come. We believe this paper addresses an important issue and needs to be presented to the spinal community as soon as possible.

To demonstrate how we addressed the reviewer's comments, in the following in bold type are the reviewer's comments with our response in regular type:

This study should not be published in its current form. As noted by both Reviewer A and B, there is very little statistical significance differentiating the two groups, but the authors and/or company sponsoring this study have attempted to use any possible positive trend to promote this technique. Unless the authors can discuss the results of this study in an unbiased manner, which they have been unable to do in its present form, this data should not be published.

We believe we have discussed the results in an unbiased, objective manner and are not quite sure what the specific problem is here, nor do we believe we are trying to promote this technique. We believe the data speaks for itself and the readers can make up their own mind as to whether to use this technique. In our mind, we believe the article warns potential users about performing it. There will be more comments on this subject later in our response.

This is a very important study, but there are some problems with the study's execution and with the data as it is presented. First, why was this "2-year study" stopped after 9 months?

Our paper did not say that the study was stopped after 9 months. It said that all the patients were entered in a 9 month period. As the discussion says the size of this study represents in essence a pilot study. We assumed The Spine Journal would want 2-year follow-up. Nevertheless, we have added a footnote to the text to explain why more patients were not entered into the study.

The authors state that larger numbers might have helped show greater differences between the two groups, so the question remains, why stop at 67 patients after 9 months (other rhBMP-2 studies included over 300 patients)?

Performing large-scale studies is very expensive and not all studies need to be large scale. What is the reviewer suggesting is the proper alternative here? To not publish this data? We believe this information is important and should be shared with the spinal community. As was mentioned, the added footnote addresses this reviewer's comment.

Also, the authors cannot talk about "greater differences" and "better outcomes" in the results unless the differences are statistically significant.

We did a search of the manuscript and cannot find the phrase "greater differences" or "better outcomes" in the text. So we do not know how to address this issue. The manuscript had the phrase "although not statistically significant" six times in the text.

They analyzed statistically almost every conceivable outcome variable, except for the one finding strongly against rhBMP-2 – that is, a higher rate of new bone growth in the spinal canal! This is the greatest fear that surgeons have regarding BMP's -- uncontrolled new bone formation. It happened in 23/34 BMP patients, versus 5/33 bone graft patients. They did not do a statistical analysis of this, but I ran a Fisher's exact 2-tailed test for this data....and P<0.0001, the most significant of

all differences found in this study, yet the authors did not even run this analysis! This is very troubling, and raises the issues of commercial support of such a study leading to a biased reporting of results. I ask the authors to explain this point, and include and emphasize its importance prior to acceptance for publication.

As we understand this comment the reviewer is in essence saying that we have statistically analyzed too many outcomes parameters and then asks us to do one more. We believe the point about bone formation is obvious, but we have added the statistical analysis he has asked for in the revised manuscript.

We are not quite sure what the reviewer is saying about "commercial support" since any human study of recombinant proteins will be very expensive and require some type of commercial support in order to be performed. The reviewer seems to think that this paper is advocating the use of rhBMP-2 in PLIF procedures. Readers of this paper, once published, will see that such use, which is not FDA approved and may never be, can have unexpected radiographic findings, and surgeons will hesitate performing surgeries in the same manner as used in the study without further study or without modifying their technique. Without any publications of any kind on this subject, surgeons may have a false sense of security that rhBMP-2 can be used in PLIF procedures just as in ALIF cages.

As was mentioned, we do not believe our independent review of these results encourages or discourages the procedure in either the investigational or control groups. Rather we

just report the facts that until this paper gets published are only known about with rhBMP and PLIF cages through hearsay and rumor. Although we do not come out and say it (because we felt such comments would be inappropriate in a scientific publicaton) the use of stand alone cylindrical cages in PLIF procedures seems to have gone into disfavor in the US. We believe the net effect to the reader on the use of rhBMP inside a PLIF cage will be discouragement (which ironically will probably not be favorable to the to the industrial community, although some may view the posterior bone formation as proof that rhBMP-2 does form bone), as will the reader for the use of stand alone cylindrical PLIF cages with autograft.

Nevertheless, we have added the statistical analysis the reviewer has requested to the revised text in the results section.

They also need to specify how many patients with ectopic bone had new or persistent leg pain, not just overall average leg pain scores.

We did not ever use the term "ectopic" in the original paper. In the re-write we added the term "unexpected". We have expanded our discussion on the bone formation outside the disc space to be more descriptive and added a discussion of recurrent leg pain.

Page 16, Patient Satisfaction: Please give patient satisfaction data in tabular form, as it is given for all of the other clinical outcomes.

Table 4 has been added per this reviewer's request.

Page 18, end 1st paragraph: "Positive trend" usually refers to a P value between 0.05 and 0.10. If this is not true, then this term "positive trend" probably should not be used.

We have eliminated the term "positive trend" from the revised text.

Page 18, 2nd paragraph: Regarding bone formation outside of the disc space, it is surprising that 23 of 34 investigational patients versus 5 of 33 control patients had this problem. This appeared to me to be a statistically significant difference and in fact by Fisher's Exact Test the difference was highly significant with a P value of less than 0.0001. Why is this not stated in the text? A statistical analysis and description of these results, both in tabular format and in the text of the Results and Discussion is necessary.

This analysis was added to the text. We also found a small error in the calculations and have corrected it in the revised text.

Page 19, 1st paragraph: Did any patients who had new bone formation have residual leg pain or new leg pain? The results describe overall average scores for leg pain, but we do not know specifically how many of the patients in each group still had leg pain or developed leg pain following surgery. This is important as this might suggest that there was a clinical impact to the new bone formation.

The revised manuscript addresses this issue. There was no correlation.

Page 19, 3rd & 4th paragraph: What are spine surgery failures? Does this mean pseudoarthrosis? Does this mean the patients had recurrent or residual leg pain?

Second surgery spine failures are defined as patients who have had a revision, removal, or supplemental fixation. These cases could include pseudarthrosis and included 3 controls and 2 investigational. One additional investigational patient had recurrent leg pain. We added text about the recurrent leg pain.

Page 21, middle of 2nd paragraph: It is again confusing that 60% of patients had some pain in the bone graft site and yet only one patient is mentioned in the Abstract and Results section as having pain on follow-up.

A 20-point scale was used to quantify hip donor site pain. At 2 years, 60% of the patients had a score of 1 or greater. This is different from a reported complication of graft site discomfort. To make the paper more clear, we will eliminate the graft site discomfort reference from the text.

Page 22, 2nd paragraph: Here there should be a discussion regarding the greater likelihood of bone formation in the canal with rhBMP-2. Please discuss whether this new bone formation may have caused leg pain in any of the patients.

The revised manuscript addresses this point.

Page 23, 2nd paragraph: I would agree with this point of the discussion if there truly were no patients with post op leg pain and bone in the canal, whether or not the two were related.

The revised manuscript addresses this point.

Page 23, 3rd paragraph: The authors cannot state that "all the outcomes measured favored the investigational group", unless these differences were statistically significant. Since they were not, this statement is not accurate.

We have revised the text to tone down this sentence and add the phrases "on average" and "although not statistically different".

General Comments:

This is described as a two-year study yet it seems that small numbers of patients were enrolled and only over a short nine-month period. Why is this? Was the study ended prematurely? If so, this should be stated at least in the body of the paper.

The revised manuscript addresses this point.

Page 3, end of 3rd paragraph: 3.0% of patients reporting graft site discomfort is one patient and should be stated as such instead of with percentage.

As was mentioned, the revised manuscript addresses this point.

Page 5, Introduction, 1st paragraph: references are needed regarding the clinical results of PLIF, as well as clinical results for DDD, spondylolisthesis, etc.

References were added to the revised text.

Page 5, Introduction: How is sagittal balance restored in the setting of stand-alone PLIF? Please reference the biomechanical studies which demonstrate this.

References were added to the text.

Page 5, 2nd paragraph: Can the authors reference papers describing the restoration of normal anatomic alignment with PLIF?

We added several references to this paragraph, although none may specifically address the reviewer's question.

Page 12, Complications: Were there are dural tears? Were there any neuropraxic injuries, i.e. patients with postoperative weakness or postoperative numbness? These should also be cited under Complications.

Three investigational (8.8%) and 2 controls (6.1%) had dural tears. As far as neurological complications, in the investigational patients 16 events occurred in 14 patients, while in the control 18 events occurred in 14 patients. We have added these figures to the revised text.

Page 12, 2nd paragraph: It is confusing that the authors describe one patient having graft site discomfort two years out from surgery yet they in the same paragraph state that 60% of patients who had a graft harvested had pain. They state that at two years the graft site pain scores averaged 5.5 points out of 20, yet

they stated only one patient had graft site discomfort. Please explain these apparently confusing results.

This issue has been addressed in the revised text by eliminating the discussion of the graft site discomfort for the sake of clarity.

Page 13: Please discuss why there might have been such a high percentage of antibody formation to bovine type I collagen in the control group. Was this related to the use of gel foam?

GELFOAM sponge was used in 15 of the 34 (44%) investigational patients. Of these 15, 2 developed antibody formations to bovine collagen. GELFOAM sponge was also used in 20 of 33 (61%) of the controls. Of these 20, 7 had antibody formation to the bovine collagen. This result was added to the text as was a discussion on whether this was related to antibody formation.

Page 14 & 15: Throughout the Clinical Outcomes section the authors cannot describe "greater improvements", and "better" scores when there is no signficant difference. For example, in the 1st paragraph of page 14 the 4th sentence should read "after the first six week follow-up the investigational group showed no significant differences over the control group in the mean overall Oswestry scores". This can then be followed by giving the actual scores that were obtained for each group. The reader can then interpret the difference in numbers as they wish, but

the fact that it is not statistically significant needs to be stated rather than stating that there were greater improvements when these differences were not statistically significant. The same is true for the results under Back Pain, Leg Pain, and Short Form SF-36.

We believe the revised paper addresses this issue.

Reviewer A

This manuscript is not worthy of publication in its current form. There are many issues which I will develop to this end, but the most significant is that the conclusions do not support the data contained therein. I will outline the concepts for the authors. First, none of the differences, in the end, are statistically significant, yet the authors take the liberty to interject statements that there are "trends that the investigational group showed better results" when there is no evidence for this. Whenever the control group has a similar positive trend, no mention of this is made (which is appropriate, but not consistent).

The revised manuscript addresses this point, as was previously mentioned, and we believe is now worthy of publication.

The manuscript is full of biased statements that are a reflection of the data evaluators - the company that markets the product. No mention is made in the

discussion, or methods section about the introduction of bias (which is well documented in the scientific literature, I refer the authors to this months AMA News as one of many articles), which may occur when the data is collated, collected and analyzed by industry personnel. While this cannot be proven, it must at least be discussed and the potential for bias stated. We do not have disclosures of the authors or the surgeons in the multiple centers who participated, and this should have been clearly identified.

To help eliminate any potential bias, only one of the co-authors was a clinical investigator—the other three were independent reviewers of all the data. Since these data are taken from a clinical IDE study sponsored by a company, only the company would have all the data in its database—data that is reviewed by FDA auditors. We don't believe any discussion of bias is needed for the text.

Was this IRB approved at all centers? If not, why? Was consent obtained in all patients prior to inclusion into the study? All questions which should be answered via the methods section.

Of course since this study was an IDE study, IRB approval and informed consent was obtained. Text was added to the revised manuscript to state this.

There is no data given for the economic impact of the use of this product (does the cost to the insurance company or patient justify it's use at this point?) Yes, OR time is greater if a bone graft is taken, and blood loss slightly higher, but patient satisfaction was actually higher (although not statistically significant) in the control

patients. This fact is very important, but glossed over and not discussed, as it should be.

An economic analysis is beyond the scope of this study and would require much more data than can be presented here. Besides, this product is not FDA approved and any economic analysis would be purely academic.

The methods section is grossly lacking. There is no control for diagnosis. What were the entry criteria? This is really a consecutive series of cases using a specific product versus autograft. The authors state that degenerative disc disease was the diagnosis in all cases, yet in the results section discuss spondylolisthesis, spondylolysis as well as degenerative disc disease, but no data is given as to the breakdown of the two groups. Did all of the investigational patients have spondylolisthesis or visa versa? This may impact the results.

The revised manuscript makes the indications section more clear and says that spondylolisthesis patients could be entered into the study.

The definition of fusion is not clearly defined and the lucency of the implant data needs to be better delineated and quantified. The concept that reoperations, if felt to be *clinically* failed fusions, were so documented is not logical, and not *scientifically* based.

The definitions used were the same as given by the FDA. We did not change the definitions.

The postoperative recovery of patients was not controlled and very well in such a small group affected the outcome. For example, if all patients in the control group were ambulated earlier than the investigational group a higher pseudo rate may have an effect.

The study protocol allowed the surgeons to decide the post-op recovery. [NOTE: Is this true?]

This group of patients overall had a very high rate of reoperation, and is very concerning, and bears further discussion. This rate is much higher than the literature would suggest. The author's statements about the effects of isolated PLIF procedures decreasing biomechanical stability of the motion segment is in fact true, and when the facet joints are compromised instability results. This operation is not recommended unless posterior stability is provided by supplemental instrumentation and is likely why the failure/reoperation rate was so high. The exceedingly high reoperation rate needs to be clearly discussed. Based upon these results, the authors should recommend abandonment of the procedure.

We believe the revised manuscript and its closing sentence addresses this point.

IF the shortcomings and bias of this manuscript are clearly incorporated it may have benefit to the readership. As it stands it is an advertisement for a specific product without significant scientific merit.

The purpose of the paper was not to evaluate the viability of using stand-alone cylindrical PLIF cages. Instead, its purpose was to investigate the feasibility of using rhBMP-2 to replace autograft in a PLIF procedure. We feel that our comments in the discussion is appropriate—more research is needed, and if performed should be carried out making the changes in the protocol described. We do not believe the revised or original paper is an advertisement for a specific product. In general though, the data show reasons to be encouraged and cautioned about in the use of rhBMP-2 in PLIF procedures. Encouraged because the need is so great and the preliminary data are trending favorably, but cautionary in nature because of the occurrence of posterior bone formation.

We have modified the revised manuscript to include some language advising the reader that this use is not FDA approved and its use is not recommended by the method described. If the reader decides to use BMP in this manner anyway, extreme caution should be taken (like countersinking the cages) and the patients carefully followed.

Please let us know if you need us to clarify anything else in this manuscript, for we feel that the changes made now make this paper acceptable for publication.

Thank you.

Sincerely,

Ken Burkus, M.D.

From: Ma, Guorong
Sent: Monday, June 26, 2006 10:04:12 AM
To: Bearcroft, Julie, PhD
CC: Keller, Jim
Subject: FW: Please review '2YrBMP-CRMSRS2006_06-07-06v2_MSD'

Attachments: 2YrBMP-CRMSRS2006_06-07-06v2_MSD.doc

Julie,

I made a couple of comments on Pages 5 and 7, regarding to CT, fusion and bridging bone assessments.

Remember, in the table made for Dr. Boden, results for bridging bone did not consider motion and radiolucency measures. He wanted results just based on bridging bone!

In terms of the IDE-defined fusion, if any one of measurements (components) is missing and all the others are successes, then fusion is missing. But, if any of the components is failures, then fusion is a failure, regardless of whether the others are missing or not.

Thanks,

Guorong

From: Bearcroft, Julie, PhD
Sent: Monday, June 26, 2006 7:34 AM
To: Ma, Guorong; Keller, Jim
Cc: McKay, Bill; Beals, Neil; Meyer, Matt; Lanctot, Rodney; Hatcher, Brian
Subject: Please review '2YrBMP-CRMSRS2006_06-07-06v2_MSD'
Importance: High

Guorong, thank you for reviewing the initial draft of this manuscript prepared by John Dimar. I started with your edited version and went a step further. The key to commentary is that Guorong's comments are in green, mine are in blue and the highlighted areas are sections that need to be verified. (Brian is helping me on those sections)

This is the version that I plan to provide to Carol tomorrow morning (Tuesday) unless other suggestions are made. Jim and Guorong, please pay careful attention to the segments describing the radiographic fusion success and CT bridging bone, since I do want to make this as clear as possible as well as accurate.

I want to thank everyone in advance for their time and effort in reviewing this manuscript.

julie

Please review the attached document.

A large-scale, level 1, clinical and radiographic analysis of an optimized rhBMP-2 formulation as an autograft replacement in posterolateral lumbar spine fusion

John R. Dimar II, MD*, Steven D. Glassman, MD*, J. Kenneth Burkus, MD†, Philip W. Pryor‡, MD, James W. Hardacker. MD‡, Scott D. Boden, MD§

*Spine Institute for Special Surgery, Louisville, KY; †The Hughston Clinic, Columbus, GA; ‡The Spine Institute, Carmel, IN; § Emory Spine Center, Emory University School of Medicine, Atlanta, GA

Purpose: To determine the feasibility of using a new recombinant human bone morphogenetic protein-2 formulation utilizing a new compression resistant matrix (rhBMP-2 matrix) as an iliac crest bone graft (ICBG) substitute in patients undergoing posterolateral fusion.

Methods: In this ongoing prospective study, 463 patients with symptomatic single-level degenerative disc disease with ≤ Grade 1 spondylolisthesis were treated with decompression and instrumented single-level posterolateral fusion through an open midline approach. Patients were randomly assigned to either the rhBMP-2 matrix (AMPLIFY™, Medtronic Sofamor Danek) group (239 patients) or the ICBG group (224 patients). ODI, SF-36, and back and leg pain scores were determined preoperatively and at 1.5, 3, 6, 12 and 24 months postoperatively. Two independent radiologists reviewed radiographs and CT scans taken at 6, 12, and 24 months postoperatively. Fusion was defined as the presence of bilateral, continuous trabeculated bone connecting the transverse processes, translation of ≤3 mm and angulation of <5° on flexion-extension radiographs, and absence of cracking as evidenced by radiolucent lines completely through the fusion mass.

Results: No significant differences in demographics existed between the groups. The mean operative time in the rhBMP-2 group (2.5 hours) was less than in the ICBG group (2.9 hours) ($p<0.001$). Average blood loss in the rhBMP-2 group was 343.1 ml compared with 448.6 ml in the ICBG group ($p<0.001$). Average hospital stay was similar in both groups. No differences existed between groups in adverse events except cumulative nonunion rate reported by the investigators was higher in the ICBG group (7.1%;16 patients) ($p=.042$) than in the rhBMP-2 group (2.5%; 6 patients). Based on fine-cut CT Scans with coronal and sagittal reconstructions, at 12 months, 86.9% of patients in the rhBMP-2 group and 71.3% in the ICBG group had evidence of bilateral bridging bone ($p<0.001$). At 24 months, 93.6% in the rhBMP-2 group had bilateral bridging bone compared with 82.6% in the ICBG group ($p=0.024$). Both groups showed similar improvements in clinical outcomes and reduced pain. At 24 months, 54% of the ICBG group reported enduring donor site pain.

Conclusions: The use of rhBMP-2 can eliminate the need for harvesting iliac crest bone in successful posterolateral lumbar fusions.

Deleted: with
Deleted: rhBMP-2/CRM
Deleted: rhBMP-2/CRM
Deleted: and
Deleted: Mean
Deleted: lower
Deleted: in the rhBMP-2 group (2.5%; 6 patients)
Deleted: in the ICBG group (7.1%;16 patients) (p=.042)
Deleted: fusion
Deleted: were fused
Deleted:

INTRODUCTION

Posterolateral fusion combined with pedicle instrumentation is frequently employed for the treatment of degenerative disease of the lumbosacral spine. Various indications include degenerative disc disease, spondylolisthesis, and instability. The results of instrumented posterolateral fusions in large clinical studies have shown varying rates of fusion and clinical outcomes [1-6]. Traditional sources of grafting material include autograft obtained locally from the iliac crest or from distal sources and different types of allograft [3-6].

Previous studies have demonstrated the ability of recombinant human bone morphogenetic protein (rhBMP-2) to achieve a solid fusion [7-9]. Recently, prospective randomized human clinical studies demonstrated superior fusion rates and clinical outcomes with rhBMP-2 and a collagen sponge (INFUSE® Bone Graft) versus autograft when using either cortical bone dowels or threaded interbody cages in anterior lumbar interbody techniques [10-11]. Nonhuman primate studies have demonstrated that rhBMP-2/ACS required additional osteoconductive bulking agents in order to achieve successful posterolateral spine fusion (11A-11C). A new formulation using an optimized rhBMP-2 concentration and a compression resistant carrier developed specifically for posterolateral fusions demonstrated excellent results in nonhuman primates (11D). A small pilot study on humans demonstrated similar results with rhBMP-2 combined with biphasic calcium phosphate versus iliac crest autograft for posterolateral fusions [12]. Currently, a prospective randomized FDA IDE study comparing iliac crest bone graft (ICBG) to rhBMP-2 combined with a carrier consisting of bovine collagen and tricalcium/hydroxyapatite to create a compression resistant matrix for single-level posterolateral fusions is ongoing. The purpose of our report is to present the two year radiographic results and clinical outcomes using rhBMP-2 matrix or ICBG in single-level instrumented fusions for lumbosacral degenerative disease.

MATERIAL AND METHODS

There were 463 patients enrolled in a multi-center prospective, randomized, nonblinded, FDA IDE study. There were 29 participating investigational sites with 83 spine surgeons. All of the patients were treated with a single-level instrumented fusion using CD Horizon® (I need to make this match the IDE and will provide proper language ASAP.) (Medtronic Sofamor Danek, Memphis, TN USA) pedicle screw and rod instrumentation. Exclusion criteria included a previous attempt at fusion at the intended surgical level, significant osteoporosis (less than 2 SD below normal on DEXA), autoimmune disease, malignancy, pregnancy, or the inability to harvest graft due to previous surgical procurement. Patients were randomly assigned to one of two groups: the control group received autogenous iliac crest bone graft (ICBG) and the investigational group received rhBMP-2 matrix (Medtronic Sofamor Danek, Memphis, TN, USA). The dose and concentration of rhBMP-2 used in this study is higher (2.0mg/cc for a total dose of 40mg, 20mg per side) than that of commercially available INFUSE® Bone Graft (1.5mg/cc for a total dose of 12mg per large kit).

The indications for surgery were symptomatic, single-level lumbosacral degenerative disease from L2/3 to L5/S1 of at least six months duration that had not responded to conservative care. The clinical symptoms included low back pain with or without radicular leg pain. Additional enrollment criteria were a Grade I or less spondylolisthesis and no previous fusion.

Deleted: equivalent
Deleted: Infuse
Formatted: Superscript
Deleted: (
Deleted: Compression
Deleted: , CRM)
Deleted: /CRM
Deleted: 476
Deleted: M8
Deleted: is this accurate?
Deleted: /CRM
Deleted: Infuse
Deleted: 6
Deleted: , 8 mg per side
Deleted: ,
Deleted: , or both
Deleted: , although degenerative disease adjacent to a previous fusion was acceptable

A standard open posterior approach was used for both the ICBG and rhBMP-2 matrix groups. Local bone graft obtained during the decompression was discarded. Bone graft from the iliac crest in the ICBG group was obtained in a standard open fashion. The bone graft was morselized and placed in the lateral gutters on the decorticated bony surface of the transverse processes and along the pars interarticularis.

The rhBMP-2 was reconstituted using sterile water into two 5 ml syringes containing 20mg of rhBMP-2. The matrix was cut lengthwise with a scalpel into two equal pieces using a cutting template. The reconstituted rhBMP-2 from each syringe was then uniformly distributed to each piece of the matrix and allowed to stand for a minimum of five minutes. The rhBMP-2 matrices were all implanted within 60 minutes following preparation. In no instance was the matrix of insufficient length to span the transverse processes in a single-level fusion. As required by the protocol, any local bone graft obtained from the decompression was discarded in the rhBMP-2 matrix group.

Clinical data were collected preoperatively and post operatively at six weeks, 3 months, 6 months, 12months, and 24 months. The validated outcome instruments employed included the Oswestry Low Back Pain Disability Index (ODI), the Short Form 36 (SF-36). Back pain, leg pain, and donor graft site pain in the control group were also monitored. Patients were asked to rate the frequency and intensity of their pain on a scale of 0 to 10 and the scores were summed to derive a 20 point numerical rating scale. Data on work status, patient satisfaction, and adverse events were also recorded. Neurological examination including motor function, sensory function, reflexes, and straight leg raise were recorded.

Plain radiographs, lateral flexion and extension radiographs, and CT Scans with sagittal and coronal reconstruction were used to evaluate the fusion in both groups post operatively at 6, 12, and 24 months. The CT imaging protocol consisted of one millimeter continuous non-overlapping axial slices that were taken without bone filter. The window and level settings were set to optimize trabecular bone detail (2000/350 on GE Scanners). The field of view was made as small as possible but still encompassed the complete vertebra in between and including the transverse processes. The radiographs and CT scans were evaluated by two independent radiologists who were blinded to which patient group they were evaluating (is this true?).

The rhBMP-2 matrix and ICBG group values were compared using ANOVA for continuous variables and Fisher's exact test for categorical variables for independent samples across each time interval.

RESULTS

All the patients were past the 12-month evaluation point, but the 24-month follow-ups are ongoing. There were 282 subjects available for assessment at two years postoperatively, 137 in the ICBG group and 145 in the rhBMP-2 matrix group. Randomization resulted in a similar distribution of baseline characteristics in the two study groups as shown in Table 1.

The average surgical time for the control patients was 2.9 hours which was significantly longer ($p<0.001$) than the 2.5 hours observed in the rhBMP-2 matrix group (Table 2). The average blood loss was 448.6 ml for the control patients which was also significantly greater ($p<0.001$) than the 343.1 ml blood loss observed with the rhBMP-2 matrix group. There was no statistically significant difference in length of hospital stay between the two groups. No surgeries were abandoned due to technical problems. There were no unanticipated intra-operative complications related to the fusion procedure.

Deleted: /CRM
Deleted: CRM
Deleted: CRM
Deleted: /CRM sponges
Deleted: sponge
Deleted: /CRM
Deleted: was
Deleted: post operatively
Deleted:
Deleted: , b
Deleted: and
Deleted: scores
Deleted: the Oswestry Low Back Pain Disability Index (ODI),
Deleted: , back pain and leg pain scores
Deleted: Scans
Deleted: an
Deleted: as
Deleted: /CRM
Deleted: initial review
Deleted: /CRM
Deleted: that might be independently related to the study outcomes
Deleted: =
Deleted: rhBMP-2/CRM
Deleted: cc
Deleted: s
Deleted: cc
Deleted: rhBMP-2/CRM

The ODI scores were similar in both groups over all time intervals (Figure 2) and showed statistically significant improvement compared to pre-operative scores in both the ICBG and rhBMP-2 matrix groups Table 4 [Comments: p-values showing significant improvement for within groups are not shown, but p-values comparing between the groups are shown, which are not significant. I would not show those between groups.]. The SF-36 physical component summary (PCS) scores were similar in both groups at all time intervals (Figure 1) and showed statistically significant improvement compared to pre-operative scores in both the ICBG and rhBMP-2 matrix groups Table 3 [Comments: p-values showing significant improvement for within groups are not shown, but p-values comparing between the groups are shown, which are not significant. I would not show those between groups.].

The back pain scores for the ICBG and rhBMP-2 matrix groups improved significantly from pre operative scores of 15.8 and 15.6 to 8.1 and 7.8 at 24 months, respectively. Both groups showed similar improvements over all time intervals (Figure 3) with no statistically significant difference in their 24 month back pain scores. The leg pain scores following surgery demonstrated that both the ICBG and rhBMP-2 matrix groups improved in a similar manner over all time intervals (Figure 4). Leg pain scores improved from 14.0 in both groups, to 7.4 in the ICBG group and 7.1 in the rhBMP-2 matrix group at 24 months. There was no statistically significant difference in their 24 month leg pain scores.

Pain resulting from iliac crest harvest was measured using donor site pain scores. These were collected only from the ICBG group. The mean donor site score after discharge was 11.3, which improved to 7.9 six weeks after surgery. There was minimal improvement on subsequent follow-up periods up to 24 months. A large number of patients in the ICBG group (54%) still had persistent donor site pain with a mean pain score of 5.0 at 24 months after surgery (Figure 5).

41.1% of subjects in the ICBG group were working prior to surgery and 48.5% were able to return to work at 24 months (Figure 6). 34.7% of the subjects in the rhBMP-2 matrix group were working prior to surgery as compared to 40.7% at 24 months postoperatively.

All plain films and CT scans were read by the independent radiologists. Fusion success was determined by the IDE protocol-defined analysis whereby assessment per plain films were considered first. In cases where the plain films did not exhibit bridging bone, CT scans were then considered and used for bridging bone determination. If any views were missing or of insufficient quality for reading such that each criterion could not be determined, the patient was deemed a missing in fusion regardless of the interpretation of other films [I suggest to delete this sentence. It is still not accurate.]. Assessment in this manner showed that 87.4% of patients in the rhBMP-2 group and 82.4% in the ICBG group achieved fusion success (p=.199) at 12 months. At 24 months, 94.9% in the rhBMP-2 matrix group achieved fusion success compared with 86.8% in the ICBG group (p=.074). Fine-cut CT scans with sagittal and coronal reconstructions showed that 74.4% of the subjects in the rhBMP-2 matrix group and 56.4% in the ICBG group had evidence of bilateral bridging bone at 6 months (p<0.001). At 12 months, 86.9% of subjects in the rhBMP-2 matrix group and 71.3% in the ICBG group had evidence of bilateral bridging bone (p<0.001) At 24 months, the rate was 93.6% in the rhBMP-2 group compared to 82.6% in the ICBG group (p=0.024)(Figure 7).

The most common complication which may have been related to the surgery were infections of various types at different sites. There was a higher incidence of superficial

5

Deleted: (PCS)
Deleted: rhBMP-2/CRM
Deleted:
Deleted: The ODI scores were similar in both groups over all time intervals (Figure 2) and showed statistically ... [1]
Deleted: rhBMP-2/CRM
Deleted: and
Deleted: rhBMP-2/CRM
Deleted: rhBMP-2/CRM
Deleted: hip
Deleted: hip pain
Deleted: Patients
Deleted: hip
Deleted: rhBMP-2/CRM
Deleted: , and
Deleted: 16
Deleted: returned to work
Deleted: T
Deleted: fusion
Deleted: fusion
Deleted: fusion success
Deleted: fusion failure
Deleted: [which utilized both
Deleted: P
Deleted: plain radiographs and CTs]
Formatted: Font: Not Bold
Deleted: at 12 months
Deleted: had evidence of fusion
Deleted: 2
Deleted: rhBMP-2/CRM
Deleted: were fused
Deleted: 37
Deleted: Scans
Deleted: rhBMP-2/CRM
Deleted: fusion
Deleted: rhBMP-2/CRM
Deleted: fusion
Deleted: of
Deleted: were fused
Deleted: of
Deleted: There were twice as mf ... [2]
Deleted: ¶
Formatted: Indent: First line: 36 pt
Formatted: Highlight

wound infections in the ICBG group. There was no difference in the incidence of deep wound infections, wound drainage or development of wound hematoma. Sixteen patients in the ICBG group complained of continued pain from the bone graft donor site that required active treatment. One patient developed a donor site infection. No adverse events were observed that could be directly attributable to the use of rhBMP-2 matrix.

DISCUSSION

The guiding principle for the surgical treatment of painful or unstable lumbosacral degenerative spinal disease remains the ability to achieve a solid fusion. Although autologous ICBG is the gold standard, the morbidity associated with graft harvest has led surgeons to seek viable alternatives, such as allografts, ceramics, and various types of growth factors [16-20]. These graft substitutes have demonstrated great variability in achieving fusion with the best success achieved when used in addition to iliac crest bone graft and not as an alternative to iliac crest bone graft. Additionally, they present their own unique problems including decreased success of fusion [21], limited availability, and the potential for rejection or immunologic reaction [17, 18].

The development of osteoinductive biologics has resulted in the clinical availability of recombinant human bone morphogenetic protein (rhBMP-2 and rhBMP-7) for spinal fusion [22]. These naturally occurring bone proteins stimulate bone healing via a cascade mechanism that results in the differentiation of primitive mesenchymal cells and preosteoblasts into osteoblasts that promote bone formation and ultimately, healing [23]. The effectiveness of rhBMP-2 in achieving a solid interbody fusion has been demonstrated in numerous experimental animal studies [7-9]. Subsequently, clinical trials have demonstrated similar fusion rates and clinical outcomes when ICBG was compared to rhBMP-2 combined with a collagen sponge carrier (INFUSE® Bone Graft) and a lordotic threaded interbody cage (LT-cage) [10, 11]. As a result of these findings the FDA approved the use of rhBMP-2 as a iliac crest bone graft replacement for lumbar interbody fusions in 2002.

A recent randomized human pilot study evaluated rhBMP-2 combined with biphasic calcium phosphate granules versus autograft in achieving a successful posterolateral fusion [11F]. The study demonstrated a 40% fusion rate in the autograft group versus a 100% fusion rate with the investigational group when evaluated by radiographs and CT scans. Oswestry and SF-36 outcome measures demonstrated significant but similar improvement of all groups at the end of the study. Although the authors sited several deficiencies, most notably the lack of a 24 month follow-up on all the subjects, the study presented strong evidence of the efficacy of rhBMP-2 in achieving a successful radiographically confirmed fusion in humans.

As part of an ongoing FDA regulated IDE study, rhBMP-2 is now being evaluated for use in single-level posterolateral fusions combined with pedicle screw/rod instrumentation. This report reviews our two-year clinical outcomes and fusion rates based on CT scans. This study utilizes a specifically designed carrier, that combines tricalcium phosphate and hydroxyapatite granules with a collagen matrix. This combination provides significant resistance to compression when placed in the lateral gutters. It is also important to emphasize that this study uses a higher concentration of rhBMP-2 (2.0mg/cc vs 1.5mg/cc) when compared to the concentration utilized in previous clinical studies with an absorbable collagen sponge carrier.

Although local bone graft is rarely discarded in clinical practice, the quality and quantity of local bone grafts are highly variable. In this study, local bone graft was

Deleted: rhBMP-2/ACM

Deleted: tissue

Deleted: appear to

Deleted: de

Deleted: 24

Deleted: Infuse

Deleted: bone graft substitute

Deleted: anterior

Deleted: posterior

Deleted: 10

Deleted: two

Deleted: for 282 subjects

Comment [LYC1]: Pre-clinical studies have shown that the concentration per carrier is more critical than the actual amount of BMP)

Deleted: ml

Deleted: ml

discarded in both groups to allow for a direct comparison of the fusion rates of rhBMP-2 matrix to ICBG without local bone graft as a confounding variable.

Perioperative measures indicate improvements in operative time and blood loss, which were significantly less in the rhBMP-2 matrix group as compared to the ICBG group. The length of hospital stay was the same for both groups. The incidence of deep wound infections, wound drainage or development of wound hematoma was similar in both groups. There was a higher incidence of superficial wound infections in the ICBG group which may be due to the need for significant retraction to access the iliac crest through the same incision for bone graft harvest.

An equally important measure of the success of a fusion procedure, beyond the radiographic evidence of fusion, is how the patient feels and functions after surgery. The use of validated patient-based clinical outcome measures such as the Oswestry Disability Index and the SF-36 provide a self-assessment of the patient's functional improvement rather than the clinician's perception [13]. Most of the improvement in ODI scores and SF-36 PCS occurred within the first three months after surgery, in both groups. This improvement was maintained through the subsequent follow-up periods up to 24 months. The improvement in PCS at 24 months in both groups was well above the 5.41 point threshold in the literature for clinically significant improvement [26? check reference?]. The average decrease in ODI scores at 24 months in both groups was greater than 25 points [comments: I think the 15-point value refers to patient-based meaningful improvement. The group-based value would be 4-5 points], which is also above that necessary to demonstrate treatment efficacy [27].

Most of the improvement in back pain and leg pain scores was noted within the first six weeks after surgery, and was maintained throughout the entire follow-up period. The 6.9 point decrease in back pain in the rhBMP-2 matrix group and 7.7 in the ICBG group indicates a clinically significant diminution in back pain following surgery. The 7.9 point decrease in leg pain in the rhBMP-2 matrix group and 8.4 in the ICBG group indicates a clinically significant diminution in leg pain following surgery.

The rates of fusion in previously published articles vary widely from 60% to 98%. This may be due to the use of plain radiographs with flexion extension views which are known to be inaccurate with error rates estimated from 20 to 40% [citation?]. When fusion success was determined using the IDE protocol-defined criteria, the rhBMP-2 matrix group had smaller differences in fusion success rates as compared with the ICBG group. Using thin-cut CT scans, bilateral bridging bone was reported by the independent, blinded radiologists significantly more often in the rhBMP-2 matrix group as compared to the ICBG group at all three time points. [include statement referencing Steve Glassman's work (SPINE 2005) on the quality of fusion? Perhaps -- In a separate study derived from a subset of this patient population, it was reported that rhBMP-2 matrix produced a more robust fusion mass as compared to iliac crest bone graft as judged from CT scans alone.] This suggests that the use of fine-cut CT scans with sagittal and coronal reconstructions may increase its ability to demonstrate the robustness of the fusion and the presence of bilateral confluent bridging bone. At the 24 month follow-up period, there were twice as many patients in the ICBG group with established nonunions [what is the source for this comment? Is this the adverse event nonunion rate? I would move this statement earlier in the discussion, perhaps with the adverse events above, to help end on a strong note.].

Deleted: rhBMP-2/CRM

Deleted: The results of this study demonstrate significant improvement of the ODI, SF-36,

Deleted: ODI,

Deleted: leg and back pain scores in both groups over all time intervals. There were differences in

Deleted: /CRM

Deleted: all

Deleted: 25

Deleted: 15

Deleted: 26,

Deleted: rhBMP-2/CRM

Deleted: rhBMP-2/CRM

Deleted: rates of fusion in previously published articles varies

Deleted: form

Deleted: 1

Deleted: and CT Scans

Deleted: assessed

Deleted: that use plain radiographs and CTs

Deleted: rhBMP-2/CRM

Deleted: both groups

Deleted: similar

Deleted: without radiolucencies or clefts within the fusion mass

Deleted: and these rates were higher than that observed when fine-cut CT Scans were used. [Comments: if just plain radiographs are used, the fusion rates would be lower than those just from CTs. The IDE fusion rates use both for determining bridging bone.] Subjects in the ICBG group demonstrated lower fusion rates over all time intervals compared to the rhBMP-2/CRM group when fine-cut CT Scans with reconstructions were used to assess fusions.

Deleted: 7

Deleted: the accuracy by which fusions are assessed by

Deleted: The incidence of deep wound infections, wound drainage or development of wound hematoma was similar in both groups. There was a higher incidence of superficial wound infections in the ICBG group which may be due to the need for significant retraction to access the iliac crest through the same incision for bone graft harvest.

CONCLUSION

This study demonstrates that, for patients with a single-level degenerative disease, an instrumented posterolateral fusion with ICBG and rhBMP-2 matrix provide excellent clinical improvement and exhibit similar clinical outcomes two years after surgery. The rhBMP-2 matrix group demonstrated significantly decreased intraoperative blood loss and decreased operative time when compared to the ICBG group. The rhBMP-2 matrix demonstrated an improved fusion success rate when compared to the ICBG group at 24 months. There were no significant differences in complications between the two groups. In conclusion, rhBMP-2 matrix demonstrated similar clinical outcomes and increased fusion rates when compared to ICBG for a single-level instrumented posterolateral fusion.

Deleted: rhBMP-2/CRM

Deleted: rhBMP-2/CRM

Deleted:

Deleted: rhBMP-2/CRM

Deleted: rhBMP-2/CRM

Table 1. Patient Demographic Data

	rhBMP-2 matrix	ICBG
Age (years)	53.2	52.3
Gender (%Male)	45.2	42.4
Workmen's Comp (%)	11.3	12.5
Smoker (%)	26.4	26.3

Table 2. Surgical data

	rhBMP-2 matrix	ICBG	p=value
OR Time	2.5	2.9	<0.001
EBL	343.1	448.6	<0.001
Hospital Stay	4.1	4.0	0.609

Table 3. Mean change in SF-36 PCS compared to pre-operatively on each follow-up period

Mean Change in SF-36 PCS	rhBMP-2 matrix	ICBG	p=value
6 weeks	3.8	4.5	0.378
3 months	9.5	8.8	0.465
6 months	12.9	10.9	0.073
12 months	13.7	11.6	0.070
24 months	12.7	12.8	0.990

Table 4. Mean Improvement in ODI compared to pre-operatively on each follow-up period

Mean Improvement in ODI	rhBMP-2 matrix	ICBG	p=value
6 weeks	12.9	13.9	0.580
3 months	22.1	21.2	0.610
6 months	26.0	24.4	0.382
12 months	26.9	25.4	0.452
24 months	27.2	25.6	0.582

Deleted: rhBMP-2/CRM
Deleted: 9
Deleted: rhBMP-2/CRM
Deleted: 4
Deleted: rhBMP-2/CRM
Deleted: 9
Deleted: 7
Deleted: 1
Deleted: 3
Deleted: change
Deleted: Change
Deleted: rhBMP-2/CRM
Deleted: 5
Deleted: 5.8
Deleted: 2

Table 5. Complications

	rhBMP-2 matrix	ICBG
Wound Drainage	4	3
Superficial Infection	5	15
Deep Infection	5	5
Wound Hematoma	1	0
Epidural Hematoma	2	0
Malignancy*	7	4
Anemia	26	29
UTI	8	9
Infection (Other sites)	27	19
Infection (Total)	46	48
Nonunion	11	22
AIF	6	10
PSF	0	6
Symptomatic	2	5
Asymptomatic	3	1
Dural Tear	14	18
Adjacent Level Degeneration	3	7
Surgical	2	5
Nonsurgical	1	2
Renal Stones	7	4
Pulmonary	17	9
Ileus	10	4
Technical Problems	9	6
Death	3	4
Donor Site Complaints	0	16
Donor Site Infection	0	1

*Cancer types in the rhBMP-2 matrix group include Follicular, Squamous Cell, Laryngeal, Pancreatic, Prostate, Lung and Basal Cell; in the ICBG group types include NonHodgkin's Lymphoma, Breast, Colon and an unknown Primary

Formatted: Highlight

Deleted: rhBMP-2/CRM

Deleted: rhBMP-2/CRM

FIGURES

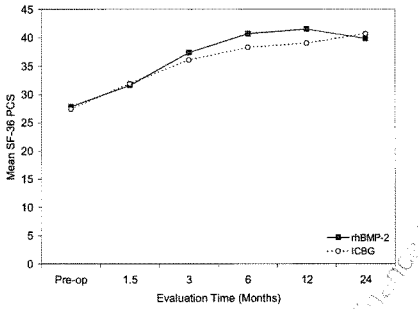


Figure 1. Comparison of SF-36 PCS in the ICBG and rhBMP-2 matrix groups.

Deleted: rhBMP-2/CRM

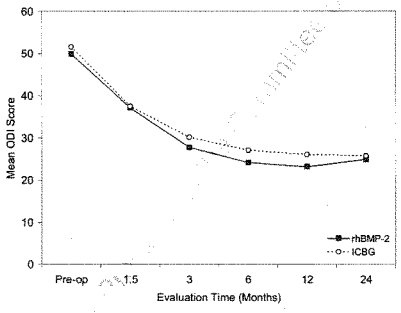


Figure 2. Comparison of ODI in the ICBG and rhBMP-2 matrix groups. I would recommend substituting the plot showing average improvement here rather than average scores. I think it will be more compelling to surgeons and payers alike.

Deleted: rhBMP-2/CRM

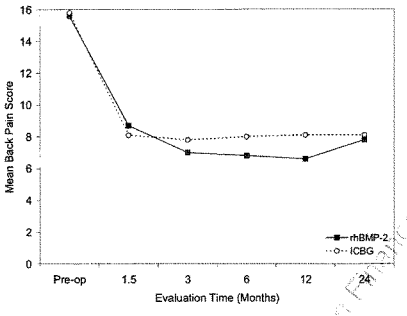


Figure 3. Comparison of mean back pain scores in the ICBG and rhBMP-2 matrix groups.

Deleted: rhBMP-2/CRM

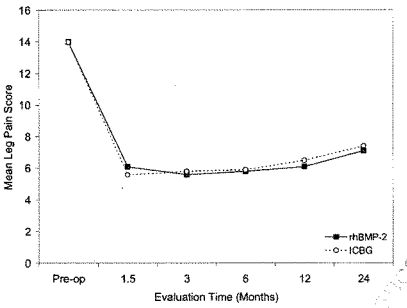


Figure 4. Comparison of mean leg pain scores in the ICBG and rhBMP-2 matrix groups. **Deleted:** rhBMP-2/CRM

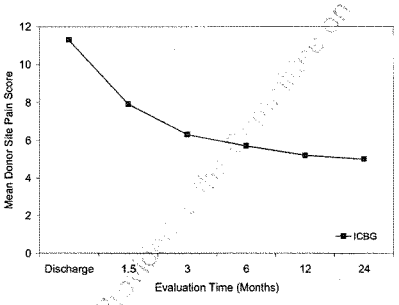


Figure 5. Mean donor site pain scores in the ICBG group. **Deleted:** bip

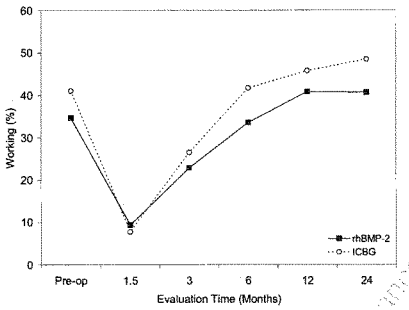


Figure 6. Percentage of subjects working in the ICBG and rhBMP-2 matrix groups.

Deleted: rhBMP-2/CRM

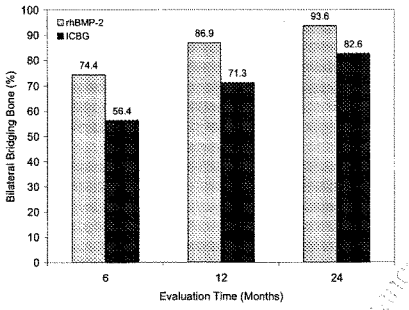


Figure 7. Percentage of subjects with bilateral confluent bridging bone reported by independent radiologists as observed on fine-cut CT scans with reconstructions for the ICBG and rhBMP-2 matrix groups.

Deleted: Scans

Deleted: rhBMP-2/CRM

REFERENCES

1. Bono CM, Lee CK: Critical Analysis of Trends in Fusion for Degenerative Disc Disease Over the Past 20 Years. Spine. Feb 15;29(4):455-63.
2. An HS, Lynch K, Toth J: Prospective Compatison of Autograft vs. Allograft for Adult Posterolateral Lumbar Spine Fusion: Differences Among Freeze-Dried, Frozen, and Mixed Grafts. J Spinal Disord. Apr;8(2):131-5, 1995
3. An HS, Lynch K, Toth J: Prospective Compatison of Autograft vs. Allograft for Adult Posterolateral Lumbar Spine Fusion: Differences Among Freeze-Dried, Frozen, and Mixed Grafts. J Spinal Disord. Apr;8(2):131-5, 1995
4. Dawson EG, Lotysch M 3rd, Urist MR: Intertransverse Process Lumbar Arthrodesis with Autogenous Bone Graft. Clin Orthop Jan-Feb;(154):90-6,1981
5. Dimar, Glassman, Burkus, Carreon: A Comparison of Prospective Clincial Outcome Measures for Anterior vs. Posterior Single-level Spine Fusion. IMAST Program July 2004
6. Jorgenson SS, Lowe TG, France J, Sabin J: A prospective analysis of autograft versus allograft in posterolateral lumbar fusion in the same patient. A minimum of 1 – year follow-up in 144 patients. Spine Sep 15;19(18):2048-53, 1994
7. consider using this citation instead: Sandhu HS, Toth JM, Diwan AD, Seim HB III, Kanim LEA, Kabo JM, Turner AS "Histological evaluation of the efficacy of rhBMP-2 compared with autograft bone in sheep spinal anterior interbody fusion" *Spine*, 27 (6): 567 – 575, 2002
Rather than
Martin GJ Jr, Boden SD, Marone MA, Moskovitz PA: Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: important lessons learned regarding dose, carrier, and safety. J Spinal Disord. Jun;12(3):179-86, 1999

8. Boden SD, Martin GJ Jr., Horton WC, Truss TL, Sandhu HS "Laparoscopic anterior spinal arthrodesis with rhBMP-2 in a titanium interbody threaded cage" *J Spinal Disorders*, 11 (2): 95 – 101, 1998

9. consider using this citation as an alternate: Hecht BP, Fischgrund JS, Herkovitz HN, Penman L, Toth JM, Shirkhoda A "The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model" *Spine*, 24 (7): 629 – 636, 1999
Rather than
Boden SD, Schimandle JH, Hutton WC, Chen MI: 1995 Volvo Award in Basic Science. The Use of an Osteoinductive Growth Factor for Lumbar Spine Fusion. Part I: Biology of Spinal Fusion. Spine 15; 20(24):2626-32, 1995
10. Burkus JK, et al. "Is INFUSE Bone Graft superior to iliac crest bone graft? ..." J Spinal Disord Tech, 2003
11. Burkus JK, Dorchak JD, Sanders DL,: Radiographic Assessment of Interbody Fusion Using Recombinant Human Bone Morphogenetic Protein Type 2. Spine 15; 8(4):372-7, 2003
11A Martin GJ Jr., Boden SD, Marone MA, Moskovitz PA "Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: important lessons learned regarding dose, carrier, and safety" *J Spinal Disorders*, 12 (3): 179 – 186, 1999

Deleted: 8. Yoon ST, Park JS, Kim KS, Li J, Attallah-Wasif ES, Hutton WC, Boden SD, ISSLS Prize Winner: LMP-1 Upregulates Intervertebral Disc Cell Production of Proteoglycans and BMPs in Vitro and in Vivo. Spine 29(23):2603-11, 2004¶

Deleted: Gornet MF, Dickman CA, Zdeblick TA: Anterior Lumbar Interbody Fusion Using rhBMP-2 with Tapered Interbody Cages.

Deleted: 15(5):337-49

Deleted: 2002

Formatted: Normal, Justified, Space After: 12 pt, Keep lines together

11B Barnes B, Boden SB, Louis-Ugbo J, Tomak PR, Park J, Park M, Minamide A "Lower dose of rhBMP-2 achieves spine fusion when combined with an osteoconductive bulking agent in non-human primates" *Spine*, 30 (10): 1127-1133, 2005

11C Akamaru T, Suh D, Boden SD, Kim H-S, Minamide A, Louis-Ugbo J "Simple carrier matrix modifications can enhance delivery of recombinant human bone morphogenetic protein-2 for posterolateral spine fusion" *Spine*, 28 (5): 429 – 434, 2003

11 D Suh DY, Boden SD, Louis-Ugbo J, Mayr M, Murakami H, Kim HS, Minamide A, Hutton WC "Delivery of recombinant human bone morphogenetic protein – 2 using a compression-resistant matrix in posterolateral spine fusion in the rabbit and in the non-human primate" *Spine*, 27 (4): 353 – 360, 2002

11E Boden SD, Martin GJ Jr., Morone MA, Ugbo JL, Moskovitz PA "Posterolateral lumbar intertransverse process arthrodesis with recombinant human bone morphogenetic protein 2 / hydroxyapatite – tricalcium phosphate after laminectomy in the nonhuman primate" *Spine*, 24 (12): 1179 – 1185, 1999

11F Boden SD, Kang J, Sandhu H, Heller JG "Use of rhBMP-2 to achieve posterolateral lumbar spine fusion in humans: A prospective and randomized clinical pilot trial" *Spine*, 27 (23): 2662 – 2673, 2002

12. Boden SD, Kang J, Harvinder S, Heller JG: Use of Recombinant Human Bone Morphogenetic Protein-2 to Achieve Posterolateral Lumbar Spine. Spine. Dec 1;27(23):2662-73, 2002
13. Ware JE Jr, Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. Jun;30(6):473-83, 1992
14. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD: The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. Jan;32(1):40-66, 1994
15. Fairbank JC, Couper J, Davies JB, O'Brien JP: The Oswestry low back pain disability questionnaire. Physiotherapy. Aug;66(8):271-3, 1980
16. Glassman SD, Dimar JR, Carreon LY, Campbell MJ, Johnson JR and Puno RM. Initial fusion rates with rh-BMP-2 and HA-TCP/Collagen carrier in posterolateral fusion. In Publication.
17. Boden SD. Overview of the biology of lumbar spine fusion and principles for selecting a bone graft substitute. Spine, 2002; 27(16S):S26-S31.
18. Ludwig SC, Kowalski JM and Boden SD. Osteoinductive bone graft substitutes. Eur Spine J, 2000; 9(Suppl 1):S119-S125.
19. Lind M and Bunger C. Factors stimulating bone formation. Eur Spine J, 2000; 9(Suppl 1):S102-S109.
21. Vaccaro AR, Sharon AD, Tuan RS, Kang JD, An HS, et al. The use of biologic materials in spinal fusion. Orthopedics, 2001; 24(2):191-197.
22. Carreon LY, Glassman SD, Anekstein Y, Puno RM. Platelet gel (AGF) fails to increase fusion rates in instrumented posterolateral fusions. Spine. 2005 May 1;30(9):E243-6.
23. Urist MR: Bone: formation by autoinduction. Science. 1965 Nov 12;150(698):893-9
24. Martin GJ Jr, Boden SD, Marone MA, Marone MA, Moskovitz PA: Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: important lessons learned regarding dose, carrier, and safety. J Spinal Disord. Jun;12(3):179-86, 1999
25. Suh DY, Boden SD, Louis-Ugbo J, Mayr M, Murakami H, Kim HS, Minamide A, Hutton WC. Delivery of recombinant human bone morphogenetic protein-2 using a

compression-resistant matrix in posterolateral spine fusion in the rabbit and in the non-human primate. Spine. 2002 Feb 15;27(4):353-60.
26. Ware JE, Kosinski M, Keller SK. SF-36® Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: The Health Institute, 1994.
27. Fairbank JCT, Pynsent PB: The Oswestry Disability Index. SPINE 2000;25(22):2940-2953.
28. Walsh TL, Hanscom B, Lurie JD, Weinstein JN: Is a condition-specific instrument for patients with low back pain/leg symptoms really necessary? The responsiveness of the Oswestry Disability index, MODEMS and the SF-36. Spine 2003 Mar 15;28(6):607-15.

Page 5: [1] Deleted bearcj1 6/26/2006 5:50:00 AM

The ODI scores were similar in both groups over all time intervals (Figure 2) and showed statistically significant improvement compared to pre-operative scores in both the ICBG and rhBMP-2/CRM groups Table 4 [Comments: p-values showing significant improvement for within groups are not shown, but p-values comparing between the groups are shown, which are not significant. I would not show those between groups.]. [I would change the order ODI and PCS]

Page 5: [2] Deleted bearcj1 6/26/2006 6:08:00 AM

There were twice as many nonunions in the ICBG group compared to the rhBMP-2/CRM group.

From: sdg[redacted]
Sent: Monday, September 4, 2006 09:45:09 AM
To: Bearcroft, Julie, PhD
CC: lcarreon[redacted]; tallgeye[redacted]
Subject: Re: smoking paper

Attachments: THE_EFFICACY_OF_rhBMP-2_9-05-06.doc

Hi Julie
Thanks for your additional input. I have incorporated mostof your suggestions. I think you added too many words for the abstract, so I left out a few. Also, in the introduction I am refering to BMP generically, not just rhBMP or rhBMP-2.
I understand your point about BMP formulation. I incorporated your suggestions on that and added the thought again in the discussion (see paragraph beginning with "Given the constraints").
As far as the issue of quantifying DDD, I don't believe that adding anatomic descriptors will achieve your goal. That is just not a way in which specific diagnosis is presented or understood. If you want to make that arguement, you will need to start with a paper looking specifically at the relationship between those anatomic parameters and some known diagnoses. I doubt it will work because the characteristics you identify are as much a part of normal aging as they are assocoated with pathology. Sorry.
Let me know about the numbers and we can get this submitted this week.
Regards
Steve
Tana - this is an updated version.

-----Original Message-----
From: julie[redacted]bearcroft[redacted]
To: sdg[redacted]
Cc: matt[redacted]meyer[redacted]
Sent: Fri, 1 Sep 2006 1:49 PM
Subject: RE: smoking paper

Steve -

I read through the manuscript and inserted some comments for consideration. I also inserted some commentary about the dose notation that I raised in an earlier email.

To help you understand my thought process, let me outline some of my thoughts.

- <![endif]>We only studied one formulation (carrier + dose) in one application (posterolateral) in this study and found that it appears to have a benefit even in smokers.
- <![endif]>We have not studied other formulations (INFUSE) or dose (# kits/level) in a systematic way so we don't know the answer for that circumstance.
- <![endif]>I think graft volume may also be an important factor. AMPLIFY delivers 10 cc per side in final graft volume. Since INFUSE is so malleable, I think the graft volume is realistically equal to the bulking agent volume. So I think these may be apples and oranges w.r.t. this issue.

You are right in that I think you did do an excellent job to distinguish AMPLIFY from INFUSE in the paper. I am just questioning the validity of commenting on rhBMP-2 dose when some data points are missing.

An edited version and I think my changes are in green. I did make a couple other changes.

Another thought I had was to add some commentary defining DDD. Insurers don't like it because it is not a diagnostic code. I asked Youjun to provide some diagnostic info to help fill in the blanks. I will admit that it is difficult to interpret but I think if we include language about the characteristics of these patients and how many had multiple characteristics identified, it may be more impactful to the insurers. (Youjun's new data is attached.) I'm interested in your thoughts from the surgeon perspective.

I also have to confess that I have not yet validated every single number in the document. I will do that last quality check this weekend and reply back on Tuesday.

Call me if you have any questions,
julie

From: sdg[redacted]
Sent: Wednesday, August 30, 2006 8:11 AM
To: Bearcroft, Julie, PhD
Cc: Meyer, Matt
Subject: smoking paper

Hi Julie
I have not heard from anyone, which I will interpret as a go ahead. My plan is to submit to SPINE on Friday. If you have any last minute issues, let me know. I will be in Memphis on Thursday if you need me.
Steve

Check out AOL.com today. Breaking news, video search, pictures, email and IM. All on demand. Always Free.

Formatted: Different first page

The Efficacy of rhBMP-2 for Posterolateral Lumbar Fusion in Smokers

Deleted: THE IMPACT OF SMOKING ON LUMBAR FUSION USING A
Formatted: Font: 14 pt
Deleted: MATRIX
Formatted: Font: 14 pt
Formatted: Font: 14 pt
Formatted: Superscript

[†]Steven D. Glassman, M.D., [†]John R. Dimar, III, M.D., **Kenneth Burkus, M.D., [†]James W. Hardacker, M.D., [†]Philip W. Pryor, M.D., *Scott D. Boden, [†]Leah Y. Carreon, M.D., M.Sc.

Formatted: Superscript

[†]Department of Orthopaedic Surgery, University of Louisville School of Medicine and the Kenton D. Leatherman Spine Center, Louisville, Kentucky
**The Hughston Clinic, Columbus, Georgia
[†]The Spine Institute, Carmel, Indiana
*Emory Spine Center, Emory University School of Medicine, Atlanta, Georgia

Formatted: Left

Reprint Requests:
Steven D. Glassman, M.D.
[redacted]
Louisville, Kentucky 40202
Fax: [redacted]

Formatted: Italian (Italy)

Formatted: Left
Formatted: Right

Formatted: Right

Abstract

Deleted: ¶
Formatted: Line spacing: Double

Study Design: Retrospective review of prospectively collected data, as part of an IRB approved, at three spine centers FDA regulated, randomized nonblinded IDE trial of rhBMP-2 matrix for lumbar spinal fusion.

Objectives: The purpose of this study is to examine the influence of smoking on fusion rate and outcome in a large series of patients treated with an rhBMP-2 matrix (AMPLIFY) or iliac crest bone graft as part of a randomized IDE trial for single level lumbar fusion.

Summary of Background Data: Preclinical studies suggest that BMPs are able to reverse the negative influence of nicotine on fusion healing in animal models. It remains unclear if a similar benefit will be seen in humans, and if so, what formulation and amount of BMP will be required to achieve that improvement.

Deleted: amount

Methods: We reviewed the clinical and radiographic records of 148 patients who underwent single level instrumented lumbar fusion at three spine centers as part of an ongoing FDA regulated IDE trial. Clinical outcome measures included ODI, SF-36, back and leg pain scores. Radiographic measures were plain x-ray with flexion/extension views and fine cut CT scan with sagittal and coronal reconstruction. Fusion success was determined by independent radiologist readings.

Deleted: at one of three spine centers

Results: At 2 years post-op, solid fusion was demonstrated in all 55 nonsmokers in the rhBMP-2 group (100%). Successful fusion was seen in 20 of 21 smokers in the rhBMP-2 group (95.2%),

Formatted: Right

Fusion was achieved in 48 of 51 nonsmokers in the ICBG group (94.1%), but only 16 of 21 smokers (76.2%) in the ICBG group.

Conclusions: The results of this study suggest that rhBMP-2 enhances fusion rate in cigarette smokers undergoing single level instrumented posterolateral lumbar fusion. Despite the improvement in fusion rate with rhBMP-2, clinical outcomes measures were still adversely affected in smokers.

Key words: Lumbar fusion, rhBMP-2, smoking, bone graft

Key points

Formatted: Bullets and Numbering

- rhBMP-2 enhances fusion rate in smokers
- Clinical outcome measures are worse in smokers
- Smoking abatement prior to lumbar fusion surgery is recommended.

 Formatted: Right

Mini-abstract:

This study examines the influence of smoking on fusion rate and outcome in patients treated with rhBMP-2 or ICBG as part of a randomized IDE trial for single level lumbar fusion. The results suggest that rhBMP-2 enhances fusion rate in smokers. Clinical outcomes measures were still adversely affected in smokers.

Formatted: Right

INTRODUCTION

Deleted: Introduction.

Cigarette smoking has been identified as an important risk factor for both nonunion and poor clinical outcome in lumbar spine fusion surgery (Glassman, Anderson, Kwon and Brown). In particular, smoking has been shown to markedly diminish fusion rate for the challenging healing environment associated with posterolateral spine fusion procedures. A variety of strategies have been advocated to offset this negative impact of cigarette smoking. They include smoking abatement (Glassman, Whitesides), spinal instrumentation and circumferential fusion. (Mirovski, Kwon) The advent of biologic osteoinductive graft alternatives has introduced a new set of potential options in the management of this difficult clinical problem.

Deleted:

Deleted: Canadian study etc

Recent experience with bone morphogenic proteins (BMP) has documented their potency as an iliac crest bone graft (ICBG) substitute (Burkus 1,Burkus 2, Glassman, Abraham EP, Alexander DI) and generated high expectations for achieving fusion in complex and difficult cases. The question, therefore, is whether BMPs can overcome the adverse effect of smoking on lumbar fusion. Preclinical studies suggest that BMPs are able to reverse the negative influence of nicotine on fusion healing in animal models (Patel, Silcox). It remains unclear if a similar benefit will be seen in humans and, if so, what formulation and amount of BMP will be required to achieve that improvement. The purpose of this study is to examine the influence of smoking on fusion rate and outcome in a large series of patients treated with an rhBMP-2 matrix (AMPLIFY™ rhBMP-2 Matrix, Medtronic, Memphis TN) or iliac crest bone graft as part of a randomized IDE trial for single level lumbar fusion.

Deleted:

Deleted: .

METHODS

We reviewed the clinical and radiographic records of 148 patients who underwent single level lumbar fusion at three spine centers. Patients were studied as part of an IRB approved, FDA regulated, randomized nonblinded IDE trial of rhBMP-2 matrix for posterolateral lumbar spinal fusion. It is important to note that the patients were randomized based upon bone graft technique (rhBMP-2 vs. ICBG), not smoking status, and that this is a retrospective review of that data.

Inclusion criteria for this study were single level lumbar degenerative disc disease in patients over 18 years of age with no greater than Grade I spondylolisthesis. Exclusion criteria included autoimmune diseases, chronic steroid dependence, ODI less than 30, and high risk for noncompliance with study protocol. All patients underwent single level fusion with adjunctive screw/rod instrumentation. All patients were evaluated at a minimum two year follow-up.

Posterior lumbar decompression and instrumentation was performed according to a standardized technique based on the IDE study protocol. In the ICGB group, a bone graft harvest was performed through a separate fascial incision over the iliac crest and the quantity of bone obtained was recorded. In the rhBMP-2 group, a 10 cc HA/TCP and collagen compression resistant matrix was combined with 20 mg. rhBMP-2 per side at a final graft concentration of 2 mg/ml. Local bone was excluded as per IDE protocol in both groups.

Clinical outcome measures included ODI, SF-36, back and leg pain scores. Outcome measures were performed at 6 weeks, 3 months, 6 months, and 1 and 2 years post-op. Radiographic

Formatted: Right
Deleted: Methods
Deleted: one of
Deleted: erous ICGB
Deleted: DDD
Deleted: 50
Deleted: a
Deleted: the
Deleted: rhBMP-2
Formatted: Line spacing: Double

Formatted: Right

measures were plain x-ray with flexion/extension views and fine cut CT scan with sagittal and coronal reconstruction. CT scans were performed at 6 months, 1 year and 2 years post-op. Fusion success, evaluated as per the IDE protocol, was defined as bilateral bridging trabecular bone on plain radiographs with less than 3 degrees of translation and less than 5 degrees of angulation on flexion/extension views. CT scans were used as a secondary measure when bridging trabecular bone was not observed on plain radiographs. Fusion status was separately evaluated for all patients based primarily upon the presence or absence of contiguous bridging bone on fine cut CT scan with coronal and sagittal reconstructions. Assessment of all radiographic parameters was conducted by independent radiologists, blinded to treatment group.

Deleted: CT

Deleted: as

Deleted: if the presence of

Deleted: could not be evaluated

Deleted: also

Deleted: , as per the standard of

Deleted: more

Deleted: recent literature,

Deleted:

Deleted: Both fusion criteria were assessed

Deleted: 's review

Deleted: Clinical outcome measures included ODI, SF-36, back and leg pain scores. Outcome measures were performed at 6 weeks, 3 months, 6 months, and 1 and 2 years post-op. Radiographic measures were plain x-ray with flexion/extension views and fine cut CT scan with sagittal and coronal reconstruction. CT scans were performed at 6 months, 1 year and 2 years post-op. Fusion was defined by the IDE protocol as contiguous bony bridging

Deleted: on CT scan

Deleted: with less than 3 degrees of motion on flexion/extension views by independent radiologist's review.

Formatted: Right

Deleted: Results

RESULTS

Deleted: 50.5 (

Deleted: 2 for all of the 148 patients)

Deleted: (table 3 don't have the exact numbers)

The 148 patients studied included 71 males and 77 females. Mean age was 51.1 (range 18-78) years. Overall, there were 42 smokers and 106 nonsmokers. There were 21 smokers and 55 nonsmokers in the rhBMP-2 group and 21 smokers and 51 nonsmokers in the ICBG group. There were no statistically significant differences in demographic parameters between the four smoking/graft montage subgroups (Table 1).

Deleted: ,

Deleted: ,

At 2 years post-op, successful fusion by IDE protocol criteria was demonstrated in all 55 nonsmokers in the rhBMP-2 group (100%). Successful fusion was seen in 20 of 21 smokers in the rhBMP-2 group (95.2%). Fusion was achieved in 48 of 51 nonsmokers in the ICBG group (94.1%), but only 16 of 21 smokers (76.2%) in the ICBG group (Figure 1). There was a statistically significant difference between fusion rate in the smoker/ICBG group versus the nonsmoker/ICBG group (p=0.042), but no statistically significant difference between the smoker/rhBMP-2 and nonsmoker/rhBMP-2 groups (p=0.276). There was also a significant difference in fusion rate between all smokers (85.7%) and all nonsmokers (97.2%) (p=0.016). The higher fusion rate in the smoker/rhBMP-2 group versus the smoker/ICBG group was not significant (p=0.184).

Deleted: fusion status

Deleted: Solid fusion

Deleted: Solid fusion

Assessment of contiguous bridging bone based on CT scan criteria demonstrated similar findings. Bridging bone was identified in 54 of 55 nonsmokers (98.1%) and 20 of 21 smokers (95.2%) in the rhBMP-2 group. Bridging bone was documented less frequently in ICBG cases.

specifically 46 of 51 (90.2%) nonsmokers and 16 of 21 smokers (76.2%) (Figure 2). None of the differences were statistically significant.

At every post-operative interval, statistically significant improvement from baseline was observed for ODI and SF-36 PCS measures in both smokers and nonsmokers. (Figure 3) Statistically significant improvement was also seen for VAS back and leg pain scores in both smokers and nonsmokers (Figure 4). Although improvement was statistically significant in both groups, the mean SF-36, ODI scores were consistently better for nonsmokers (Figure 5).

At two years post-op, ODI improved a mean 26.4 points in rhBMP-2 nonsmokers, 24.6 points in ICBG nonsmokers, 22.1 points in rhBMP-2 smokers and 21.0 points in ICBG smokers. SF-36 PCS improved a mean 10.2 points in rhBMP-2 nonsmokers, 11.2 points in ICBG nonsmokers, 7.1 points in rhBMP-2 smokers and 11.6 points in ICBG smokers. Improvement in back pain scores was a mean 7.4 points in rh-BMP-2 nonsmokers, 7.5 points in ICBG nonsmokers, 7.9 points in rhBMP-2 smokers, and 6.1 points in ICBG smokers.

Assessment of SF-36 MCS scores revealed a statistically significant improvement at 2 years post-op in nonsmokers but only a trend toward improvement in smokers. Magnitude of SF-36 MCS improvement at 2 years post-op was 7.0 points in rhBMP-2 nonsmokers, 6.1 points in ICBG nonsmokers, 5.5 points in rhBMP-2 smokers and 6.5 points in ICBG smokers. While there were no statistically significant differences in return to work rate comparing rhBMP-2 and ICBG subgroups, nonsmokers were more likely to be working both preoperatively (44.3% vs. 21.4%) (p=0.014) and post-operatively (46.7% vs. 27.5%) (p=0.074).

Formatted: Right

Deleted: in

Deleted: CHECK DATA

Deleted: in the ICBG group

Deleted: At 2 years postop, solid fusion was demonstrated in all 55 nonsmokers in the rhBMP-2 group (100%). Successful fusion was seen in 20 of 21 smokers in the rhBMP-2 group (95.2%). Fusion was achieved in 48 of 51 nonsmokers in the ICBG group (94.1%), but only 16 of 21 smokers (76.2%) in the ICBG group (Figure 1.). There was a statistically significant difference between fusion rate in the smoker/ICBG group versus the

Deleted: other three groups(the p-value only for smoking vs nonsmoking in the control group)

Deleted: nonsmoker/ICBG group (p=0.042), but no statistically significant difference between the smoker/rhBMP-2 and nonsmoker/rhBMP-2 groups (p=0.276).

Deleted: (Julie – Have I presented the stat accurately?)

Deleted: There was also a significant difference in fusion rate between all smokers (85.7%) and all nonsmokers (97.2%) (p=0.016). The higher fusion rate in the smoker/rhBMP-2 group versus the smoker/ICBG group was not significant (p=0.184).

Deleted: There was not a statistically significant difference in fusion success when comparing the nonsmoker/rhBMP-2 and nonsmoker/rhBMP-2 groups [1]

Deleted: ¶
¶ [2]

Deleted: 10.3(…)…11.0(…)…11.8 (…)…7.5 (…)…7.2 (…)…7.8 (… [3]

Deleted: postop

Deleted: 6.8 (…)…6.3 (…)…4.9 (…)…5.0(…) [4]

Deleted: (Julie – I don't have MCS data in this version. Should I exclude [5]

Deleted: (

Deleted: in each group between smoking and

Deleted: nosmoking

Deleted: nonsmoking

Deleted:)

Deleted: ,

Deleted: postop

Deleted: (p=0.027)

Deleted: ¶

Formatted: Right

DISCUSSION

Cigarette smoking is detrimental in patients undergoing lumbar fusion surgery. Smoking has been associated with decreased fusion rate, diminished clinical outcomes, limitation in functional rehabilitation and poorer overall patient satisfaction (Glassman, Anderson, McGeary, Kwon, Mooney). Most of the attention has been focused on fusion status, particularly for posterolateral fusion procedures where healing is a challenge even in an ideal host.

The relationship between smoking and spinal fusion has been investigated in a variety of animal models (Lee, Daftari, Silcox, Wing, Theiss). The mechanism by which nicotine inhibits fusion healing appears to be multifactorial. The effect of nicotine has been demonstrated to include decreased revascularization of the bone graft (Daftari) and an alteration in gene expression (Theiss). More recently, nicotine receptors with an anti-inflammatory function have been identified (Wang, Miao). Given the known inhibition of spine fusion associated with nonsteroidal anti-inflammatory medications (Glassman 2, Reuben, Park), this pathway may represent an additional mechanism whereby nicotine interferes with fusion healing.

Deleted: second
Deleted:
Deleted:

Importantly, cigarette smoking has been shown to adversely affect clinical outcomes independent of the diminution in fusion rate (Glassman, Anderson, Kwon). Contributing factors may include an accelerated rate of disc degeneration (Battie) or a compromised general health status. Preoperative smoking abatement is the ideal solution because it has been demonstrated to increase fusion rate and to improve outcomes. (Wing, Glassman) Unfortunately, not all patients

Deleted: , Hilibrand
Formatted: Highlight

Formatted: Right

Deleted: .

are able or willing to quit smoking, therefore, alternative surgical strategies which may offset the negative influence of smoking have been sought.

Initially, pedicle screw fixation was seen as a mechanism to avoid nonunion in complex cases and compromised hosts. Unfortunately, rigid stabilization alone has been insufficient to assure fusion in cigarette smokers (Anderson, Kwon, Hadley). Lumbar interbody fusion has also been advocated to enhance fusion rate in smokers (Mirovsky). Higher fusion rates are routinely reported with interbody grafting techniques, but the accuracy of radiographic assessment has been questioned. (Cook). From a clinical standpoint, the occurrence of surgical nonunion in smokers remains a substantial unresolved issue.

Deleted:

The advent of osteoinductive biologic bone graft alternatives, particularly BMPs, offers another potential tool to achieve fusion in difficult hosts such as cigarette smokers. Preclinical studies have heightened expectations by demonstrating a reversal of the nicotinic effect in rabbits with both rhBMP-2 (Silcox) and rhBMP-7 (Patel). A small human pilot study suggested that rhBMP-7 might generate a similar effect in clinical application (Govender). The authors caution that the study, which included only four smokers, must be considered very preliminary. A study of early fusion rates with high dose rhBMP-2 (2 mg/ml, 20 mg per side) versus ICBG, was also encouraging (Glassman 3). This study, which included 16 smokers, demonstrated a more robust fusion among smokers in the rhBMP-2 group, but the differences were not statistically significant.

Deleted: also

Formatted: Right

In the present study, fusion rate based on plain radiographs and CT scan assessment was analyzed in 148 patients at 2 year follow-up after single level posterolateral lumbar fusion. The data was collected as part of a prospective randomized trial of rhBMP-2 versus iliac crest bone graft. The study cohort, from three spine centers, included 42 smokers and 106 nonsmokers. It is important to recognize that patients were not randomized based upon smoking status, and that this is a retrospective review of a limited subset from the overall IDE trial. Also, the dose and concentration of rhBMP-2 (2 mg/ml, 20 mg per side) is substantially greater than that in commercially available INFUSE Bone Graft.

Given these constraints, the use of the specific dose and formulation of rhBMP-2 studied appears to enhance fusion rate in smokers. The fusion rate was 100% in the nonsmoker/rhBMP-2 group, 94.1% in the nonsmoker/ICBG group, 95.2% in the smoker/rhBMP-2 group and only 76.2% in the smoker/ICBG group based on IDE protocol criteria. The difference in fusion rate at 24 months between rhBMP-2 (20/21) and ICBG (16/21) in the smokers did not reach statistical significance (p=0.184), but this is likely due to limited power given the number of subjects in this subset of patients. There was, however, a significant difference in fusion rate comparing all smokers (85.7%) and all nonsmokers (97.2%) (p=0.016). A similar disparity in fusion status was demonstrated using the criteria of bridging bone on fine cut CT scan with coronal and sagittal reconstructions. This is the present "state of the art" for fusion assessment (Molinari, Glassman SPINE 2005, Burkus 3, Cizek).

Despite the excellent fusion rate with rhBMP-2, clinical outcomes measures were still adversely affected in smokers. Although the differences were generally not statistically significant,

Deleted: th

Formatted: Font: (Default) Times New Roman, 12 pt, No underline

Deleted: a

Deleted: ,

Deleted: which

Deleted: – Initial fusion rates

Deleted: rtius – with Dorchak

Deleted: Given these constraints, the use of rhBMP-2 appears to enhance fusion rate in smokers. The fusion rate was 100% in the nonsmoker/rhBMP-2 group, 94.1% in the nonsmoker/ICBG group, 95.2% in the smoker/rhBMP-2 group and only 76.2% in the smoker/ICBG group. The difference in fusion rate at 24 months between rhBMP-2 (20/21) and ICBG (16/21) in the smokers

Deleted: was

Deleted: did

Deleted: (

Deleted: not

Deleted:)

Deleted: reach statistical

Deleted: ly

Deleted: significance

Deleted: (

Deleted:

Deleted: (p=0.042

Deleted: (p=0.184

Deleted:)

Deleted:).

Deleted: (Julie – I'm not sure that this is exactly the comparison that you did.)

Deleted: There was, however,

Deleted: also

Deleted: a significant difference in fusion rate comparing all smokers (85.7%) and all nonsmokers (97.2%) (p=0.016). ¶

Deleted: improvement in

nonsmokers had better ODI and SF-36 PCS scores at all intervals. Nonsmokers were also significantly more likely to be working both pre and post-operatively.

The results of this study suggest that AMPLIFY™ rhBMP-2 Matrix (2 mg/ml, 20 mg. per side) may enhance fusion rate in cigarette smokers undergoing single level instrumented posterolateral lumbar fusion. The findings are also consistent with prior studies which indicate that smoking is detrimental to clinical outcome independent of fusion status. (Glassman, Anderson) Therefore, the authors conclude that while rhBMP-2 matrix is a valuable tool for lumbar fusion in smokers, smoking abatement is still the optimal management technique for patients undergoing lumbar fusion surgery.

Formatted: Right

Deleted: postop

Deleted: matrix

Deleted: substantially

Deleted: s

Deleted: .

Deleted: , however,

Formatted: Right

FIGURE LEGEND

Formatted: Indent: Left: 0 pt, Hanging: 72 pt

Figure 1 Graph showing the percentage of patients fused at 12 months and 24 months among the four subgroups based on the IDE fusion success criteria.

Figure 2 Graph showing the percentage of patients fused at 12 months and 24 months among the four subgroups based on CT scan bridging bone criteria.

Figure 3 Graph showing the mean ODI scores (a) and the mean SF-36 PCS (b) of the four subgroups pre-operatively and at the different follow-up intervals.

Deleted: s

Figure 4 Graph showing the mean back pain VAS (a) and the mean leg pain VAS (b) of the four subgroups pre-operatively and at the different follow-up intervals.

Figure 5 Graph showing the mean ODI scores (a) and the mean SF-36 PCS (b) for the entire cohort based on smoking status.

Deleted: of the all

Deleted: the smokers and nonsmokers

Deleted: in each bone graft group combined

Formatted: Right

Table 1. Demographic data of the four subgroups.

Formatted: Line spacing: single

Formatted: Centered

	rhBMP-2 Matrix		ICBG	
	Smokers	Nonsmokers	Smokers	Nonsmokers
N	21	55	21	51
Mean Age (years)	50.8	51.8	48.1	51.7
Mean Weight (lbs)	180.2	189.2	187.7	187.8
Male/Female Ratio	11/10	25/30	13/8	22/29
Workmens' Compensation (%)	4.8	14.5	23.8	13.7
Spinal Litigation (%)	4.8	3.6	4.8	13.7

Formatted: Right

Formatted: Font: Bold

BIBLIOGRAPHY

Glassman SD, Anagnost SC, Parker A, et al: The effect of cigarette smoking and smoking cessation on spinal fusion. Spine 2000;20:2608-2615.

Andersen T, Christensen FB, Laursen M et al: Smoking as a predictor of negative outcome in lumbar spinal fusion. Spine 2001;23:2623-2628.

Kwon BK, Hilibrand AS, Malloy K et al: A critical analysis of the literature regarding surgical approach and outcome for adult low-grade isthmic spondylolisthesis. J Spinal Disord Tech 2005;18:S30-40.

Brown CW, Orme TJ, Richardson HD: The rate of pseudoarthrosis (surgical nonunion) in patients who are smokers and patients who are nonsmokers: a comparison study. Spine 1986;11(9):942-943.

Whitesides TE, Hanley EN, Fellrath RF: Controversies Smoking Abstinence. Is it necessary before spinal fusion? Spine 1994;17:2012-2014.

Mirovsky Y, Halperin N, Anekstein Y et al: Good results of circumferential spine fusion in smokers, using autograft and allograft. Cell and Tissue Banking 2002;3:169-173.

Burkus J JK, Gornet MF, Dickman CA et al: Anterior lumbar interbody fusion using rhBMP-2 with tapered inter body cages. J Spinal Disord Tech 2002;15(5):337-347.

Burkus 2 JK, Sandhu HS, Gornet MF et al: Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery. J Bone Joint Surg AM 2005;87(6):1205-1212.

Burkus 3 JK, Dorchak JD, Sanders DL: Radiographic assessment of interbody fusion using recombinant human bone morphogenetic protein Type 2. Spine 2003;28(4):372-377.

Abraham EP, Alexander DL Bailey SI et al: Evaluation of a new rhBMP-2 formulation in two-level posterolateral lumbar spine fusion. Abstract presented to the American Academy of Orthopaedic Surgeons. 2005:No. 002.

Alexander DL Abraham EP, Bailey SI et al: A new rhBMP-2 formulation in posterolateral lumbar spine fusion: a prospective, randomized study. Abstract presented to the American Academy of Orthopaedic Surgeons. 2005:No. 003.

Patel TC, Erulkar JS, Grauer JN et al: Osteogenic protein-1 overcomes the inhibitory effect of nicotine on posterolateral lumbar fusion. Spine 2001;15:1656-1661.

Silcox DH, Boden SD, Schimandle JH, et al: Reversing the inhibitory effect of nicotine on spinal fusion using an osteoinductive protein extract. Spine 1998;23(3):291-296.

Formatted: Right

McGeary DD, Mayer TG, Gatchel RJ et al: Smoking status and psychosocioeconomic outcomes of functional restoration in patients with chronic spinal disability. Spine J 2004;4(2):170-175.

Mooney V, McDermott KL, Song J: Effects of smoking and maturation on long-term maintenance of lumbar spinal fusion success. J Spinal Disord 1999;5:380-385.

Lee TC, Ueng SWN, Chen HH, et al: The effect of acute smoking on spinal fusion: An experimental study among rabbits. J Trauma 2005;59(2):401-407.

Daftari TK, Whitesides TE,Heller JG et al: Nicotine on the revascularization of bone graft. Spine 1994;8:904-911.

Wing KJ, Fisher CG, O'Connell JX et al: Stopping nicotine exposure before surgery. Spine 2000;1:30-34.

Theiss SM, Boden SD, Hair G et al: The effect of nicotine on gene expression during spine fusion. Spine 2000;20:2588-2594.

Wang H, Yu MJ, Ochani M et al: Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. Nature 2003;421:384-388.

Miao FJ, Green PG, Benowitz N et al: Central terminals of nociceptors are targets for nicotine suppression of inflammation. Neuroscience 2004;123(3):777-784.

Glassman SD, Rose SM, Dimar JR et al: The Effect of Postoperative Nonsteroidal Anti-inflammatory Drug Administration on Spinal Fusion. Spine 1998;23(7):834-838.

Reuben SS, Ablett D, Kaye R: High dose nonsteroidal anti-inflammatory drugs compromise spinal fusion. Can J Anesth 2005;52:5:506-512.

Park SY, Moon SH, Park MS et al: The effects of Ketorolac injected via patient controlled analgesic postoperatively on spinal fusion. Yonsei Med J 2005;2:245-251.

Battie MC, Videman T, Gill K et al: Smoking and lumbar intervertebral disc degeneration: an MRI study of identical twins. Spine 1991;16:1015-1021.

Hadley M, Reddy S: Smoking and the human vertebral column: A review of the impact of cigarette use on vertebral bone metabolism and spinal fusion. Neurosurgery 1997;41:116-124.

Cook SD, Patron LP, Christakis PM et al: Comparison of methods for determining the presence and extent of anterior lumbar interbody fusion. SPINE 2004;29(10):1118-1123.

Fusion with rhBMP-2 in Smokers

Govender PV, Rampersaud YR, Rickards L et al: Use of Osteogenic protein-1 in spinal fusion: literature review and preliminary results in a prospective series of high-risk cases. Neurosurg Focus 2002;13(6):e4:1-6.

Glassman S, Dimar J, Carreon L et al: Initial Fusion Rates with rh-BMP-2 and an HA-TCP/Collagen Carrier in Posterolateral Fusion. Spine 2005;30(15):1694-1698.

Molinari RW, Bridwell KH, Klepps SJ, Baldus C: Minimum 5-year follow-up of anterior column structural allografts in the thoracic and lumbar spine. Spine 1999;24(10):967-972.

Cizek GR, Boyd LM: Imaging pitfalls of interbody spinal implants. Spine 2000;25(20):2633-2636.

Formatted: Right

Formatted: Indent: Left: 0 pt, Hanging: 36 pt

Formatted: Font: 12 pt, Not Bold, No underline

Formatted: Justified, Indent: Left: 0 pt, Hanging: 36 pt

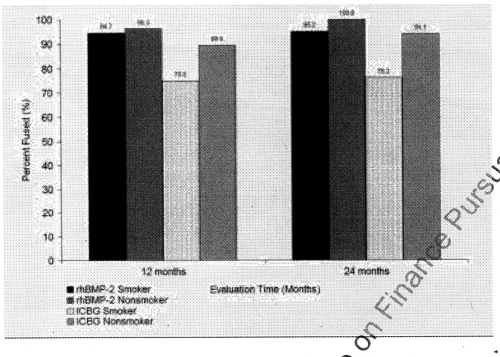
Formatted: Font: 12 pt

Formatted: Font: 12 pt

Fusion with rhBMP-2 in Smokers

Formatted: Right

Figure 1

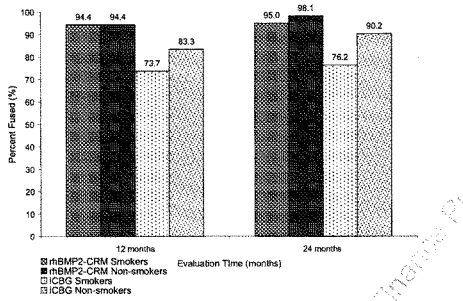


Formatted: Justified, Indent: Left: 0 pt, Hanging: 36 pt

Fusion with rhBMP-2 in Smokers

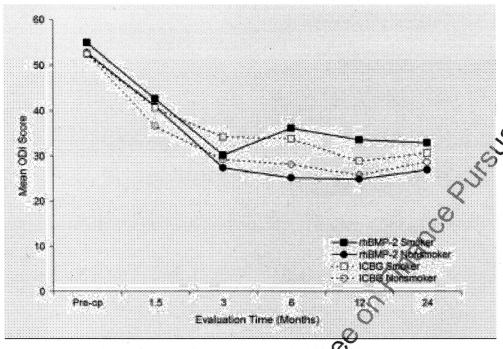
Formatted: Right

Figure 2



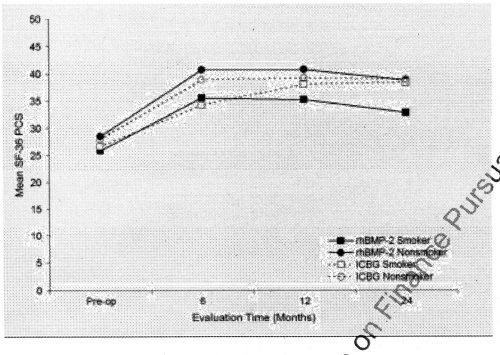
Formatted: Right

Figure 3a



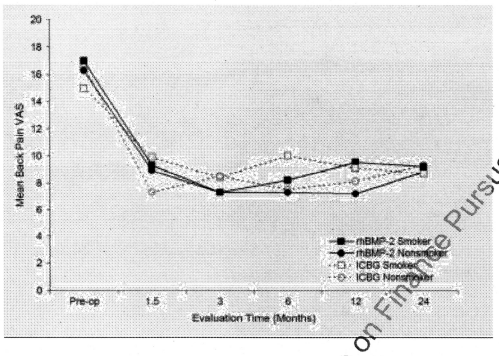
Formatted: Right

Figure 3b



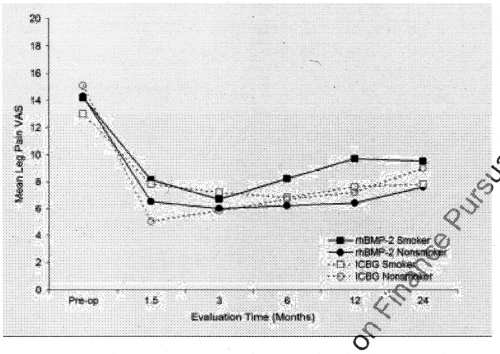
Formatted: Right

Figure 4a



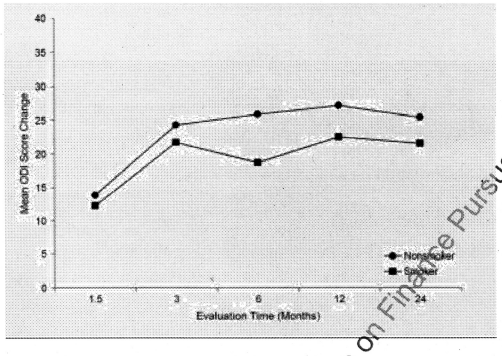
Formatted: Right

Figure 4b



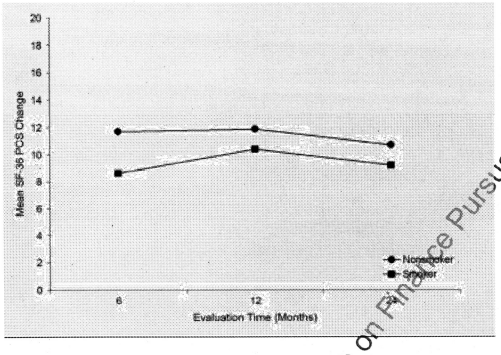
Formatted: Right

Figure 5a



Formatted: Right

Figure5



Page 9: [1] Deleted 8/10/2006 9:20:00 AM
There was not a statistically significant difference in fusion success when comparing the

nonsmoker/rhBMP-2 and nonsmoker/rhBMP-2 groups (p=0.276)

Page 9: [2] Deleted 8/10/2006 9:20:00 AM

Page 9: [2] Deleted 6/27/2006 12:06:00 PM
postop

Page 9: [2] Deleted 8/16/2006 11:06:00 AM
. 2

Page 9: [2] Deleted 8/16/2006 11:07:00 AM
. 3

Page 9: [2] Deleted 8/16/2006 11:07:00 AM
. 4

Page 9: [3] Deleted bearcj1 6/18/2006 6:04:00 PM
10.3(

Page 9: [3] Deleted bearcj1 6/18/2006 6:04:00 PM
)

Page 9: [3] Deleted bearcj1 6/18/2006 6:04:00 PM
11.0(

Page 9: [3] Deleted bearcj1 6/18/2006 6:04:00 PM
)

Page 9: [3] Deleted bearcj1 6/18/2006 6:04:00 PM
11.8 (

Page 9: [3] Deleted bearcj1 6/18/2006 6:04:00 PM
)

Page 9: [3] Deleted	bearcj1	6/18/2006 6:04:00 PM

7.5 (

Page 9: [3] Deleted	bearcj1	6/18/2006 6:04:00 PM

)

Page 9: [3] Deleted	bearcj1	6/18/2006 6:04:00 PM

7.2 (

Page 9: [3] Deleted	bearcj1	6/18/2006 6:04:00 PM

)

Page 9: [3] Deleted	bearcj1	6/18/2006 6:04:00 PM

7.8 (

Page 9: [3] Deleted	bearcj1	6/18/2006 6:04:00 PM

)

Page 9: [3] Deleted	bearcj1	6/18/2006 6:05:00 PM

6.3 (

Page 9: [3] Deleted	bearcj1	6/18/2006 6:05:00 PM

)

Page 9: [4] Deleted	bearcj1	6/18/2006 6:03:00 PM

6.8 (

Page 9: [4] Deleted	bearcj1	6/18/2006 6:03:00 PM

)

Page 9: [4] Deleted	bearcj1	6/18/2006 6:03:00 PM

6.3 (

Page 9: [4] Deleted	bearcj1	6/18/2006 6:03:00 PM

)

Page 9: [4] Deleted	bearcj1	6/18/2006 6:03:00 PM

4.9 (

Page 9: [4] Deleted	bearcj1	6/18/2006 6:03:00 PM

)

Page 9: [4] Deleted bearcj1 6/18/2006 6:03:00 PM

5.0(

Page 9: [4] Deleted bearcj1 6/18/2006 6:03:00 PM

)

Page 9: [5] Deleted 6/27/2006 12:04:00 PM

(Julie – I don't have MCS data in this version. Should I exclude it? You can include it but it does not show a trend in its behavior making it difficult to interpret relative to the smoking/nonsmoking issue?)

From: Hatcher, Brian, PhD.
Sent: Tuesday, October 9, 2007 03:43:29 PM
To: 'Ken Burkus [redacted]
CC: Bearcroft, Julie, PhD
Subject: INFUSE/LT 6 year paper

Attachments: BMP LT Cage 72 months jkb first.doc

Hello Dr. Burkus,
Please find attached the edited version of the manuscript you prepared on the 6 year follow up from the INFUSE/LT Cage study. There is really only 1 major change that I want to make you aware of:

With regards to the second surgery information, we have reported the overall second surgery failure rate for the study (10.4%). You had also included 2 tables that discussed what category the 2nd surgery was (revision, removal, or supplemental fixation), the reason for the surgery, the time of the event, and the level (index or index/adjacent). Instead of presenting this level of detail in tabular format, does it seem reasonable to summarize it and report it only in the body of the text? Would this still provide the reader with the information they need to draw their own conclusions about the relationship between the 2nd surgery rates and the bone graft? For your convience, I have provided the commentary from the paper that discusses this (see below).

There were a total of 25 second surgery failures over the 6 year follow-up, including 16 in the open group and 9 in the laparoscopic group. These second surgery failures included 23 supplemental fixations, 1 removal and 1 revision. Reasons for second surgeries were reported by the enrolling surgeon, and included implant positioning, migration or loosening, nonunions, pending nonunions, subsidence, stenosis, radiculopathy, adjacent segment degeneration and post laminectomy syndrome. Second surgery failures occurred between 5 days and 62 months postoperative.

Adjusting for the patients available at each follow-up by a time to event analysis, the overall second surgery failure rate was 10.4% (13.7% in the open group and 7.1% in the laparoscopic group; Fig 7). The second surgery failure rate prior to 2 years for the combined group was 6.7% (6.4% open and 7.1% laparoscopic). Between 2 and 6 years, the rate of second surgery failure for the combined group was 3.7% (7.3% open and 0% laparoscopic).

Please let me know if this is acceptable.
Additionally, would you like to include any images in this publication? I have a series of x-rays and CTs from 1 of your patients that we could select from if you would like. As it stands now, this is not included in the paper.

I would also respectfully ask if you would be willing to send this to the co-authors for their comments as well.

Once again, I would like to thank you for all of the hard work that you have put into this study. I have enjoyed working on these last couple of papers with you and look forward to the next one!

Brian

Brian Hatcher, Ph.D.
Technology Manager, Biologics
Medtronic
Spinal and Biologics
1800 Pyramid Place
Memphis, TN 38132
O: [redacted]
M: [redacted]
F: [redacted]

Long -Term Follow-up of Patients Treated with Stand Alone Anterior Lumbar Interbody Fusion Cages and Recombinant Human Bone Morphogenetic Protein-2

J. Kenneth Burkus, M.D.*

Matthew F. Gornet MD†

Thomas C. Schuler, MD††

Thomas A. Kleeman, MD#

Thomas A. Zdeblick MD§

* Staff Physician, Spine Service, The Hughston Clinic, [redacted]

† The Orthopedic Center of St. Louis, St. Louis, MO

†† Virginia Spine Institute, Reston, Virginia

New Hampshire Spine Institute, Bedford, New Hampshire

§Chairman, Department of Orthopedics and Rehabilitation, University of Wisconsin, Madison, Wisconsin

FDA device/drug status: Approved for this indication.

Statement of Financial Relationship: The authors are consultants and clinical investigators for the company distributing the device studied.

Address correspondence and reprint requests to: J. K. Burkus, M.D., The Hughston Clinic, [redacted] Columbus, Georgia 31908-9517

ABSTRACT

Background: Stand alone anterior lumbar interbody fusion using dual tapered interbody fusion cages and recombinant human bone morphogenetic protein-2 on an absorbable collagen sponge (rhBMP-2/ACS) has been reported with 24-month outcomes. Longer clinical and radiographic follow-up is needed to verify the sustained improvements in outcomes in the surgical treatment of degenerative lumbar disc disease.

Methods: An integrated analysis was performed following two prospective clinical studies in which patients received rhBMP-2/ACS with lumbar fusion cage implants and had 6 year follow up. A total of 146 patients were treated for single-level degenerative disc disease with up to grade 1 spondylolisthesis by either an open or a laparoscopic surgical procedure. Patient outcomes were determined using well-established clinical outcome measurements and radiographic assessments.

Results: Patients treated with rhBMP-2 and stand alone fusion cages showed high rates of fusion and low rates of additional surgery. For patients with 6 year follow-up, radiographic evidence of fusion was documented in 98.5% of patients at 6 years. Additionally, significant improvements in clinical outcomes, including Oswestry Disability Index scores (ODI), SF-36® Health Survey Physical Component Summary scores, and back and leg pain scores were achieved by 6 weeks and were sustained out to 6 years. A higher percentage of patients were working than were working preoperatively by 6 months, and this improvement was sustained out to 6 years. There was a trend towards greater improvement in ODI, back pain, and SF-36 PCS scores in the laparoscopic group compared to the open group.

Conclusions: The use of dual tapered threaded fusion cages and rhBMP-2 on an absorbable collagen sponge facilitates and maintains intervertebral spinal fusion, sustained improvements in clinical outcomes and reduction of pain following anterior lumbar interbody fusion for degenerative lumbar disc disease.

Keywords: Anterior lumbar interbody fusion, INFUSE Bone Graft, bone morphogenetic protein, fusion cage, degenerative disc disease, lumbar spine

INTRODUCTION

Discogenic low back pain results, in part, from abnormal intersegmental load patterns and movement within a degenerative disc [1]. Clinically painful discs have been shown to display specific patterns of altered stresses in the annulus and vertebral endplates, reflecting abnormal loading [2]. Lumbar interbody fusion can eliminate abnormal stress patterns associated with degenerative disc disease and normalize stress distribution patterns [3, 4]. Threaded interbody fusion cages stabilize the spinal motion segment and provide a mechanical environment that optimizes fusion [5]. New bone formation in and around the cages increases the contact area and decreases the magnitude of abnormal load in the adjacent vertebrae.

Various bone grafts have been used in an effort to enhance bone formation within the interverterbal disc space. Recombinant human bone morphogenetic protein (rhBMP-2) is an osteoinductive growth factor that stimulates pleuripotential cells to form bone. In animal and human studies, rhBMP-2 has been shown to be capable of inducing new bone formation [6, 7]. At 24 months in randomized anterior lumbar interbody fusion (ALIF) clinical trials, the use of rhBMP-2 as an iliac crest bone graft (ICBG) replacement has been shown to increase rates of interbody fusion, and its use has been associated with decreased pain and improved clinical outcomes [8-10]. When used in combination with the LT CAGE® Device (Medtronic Sofamor Danek, Memphis, Tennessee), patients treated with rhBMP-2 had significantly higher fusion rates than patients treated with ICBG (94.4% vs. 89.4%; p=0.022) [11]. Additional studies with rhBMP-2/ACS in lumbar interbody fusion have also shown similar rates of fusion success [8-10, 12-19].

The purpose of our analysis was to investigate the post-approval long-term clinical and radiographic outcomes in those investigational patients enrolled in these initial FDA trials using stand alone interbody fusion cages and rhBMP-2 as an iliac crest bone graft replacement. Patients who received INFUSE® Bone Graft were followed for a period of 6 years to determine the long term efficacy as a replacement to ICBG.

MATERIALS and METHODS

Two prospective, multi-center FDA-approved IDE studies of patients undergoing treatment for single-level lumbar degenerative disc disease were conducted, utilizing a similar fusion technique through two different surgical approaches [9, 20]. All patients were entered into these studies between 1997 and 1999. Our analysis combines data from the patients who received treatment with the INFUSE® Bone Graft/LT-CAGE® Device in the two FDA IDE trials (Table 1). These studies used the identical inclusion-exclusion criteria (Table 2); however, the laparoscopic cohort was a non randomized, single-arm study whereas patients in the open study were randomized to rhBMP-2/ACS or ICBG.

Inclusion Exclusion Criteria

At the time of surgery, all patients were between the ages of 19 and 70 years and had symptomatic degenerative disc disease at the L4-L5 or L5-S1 levels. All had low back pain for at least 6 months before their surgery that was recalcitrant to nonoperative treatment modalities, such as physical therapy, bed rest, and anti-inflammatory medications. Patients were included in the study if their plain radiographic findings documented single-level disc disease, and they had undergone at least one additional confirmatory neuroradiographic study, such as MRI, CT-enhanced myelography, or discography. All patients were considered candidates for a single-level stand-alone ALIF.

Patients were excluded from the study if they had spinal conditions other than single-level symptomatic degenerative disc disease or greater than Grade 1 spondylolisthesis. Other exclusion criteria were symptomatic disc disease at a level other than the L4-L5 or L5-S1, obesity (more than 40% above ideal body weight), or a medical

condition that required medication, such as steroids or nonsteroidal anti-inflammatory medications, that could interfere with fusion.

Patient Accountability and Demographics

There were 277 patients enrolled in both the open (143 patients) and laparoscopic (134 patients) groups in the initial FDA IDE studies. A total of 23 out of the 31 initial sites elected to participate in the long-term follow-up. As a result of second surgery failures and non participating sites, 58 patients were excluded from this study leaving a total of 219 patients who were eligible for the FDA IDE post-approval follow-ups (109 in the open arm and 110 in the laparoscopic arm). A total of 146 patients completed the 72-month follow-ups. This subgroup of patients was evaluated to determine the clinical outcome measures and fusion status at each time point (preoperative through 72 months).

Surgical Procedures

Patients underwent an ALIF procedure using either an open [9]or a laparoscopic approach [20]. In the open group, either transperitoneal or retroperitoneal approaches to the lumbosacral spine were utilized; in the laparoscopic group, all approaches were transperitoneal. Patients had two LT-CAGE® Devices implanted anteriorly at one lumbar interspace (either L4-L5 or L5-S1).

rhBMP-2 on the ACS was used exclusively as an ICBG replacement. No autogenous grafts and no local host bone reamings were used. The method of use of rhBMP-2 has been reviewed [9, 20]. The genetically engineered the rhBMP-2 component (Wyeth BioPharma, Cambridge, MA) and ACS component (Integra LifeSciences, Plainsboro, NJ) are distributed commercially under the trade name INFUSE® Bone Graft (Medtronic Sofamor Danek, Memphis, TN). The rhBMP-2 was

reconstituted to a concentration of 1.5mg/ml using sterile water and applied to the appropriate number of ACS's. The rhBMP-2 was allowed to bind to the ACS for a minimum of 15 minutes, which results in 95% of the protein being bound to the sponge [21]. The rhBMP-2 soaked sponges were placed into the central portion of each LT-CAGE® Device. No additional rhBMP-2-bound sponges were placed outside of the fusion cages. The total dose of rhBMP-2 ranged from 4.2 to 8 mg and was determined by matching the volume of the prepared ACS to the internal volume of the LT-CAGE® Device.

The results from the two surgical approaches were pooled and analyzed independently to better define the effects of surgical approach in surgical parameters, hospital stay, and the long-term clinical and radiographic outcomes.

Clinical Outcome Measures

Clinical outcome measures, including Oswestry Disability Index (ODI) [22], Short Form 36 questionnaire [23, 24], back and leg pain scores and return to work status were self administered preoperatively and at 1.5, 3, 6, 12, 24, 48, and 72 months. Back and leg pain scores were determined using a 20 point scale (10 points frequency and 10 points intensity).

Radiographic Assessment

The presence of continuous trabecular bone formation between the vertebral bodies was assessed using radiographs and computed tomography (CT) scans. Fusion was defined as bridging bone connecting the adjacent vertebral bodies either through the implants or around the implants, less than 5° of angular motion, less than or equal to 3 mm of translation, and an absence of radiolucent lines around more than 50% of either

implant. Fusion was assessed at 6, 12, 24, 48, and 72 months, and was considered successful only if all four criteria were achieved.

Additional Surgical Procedures

Secondary surgical procedures performed subsequent to the index operation were classified as revisions, removals, supplemental fixations, or reoperations. A revision surgery was defined as any procedure that adjusts or modifies the original implant configuration; a removal was defined as a procedure that removes one or more components of the original implant and replaces it with a different type of implant; supplemental fixation was defined as a procedure in which additional spinal devices not approved as part of the protocol are placed; and reoperation was defined as any surgical procedure at the treated level that does not remove, modify, or add any components, for example a posterior foraminotomy. A survivorship analysis was used to determine the percentage of patients who were second surgery failures, taking into account all available patients at each follow-up time point.

Adverse Events

Adverse events were studied and classified as to their severity and relationship with the implants and with surgical procedures.

RESULTS

Patient Accountability

A total of 146 patients (68 in the laparoscopic group and 78 in the open group) completed the 6 year follow-up. The overall follow-up rate was 52.7% (146/277), and the follow-up rate for available patients at 6 years was 66.7% (146/219). A comparison of this subgroup of patients with the entire patient population prior to 24 months indicated similar clinical outcomes between the groups, suggesting that this group of patients serves as a representative subset of the entire patient population.

Demographic data were compiled for the patients included in the analysis (Table 3). The two prospective study groups were not randomized; however, the patients' demographic characteristics and prognostic factors were similar except for sex and alcohol use.

Surgical Data

Surgical, hospitalization and clinical outcomes were analyzed for each surgical technique and the outcomes were combined. Analysis of surgical and hospitalization data for the two surgical treatment groups shows the laparoscopic group spent an average of 18 minutes longer under anesthesia and lost an average of 7.3 mL more blood (Table 4). However, the laparoscopic group left the hospital 1.7 days earlier than the open group, on average.

Clinical Outcomes

Oswestry Disability Scores:

The Oswestry Disability Index (ODI) Questionnaire measures the level of pain and disability associated with various activities. ODI scores improved significantly from

preoperative values by 6 weeks, and these improvements were maintained out to 6 years ($p<0.001$). For the combined group, ODI scores improved an average of 33.6 points and 31.0 points at 48 and 72 months, respectively, from a preoperative score of 52.0. These improvements were similar to those observed at 24 months (31.7 points). There was a trend towards slightly greater improvements in ODI scores in the laparoscopic group compared to the open group at 72 months (Fig 1).

Back Pain:

Back pain scores improved significantly from preoperative values by 6 weeks, and these improvements were maintained out to 6 years ($p<0.001$). For the combined group, back pain scores improved an average of 9.3 points and 8.6 points at 48 and 72 months, respectively. These improvements were similar to those observed at 24 months (9.3 points). There was a trend towards slightly greater improvements in back pain scores in the laparoscopic group compared to the open group and 48 and 72 months (Fig 2).

Leg Pain:

Leg pain scores improved significantly from preoperative values by 6 weeks, and these improvements were maintained out to 6 years ($p<0.001$). For the combined group, leg pain scores improved an average of 6.4 points and 6.7 points at 48 and 72 months, respectively. These improvements were similar to those observed at 24 months (6.4 points). The improvement from the preoperative score at 72 months was similar in the laparoscopic and open group (Fig 3).

SF-36:

The SF-36 measures specific health concepts related to physical functioning, social functioning and health perceptions. For the combined group, Physical Component Scores (PCS) improved an average of 17.3 points and 15.1 points at 48 and 72 months, respectively. These improvements were similar to those observed at 24 months (16.1 points). There was a trend towards slightly greater improvements in SF-36 PCS scores in the laparoscopic group compared to the open group at 48 and 72 months (Fig 4).

For the combined group, all SF-36 outcomes except for general health perception improved significantly ($p<0.001$) from the preoperative values at 72 months (Table 5). Additionally, SF-36 scores were maintained between 24 and 72 months. There was a trend towards greater improvement in SF-36 scores in the laparoscopic group compared to the open group.

Radiographic Outcomes:

At 72 months, 130 patients had complete radiographic follow-up. At 48 and 72 months, 97.9% and 98.5% of patients had radiographic evidence of fusion (Figure 5). The high rates of fusion seen at these later time points were similar to the rates of arthrodesis seen at 6, 12, and 24 months. Fusion rates were similar between the open and laparoscopic groups.

Second Surgery Failures:

There were a total of 25 second surgery failures over the 6 year follow-up, including 16 in the open group and 9 in the laparoscopic group. These second surgery failures included 23 supplemental fixations, 1 removal and 1 revision. Reasons for second surgeries were reported by the enrolling surgeon, and included implant positioning, migration or loosening, nonunions, pending nonunions, subsidence, stenosis,

radiculopathy, adjacent segment degeneration and post laminectomy syndrome. Second surgery failures occurred between 5 days and 62 months postoperative.

Adjusting for the patients available at each follow-up by a time to event analysis, the overall second surgery failure rate was 10.4% (13.7% in the open group and 7.1% in the laparoscopic group; Fig 7). The second surgery failure rate prior to 2 years for the combined group was 6.7% (6.4% open and 7.1% laparoscopic). Between 2 and 6 years, the rate of second surgery failure for the combined group was 3.7% (7.3% open and 0% laparoscopic).

Return-to-Work Status:

At 48 and 72 months, more patients were working than were working preoperatively (69.2% and 68.1% at 48 and 72 months, respectively compared to 52.1% preoperatively). The percentage of patients working at the later time points was similar to what was seen at 24 months (70.3%, Figure 6). By 6 months, approximately 90% of the patients who were working preoperatively had returned to work, and this was maintained though the 72 month time point.

Adverse events:

No unanticipated adverse events related to the use of rhBMP-2/ACS occurred during the course of the study. Since the ICBG control group was not followed during the 24 and 72 month time frame, no analysis of adverse events between the investigational and control group could be completed.

DISCUSSION

Results from prospective studies of the LT-CAGE® Device have shown a trend towards faster fusion with INFUSE® Bone Graft and improved clinical outcomes when compared with patients who received autograft ICBG [11]. These improved outcomes are related, in part, to the successful combination of the surgical approach, the advanced cage designs, the avoidance of bone graft harvesting morbidity, and the high rate of successful interbody fusion. This study represents the longest follow-up to date of patients undergoing spine fusion with INFUSE® Bone Graft [9-20]. In patients followed out to 6 years, it was observed that radiographic fusion rates were high, rates of second surgery were low, and improvements in clinical outcomes were maintained.

Other studies have reported on the long term radiographic and clinical results following lumbar interbody fusion [25-30]. Kuslich et al. reported on 4 year results from a study enrolling 947 patients who received Bagby and Kuslich (BAK) cages and ICBG [29]. Only 20.7% (196/947) of patients completed the 4 year follow-up, however, which included both anterior (n=122) and posterior (n=74) approaches and single-level (n=116) and 2-level (n=80) fusions. Fusion success allowed for up to 7° of angulation on flexion extension films, and no thin cut CT scans with reconstructed images were obtained to assess fusion. At 4 years, the authors reported an overall fusion success of 98% and a repeat surgery rate of 8.7%. Pain scores were maintained out to 4 years.

In a similar study, clinical and radiographic outcomes following ALIF with stand alone BAK cages implanted by a single author were evaluated [28]. Patients underwent single-level (n=40) or 2-level (n=6) ALIF with BAK Cages and autograft, allograft, or a combination of both. A total of 33 out of 46 patients (71.7%) reached a mean follow-up

of 55 months (range = 36-65 months). The authors reported an overall nonunion rate of 30% and a revision rate of 22%. Mean ODI score at final follow-up was 41, with only 42% of patients having an ODI ≤ 40. The fusion rates and improvement in ODI scores at 4 and 6 years in patients treated with INFUSE® Bone Graft and the LT CAGE® Device indicate an improvement relative to this published report.

Brantigan also investigated the long term results following instrumented posterior lumbar interbody fusion (PLIF). The initial study enrolled a total of 110 patients with degenerative disc disease at 6 centers. A total of 33 patients selected from 2 centers completed the 10 year follow-up (30%). Radiographic evidence of fusion, as defined by bridging bone and the absence of radiolucencies was reported in 96.7% of the patients at 10 years. At 2 years, elective removal of pedicle screws indicated that 90% (104/115) of the examined levels were fused. Clinical outcomes were determined using a 20 point Prolo scale. A clinical success was defined as a patient with an excellent, good or fair outcome and a minimum of a 3 point improvement. Preoperatively, 76% of patients had a rating of good or fair. At 10 years, 87.8% (29/33) of patients had a rating of excellent, good or fair and achieved clinical success. In the current study, 79% (109/138) of patients treated with INFUSE Bone Graft had an ODI improvement of greater than 15 points at 6 years.

Martin [31] compared reoperations rates in the early 90s with the late 90s. The study included approximately 25,000 patients who underwent primary lumbar surgery for degenerative disc disease, herniated lumbar disc, stenosis or spondylolisthesis. The primary surgical procedure was fusion in 19.1% of patients and decompression or discectomy in 90.9%. A reoperation was defined as any secondary

operation of the lumbar spine. For patients whose primary procedure was a fusion, these authors found a general overall reoperation rate of 14% at 4 years, and for patients whose primary diagnosis was herniated disc or degenerative disc disease, the reoperation rate was approximately 15%. For patients treated with INFUSE® Bone Graft and the LT CAGE® Device, the secondary surgery failure rate of 9% at 4 years and 10% at 6 years compares favorably to overall failure rates cited for the 1990s.

Patients treated by the laparoscopic surgical technique in the current study trended to have improved outcomes in shortened hospital stay, better Oswestry Low Back Pain Disability Questionnaire scores, improved scores on the SF-36 Health Survey, reduced low back pain, and fewer reoperations when compared to the open surgically treated group. There are potential benefits of the laparoscopic surgical approach that may have contributed to this, which include less muscle damage and tissue retraction, shorter hospital stay, and a quicker return to normal activities. Preoperative differences in patient demographics, including sex and alcohol use, also may have contributed in part to these differences. Additionally, more patients in the open group had substantial changes in their ODI scores between 24 and 72 months, which may have contributed bias (18 patients in the open group had an ODI increase of 20 points or more, compared to only 1 patient in the laparoscopic group). Review of Case Report Forms for patients in the open group revealed the occurrence of falls, motor vehicle accidents, adjacent level disease, and a high percentage of patients with a BMI of >25, which may have contributed to the slight differences in clinical outcomes. Finally, the lack of randomization between the open and laparoscopic groups make it difficult to draw definitive conclusions as to the etiology or clinical significance of this difference. Importantly, the mean improvement

scores for both groups in Oswestry pain scores, PCS scores, and back and leg pain scores were significantly improved from preoperative and were maintained between the 24 and 72 month follow-up period.

A comparison of three outcome parameters including fusion status, operative time, and hospital stay show an improvement in care for treatment of degenerative disc disease in the lumbar spine with an advancement in therapy options [5]. Additionally, 24 month data comparing INFUSE® Bone Graft with ICBG has shown superior rates of fusion and clinical outcomes in patients treated with rhBMP-2 [11]. The improvement in functional outcomes is maintained out to 6 years following treatment with rhBMP-2, and is also reflected in the high rates of employment in both the open and laparoscopic groups. In particular, the high rate of segmental arthrodesis may serve to provide long term maintenance of these significant improvements in clinical outcomes [32].

The use of rhBMP-2 on an absorbable collagen-soaked sponge (INFUSE® Bone Graft) is an effective method of facilitating anterior intervertebral spinal fusion using a stand-alone interbody fusion device. Fusion success and improved clinical outcomes were maintained out to 6 years. INFUSE® Bone Graft demonstrates long term efficacy as a replacement to ICBG for lumbar spine fusion.

CONCLUSIONS

This paper reports the clinical and radiographic outcomes from patients treated with INFUSE® Bone Graft and threaded titanium cages with 6 years follow-up. rhBMP-2 was shown to lead to high rates of fusion that were maintained out to 6 years. Additionally, significant improvements in clinical outcome measures, including ODI, SF-36 PCS, and back and leg pain scores were maintained out to 6 years. These results further substantiate the use of rhBMP-2 as a replacement to autograft for lumbar interbody fusion.

Table 1. Summary of study groups analyzed.

Surgical approach	Randomized	Prospective	Total Patients	Patients w/ 72 mo f/u
Open	Y	Y	143	78
Laparoscopic	N	Y	134	68

Table 2. Patient inclusion/exclusion criteria

Inclusion Criteria	Exclusion Criteria
▪ ≥ 18 yrs old ▪ Single-level symptomatic DDD ▪ ≤ Grade 1 spondylolisthesis ▪ Disabling back pain and/or leg pain for greater than 6 months unresolved by nonoperative treatment	▪ Spinal conditions other than DDD ▪ DDD at disc space levels other than L4-L5 or L5-S1 ▪ Previous anterior fusion at involved level ▪ Obesity (>40% above ideal weight) ▪ Active bacterial infection ▪ Medical condition requiring medication that could interfere with fusion (e.g. steroids or NSAIDS)

DDD = degenerative disc disease; NSAID = nonsteroidal anti-inflammatory medication

Table 3. Patient demographics.

	Open	Laparoscopic	Combined
Number	78	68	146
Age (yr)	43.1	43.3	43.2
Weight (lbs)	181.1	172.6	177.2
Gender (% male)*	56.4	38.2	47.9
Smoking (%)	26.9	27.9	27.4
Worker's Compensation (%)	30.8	25.0	28.1
Unresolved litigation (%)	10.3	10.3	10.3
Alcohol use (%)**	21.8	54.4	37.0

*p<0.05; **p<0.001

Table 4. Surgical data

	Open	Laparoscopic	Combined
OR Time (hr)	1.6	1.9	1.8
Blood Loss (ml)	118.7	126.0	122.1
Length of Stay (days)	3.1	1.4	2.3

Table 5: Mean (S.D.) change in SF-36 scores from preoperative to 72 months.

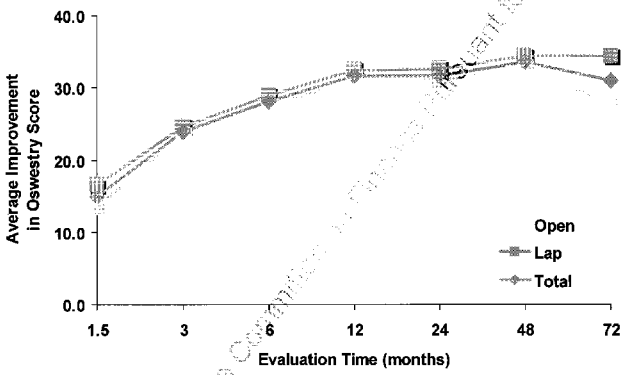
	Open	Laparoscopic	Combined
PCS	12.4 (12.6)	17.8 (10.2)	15.1 (11.7)
MCS	4.9 (13.2)	7.3 (10.2)	6.1 (11.8)
Physical Function	31.5 (30.4)	42.8 (26.8)	37.0 (29.1)
Role Physical	50.7 (46.2)	64.3 (43.0)	57.4 (45.0)
Pain Index	34.8 (27.6)	43.9 (25.8)	39.3 (27.0)
General Health Perception	-8.3 (27.0)	5.0 (17.3)	-1.7 (23.6)
Social Function	29.8 (31.7)	41.2 (27.7)	35.4 (30.2)
Mental Health	15.8 (23.5)	16.4 (20.1)	16.1 (21.8)
Role Emotional	10.1 (52.5)	26.0 (40.7)	18.0 (47.5)
Vitality	18.8 (24.6)	27.1 (23.0)	22.9 (24.1)

Note: Changes in SF-36 scores from preoperative to 24 months were similar between groups.

Long Term LT CAGE/InFUSE Outcomes
JK Burkus, MF Gornet, TC Schuler, TA Kleeman,TA Zdeblick

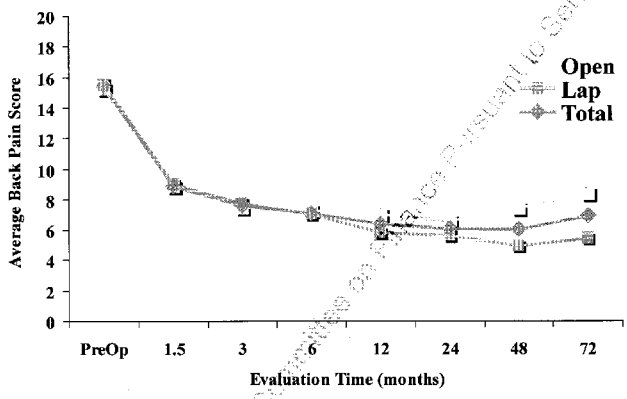
25

Figure 1: Improvement in Oswestry Disability Index.



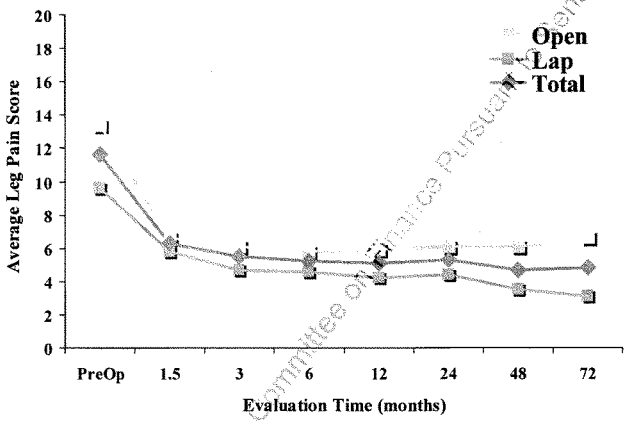
Long Term LT CAGE/InFUSE Outcomes
JK Burkus, MF Gornet, TC Schuler, TA Kleeman,TA Zdeblick

Figure 2: Back pain scores.



Long Term LT CAGE/InFUSE Outcomes
JK Burkus, MF Gornet, TC Schuler, TA Kleeman,TA Zdeblick

Figure 3: Leg pain scores.



Long Term LT CAGE/InFUSE Outcomes
JK Burkus, MF Gornet, TC Schuler, TA Kleeman,TA Zdeblick

28

Figure 4: SF-36 PCS.

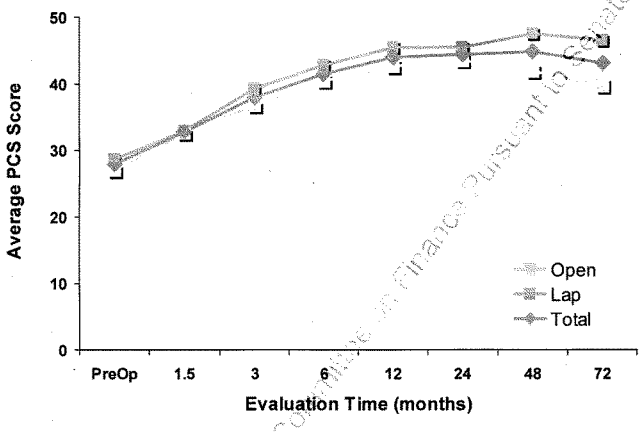
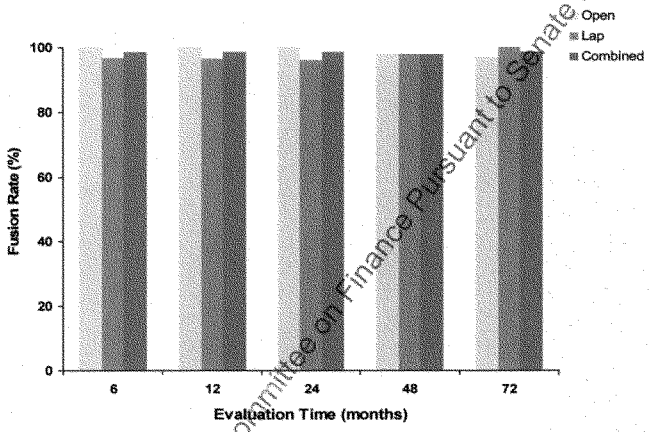
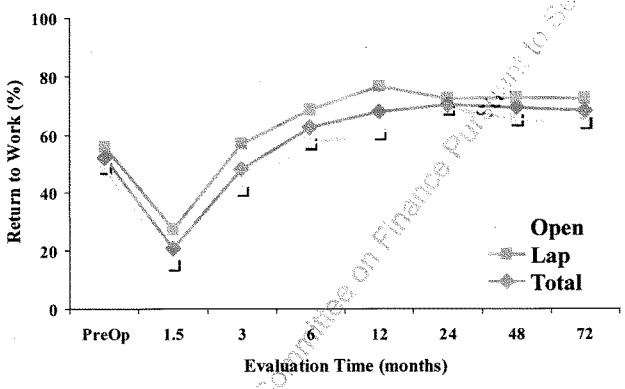


Figure 5: Radiographic fusion success.



Long Term LT CAGE/InFUSE Outcomes
JK Burkus, MF Gornet, TC Schuler, TA Kleeman,TA Zdeblick

Figure 6: Return to work status.



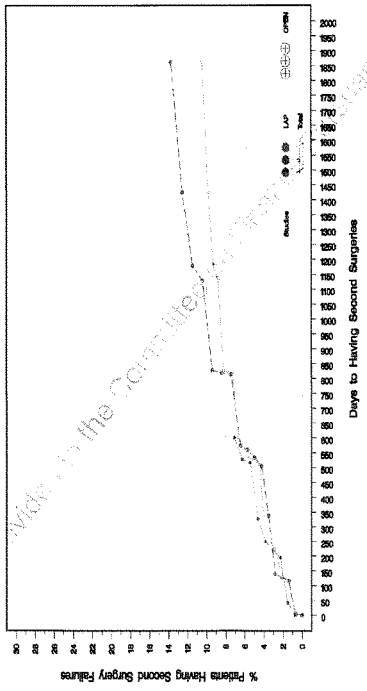


Figure 7: Second surgery failures

1. Adams, M.A. and P.J. Roughley, *What is intervertebral disc degeneration, and what causes it?* Spine, 2006. **31**(18): p. 2151-61.
2. Videman, T. and M. Nurminen, *The occurrence of anular tears and their relation to lifetime back pain history: a cadaveric study using barium sulfate discography.* Spine, 2004. **29**(23): p. 2668-76.
3. Kumar, N., M.R. Judith, A. Kumar, V. Mishra, and M.C. Robert, *Analysis of stress distribution in lumbar interbody fusion.* Spine, 2005. **30**(15): p. 1731-5.
4. Palm, W.J.t., W.S. Rosenberg, and T.M. Keaveny, *Load transfer mechanisms in cylindrical interbody cage constructs.* Spine, 2002. **27**(19): p. 2101-7.
5. Burkus, J.K., *Stand-alone anterior lumbar interbody fusion constructs: effect of interbody design, bone graft and bone morphogenetic protein on clinical and radiographic outcomes*, in *Advances in Spinal Fusion: Clinical Applications of Basic Science, Molecular Biology, Biomechanics, and Engineering*, K. Lewandrowski, et al., Editors. 2003, Marcel Dekker, Inc.: New York. p. 69-84.
6. Boden, S.D., G.J. Martin, Jr., W.C. Horton, T.L. Truss, and H.S. Sandhu, *Laparoscopic anterior spinal arthrodesis with rhBMP-2 in a titanium interbody threaded cage.* J Spinal Disord, 1998. **11**(2): p. 95-101.
7. Hecht, B.P., J.S. Fischgrund, H.N. Herkowitz, L. Penman, J.M. Toth, and A. Shirkhoda, *The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model.* Spine, 1999. **24**(7): p. 629-36.
8. Boden, S.D., T.A. Zdeblick, H.S. Sandhu, and S.E. Heim, *The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report.* Spine, 2000. **25**(3): p. 376-81.
9. Burkus, J.K., M.F. Gornet, C.A. Dickman, and T.A. Zdeblick, *Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages.* J Spinal Disord Tech, 2002. **15**(5): p. 337-49.
10. Burkus, J.K., H.S. Sandhu, M.F. Gornet, and M.C. Longley, *Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery.* J Bone Joint Surg Am, 2005. **87**(6): p. 1205-12.
11. Burkus, J.K., S.E. Heim, M.F. Gornet, and T.A. Zdeblick, *Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-CAGE lumbar tapered fusion device.* J Spinal Disord Tech, 2003. **16**(2): p. 113-22.
12. Anand, N., J.F. Hamilton, B. Perri, H. Miraliakbar, and T. Goldstein, *Cantilever TLIF with structural allograft and RhBMP2 for correction and maintenance of segmental sagittal lordosis: long-term clinical, radiographic, and functional outcome.* Spine, 2006. **31**(20): p. E748-53.
13. Kuklo, T.R., M.K. Rosner, and D.W. Polly, Jr., *Computerized tomography evaluation of a resorbable implant after transforaminal lumbar interbody fusion.* Neurosurg Focus, 2004. **16**(3): p. E10.
14. Lanman, T.H. and T.J. Hopkins, *Lumbar interbody fusion after treatment with recombinant human bone morphogenetic protein-2 added to poly(L-lactide-co-D,L-lactide) bioresorbable implants.* Neurosurg Focus, 2004. **16**(3): p. E9.
15. Mummaneni, P.V., J. Pan, R.W. Haid, and G.E. Rodts, *Contribution of recombinant human bone morphogenetic protein-2 to the rapid creation of interbody fusion when used in transforaminal lumbar interbody fusion: a preliminary report. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2004.* J Neurosurg Spine, 2004. **1**(1): p. 19-23.
16. Potter, B.K., B.A. Freedman, E.G. Verwiebe, J.M. Hall, D.W. Polly, Jr., and T.R. Kuklo, *Transforaminal lumbar interbody fusion: clinical and radiographic results and complications in 100 consecutive patients.* J Spinal Disord Tech, 2005. **18**(4): p. 337-46.
17. Schwender, J.D., L.T. Holly, D.P. Rouben, and K.T. Foley, *Minimally invasive transforaminal lumbar interbody fusion (TLIF): technical feasibility and initial results.* J Spinal Disord Tech, 2005. **18 Suppl**: p. S1-6.
18. Slosar, P.J., R. Josey, and J. Reynolds, *Accelerating lumbar fusions by combining rhBMP-2 with allograft bone: a prospective analysis of interbody fusion rates and clinical outcomes.* Spine J, 2007. **7**(3): p. 301-7.

19. Villavicencio, A.T., S. Burneikiene, E.L. Nelson, K.R. Bulsara, M. Favors, and J. Thramann, *Safety of transforaminal lumbar interbody fusion and intervertebral recombinant human bone morphogenetic protein-2.* J Neurosurg Spine, 2005. **3**(6): p. 436-43.
20. Kleeman, T.J., U.M. Ahn, and A. Talbot-Kleeman, *Laparoscopic anterior lumbar interbody fusion with rhBMP-2: a prospective study of clinical and radiographic outcomes.* Spine, 2001. **26**(24): p. 2751-6.
21. Hsu, H.P., J.M. Zanella, S.M. Peckham, and M. Spector, *Comparing ectopic bone growth induced by rhBMP-2 on an absorbable collagen sponge in rat and rabbit models.* J Orthop Res, 2006. **24**(8): p. 1660-9.
22. Fairbank, J.C., J. Couper, J.B. Davies, and J.P. O'Brien, *The Oswestry low back pain disability questionnaire.* Physiotherapy, 1980. **66**(8): p. 271-3.
23. McHorney, C.A., J.E. Ware, Jr., J.F. Lu, and C.D. Sherbourne, *The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups.* Med Care, 1994. **32**(1): p. 40-66.
24. Ware, J.E., Jr. and C.D. Sherbourne, *The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection.* Med Care, 1992. **30**(6): p. 473-83.
25. Bagby, G., *The Bagby and Kuslich (BAK) method of lumbar interbody fusion.* Spine, 1999. **24**(17): p. 1857.
26. Brantigan, J.W., A. Neidre, and J.S. Toohey, *The Lumbar I/F Cage for posterior lumbar interbody fusion with the variable screw placement system: 10-year results of a Food and Drug Administration clinical trial.* Spine J, 2004. **4**(6): p. 681-8.
27. Brantigan, J.W., A.D. Steffee, M.L. Lewis, L.M. Quinn, and J.M. Persenaire, *Lumbar interbody fusion using the Brantigan I/F cage for posterior lumbar interbody fusion and the variable pedicle screw placement system: two-year results from a Food and Drug Administration investigational device exemption clinical trial.* Spine, 2000. **25**(11): p. 1437-46.
28. Button, G., M. Gupta, C. Barrett, P. Cammack, and D. Benson, *Three- to six-year follow-up of stand-alone BAK cages implanted by a single surgeon.* Spine J, 2005. **5**(2): p. 155-60.
29. Kuslich, S.D., G. Danielson, J.D. Dowdle, J. Sherman, B. Fredrickson, H. Yuan, and S.L. Griffith, *Four-year follow-up results of lumbar spine arthrodesis using the Bagby and Kuslich lumbar fusion cage.* Spine, 2000. **25**(20): p. 2656-62.
30. Kuslich, S.D., C.L. Ulstrom, S.L. Griffith, J.W. Ahern, and J.D. Dowdle, *The Bagby and Kuslich method of lumbar interbody fusion. History, techniques, and 2-year follow-up results of a United States prospective, multicenter trial.* Spine, 1998. **23**(11): p. 1267-78; discussion 1279.
31. Martin, B.I., S.K. Mirza, B.A. Comstock, D.T. Gray, W. Kreuter, and R.A. Deyo, *Are lumbar spine reoperation rates falling with greater use of fusion surgery and new surgical technology?* Spine, 2007. **32**(19): p. 2119-26.
32. Kornblum, M.B., J.S. Fischgrund, H.N. Herkowitz, D.A. Abraham, D.L. Berkower, and J.S. Ditkoff, *Degenerative lumbar spondylolisthesis with spinal stenosis: a prospective long-term study comparing fusion and pseudarthrosis.* Spine, 2004. **29**(7): p. 726-33; discussion 733-4.

From: Hatcher, Brian, PhD.
Sent: Wednesday, October 10, 2007 08:22:05 AM
To: Bearcroft, Julie, PhD; Meyer, Matt; Beals, Neil
Subject: FW: Long term LT CAGE BMP manuscript

Attachments: BMP LT Cage 72 months.ready.to.submit.doc

FYI, see note below from Dr. Burkus to other co-authors regarding the INFUSE/LT Cage 6 year paper. We should be looking to submit this manuscript in the next few weeks.
Brian

From: Ken Burkus [mailto[redacted]
Sent: Wednesday, October 10, 2007 5:15 AM
To: Tom Kleeman; Thomas Kleeman [redacted]); Tom Schuler; Matthew F Gornet; Thomas Zdeblick
Cc: Carol Binns; Hatcher, Brian, PhD.; Vicki K Earnest; Lynn Sanders
Subject: Long term LT CAGE BMP manuscript

Sirs,

For one thing we have too many Tom's on this manuscript.

Please see attached - a manuscript prepared for submission to JBJS. This is the 6-year LT CAGE BMP data. I will find an radiographic case to include.

Please make you comments on the WORD document and return it to Carol Binns. I would like to submit it before the end of the month. It is possible that ND may have won their second game by then - you know how many upsets there have been this year.

At MSD, Brain Hatcher has been the driving force behind getting the data and the manuscript to this point.

Best regards,
Ken Burkus

Long -Term Follow-up of Patients Treated with Stand Alone Anterior Lumbar Interbody Fusion Cages and Recombinant Human Bone Morphogenetic Protein-2

J. Kenneth Burkus, M.D.*

Matthew F. Gornet MD†

Thomas C. Schuler, MD††

Thomas A. Kleeman, MD#

Thomas A. Zdeblick MD§

* Staff Physician, Spine Service, The Hughston Clinic, [redacted]

† The Orthopedic Center of St. Louis, St. Louis, MO

†† Virginia Spine Institute, Reston, Virginia

New Hampshire Spine Institute, Bedford, New Hampshire

§Chairman, Department of Orthopedics and Rehabilitation, University of Wisconsin, Madison, Wisconsin

FDA device/drug status: Approved for this indication.

Statement of Financial Relationship: The authors are consultants and clinical investigators for the company distributing the device studied.

Address correspondence and reprint requests to: J. K. Burkus, M.D., The Hughston Clinic, [redacted] Columbus, Georgia 31908-9517

ABSTRACT

Background: Stand alone anterior lumbar interbody fusion using dual tapered interbody fusion cages and recombinant human bone morphogenetic protein-2 on an absorbable collagen sponge (rhBMP-2/ACS) has been reported with 24-month outcomes. Longer clinical and radiographic follow-up is needed to verify the sustained improvements in outcomes in the surgical treatment of degenerative lumbar disc disease.

Methods: An integrated analysis was performed following two prospective clinical studies in which patients received rhBMP-2/ACS with lumbar fusion cage implants and had 6 year follow up. A total of 146 patients were treated for single-level degenerative disc disease with up to grade 1 spondylolisthesis by either an open or a laparoscopic surgical procedure. Patient outcomes were determined using well-established clinical outcome measurements and radiographic assessments.

Results: Patients treated with rhBMP-2 and stand alone fusion cages showed high rates of fusion and low rates of additional surgery. For patients with 6 year follow-up, radiographic evidence of fusion was documented in 98.5% of patients at 6 years. Additionally, significant improvements in clinical outcomes, including Oswestry Disability Index scores (ODI), SF-36® Health Survey Physical Component Summary scores, and back and leg pain scores were achieved by 6 weeks and were sustained out to 6 years. A higher percentage of patients were working than were working preoperatively by 6 months, and this improvement was sustained out to 6 years. There was a trend towards greater improvement in ODI, back pain, and SF-36 PCS scores in the laparoscopic group compared to the open group.

Conclusions: The use of dual tapered threaded fusion cages and rhBMP-2 on an absorbable collagen sponge facilitates and maintains intervertebral spinal fusion, sustained improvements in clinical outcomes and reduction of pain following anterior lumbar interbody fusion for degenerative lumbar disc disease.

Keywords: Anterior lumbar interbody fusion, INFUSE Bone Graft, bone morphogenetic protein, fusion cage, degenerative disc disease, lumbar spine

INTRODUCTION

Discogenic low back pain results, in part, from abnormal intersegmental load patterns and movement within a degenerative disc [1]. Clinically painful discs have been shown to display specific patterns of altered stresses in the annulus and vertebral endplates, reflecting abnormal loading [2]. Lumbar interbody fusion can eliminate abnormal stress patterns associated with degenerative disc disease and normalize stress distribution patterns [3, 4]. Threaded interbody fusion cages stabilize the spinal motion segment and provide a mechanical environment that optimizes fusion [5]. New bone formation in and around the cages increases the contact area and decreases the magnitude of abnormal load in the adjacent vertebrae.

Various bone grafts have been used in an effort to enhance bone formation within the interverterbal disc space. Recombinant human bone morphogenetic protein (rhBMP-2) is an osteoinductive growth factor that stimulates pleuripotential cells to form bone. In animal and human studies, rhBMP-2 has been shown to be capable of inducing new bone formation [6, 7]. At 24 months in randomized anterior lumbar interbody fusion (ALIF) clinical trials, the use of rhBMP-2 as an iliac crest bone graft (ICBG) replacement has been shown to increase rates of interbody fusion, and its use has been associated with decreased pain and improved clinical outcomes [8-10]. When used in combination with the LT CAGE® Device (Medtronic Sofamor Danek, Memphis, Tennessee), patients treated with rhBMP-2 had significantly higher fusion rates than patients treated with ICBG (94.4% vs. 89.4%; p=0.022) [11]. Additional studies with rhBMP-2/ACS in lumbar interbody fusion have also shown similar rates of fusion success [8-10, 12-19].

The purpose of our analysis was to investigate the post-approval long-term clinical and radiographic outcomes in those investigational patients enrolled in these initial FDA trials using stand alone interbody fusion cages and rhBMP-2 as an iliac crest bone graft replacement. Patients who received INFUSE® Bone Graft were followed for a period of 6 years to determine the long term efficacy as a replacement to ICBG.

MATERIALS and METHODS

Two prospective, multi-center FDA-approved IDE studies of patients undergoing treatment for single-level lumbar degenerative disc disease were conducted, utilizing a similar fusion technique through two different surgical approaches [9, 20]. All patients were entered into these studies between 1997 and 1999. Our analysis combines data from the patients who received treatment with the INFUSE® Bone Graft/LT-CAGE® Device in the two FDA IDE trials (Table 1). These studies used the identical inclusion-exclusion criteria (Table 2); however, the laparoscopic cohort was a non randomized, single-arm study whereas patients in the open study were randomized to rhBMP-2/ACS or ICBG.

Inclusion Exclusion Criteria

At the time of surgery, all patients were between the ages of 19 and 70 years and had symptomatic degenerative disc disease at the L4-L5 or L5-S1 levels. All had low back pain for at least 6 months before their surgery that was recalcitrant to nonoperative treatment modalities, such as physical therapy, bed rest, and anti-inflammatory medications. Patients were included in the study if their plain radiographic findings documented single-level disc disease, and they had undergone at least one additional confirmatory neuroradiographic study, such as MRI, CT-enhanced myelography, or discography. All patients were considered candidates for a single-level stand-alone ALIF.

Patients were excluded from the study if they had spinal conditions other than single-level symptomatic degenerative disc disease or greater than Grade 1 spondylolisthesis. Other exclusion criteria were symptomatic disc disease at a level other than the L4-L5 or L5-S1, obesity (more than 40% above ideal body weight), or a medical

condition that required medication, such as steroids or nonsteroidal anti-inflammatory medications, that could interfere with fusion.

Patient Accountability and Demographics

There were 277 patients enrolled in both the open (143 patients) and laparoscopic (134 patients) groups in the initial FDA IDE studies. A total of 23 out of the 31 initial sites elected to participate in the long-term follow-up. As a result of second surgery failures and non participating sites, 58 patients were excluded from this study leaving a total of 219 patients who were eligible for the FDA IDE post-approval follow-ups (109 in the open arm and 110 in the laparoscopic arm). A total of 146 patients completed the 72-month follow-ups. This subgroup of patients was evaluated to determine the clinical outcome measures and fusion status at each time point (preoperative through 72 months).

Surgical Procedures

Patients underwent an ALIF procedure using either an open [9]or a laparoscopic approach [20]. In the open group, either transperitoneal or retroperitoneal approaches to the lumbosacral spine were utilized; in the laparoscopic group, all approaches were transperitoneal. Patients had two LT-CAGE® Devices implanted anteriorly at one lumbar interspace (either L4-L5 or L5-S1).

rhBMP-2 on the ACS was used exclusively as an ICBG replacement. No autogenous grafts and no local host bone reamings were used. The method of use of rhBMP-2 has been reviewed [9, 20]. The genetically engineered the rhBMP-2 component (Wyeth BioPharma, Cambridge, MA) and ACS component (Integra LifeSciences, Plainsboro, NJ) are distributed commercially under the trade name INFUSE® Bone Graft (Medtronic Sofamor Danek, Memphis, TN). The rhBMP-2 was

reconstituted to a concentration of 1.5mg/ml using sterile water and applied to the appropriate number of ACS's. The rhBMP-2 was allowed to bind to the ACS for a minimum of 15 minutes, which results in 95% of the protein being bound to the sponge [21]. The rhBMP-2 soaked sponges were placed into the central portion of each LT-CAGE® Device. No additional rhBMP-2-bound sponges were placed outside of the fusion cages. The total dose of rhBMP-2 ranged from 4.2 to 8 mg and was determined by matching the volume of the prepared ACS to the internal volume of the LT-CAGE® Device.

The results from the two surgical approaches were pooled and analyzed independently to better define the effects of surgical approach in surgical parameters, hospital stay, and the long-term clinical and radiographic outcomes.

Clinical Outcome Measures

Clinical outcome measures, including Oswestry Disability Index (ODI) [22], Short Form 36 questionnaire [23, 24], back and leg pain scores and return to work status were self administered preoperatively and at 1.5, 3, 6, 12, 24, 48, and 72 months. Back and leg pain scores were determined using a 20 point scale (10 points frequency and 10 points intensity).

Radiographic Assessment

The presence of continuous trabecular bone formation between the vertebral bodies was assessed using radiographs and computed tomography (CT) scans. Fusion was defined as bridging bone connecting the adjacent vertebral bodies either through the implants or around the implants, less than 5° of angular motion, less than or equal to 3 mm of translation, and an absence of radiolucent lines around more than 50% of either

implant. Fusion was assessed at 6, 12, 24, 48, and 72 months, and was considered successful only if all four criteria were achieved.

Additional Surgical Procedures

Secondary surgical procedures performed subsequent to the index operation were classified as revisions, removals, supplemental fixations, or reoperations. A revision surgery was defined as any procedure that adjusts or modifies the original implant configuration; a removal was defined as a procedure that removes one or more components of the original implant and replaces it with a different type of implant; supplemental fixation was defined as a procedure in which additional spinal devices not approved as part of the protocol are placed; and reoperation was defined as any surgical procedure at the treated level that does not remove, modify, or add any components, for example a posterior foraminotomy. A survivorship analysis was used to determine the percentage of patients who were second surgery failures, taking into account all available patients at each follow-up time point.

Adverse Events

Adverse events were studied and classified as to their severity and relationship with the implants and with surgical procedures.

RESULTS

Patient Accountability

A total of 146 patients (68 in the laparoscopic group and 78 in the open group) completed the 6 year follow-up. The overall follow-up rate was 52.7% (146/277), and the follow-up rate for available patients at 6 years was 66.7% (146/219). A comparison of this subgroup of patients with the entire patient population prior to 24 months indicated similar clinical outcomes between the groups, suggesting that this group of patients serves as a representative subset of the entire patient population.

Demographic data were compiled for the patients included in the analysis (Table 3). The two prospective study groups were not randomized; however, the patients' demographic characteristics and prognostic factors were similar except for sex and alcohol use.

Surgical Data

Surgical, hospitalization and clinical outcomes were analyzed for each surgical technique and the outcomes were combined. Analysis of surgical and hospitalization data for the two surgical treatment groups shows the laparoscopic group spent an average of 18 minutes longer under anesthesia and lost an average of 7.3 mL more blood (Table 4). However, the laparoscopic group left the hospital 1.7 days earlier than the open group, on average.

Clinical Outcomes

Oswestry Disability Scores:

The Oswestry Disability Index (ODI) Questionnaire measures the level of pain and disability associated with various activities. ODI scores improved significantly from

preoperative values by 6 weeks, and these improvements were maintained out to 6 years ($p<0.001$). For the combined group, ODI scores improved an average of 33.6 points and 31.0 points at 48 and 72 months, respectively, from a preoperative score of 52.0. These improvements were similar to those observed at 24 months (31.7 points). There was a trend towards slightly greater improvements in ODI scores in the laparoscopic group compared to the open group at 72 months (Fig 1).

Back Pain:

Back pain scores improved significantly from preoperative values by 6 weeks, and these improvements were maintained out to 6 years ($p<0.001$). For the combined group, back pain scores improved an average of 9.3 points and 8.6 points at 48 and 72 months, respectively. These improvements were similar to those observed at 24 months (9.3 points). There was a trend towards slightly greater improvements in back pain scores in the laparoscopic group compared to the open group and 48 and 72 months (Fig 2).

Leg Pain:

Leg pain scores improved significantly from preoperative values by 6 weeks, and these improvements were maintained out to 6 years ($p<0.001$). For the combined group, leg pain scores improved an average of 6.4 points and 6.7 points at 48 and 72 months, respectively. These improvements were similar to those observed at 24 months (6.4 points). The improvement from the preoperative score at 72 months was similar in the laparoscopic and open group (Fig 3).

SF-36:

The SF-36 measures specific health concepts related to physical functioning, social functioning and health perceptions. For the combined group, Physical Component Scores (PCS) improved an average of 17.3 points and 15.1 points at 48 and 72 months, respectively. These improvements were similar to those observed at 24 months (16.1 points). There was a trend towards slightly greater improvements in SF-36 PCS scores in the laparoscopic group compared to the open group at 48 and 72 months (Fig 4).

For the combined group, all SF-36 outcomes except for general health perception improved significantly ($p<0.001$) from the preoperative values at 72 months (Table 5). Additionally, SF-36 scores were maintained between 24 and 72 months. There was a trend towards greater improvement in SF-36 scores in the laparoscopic group compared to the open group.

Radiographic Outcomes:

At 72 months, 130 patients had complete radiographic follow-up. At 48 and 72 months, 97.9% and 98.5% of patients had radiographic evidence of fusion (Figure 5). The high rates of fusion seen at these later time points were similar to the rates of arthrodesis seen at 6, 12, and 24 months. Fusion rates were similar between the open and laparoscopic groups.

Second Surgery Failures:

There were a total of 25 second surgery failures over the 6 year follow-up, including 16 in the open group and 9 in the laparoscopic group. These second surgery failures included 23 supplemental fixations, 1 removal and 1 revision. Reasons for second surgeries were reported by the enrolling surgeon, and included implant positioning, migration or loosening, nonunions, pending nonunions, subsidence, stenosis,

radiculopathy, adjacent segment degeneration and post laminectomy syndrome. Second surgery failures occurred between 5 days and 62 months postoperative.

Adjusting for the patients available at each follow-up by a time to event analysis, the overall second surgery failure rate was 10.4% (13.7% in the open group and 7.1% in the laparoscopic group; Fig 7). The second surgery failure rate prior to 2 years for the combined group was 6.7% (6.4% open and 7.1% laparoscopic). Between 2 and 6 years, the rate of second surgery failure for the combined group was 3.7% (7.3% open and 0% laparoscopic).

Return-to-Work Status:

At 48 and 72 months, more patients were working than were working preoperatively (69.2% and 68.1% at 48 and 72 months, respectively compared to 52.1% preoperatively). The percentage of patients working at the later time points was similar to what was seen at 24 months (70.3%, Figure 6). By 6 months, approximately 90% of the patients who were working preoperatively had returned to work, and this was maintained though the 72 month time point.

Adverse events:

No unanticipated adverse events related to the use of rhBMP-2/ACS occurred during the course of the study. Since the ICBG control group was not followed during the 24 and 72 month time frame, no analysis of adverse events between the investigational and control group could be completed.

DISCUSSION

Results from prospective studies of the LT-CAGE® Device have shown a trend towards faster fusion with INFUSE® Bone Graft and improved clinical outcomes when compared with patients who received autograft ICBG [11]. These improved outcomes are related, in part, to the successful combination of the surgical approach, the advanced cage designs, the avoidance of bone graft harvesting morbidity, and the high rate of successful interbody fusion. This study represents the longest follow-up to date of patients undergoing spine fusion with INFUSE® Bone Graft [9-20]. In patients followed out to 6 years, it was observed that radiographic fusion rates were high, rates of second surgery were low, and improvements in clinical outcomes were maintained.

Other studies have reported on the long term radiographic and clinical results following lumbar interbody fusion [25-30]. Kuslich et al. reported on 4 year results from a study enrolling 947 patients who received Bagby and Kuslich (BAK) cages and ICBG [29]. Only 20.7% (196/947) of patients completed the 4 year follow-up, however, which included both anterior (n=122) and posterior (n=74) approaches and single-level (n=116) and 2-level (n=80) fusions. Fusion success allowed for up to 7° of angulation on flexion extension films, and no thin cut CT scans with reconstructed images were obtained to assess fusion. At 4 years, the authors reported an overall fusion success of 98% and a repeat surgery rate of 8.7%. Pain scores were maintained out to 4 years.

In a similar study, clinical and radiographic outcomes following ALIF with stand alone BAK cages implanted by a single author were evaluated [28]. Patients underwent single-level (n=40) or 2-level (n=6) ALIF with BAK Cages and autograft, allograft, or a combination of both. A total of 33 out of 46 patients (71.7%) reached a mean follow-up

of 55 months (range = 36-65 months). The authors reported an overall nonunion rate of 30% and a revision rate of 22%. Mean ODI score at final follow-up was 41, with only 42% of patients having an ODI ≤ 40. The fusion rates and improvement in ODI scores at 4 and 6 years in patients treated with INFUSE® Bone Graft and the LT CAGE® Device indicate an improvement relative to this published report.

Brantigan also investigated the long term results following instrumented posterior lumbar interbody fusion (PLIF). The initial study enrolled a total of 110 patients with degenerative disc disease at 6 centers. A total of 33 patients selected from 2 centers completed the 10 year follow-up (30%). Radiographic evidence of fusion, as defined by bridging bone and the absence of radiolucencies was reported in 96.7% of the patients at 10 years. At 2 years, elective removal of pedicle screws indicated that 90% (104/115) of the examined levels were fused. Clinical outcomes were determined using a 20 point Prolo scale. A clinical success was defined as a patient with an excellent, good or fair outcome and a minimum of a 3 point improvement. Preoperatively, 76% of patients had a rating of good or fair. At 10 years, 87.8% (29/33) of patients had a rating of excellent, good or fair and achieved clinical success. In the current study, 79% (109/138) of patients treated with INFUSE Bone Graft had an ODI improvement of greater than 15 points at 6 years.

Martin [31] compared reoperations rates in the early 90s with the late 90s. The study included approximately 25,000 patients who underwent primary lumbar surgery for degenerative disc disease, herniated lumbar disc, stenosis or spondylolisthesis. The primary surgical procedure was fusion in 19.1% of patients and decompression or discectomy in 90.9%. A reoperation was defined as any secondary

operation of the lumbar spine. For patients whose primary procedure was a fusion, these authors found a general overall reoperation rate of 14% at 4 years, and for patients whose primary diagnosis was herniated disc or degenerative disc disease, the reoperation rate was approximately 15%. For patients treated with INFUSE® Bone Graft and the LT CAGE® Device, the secondary surgery failure rate of 9% at 4 years and 10% at 6 years compares favorably to overall failure rates cited for the 1990s.

Patients treated by the laparoscopic surgical technique in the current study trended to have improved outcomes in shortened hospital stay, better Oswestry Low Back Pain Disability Questionnaire scores, improved scores on the SF-36 Health Survey, reduced low back pain, and fewer reoperations when compared to the open surgically treated group. There are potential benefits of the laparoscopic surgical approach that may have contributed to this, which include less muscle damage and tissue retraction, shorter hospital stay, and a quicker return to normal activities. Preoperative differences in patient demographics, including sex and alcohol use, also may have contributed in part to these differences. Additionally, more patients in the open group had substantial changes in their ODI scores between 24 and 72 months, which may have contributed bias (18 patients in the open group had an ODI increase of 20 points or more, compared to only 1 patient in the laparoscopic group). Review of Case Report Forms for patients in the open group revealed the occurrence of falls, motor vehicle accidents, adjacent level disease, and a high percentage of patients with a BMI of >25, which may have contributed to the slight differences in clinical outcomes. Finally, the lack of randomization between the open and laparoscopic groups make it difficult to draw definitive conclusions as to the etiology or clinical significance of this difference. Importantly, the mean improvement

scores for both groups in Oswestry pain scores, PCS scores, and back and leg pain scores were significantly improved from preoperative and were maintained between the 24 and 72 month follow-up period.

A comparison of three outcome parameters including fusion status, operative time, and hospital stay show an improvement in care for treatment of degenerative disc disease in the lumbar spine with an advancement in therapy options [5]. Additionally, 24 month data comparing INFUSE® Bone Graft with ICBG has shown superior rates of fusion and clinical outcomes in patients treated with rhBMP-2 [11]. The improvement in functional outcomes is maintained out to 6 years following treatment with rhBMP-2, and is also reflected in the high rates of employment in both the open and laparoscopic groups. In particular, the high rate of segmental arthrodesis may serve to provide long term maintenance of these significant improvements in clinical outcomes [32].

The use of rhBMP-2 on an absorbable collagen-soaked sponge (INFUSE® Bone Graft) is an effective method of facilitating anterior intervertebral spinal fusion using a stand-alone interbody fusion device. Fusion success and improved clinical outcomes were maintained out to 6 years. INFUSE® Bone Graft demonstrates long term efficacy as a replacement to ICBG for lumbar spine fusion.

CONCLUSIONS

This paper reports the clinical and radiographic outcomes from patients treated with INFUSE® Bone Graft and threaded titanium cages with 6 years follow-up. rhBMP-2 was shown to lead to high rates of fusion that were maintained out to 6 years. Additionally, significant improvements in clinical outcome measures, including ODI, SF-36 PCS, and back and leg pain scores were maintained out to 6 years. These results further substantiate the use of rhBMP-2 as a replacement to autograft for lumbar interbody fusion.

Table 1. Summary of study groups analyzed.

Surgical approach	Randomized	Prospective	Total Patients	Patients w/ 72 mo f/u
Open	Y	Y	143	78
Laparoscopic	N	Y	134	68

Table 2. Patient inclusion/exclusion criteria

Inclusion Criteria	Exclusion Criteria
▪ ≥ 18 yrs old ▪ Single-level symptomatic DDD ▪ ≤ Grade 1 spondylolisthesis ▪ Disabling back pain and/or leg pain for greater than 6 months unresolved by nonoperative treatment	▪ Spinal conditions other than DDD ▪ DDD at disc space levels other than L4-L5 or L5-S1 ▪ Previous anterior fusion at involved level ▪ Obesity (>40% above ideal weight) ▪ Active bacterial infection ▪ Medical condition requiring medication that could interfere with fusion (e.g. steroids or NSAIDS)

DDD = degenerative disc disease; NSAID = nonsteroidal anti-inflammatory medication

Table 3. Patient demographics.

	Open	Laparoscopic	Combined
Number	78	68	146
Age (yr)	43.1	43.3	43.2
Weight (lbs)	181.1	172.6	177.2
Gender (% male)*	56.4	38.2	47.9
Smoking (%)	26.9	27.9	27.4
Worker's Compensation (%)	30.8	25.0	28.1
Unresolved litigation (%)	10.3	10.3	10.3
Alcohol use (%)**	21.8	54.4	37.0

*p<0.05; **p<0.001

Table 4. Surgical data

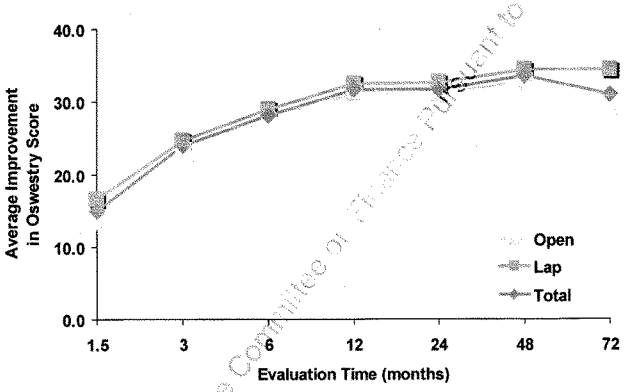
	Open	Laparoscopic	Combined
OR Time (hr)	1.6	1.9	1.8
Blood Loss (ml)	118.7	126.0	122.1
Length of Stay (days)	3.1	1.4	2.3

Table 5: Mean (S.D.) change in SF-36 scores from preoperative to 72 months.

	Open	Laparoscopic	Combined
PCS	12.4 (12.6)	17.8 (10.2)	15.1 (11.7)
MCS	4.9 (13.2)	7.3 (10.2)	6.1 (11.8)
Physical Function	31.5 (30.4)	42.8 (26.8)	37.0 (29.1)
Role Physical	50.7 (46.2)	64.3 (43.0)	57.4 (45.0)
Pain Index	34.8 (27.6)	43.9 (25.8)	39.3 (27.0)
General Health Perception	-8.3 (27.0)	5.0 (17.3)	-1.7 (23.6)
Social Function	29.8 (31.7)	41.2 (27.7)	35.4 (30.2)
Mental Health	15.8 (23.5)	16.4 (20.1)	16.1 (21.8)
Role Emotional	10.1 (52.5)	26.0 (40.7)	18.0 (47.5)
Vitality	18.8 (24.6)	27.1 (23.0)	22.9 (24.1)

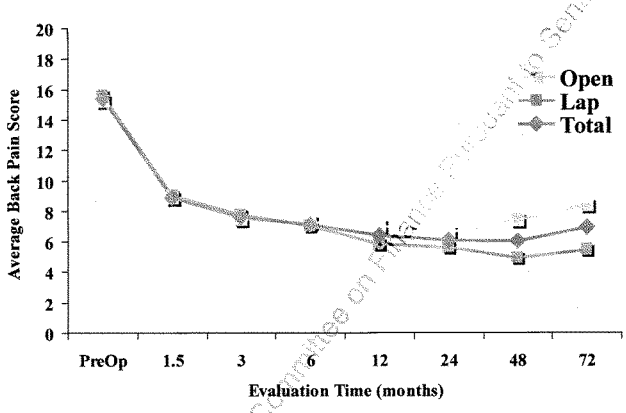
Note: Changes in SF-36 scores from preoperative to 24 months were similar between groups.

Figure 1: Improvement in Oswestry Disability Index.



Long Term LT CAGE/InFUSE Outcomes
JK Burkus, MF Gornet, TC Schuler, TA Kleeman,TA Zdeblick 26

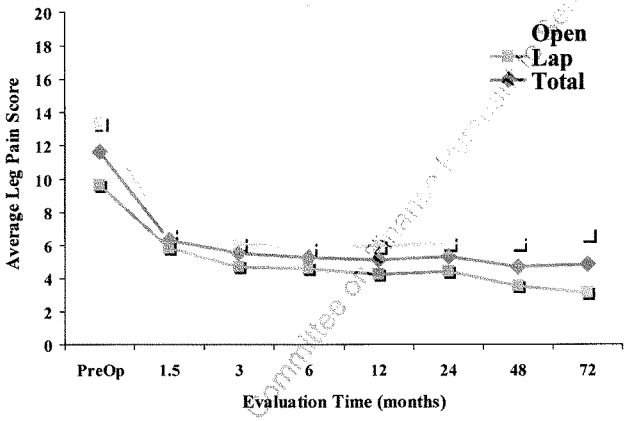
Figure 2: Back pain scores.



Long Term LT CAGE/InFUSE Outcomes
JK Burkus, MF Gornet, TC Schuler, TA Kleeman,TA Zdeblick

27

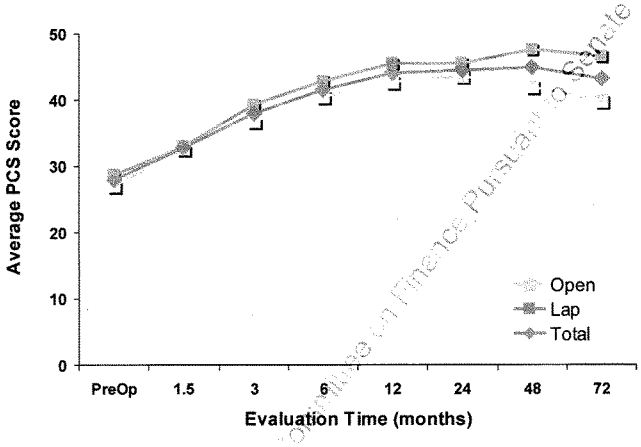
Figure 3: Leg pain scores.



Long Term LT CAGE/InFUSE Outcomes
JK Burkus, MF Gornet, TC Schuler, TA Kleeman,TA Zdeblick

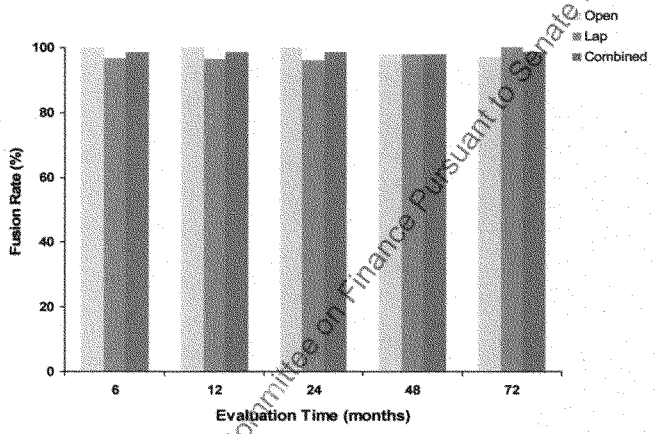
28

Figure 4: SF-36 PCS.



Long Term LT CAGE/InFUSE Outcomes
JK Burkus, MF Gornet, TC Schuler, TA Kleeman,TA Zdeblick

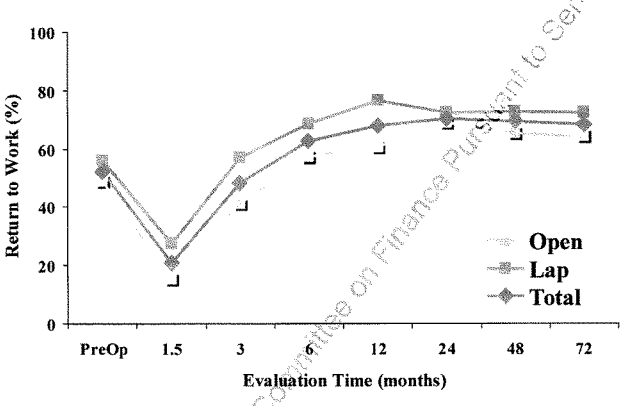
Figure 5: Radiographic fusion success.



Long Term LT CAGE/InFUSE Outcomes
JK Burkus, MF Gornet, TC Schuler, TA Kleeman,TA Zdeblick

30

Figure 6: Return to work status.



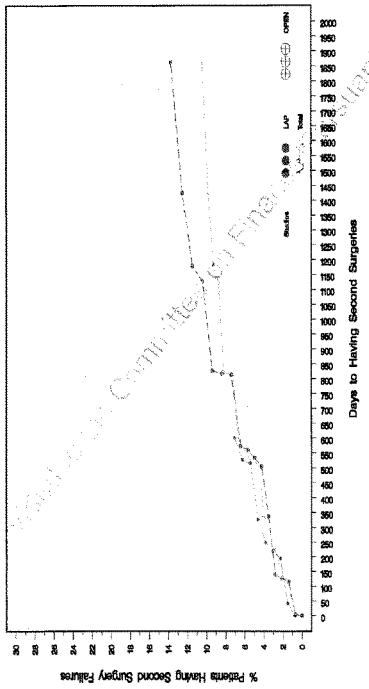


Figure 7: Second surgery failures

1. Adams, M.A. and P.J. Roughley, *What is intervertebral disc degeneration, and what causes it?* Spine, 2006. **31**(18): p. 2151-61.
2. Videman, T. and M. Nurminen, *The occurrence of anular tears and their relation to lifetime back pain history: a cadaveric study using barium sulfate discography.* Spine, 2004. **29**(23): p. 2668-76.
3. Kumar, N., M.R. Judith, A. Kumar, V. Mishra, and M.C. Robert, *Analysis of stress distribution in lumbar interbody fusion.* Spine, 2005. **30**(15): p. 1731-5.
4. Palm, W.J.t., W.S. Rosenberg, and T.M. Keaveny, *Load transfer mechanisms in cylindrical interbody cage constructs.* Spine, 2002. **27**(19): p. 2101-7.
5. Burkus, J.K., *Stand-alone anterior lumbar interbody fusion constructs: effect of interbody design, bone graft and bone morphogenetic protein on clinical and radiographic outcomes*, in *Advances in Spinal Fusion: Clinical Applications of Basic Science, Molecular Biology, Biomechanics, and Engineering*, K. Lewandrowski, et al., Editors. 2003, Marcel Dekker, Inc.: New York. p. 69-84.
6. Boden, S.D., G.J. Martin, Jr., W.C. Horton, T.L. Truss, and H.S. Sandhu, *Laparoscopic anterior spinal arthrodesis with rhBMP-2 in a titanium interbody threaded cage.* J Spinal Disord, 1998. **11**(2): p. 95-101.
7. Hecht, B.P., J.S. Fischgrund, H.N. Herkowitz, L. Penman, J.M. Toth, and A. Shirkhoda, *The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model.* Spine, 1999. **24**(7): p. 629-36.
8. Boden, S.D., T.A. Zdeblick, H.S. Sandhu, and S.E. Heim, *The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report.* Spine, 2000. **25**(3): p. 376-81.
9. Burkus, J.K., M.F. Gornet, C.A. Dickman, and T.A. Zdeblick, *Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages.* J Spinal Disord Tech, 2002. **15**(5): p. 337-49.
10. Burkus, J.K., H.S. Sandhu, M.F. Gornet, and M.C. Longley, *Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery.* J Bone Joint Surg Am, 2005. **87**(6): p. 1205-12.
11. Burkus, J.K., S.E. Heim, M.F. Gornet, and T.A. Zdeblick, *Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-CAGE lumbar tapered fusion device.* J Spinal Disord Tech, 2003. **16**(2): p. 113-22.
12. Anand, N., J.F. Hamilton, B. Perri, H. Miraliakbar, and T. Goldstein, *Cantilever TLIF with structural allograft and RhBMP2 for correction and maintenance of segmental sagittal lordosis: long-term clinical, radiographic, and functional outcome.* Spine, 2006. **31**(20): p. E748-53.
13. Kuklo, T.R., M.K. Rosner, and D.W. Polly, Jr., *Computerized tomography evaluation of a resorbable implant after transforaminal lumbar interbody fusion.* Neurosurg Focus, 2004. **16**(3): p. E10.
14. Lanman, T.H. and T.J. Hopkins, *Lumbar interbody fusion after treatment with recombinant human bone morphogenetic protein-2 added to poly(L-lactide-co-D,L-lactide) bioresorbable implants.* Neurosurg Focus, 2004. **16**(3): p. E9.
15. Mummaneni, P.V., J. Pan, R.W. Haid, and G.E. Rodts, *Contribution of recombinant human bone morphogenetic protein-2 to the rapid creation of interbody fusion when used in transforaminal lumbar interbody fusion: a preliminary report. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2004.* J Neurosurg Spine, 2004. **1**(1): p. 19-23.
16. Potter, B.K., B.A. Freedman, E.G. Verwiebe, J.M. Hall, D.W. Polly, Jr., and T.R. Kuklo, *Transforaminal lumbar interbody fusion: clinical and radiographic results and complications in 100 consecutive patients.* J Spinal Disord Tech, 2005. **18**(4): p. 337-46.
17. Schwender, J.D., L.T. Holly, D.P. Rouben, and K.T. Foley, *Minimally invasive transforaminal lumbar interbody fusion (TLIF): technical feasibility and initial results.* J Spinal Disord Tech, 2005. **18 Suppl**: p. S1-6.
18. Slosar, P.J., R. Josey, and J. Reynolds, *Accelerating lumbar fusions by combining rhBMP-2 with allograft bone: a prospective analysis of interbody fusion rates and clinical outcomes.* Spine J, 2007. **7**(3): p. 301-7.

19. Villavicencio, A.T., S. Burneikiene, E.L. Nelson, K.R. Bulsara, M. Favors, and J. Thramann, *Safety of transforaminal lumbar interbody fusion and intervertebral recombinant human bone morphogenetic protein-2.* J Neurosurg Spine, 2005. **3**(6): p. 436-43.
20. Kleeman, T.J., U.M. Ahn, and A. Talbot-Kleeman, *Laparoscopic anterior lumbar interbody fusion with rhBMP-2: a prospective study of clinical and radiographic outcomes.* Spine, 2001. **26**(24): p. 2751-6.
21. Hsu, H.P., J.M. Zanella, S.M. Peckham, and M. Spector, *Comparing ectopic bone growth induced by rhBMP-2 on an absorbable collagen sponge in rat and rabbit models.* J Orthop Res, 2006. **24**(8): p. 1660-9.
22. Fairbank, J.C., J. Couper, J.B. Davies, and J.P. O'Brien, *The Oswestry low back pain disability questionnaire.* Physiotherapy, 1980. **66**(8): p. 271-3.
23. McHorney, C.A., J.E. Ware, Jr., J.F. Lu, and C.D. Sherbourne, *The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups.* Med Care, 1994. **32**(1): p. 40-66.
24. Ware, J.E., Jr. and C.D. Sherbourne, *The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection.* Med Care, 1992. **30**(6): p. 473-83.
25. Bagby, G., *The Bagby and Kuslich (BAK) method of lumbar interbody fusion.* Spine, 1999. **24**(17): p. 1857.
26. Brantigan, J.W., A. Neidre, and J.S. Toohey, *The Lumbar I/F Cage for posterior lumbar interbody fusion with the variable screw placement system: 10-year results of a Food and Drug Administration clinical trial.* Spine J, 2004. **4**(6): p. 681-8.
27. Brantigan, J.W., A.D. Steffee, M.L. Lewis, L.M. Quinn, and J.M. Persenaire, *Lumbar interbody fusion using the Brantigan I/F cage for posterior lumbar interbody fusion and the variable pedicle screw placement system: two-year results from a Food and Drug Administration investigational device exemption clinical trial.* Spine, 2000. **25**(11): p. 1437-46.
28. Button, G., M. Gupta, C. Barrett, P. Cammack, and D. Benson, *Three- to six-year follow-up of stand-alone BAK cages implanted by a single surgeon.* Spine J, 2005. **5**(2): p. 155-60.
29. Kuslich, S.D., G. Danielson, J.D. Dowdle, J. Sherman, B. Fredrickson, H. Yuan, and S.L. Griffith, *Four-year follow-up results of lumbar spine arthrodesis using the Bagby and Kuslich lumbar fusion cage.* Spine, 2000. **25**(20): p. 2656-62.
30. Kuslich, S.D., C.L. Ulstrom, S.L. Griffith, J.W. Ahern, and J.D. Dowdle, *The Bagby and Kuslich method of lumbar interbody fusion. History, techniques, and 2-year follow-up results of a United States prospective, multicenter trial.* Spine, 1998. **23**(11): p. 1267-78; discussion 1279.
31. Martin, B.I., S.K. Mirza, B.A. Comstock, D.T. Gray, W. Kreuter, and R.A. Deyo, *Are lumbar spine reoperation rates falling with greater use of fusion surgery and new surgical technology?* Spine, 2007. **32**(19): p. 2119-26.
32. Kornblum, M.B., J.S. Fischgrund, H.N. Herkowitz, D.A. Abraham, D.L. Berkower, and J.S. Ditkoff, *Degenerative lumbar spondylolisthesis with spinal stenosis: a prospective long-term study comparing fusion and pseudarthrosis.* Spine, 2004. **29**(7): p. 726-33; discussion 733-4.

From: Bearcroft, Julie, PhD
Sent: Wednesday, November 14, 2007 05:23:25 PM
To: JDIMAR[redacted]
Subject: AMPLIFY manuscript

Attachments: ManuscriptSept07 Revision (2).doc; AE Table.doc; Second Surgery Table.doc; Table 1.doc

John -
I know this has been a long time coming but please find the collective input of several individuals here at MSB on this manuscript. I want to thank you for your efforts in putting together this first draft and also your patience in while we go through this process.

While you are working on this, I will forward this back through the committee simultaneously just to make sure that I did not introduce errors in the process. If there are changes from that process, I will certainly let you know.

You will note that there are some commentary regarding things that we could either not verify or update as well as some suggestions for further commentary in the discussion. Guorong also added some significant language in the methods section related statistical methodology. Not sure it all needs to be there but it is helpful to payers and those deep in statistics to better understand exactly how we manage this process. There is never a perfect way so it is always controversial but Guorong feels it is the best way and corresponds to our FDA protocol.

You will also note that we are supplying a more detailed demographic table (of interest to payers), a revised adverse event table (based on PMA submission) and a new second surgery table (again of interest to payers and will help in health economic assessments conducted independently from MSB).

Once you have reviewed this, please feel free to contact me if you have any questions. Once a final version for a more broad review is ready, I recommend that you manage the process through Carol Binns as we have in the past. I have not shown or discussed this manuscript with any of the co-authors to date.

Thanks again for this tremendous effort. I know that preparing the initial draft is the hardest part of the process.

julie

Last printed Last printed 4/3/2009 3:20 PM

Deleted: 11/14/2007 2:04 PM
Deleted: 10/24/2007 1:06 PM

A Large-scale, Level 1, Clinical and Radiographic Analysis of an Optimized rhBMP-2 Formulation as an Autograft Replacement in Posterolateral Lumbar Spine Fusion

Formatted: Font: Bold

ABSTRACT

Study Design: Level I therapeutic clinical study.

Deleted: feasibility

Objective: To determine the safety and efficacy of using a new recombinant human bone morphogenetic protein-2 formulation with a new compression resistant matrix (rhBMP-2 matrix) as an iliac crest bone graft (ICBG) substitute in patients undergoing posterolateral fusion.

Summary of Background Data: Nonhuman primate studies have demonstrated that rhBMP-2 and an absorbable collagen sponge required additional osteoconductive bulking agents to produce successful posterolateral spine fusion. A new formulation using an optimized rhBMP-2 concentration and a compression resistant carrier developed specifically for posterolateral fusions demonstrated excellent results in nonhuman primates. A small pilot study in humans with an all ceramic carrier demonstrated similar results. Two-year follow-up results from a pivotal, multicenter, prospective, randomized Food and Drug Administration (FDA) Investigational Device Exemption (IDE) study comparing iliac crest bone graft (ICBG) to rhBMP-2 combined with a carrier consisting of bovine collagen and tricalcium/hydroxyapatite to create a compression resistant matrix for single-level posterolateral fusions is reported

Deleted: , and a
Deleted: a
Deleted: Currently, a

Deleted: ongoing
Deleted: ongoing

Materials and Methods: In this prospective study, 463 patients with symptomatic single-level degenerative disc disease with up to Grade 1 spondylolisthesis were treated with decompression and single-level instrumented posterolateral fusion through an open midline approach. Patients were randomly assigned to either the rhBMP-2 matrix group (239 patients) or the ICBG group (224 patients). Oswestry Disability Index, SF-36, and back and leg pain scores were determined preoperatively and at 1.5, 3, 6, 12 and 24 months postoperatively. Two independent radiologists reviewed radiographs and computed tomography scans taken at 6, 12, and 24 months postoperatively. Fusion was defined as the presence of bilateral, continuous trabeculated bone connecting the transverse processes, translation of less than or equal to 3 mm and angulation of less than 5° on flexion-extension radiographs, and absence of cracking, as evidenced by radiolucent lines through the fusion mass.

Deleted: ≤
Deleted: <

Results: No significant differences in demographics existed between the groups. The mean operative time in the rhBMP-2 matrix group (2.5 hours) was less than in the ICBG group (2.9 hours) ($P < 0.001$). Average blood loss in the rhBMP-2 matrix group was 343.1 mL compared

with 448.6 ml in the ICBG group ($P < 0.001$). Average hospital stay was similar in both groups. No differences existed between the groups in adverse events except cumulative nonunion rate reported by investigators was higher in the ICBG group (8%; 8.0 %,18 patients) than in the rhBMP-2 matrix group (2.5%; 6 patients) ($P = 0.011$). Using fine-cut CT scans with coronal and sagittal reconstructions in addition to standard radiography, at 12 months, 87.5% of patients in the rhBMP-2 matrix group and 82.5% in the ICBG group exhibited fusion success ($P < 0.119$). At 24 months, 95.9% in the rhBMP-2 matrix group were solidly fused compared with 89.3% in the ICBG group ($P < 0.023$). Both groups showed similar improvements in clinical outcomes and reduced pain. At 24 months, 6% of the ICBG group reported persistent donor site pain.

Conclusions: Using rhBMP-2 decreases operative time and blood loss and produces earlier and higher fusion rates than iliac crest bone graft in posterolateral lumbar fusion procedures. Clinical outcomes are similar to those with iliac crest bone graft. Thus, the need for harvesting iliac crest bone is eliminated along with the morbidities associated with the harvest procedure.

Key words: rhBMP-2, posterolateral lumbar fusion, degenerative disc disease

Formatted: Highlight
Deleted: 7.1
Deleted: 16
Deleted: %; 16
Deleted:
Formatted: Highlight
Formatted: Highlight
Deleted: < 0.
Deleted: 042
Formatted: Highlight
Deleted: Based on
Deleted: 86.9
Formatted: Highlight
Formatted: Highlight
Deleted: 71.3
Formatted: Highlight
Formatted: Highlight
Deleted: had evidence of bilateral bridging bone
Formatted: Highlight
Deleted: 001
Formatted: Highlight
Deleted: 93.6
Formatted: Highlight
Formatted: Highlight
Deleted: had bilateral bridging bone
Deleted: 82.6
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Deleted: 4
Deleted:).
Formatted: Highlight
Formatted: Highlight
Comment [sk1]: This number doesn't seem to correspond to the data that I have to compare it to. Based on the 24 month data for Hip Pain, there are 72 pat ... [1]
Deleted: 54
Deleted: %
Deleted: Outcomes
Deleted: ICBG
Deleted: and the morbidities ass ... [2]
Deleted: is

INTRODUCTION

Posterolateral fusion combined with pedicle instrumentation is frequently employed for the treatment of degenerative disease of the lumbosacral spine. Various indications include degenerative disc disease, spondylolisthesis, and instability. The results of instrumented posterolateral fusions in large clinical studies have shown varying rates of fusion and clinical outcomes [1-5]. Traditional sources of grafting material include autograft, obtained locally from the iliac crest or from distal sources, and different types of allograft [2-5].

Previous studies have demonstrated the ability of recombinant human bone morphogenetic protein (rhBMP-2) to achieve a solid fusion [6-8]. Recently prospective randomized human clinical studies demonstrated superior fusion rates and clinical outcomes with rhBMP-2 and a collagen sponge (INFUSE® Bone Graft, Medtronic Sofamor Danek, Memphis, TN) versus autograft when using either cortical bone dowels or threaded interbody cages in anterior lumbar interbody techniques [9,10]. Nonhuman primate studies have demonstrated that rhBMP-2 delivered on an absorbable collagen sponge required additional osteoconductive bulking agents to produce successful posterolateral spine fusion [11-14]. A new formulation using an optimized rhBMP-2 concentration and a compression resistant carrier developed specifically for posterolateral fusions demonstrated excellent results in nonhuman primates [15]. A small, prospective, randomized, clinical investigation also demonstrated excellent posterolateral fusion results for rhBMP-2 combined with biphasic calcium phosphate as compared to iliac crest autograft [16]. Currently, a prospective randomized Food and Drug Administration (FDA) Investigational Device Exemption (IDE) study is ongoing comparing iliac crest bone graft (ICBG) to rhBMP-2 combined with a compression resistant carrier consisting of bovine collagen and tricalcium/hydroxyapatite (rhBMP-2 matrix) for single-level posterolateral fusions. We report the two-year radiographic results and clinical outcomes using rhBMP-2 matrix or iliac crest bone graft (ICBG) in single-level instrumented posterolateral fusions for lumbosacral degenerative disease.

Deleted: and

Deleted: pilot study on humans

Deleted: similar

Deleted: with

Deleted: versus

Deleted: for posterolateral fusions

Deleted: to create a compression resistant matrix

Deleted: is ongoing

MATERIALS AND METHODS

Four hundred sixty-three patients were treated in this multi-center prospective, randomized, FDA-approved IDE study. Sixty-three spine surgeons performed surgery in the study at 29 investigational sites.

Deleted: enrolled

Deleted: nonblinded,

Deleted: Eighty

Deleted: participated

The indications for surgery were symptomatic, single-level lumbosacral degenerative disease from L2/3 to L5/S1 of at least six months' duration that had not responded to nonoperative care. Clinical symptoms were low back pain with or without radicular leg pain. Additional enrollment criteria were a grade 1 or less spondylolisthesis, no previous fusion, and a minimum pre-operative Oswestry Disability Index score of 30. Exclusion criteria included a previous attempt at fusion at the intended surgical level, significant osteoporosis (less than 2 standard deviations below normal on DEXA bone densitometry scan), autoimmune disease, malignancy, infection, pregnancy, or the inability to harvest graft because of a previous surgical procurement.

All patients were treated with a single-level instrumented fusion using CD Horizon® (Medtronic Sofamor Danek, Memphis, TN USA) pedicle screw and rod instrumentation. Patients were randomly assigned to one of two groups: the control group who received autogenous iliac crest bone graft (ICBG) or the investigational group who received rhBMP-2 matrix (AMPLIFY rhBMP-2 Matrix™, Medtronic Sofamor Danek, Memphis, TN, USA). The dose and concentration of rhBMP-2 used in this study is higher (2.0 mg/cc for a total dose of 40 mg) than that of commercially available rhBMP-2, or INFUSE® Bone Graft (Medtronic Sofamor Danek, Memphis, TN, USA), which is 1.5 mg/cc for a total dose of 12 mg per large kit.

A standard open posterior approach was used for both the ICBG and rhBMP-2 matrix groups. Bone graft from the iliac crest in the ICBG group was obtained in a standard open fashion. ~~Was a separate incision used?~~ The bone graft was morselized and placed in the lateral gutters on the decorticated bony surface of the transverse processes and along the pars interarticularis. As required by the protocol, any local bone graft obtained from the decompression was discarded in both groups.

The rhBMP-2 was reconstituted using sterile water into two 5-mL syringes containing 20 mg of rhBMP-2 each. The matrix measuring 4.7cm in length x 3.8cm in width x 1.1cm in thickness was cut lengthwise with a scalpel into two equal pieces (1.9 cm in width) of 10 cc each using a cutting template. The reconstituted rhBMP-2 from each syringe was then uniformly distributed to each piece of the matrix producing a 2 mg/cc concentration of rhBMP-2 in the matrix. The rhBMP-2 matrices were allowed to stand for a minimum of 5 minutes and were implanted within 60 minutes after preparation. In no instance was the matrix of insufficient length to span the transverse processes in a single-level fusion.

Deleted: end

Deleted: 1

Deleted: 2

Deleted: ,

Deleted: , 20 mg per side

Formatted: Highlight

Deleted: 7

Clinical data were collected preoperatively and postoperatively at 6 weeks, 3 months, 6 months, 12 months, and 24 months. The validated outcome instruments used were the Oswestry Low Back Pain Disability Index (ODI) [17], the Medical Outcomes Study Short Form 36 (SF-36) [18,19], back pain and leg pain scores and, in the ICBG group, graft site pain scores. Patients were asked to rate the frequency and intensity of their pain on a scale of 0 to 10 and the scores were summed to derive a 20-point numerical rating scale. Data on work status, patient satisfaction, and adverse events were also recorded. Results of neurological examinations, which included motor function, sensory function, reflexes, and straight leg raise, were recorded.

Plain radiographs, lateral flexion and extension radiographs, and computed tomography (CT) scans with sagittal and coronal reconstructions were used to evaluate the fusion in both groups at 6, 12, and 24 months after surgery. The CT imaging protocol consisted of 1 millimeter continuous nonoverlapping axial slices that were taken without bone filter. The window and level settings were set to optimize trabecular bone detail (2000/350 on GE Scanners). The field of view was made as small as possible but still encompassed the complete vertebra in between and including the transverse processes.

Fusion success was defined as the presence of bilateral, continuous trabeculated bone connecting the transverse processes, translation of less than or equal to 3 mm and angulation of less than 5° on flexion-extension radiographs, and absence of cracking, as evidenced by radiolucent lines through the fusion mass. The radiographs and computed tomography scans were evaluated by 2 independent radiologists who were blinded to which patient group they were evaluating. A third adjudicate reviewer was used as needed.

The analysis dataset consisted of all patients who were surgically treated. Statistical comparisons were primarily based on the observed and recorded follow-up data. A small number of patients required an additional surgical procedure (removal, revision, or supplemental fixation); their outcomes were recorded as a treatment failure. For other outcome variables, the last observations taken before the additional surgical procedures or interventions were carried forward using the Last Observation Carried Forward technique for all future evaluation periods.

For comparing patients' demographic and preoperative measures, p values for continuous variables were from the analysis of variance, and those for categorical variables were from Fisher's exact test.

Deleted: The rhBMP-2 matrix and ICBG group values were compared using ANOVA for continuous variables and Fisher's exact test for categorical variables for independent samples across each time interval.

Formatted: Justified, Indent: First line: 36 pt, Line spacing: 1.5 lines

For comparing success or event rates, Fisher's exact test was used for assessing the superiority hypothesis. For comparing continuous outcome measurements such as the Oswestry score, analysis of covariance was used, with the preoperative score as the covariate. For assessing the statistical significance of postoperative improvement in outcome scores from preoperative status within each treatment group, a paired t test was used.

One-sided p values were reported for comparing treatment group differences in most clinical outcomes because the study hypotheses defined in the investigational device exemption protocol for those outcomes were one sided, except for surgery data, adverse events, and additional surgical procedures, as well as for days to return to work, for which two-sided p values were reported.

A p value of less than 0.05 was considered to be statistically significant.

RESULTS

Four hundred ten (90%) of expected subjects were available for assessment at 2 years after surgery; 194 in the ICBG group and 216 in the rhBMP-2 matrix group. Seven patients had died due to causes unrelated to surgery during the two-year follow-up. Randomization resulted in a similar distribution of baseline characteristics in the two study groups as shown in Table 1.

The average surgical time for the ICBG patients was 2.9 hours, which was significantly longer ($P < 0.001$) than the 2.5 hours observed in the rhBMP-2 matrix group (Table 2). The average blood loss was 448.6 mL for the ICBG patients, which was significantly greater ($P < 0.001$) than the 343.1 mL blood loss observed with the rhBMP-2 matrix group. The average volume of bone graft obtained from the iliac crest in the ICBG patients was 36mL. There was no statistically significant difference in length of hospital stay between the two groups. No surgeries were abandoned because of technical problems. There were no unanticipated intraoperative complications related to the fusion procedure.

The ODI scores were similar in both groups over all time intervals (Fig. 1) and showed statistically significant improvement when compared with preoperative scores ($P < 0.001$) in both the ICBG and rhBMP-2 matrix groups at all time intervals (Table 3). The SF-36 Physical Component Summary (PCS) scores were similar in both groups at all time intervals (Fig. 2) and showed statistically significant improvement when compared with preoperative scores ($P < 0.001$) in both the ICBG and rhBMP-2 matrix groups (Table 4).

Deleted: All patients were past the 12-month evaluation point, but 24-month follow-up examinations are ongoing.

Deleted: Two hundred eighty-two

Formatted: Highlight

Deleted: 137

Formatted: Highlight

Deleted: 145

Formatted: Highlight

Deleted: 2

Deleted: also

Formatted: Font: Italic

Average back pain scores for the ICBG and rhBMP-2 matrix groups improved significantly from preoperative scores of 15.8 and 15.6 to 7.8 and 7.1 at 24 months, respectively ($P < 0.001$). Both groups showed similar improvements over all time intervals (Fig. 3) with no statistically significant difference in their 24-month average back pain scores ($P = 0.145$). Leg pain scores after surgery in both the ICBG and rhBMP-2 matrix groups improved in a similar manner over all time intervals (Fig. 4). The average improved from 14.0 in both groups, to 6.7 in the ICBG group and 6.2 in the rhBMP-2 matrix group at 24 months ($P < 0.001$). There was no statistically significant difference in 24-month leg pain scores ($P = 0.214$).

Pain resulting from bone harvest in the ICBG group was measured using donor site pain scores. The mean pain score at discharge of 11.3 improved to 7.9 at 6 weeks after surgery and to 6.3 at 3 months postoperatively. There was minimal improvement at subsequent follow-up periods up to 24 months. A large number of patients in the ICBG group (60%) still had persistent donor site pain, with a mean pain score of 5.1, at 24 months after surgery (Fig. 5).

Of the 224 subjects in the ICBG group, 41.1% were working before surgery. At 24 months, 48.4% were able to return to work (Fig. 6). Of the 239 rhBMP-2 matrix group patients, 34.7% were working before surgery. After surgery, 42% of the subjects were working at 24 months.

Using plain radiographs and CT scans, independent radiologists determined fusion according to the IDE protocol-defined analysis, whereby assessment by plain films was considered first. In patients in whom the plain films did not exhibit bridging bone, CT scans were then used to determine the presence of bridging bone. Assessment in this manner showed that statistical differences in fusion success occurred at two time intervals between the two groups. At 6 months, 79.1% of patients in the rhBMP-2 matrix group and 65.3% in the ICBG group achieved fusion success ($P = 0.002$). At 24 months, 95.9% in the rhBMP-2 matrix group had achieved fusion success compared with 89.3% in the ICBG group ($P = 0.014$).

Fine-cut CT scans with sagittal and coronal reconstructions showed that 74.7% of the subjects in the rhBMP-2 matrix group and 56.4% in the ICBG group had evidence of bilateral bridging bone at 6 months ($P < 0.001$). At 12 months, 86.9% of subjects in the rhBMP-2 matrix group and 71.3% in the ICBG group had evidence of bilateral bridging bone ($P < 0.001$). At 24 months, the rate was 94.8% in the rhBMP-2 group compared with 83.8% in the ICBG group ($P = 0.001$) (Fig. 7).

Deleted: Back
Deleted: 8.1
Deleted: 7.1…7. … [3]
Deleted: 8
Deleted: 8
Formatted: Font: Italic
Deleted: They
Deleted: 7.4…7.1 … [4]
Formatted: Font: Italic
Deleted: 14…5.0 … [5]
Deleted: 137
Formatted: Highlight
Deleted: Of those
Deleted: 48.5
Deleted: at 24 months…195 … [6]
Formatted: Highlight
Deleted: 40.7
Deleted: returned to work
Deleted: considereded…87.5 … [7]
Deleted: 87.4
Deleted: 82.5
Deleted: 82.4
Deleted: at 12 months…199 … [8]
Deleted: 94.9…86.8 … [9]
Deleted: 23
Deleted: 0.074
Formatted: Highlight
Deleted: 4
Formatted … [10]
Deleted: 93.6
Deleted: 82.6
Formatted … [11]
Formatted … [12]
Deleted: 054

A new AE table has been added that corresponds to the IDE submission. Unfortunately, we could not verify the original table included since the categories are not those used in the IDE.

Also a second surgery table has been added as well that you may wish to incorporate.

DISCUSSION

The guiding principle for the surgical treatment of painful or unstable lumbosacral degenerative spinal disease remains the ability to achieve a solid fusion. Although autologous ICBG is the gold standard, the morbidity associated with graft harvest has led surgeons to seek viable alternatives, such as allografts, ceramics, and various types of autologous growth factors [20-24]. These graft substitutes have demonstrated great variability in achieving fusion with the greatest success achieved when used in addition to the iliac crest bone graft and not as an alternative to iliac crest bone graft. Additionally, they present their own unique problems including decreased success of fusion [25], limited availability, and the potential for rejection or immunologic reaction [21, 22].

The development of osteoinductive bone grafting options has resulted in the clinical availability of recombinant human bone morphogenetic protein (rhBMP-2 and rhBMP-7) for spinal fusion [26]. These naturally occurring bone proteins stimulate bone healing via a cascade mechanism that results in the differentiation of primitive mesenchymal cells and preosteoblasts into osteoblasts that promote bone formation and, ultimately, healing [Wozney et al.]. The effectiveness of rhBMP-2 in achieving a solid interbody fusion has been demonstrated in numerous experimental animal studies [6-8]. Subsequently, clinical trials have demonstrated similar fusion rates and clinical outcomes when ICBG was compared with rhBMP-2 combined with a collagen sponge carrier (INFUSE® Bone Graft) and a lordotic threaded interbody cage (LT-CAGE®) [9]. As a result of these findings, the FDA approved the use of rhBMP-2 as an iliac crest bone graft replacement for lumbar interbody fusion in 2002.

A recent randomized human pilot study evaluated a new rhBMP-2 formulation consisting of a 2 mg/cc concentration combined with biphasic calcium phosphate granules versus autograft in achieving a successful posterolateral fusion [16]. The study demonstrated a 40% fusion rate in the autograft group versus a 100% fusion rate with the rhBMP-2 matrix group when evaluated by

Deleted: The most common complication possibly related to the surgery was infection of various types at different sites (Table 5). There was a higher incidence of superficial wound infections in the ICBG group. There was no difference in the incidence of deep wound infections, wound drainage or development of wound hematoma. Sixteen patients in the ICBG group complained of continued pain from the bone graft donor site that required active treatment. One patient developed a donor site infection. No adverse events were observed that could be directly attributable to the use of rhBMP-2 matrix.

Formatted: Highlight

Formatted: Highlight

Formatted: Highlight

Deleted: osteoconductive

Deleted: biologics

Deleted: spine

radiographs and CT scans. ODI and SF-36 outcome measures demonstrated significant but similar improvement in both groups at the end of the study. Although the authors cited several deficiencies—most notably the lack of a 24-month follow-up on all subjects—the study presented evidence of the feasibility of rhBMP-2 in achieving a successful radiographically confirmed fusion in humans.

As part of an ongoing FDA-regulated IDE study, rhBMP-2 is now being evaluated for use in single-level posterolateral fusions combined with pedicle screw and rod instrumentation. We reviewed our two-year clinical outcomes and fusion rates based on CT scans in subjects. We used a specifically designed carrier that combines tricalcium phosphate and hydroxyapatite granules with a collagen matrix. This combination provides significant resistance to compression by the musculature when placed in the lateral gutters while providing a high binding affinity for rhBMP-2 and suitable resorption profile to optimize bone formation. It is also important to emphasize that in this study we used a higher concentration of rhBMP-2 (2.0 mg/cc versus 1.5 mg/cc) than was used in previous clinical studies with an absorbable collagen sponge carrier.

Although local bone graft is rarely discarded in clinical practice, the quality and quantity of local bone grafts are highly variable. In this study, local bone graft was discarded in both groups to allow for a direct comparison of the fusion rates of rhBMP-2 matrix to ICBG without local bone graft as a confounding variable.

Perioperative measures indicated improvements in operative time and blood loss, which were significantly less in the rhBMP-2 matrix group than in the ICBG group. The length of hospital stay was the same for both groups. Because of the nature of adverse event reporting in FDA-regulated trials, most patients experienced an adverse event over the two-year course of the study. There were no statistical differences in adverse events with the exception of iliac crest graft-related complications which occurred in 17 (7.4%) of control patients.

An equally important measure of the success of a fusion procedure, beyond the radiographic evidence of fusion, is how the patient feels and functions after surgery. The use of validated patient-based clinical outcome measures such as the Oswestry Disability Index and the SF-36 provide a self-assessment of the patient's functional improvement rather than the clinician's perception [17]. Most of the improvement in ODI scores and SF-36 PCS occurred within the first three months after surgery, in both groups. This improvement was maintained through the subsequent follow-up periods up to 24 months. The improvement in PCS at 24

Deleted: strongest

Deleted: efficacy

Deleted: The incidence of deep wound infections, wound drainage, or development of wound hematoma was similar in both groups. There was a higher incidence of superficial wound infections in the ICBG group possibly because of the need for marked retraction to allow access to the iliac crest through the same incision for bone graft harvest.

Formatted: Highlight

months in both groups was well above the 5.41 point threshold in the literature for clinically significant improvement [27]. The decrease in ODI scores at 24 months in both groups was greater than 25 points, which is also above that necessary to demonstrate treatment efficacy [28, 29].

Most of the improvement in back pain and leg pain scores was noted within the first 6 weeks after surgery, and was maintained throughout the entire follow-up period of 24 months. The 8.4-point average decrease in back pain in the rhBMP-2 matrix group and 8.1-point average decrease in the ICBG group indicates a clinically significant diminution in back pain after surgery. The 7.3-point average decrease in leg pain in the rhBMP-2 matrix group and 6.6-point average decrease in the ICBG group indicates a clinically significant diminution in leg pain after surgery.

The rates of fusion in previously published articles vary widely from 60% to 98%. This may be due to the use of plain radiographs with flexion-extension views which are known to be inaccurate with error rates estimated from 20 to 40% [30-32]. When fusion success was determined using the IDE-protocol-defined criteria, the rhBMP-2 matrix group had significantly higher fusion success rates compared to the ICBG group at 6 and 24 months postoperatively. Using thin-cut CT scans, bilateral bridging bone was reported by the independent blinded radiologists significantly more often in the rhBMP-2 matrix group than in the ICBG group at all 3 time points. At the 24-month follow-up period, there were twice as many patients in the ICBG group with established nonunions. Similarly, there were twice as many non-elective surgical procedures to remove hardware in the ICBG group. In a separate study derived from a subset of this patient population, rhBMP-2 matrix produced a more robust fusion mass than ICBG as judged from CT scans alone [20]. The use of fine-cut CT scans with sagittal and coronal reconstructions may increase the ability to demonstrate the robustness of the fusion and the presence of bilateral confluent bridging bone.

Consider including discussion about Herkowitz observations that short-term follow-up did not result in being able to correlate fusions success with clinical outcomes; however, long-term follow-up did result in a correlation between the two. Perhaps longer-term follow-up will of this series will be able to detect to differences since statistical differences in fusion success was detected.

Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Deleted: smaller differences
Deleted: in
Deleted: than
Deleted: its
Deleted: At the 24-month follow-up period, there were
Formatted: Highlight
Deleted:
Deleted: twice
Deleted: twice
Deleted: as many patients in the ICBG group with established nonunions.

CONCLUSION

This study demonstrates that, for patients with a single-level degenerative disease, an instrumented posterolateral fusion with ICBG and rhBMP-2 matrix provides excellent clinical improvement and exhibits similar clinical outcomes 2 years after surgery. The rhBMP-2 matrix group demonstrated significantly decreased intraoperative blood loss and decreased operative time relative to the ICBG group. The rhBMP-2 matrix demonstrated an improved fusion success rate when compared with the ICBG group at 24 months. There were no significant differences in complications between the two groups with the exception of graft harvesting related complications which were avoided with the use of rhBMP-2 matrix.. In conclusion, rhBMP-2 matrix decreases operative time and blood loss with earlier higher fusion rates and similar clinical outcomes as ICBG and can eliminate the need for harvesting iliac crest bone in successful posterolateral lumbar fusion surgery.

Please acknowledge all principle investigators from all sites.

Deleted: than

Formatted: Highlight

A new demographics table has been provided.

Deleted: Table 1. Patient Demographic Data¶ [... [13]]
Formatted: Highlight

Table 2. Surgical Data

Variable	rhBMP-2 matrix Group	ICBG Group	P-value
Operative time	2.5	2.9	<0.001
Blood loss	343.1	448.6	<0.001
Hospital stay	4.1	4.0	0.609

Table 3. Mean Improvement from Preoperative Score in Oswestry Disability Index Score at Each Follow-up Interval.

Deleted: Change
Formatted Table

Follow-Up Interval	rhBMP-2 matrix	ICBG	P-value
6 weeks	12.9	13.9	0.530
3 months	22.1	21.2	0.127
6 months	26.0	24.5	0.100
12 months	26.9	25.6	0.119
24 months	26.7	25.5	0.111

Deleted: 580
Deleted: 610
Deleted: 24.4
Formatted: Highlight
Deleted: 382
Formatted: Highlight
Deleted: 25.4
Formatted: Highlight
Deleted: 452
Deleted: 27.2
Deleted: 25.6
Formatted: Highlight
Deleted: 582
Deleted: Change

Statistically significant improvement from the pre-operative status was noted in both groups at all time intervals (P<0.001).

Table 4. Mean Improvement from Preoperative Score in SF-36 Physical Component Summary Score at Each Follow-Up Interval.

Formatted Table

Follow-Up Interval	rhBMP-2 matrix/ ICBG	P-value

6 weeks	3.8	4.5	0.733
3 months	9.5	8.8	0.122
6 months	12.9	11.0	0.020
12 months	13.7	11.7	0.020
24 months	13.2	12.3	0.175

Statistically significant improvement from the pre-operative status was noted in both groups at all f
intervals (P<0.001).

Deleted: 378
Deleted: 465
Deleted: 10.9
Deleted: 073
Deleted: 070
Formatted: Highlight
Deleted: 67
Formatted: Highlight
Formatted: Highlight
Deleted: 12.7
Formatted: Highlight
Formatted: Highlight
Deleted: 8
Formatted: Highlight
Deleted: 990
Formatted: Highlight

13

A new adverse event table has been provided.

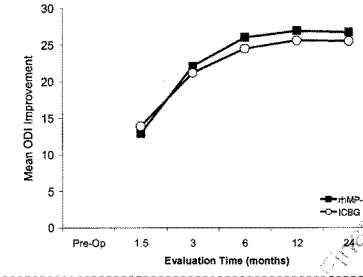


Figure 1. Comparison of mean improvement in Oswestry Disability Index scores in the ICBG and rhBMP-2 matrix groups at each follow-up interval

Comment [sk2]: See attachment for amended Table 5. I have also included a separate table for second authors.

Deleted: Table 5. Complications (events during 24-month follow-up period.)¶
Complication [141]

Formatted: Highlight

Formatted: Highlight

Deleted: ¶
¶
Page Break

Consider including Mean ODI instead of improvement since the chart already provides improvement.

Formatted: Highlight

Deleted: 1

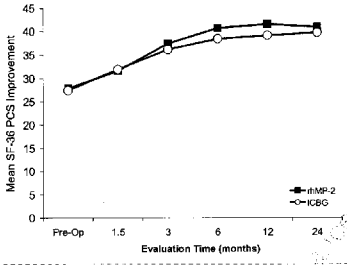
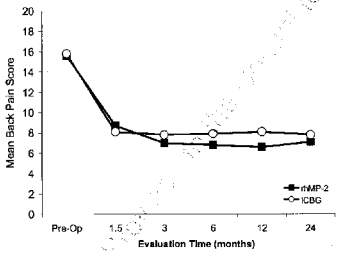


Figure 2. Comparison of SF-36 Physical Component Summary scores in the ICBG and rhBMP-2 matrix groups.

Unable to check numbers used to generate chart. Please ensure they are correct.

Formatted: Highlight



15

Figure 3. Comparison of mean back pain scores in the ICBG and rhBMP-2 matrix groups.

Unable to check numbers used to generate chart. Please ensure they are correct.

Formatted: Highlight

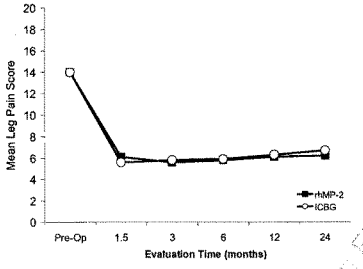


Figure 4. Comparison of mean leg pain scores in the ICBG and rhBMP-2 matrix groups.

Unable to check numbers used to generate chart. Please ensure they are correct.

Formatted: Highlight

Formatted: Body Text 2, Left

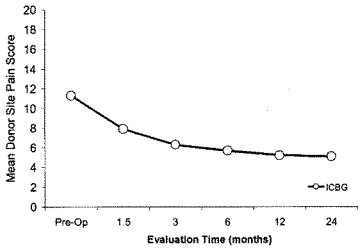
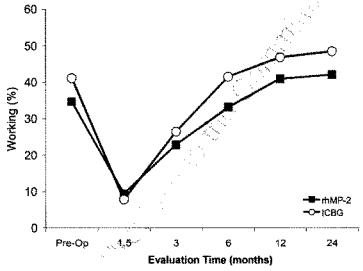


Figure 5. Mean donor site pain scores in the ICBG group.

Unable to check numbers used to generate chart. Please ensure they are correct.

Formatted: Highlight



17

Figure 6. Percentage of subjects working in the ICBG and rhBMP-2 matrix groups.

Unable to check numbers used to generate chart. Please ensure they are correct.

Formatted: Highlight

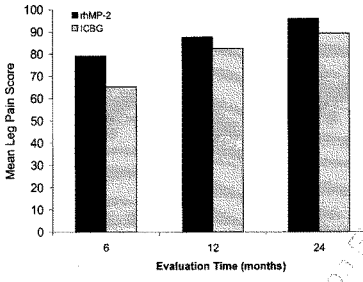


Figure 7. Percentage of subjects with bilateral confluent bridging bone reported by independent radiologists as observed on fine-cut CT scans with reconstructions for the ICBG and rhBMP-2 matrix groups. Differences between groups was statistically significant at all time points.

Y-axis title is wrong.

Formatted: Highlight

Unable to check numbers used to generate chart. Please ensure they are correct.

Please insert p values on the chart.

Fusion success table?

Formatted: Highlight

REFERENCES

1. Bono CM, Lee CK. Critical analysis of trends in fusion for degenerative disc disease over the past 20 years: influence of technique on fusion rate and clinical outcome. Spine 2004;29:455-63.

2. An HS, Lynch K, Toth J. Prospective comparison of autograft vs. allograft for adult posterolateral lumbar spine fusion: differences among freeze-dried, frozen, and mixed grafts. J Spinal Disord 1995;8:131-5.

3. Dawson EG, Lotysch M 3rd, Urist MR. Intertransverse process lumbar arthrodesis with autogenous bone graft. Clin Orthop 1981;154:90-6.

4. Dimar J, Glassman S, Burkus JK, Carreon L. A comparison of prospective clincial outcome measures for anterior vs. posterior single-level spine fusion. IMAST Program July 2004

5. Jorgenson SS, Lowe TG, France J, Sabin J. A prospective analysis of autograft versus allograft in posterolateral lumbar fusion in the same patient. A minimum of 1-year follow-up in 144 patients. Spine 1994;19:2048-53.

6. Sandhu HS, Toth JM, Diwan AD, et al. Histological evaluation of the efficacy of rhBMP-2 compared with autograft bone in sheep spinal anterior interbody fusion. Spine 2002;27:567-75.

7. Boden SD, Martin GJ Jr, Horton WC, et al. Laparoscopic anterior spinal arthrodesis with rhBMP-2 in a titanium interbody threaded cage. J Spinal Disord 1998;11:95-101.

8. Hecht BP, Fischgrund JS, Herkowitz HN, et al. The use of recombinant human bone morphogenetic protein-2)rhBMP-2) to promote spinal fusion in a nonjuman primate anterior interbody fusion model. Spine 1999;24:629-36.

9. Burkus JK, Heim SE, Gornet MF, Zdeblick TA: Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-CAGE lumbar tapered fusion device. J Spinal Disord Tech 2003;16:113-22

10. Burkus JK, Sandhu HS, Gornet MF, Longley MC. Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery. J Bone Joint Surg Am. 2005;87:1205-12.

11. Martin JG Jr, Boden SD, Marone MA, Marone MA, Moskovitz PA. Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: important lessons learned regarding dose, carrier, and safety. J Spinal Disord 1999;12:179-86.

12. Barnes B, Boden SD, Louis-Ugbo J, et al. Lower dose of rhBMP-2 achieves spine fusion when combined with an osteoconductive bulking agent in non-human primates. Spine 2005;30:1127-33.

13. Akamaru T, Suh D, Boden SD, et al. Simple carrier matrix modifications can enhance delivery of recombinant human bone morphogenetic protein-2 for posterolateral spine fusion. Spine 2003;28:429-34.

14. Suh DY, Boden SD, Louis-Ugbo J, et al. Delivery of recombinant human bone morphogenetic protein-2 using a compression-resistant matrix in posterolateral spine fusion in the rabbit and in the non-human primate. Spine. 2002;27:353-60.

15. Boden SD, Martin GJ Jr, Morone MA, et al. Posterolateral lumbar intertransverse process spine arthrodesis with recombinant human bone morphogenetic protein 2/hydroxyapatite-tricalcium phosphate after laminectomy in the nonhuman primate. Spine. 1999;24:1179-85.

16. Boden SD, Kang J, Harvinder S, Heller JG. Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial: 2002 Volvo Award in clinical studies. Spine. 2002;27:2662-73.

17. Fairbank JC, Couper J, Davies JB, O'Brien JP. The Oswestry low back pain disability questionnaire. Physiotherapy 1980; 66:271-3.

18. Ware JE Jr, Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;306:473-83.

19. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994;32:40-66.

20. Glassman SD, Dimar JR, Carreon LY, et al. Initial fusion rates with recombinant human bone morphogenetic protein-2/compression resistant matrix and a hydroxyapatite and tricalcium phosphate/collagen carrier in posterolateral spinal fusion. Spine 2005;30;1694-98.

20

21. Boden SD. Overview of the biology of lumbar spine fusion and principles for selecting a bone graft substitute. Spine 2002;27(16S):S26-S31.

22. Ludwig SC, Kowalski JM and Boden SD. Osteoinductive bone graft substitutes. Eur Spine J 2000; 9(Suppl 1):S119-S125.

23. Lind M, Bunger C. Factors stimulating bone formation. Eur Spine J 2000;9(Suppl 1):S102-S109.

24. Vaccaro AR, Sharon AD, Tuan RS, et al. The use of biologic materials in spinal fusion. Orthopedics 2001;24:191-197.

25. Carreon LY, Glassman SD, Anekstein Y, Puno RM. Platelet gel (AGF) fails to increase fusion rates in instrumented posterolateral fusions. Spine. 2005;30:E243-6.

26. Urist MR: Bone: formation by autoinduction. Science. 1965;150:893-9

27. Ware JE, Kosinski M, Keller SK. SF-36® Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: The Health Institute, 1994.

28. Fairbank JCT, Pynsent PB: The Oswestry Disability Index. Spine 2000;25:2940-53.

29. Walsh TL, Hanscom B, Lurie JD, Weinstein JN. Is a condition-specific instrument for patients with low back pain/leg symptoms really necessary? The responsiveness of the Oswestry Disability index, MODEMS and the SF-36. Spine 2003;28:607-15.

30. Blumenthal SL, Gill K. Can lumbar spine radiographs accurately determine fusion in postoperative patients? Correlation of routine radiographs with a second surgical look at lumbar fusions. Spine. 1993;18:1186-9.

31.Brodsky AE, Kovalsky ES, Kahlil MA. Correlation of radiologic assessment of lumbar spine fusions with surgical exploration. Spine. 1991;16(6 Suppl):S261-5.

32. Kant AP, Daum WJ, Dean SM, Uchida T. Evaluation of lumbar spine fusion. Plain radiographs versus direct surgical exploration and observation. Spine 1995;20:2313-7.

Wozney JM. The bone morphogenetic protein family and osteogenesis [review]. Mol Reprod Dev 1992; 32:160-167

Page 2: [1] Comment [sk1]	**kepess1**	**10/24/2007 3:19:00 PM**

This number doesn't seem to correspond to the data that I have to compare it to. Based on the 24 month data for Hip Pain, there are 72 patients that reported a score of zero, which corresponds to roughly 32% of the 224 control subjects.

Page 2: [2] Deleted	**peckhs1**	**10/3/2007 12:47:00 PM**

and the morbidities associated with

Page 7: [3] Deleted	**kepess1**	**10/24/2007 3:07:00 PM**

7.1

Page 7: [3] Deleted	**kepess1**	**10/24/2007 3:07:00 PM**

7.

Page 7: [4] Deleted	**LeahCarreon**	**9/21/2007 10:08:00 AM**

7.4

Page 7: [4] Deleted	**LeahCarreon**	**9/21/2007 10:08:00 AM**

7.1

Page 7: [5] Deleted	**LeahCarreon**	**9/21/2007 10:08:00 AM**

54

Page 7: [5] Deleted	**LeahCarreon**	**9/21/2007 10:09:00 AM**

5.0

Page 7: [6] Deleted	**bearcj1**	**11/14/2007 1:29:00 PM**

at 24 months

Page 7: [6] Deleted	**bearcj1**	**11/14/2007 1:30:00 PM**

145

Page 7: [7] Deleted	**bearcj1**	**11/14/2007 1:31:00 PM**

considereded

Page 7: [7] Deleted	**bearcj1**	**11/14/2007 1:33:00 PM**

87.5

Page 7: [8] Deleted	**bearcj1**	**11/14/2007 1:34:00 PM**

at 12 months

Page 7: [8] Deleted	**bearcj1**	**11/14/2007 1:33:00 PM**

199

Page 7: [9] Deleted	**LeahCarreon**	**9/21/2007 10:09:00 AM**

94.9

Page 7: [9] Deleted	**LeahCarreon**	**9/21/2007 10:10:00 AM**

86.8

Table 1. Patient Demographic Data

	rhBMP-2 matrix Group	ICBG Group
Age (years)	53.2	52.3
Sex (% male)	45.2	42.4
Workers' Compensation (%)	11.3	12.5
Smoker (%)	26.4	26.3

Table 5. Complications (events during 24-month follow-up period.)[sk1]

Complication	rhBMP-2 matrix Group	ICBG Group
Wound drainage	5	6
Wound infections	16	23
Wound hematoma	1	0

Epidural hematoma	2	0
Malignancy*	7	2
Anemia	25	32
UTI	5	4
Infection (other sites)	25	19
Infection (total)	46	46
Second surgeries	20	37
Revisions	2	3
Removals	12	26
Supplemental fixations	6	8
Dural tear	14	17
Renal stones	6	6
Pulmonary	14	12
Ileus	8	3
Technical complications	5	5
Malposition	4	2
Displacement/loosening	1	3
Death	3	4
Donor site complaints	0	17
Donor site infection	0	1

*Cancer types in the rhBMP-2 matrix group were follicular, squamous cell, laryngeal, pancreatic, prostate, lung, and basal cell; in the ICBG group, cancer types were non-Hodgkin's lymphoma, and colon.

Table 5. Summary of Numbers (%) of Patients Who Reported Any or Possible† Device-Related Adverse Events

Adverse Event Category	Any Adverse Event					Possible† Device-Related Adverse Event				
	Investigational (n = 239)		Control (n = 224)		p Value *	Investigational (n = 239)		Control (n = 224)		p Value *
	Operative	Up to 24 Months	Operative	Up to 24 Months		Operative	Up to 24 Months	Operative	Up to 24 Months	
Patients who had any adverse events	20 (8.4)	209 (87.4)	20 (8.9)	198(88.4)	0.777	0 (0.0)	21 (8.8)	3 (1.3)	35 (15.6)	0.032
Anatomic/ technical difficulty	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	1.000					
Arthritis/Bursitis	0 (0.0)	22 (9.2)	0 (0.0)	17 (7.6)	0.616	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	0.234
Back and/or leg pain	0 (0.0)	104 (43.5)	0 (0.0)	90 (40.2)	0.510	0 (0.0)	4 (1.7)	0 (0.0)	5 (2.2)	0.745
Cancer ◊	0 (0.0)	8 (3.3)	0 (0.0)	2 (0.9)	0.107					
Cardiovascular	2 (0.8)	52 (21.8)	0 (0.0)	54 (24.1)	0.581					
Carpal Tunnel Syndrome	0 (0.0)	9 (3.8)	0 (0.0)	6 (2.7)	0.604					
Death	0 (0.0)	3 (1.3)	0 (0.0)	4 (1.8)	0.717					
Dural Injury	13 (5.4)	14 (5.9)	18 (8.0)	18 (8.0)	0.367	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0.484
Gastrointestinal	0 (0.0)	37 (15.5)	0 (0.0)	33 (14.7)	0.897					
Graft Site Related	0 (0.0)	0 (0.0)	0 (0.0)	17 (7.6)	< 0.001					
Implant Displacement /Loosening	0 (0.0)	1 (0.4)	1 (0.4)	3 (1.3)	0.358	0 (0.0)	1 (0.4)	1 (0.4)	3 (1.3)	0.358
Infection	0 (0.0)	39 (16.3)	0 (0.0)	45 (20.1)	0.335					
Malpositioned Implant	1 (0.4)	5 (2.1)	0 (0.0)	2 (0.9)	0.451	0 (0.0)	4 (1.7)	0 (0.0)	2 (0.9)	0.686
Neurological	0 (0.0)	70 (29.3)	0 (0.0)	60 (26.8)	0.605	0 (0.0)	2 (0.8)	0 (0.0)	1 (0.4)	1.000
Non-Union	0 (0.0)	6 (2.5)	0 (0.0)	18 (8.0)	0.011	0 (0.0)	6 (2.5)	0 (0.0)	18 (8.0)	0.011
Failure										
Non-Union Outcome Pending	0 (0.0)	5 (2.1)	0 (0.0)	5 (2.2)	1.000	0 (0.0)	5 (2.1)	0 (0.0)	4 (1.8)	1.000
Other	1 (0.4)	70 (29.3)	0 (0.0)	62 (27.7)	0.758					
Other pain	0 (0.0)	29 (12.1)	0 (0.0)	28 (12.5)	1.000					
Respiratory	0 (0.0)	15 (6.3)	0 (0.0)	12 (5.4)	0.697					
Spinal Event	3 (0.7)	17 (7.1)	0 (0.0)	18 (8.0)	0.728					
Trauma	0 (0.0)	67 (28.0)	0 (0.0)	59 (26.3)	0.754					
Urogenital	0 (0.0)	26 (10.9)	0 (0.0)	21 (9.4)	0.646					
Vertebral fracture	3 (1.3)	3 (1.3)	2 (1.3)	5 (2.2)	0.492	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0.484

* p Values were obtained by Fisher's exact test for comparing the rates up to 24 months between the treatment groups.
† Possibly device-related adverse events refer to implant or implant/surgical procedure-related adverse events.
◊ Cancer types in the rhBMP-2 matrix group were basal cell carcinoma, lung, lymphoma, ovarian, pancreatic, prostate, squamous cell carcinoma, and vocal cord; in the ICBG group, cancer types were and colon, and lymphoma.

Table ?. Second Surgery Events through 24 Month Follow-Up

Type of Secondary Surgical Procedure	Total Events Through 24 Months		# of Patients Reporting			
	INV	Control	INV N=239		Control N=224	
Revisions	4	4	4	1.7%	4	1.8%
Removals, Non-Elective	10	23	10	4.2%	22	9.8%
Supplemental Fixations	6	9	6	2.5%	9	4.0%

Table 1. Patient Demographics, Preoperative Medical Conditions, and Baseline Clinical Measures

Characteristic	Investigational Group (n = 239)	Control Group (n = 224)	p Value*
Age (years), mean (range)	53.2 (20-81)	52.3 (18-86)	0.408
Height (cm), mean (range)	170.4 (149.9-200.7)	169.7 (147.3-198.1)	0.380
Weight (kg), mean (range)	84.9 (47.2-164.2)	85.5 (44.9-141.5)	0.720
Male (%)	108 (45.2)	95 (42.4)	0.575
White (%)	218 (91.2)	203 (90.6)	0.848
Married (%)	176 (73.9)	155 (69.2)	0.457
College education or higher (%)	151 (63.2)	120 (54.1)	0.136
Workers' compensation (%)	27 (11.3)	28 (12.5)	0.774
Involved in litigation (%)	6 (2.5)	15 (6.7)	0.042
Tobacco use (%)	63 (26.4	59 (26.3)	1.000
Alcohol use (%)	90 (37.7)	78 (34.8)	0.562
Working before surgery (%)	83 (34.7)	92 (41.1)	0.180
Previous back surgery (%)	73 (30.5)	62 (27.7)	0.540
Total Waddell signs, no. positive (%)	219 (91.6)	209 (93.3)	0.508
Medication use (%)			
Nonnarcotic	154 (64.7)	140 (62.5)	0.630
Weak narcotic	116 (48.5)	116 (51.8)	0.516
Strong narcotic	38 (16.0)	41 (18.4)	0.537
Muscle relaxant	55 (23.1)	55 (24.7)	0.743

*For continuous variables, p values were derived from analysis of variance for categorical variables, they were derived by Fisher's exact test.

From: Bearcroft, Julie, PhD
Sent: Wednesday, November 14, 2007 05:28:05 PM
To: Ma, Guorong; Norman, Dawn; Kepes, Steven; Peckham, Steve, Ph.D.; Zhu, Youjun
CC: Beals, Neil; Meyer, Matt; Lanctot, Rodney; McKay, Bill
Subject: AMPLIFY Manuscript

Attachments: ManuscriptSept07 Revision (2).doc; AE Table.doc; Second Surgery Table.doc; Table 1.doc

Hello everyone -

I have taken all your collective input and consolidated it into this new manuscript version. Please review and provide commentary no later than Tuesday, November 20.

I have already provided this to Dr Dimar as well since he is anxious to progress this manuscript further. Thus, the need for the short response time. At this stage, he has not shared it with other co-authors since he wanted to incorporate our input prior to distribution.

Thanks,
julie

Julie Bearcroft, PhD
Technical Director, Biologics
Medtronic Spinal and Biologics
Phone: [redacted]
Mobile: [redacted]

Last printed Last printed 4/3/2009 3:29 PM

Deleted: 11/14/2007 2:04 PM

Deleted: 10/24/2007 1:06 PM

A Large-scale, Level 1, Clinical and Radiographic Analysis of an Optimized rhBMP-2 Formulation as an Autograft Replacement in Posterolateral Lumbar Spine Fusion

ABSTRACT

Study Design: Level I therapeutic clinical study.

Objective: To determine the safety and efficacy of using a new recombinant human bone morphogenetic protein-2 formulation with a new compression resistant matrix (rhBMP-2 matrix) as an iliac crest bone graft (ICBG) substitute in patients undergoing posterolateral fusion.

Summary of Background Data: Nonhuman primate studies have demonstrated that rhBMP-2 and an absorbable collagen sponge required additional osteoconductive bulking agents to produce successful posterolateral spine fusion. A new formulation using an optimized rhBMP-2 concentration and a compression resistant carrier developed specifically for posterolateral fusions demonstrated excellent results in nonhuman primates. A small pilot study in humans with an all ceramic carrier demonstrated similar results. Two-year follow-up results from a pivotal, multicenter, prospective, randomized Food and Drug Administration (FDA) Investigational Device Exemption (IDE) study comparing iliac crest bone graft (ICBG) to rhBMP-2 combined with a carrier consisting of bovine collagen and tricalcium/hydroxyapatite to create a compression resistant matrix for single-level posterolateral fusions is reported

Materials and Methods: In this prospective study, 463 patients with symptomatic single-level degenerative disc disease with up to Grade 1 spondylolisthesis were treated with decompression and single-level instrumented posterolateral fusion through an open midline approach. Patients were randomly assigned to either the rhBMP-2 matrix group (239 patients) or the ICBG group (224 patients). Oswestry Disability Index, SF-36, and back and leg pain scores were determined preoperatively and at 1.5, 3, 6, 12 and 24 months postoperatively. Two independent radiologists reviewed radiographs and computed tomography scans taken at 6, 12, and 24 months postoperatively. Fusion was defined as the presence of bilateral, continuous trabeculated bone connecting the transverse processes, translation of less than or equal to 3 mm and angulation of less than 5° on flexion-extension radiographs, and absence of cracking, as evidenced by radiolucent lines through the fusion mass.

Results: No significant differences in demographics existed between the groups. The mean operative time in the rhBMP-2 matrix group (2.5 hours) was less than in the ICBG group (2.9 hours) ($P < 0.001$). Average blood loss in the rhBMP-2 matrix group was 343.1 mL compared

Formatted: Font: Bold

Deleted: feasibility

Deleted: , and a

Deleted: a

Deleted: Currently, a

Deleted: ongoing

Deleted: ongoing

Deleted: ≤

Deleted: ≤

Deleted: <

with 448.6 ml in the ICBG group ($P < 0.001$). Average hospital stay was similar in both groups. No differences existed between the groups in adverse events except cumulative nonunion rate reported by investigators was higher in the ICBG group (8%; 8.0 %,18 patients) than in the rhBMP-2 matrix group (2.5%; 6 patients) ($P = 0.011$). Using fine-cut CT scans with coronal and sagittal reconstructions in addition to standard radiography, at 12 months, 87.5% of patients in the rhBMP-2 matrix group and 82.5% in the ICBG group exhibited fusion success ($P < 0.119$). At 24 months, 95.9% in the rhBMP-2 matrix group were solidly fused compared with 89.3% in the ICBG group ($P < 0.023$). Both groups showed similar improvements in clinical outcomes and reduced pain. At 24 months, 60% of the ICBG group reported persistent donor site pain.

Conclusions: Using rhBMP-2 decreases operative time and blood loss and produces earlier and higher fusion rates than iliac crest bone graft in posterolateral lumbar fusion procedures. Clinical outcomes are similar to those with iliac crest bone graft. Thus, the need for harvesting iliac crest bone is eliminated along with the morbidities associated with the harvest procedure.

Key words: rhBMP-2, posterolateral lumbar fusion, degenerative disc disease

Formatted: Highlight
Deleted: 7.1
Deleted: 18
Deleted: %; 18
Deleted:
Formatted: Highlight
Formatted: Highlight
Deleted: < 0.
Deleted: 042
Formatted: Highlight
Deleted: Based on
Deleted: 86.9
Formatted: Highlight
Formatted: Highlight
Deleted: 75.3
Formatted: Highlight
Formatted: Highlight
Deleted: had evidence of bilateral bridging bone
Formatted: Highlight
Deleted: 001
Formatted: Highlight
Deleted: 93.6
Formatted: Highlight
Formatted: Highlight
Deleted: had bilateral bridging bone
Deleted: 82.6
Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Deleted: a
Deleted:)
Formatted: Highlight
Formatted: Highlight
Comment [skt1]: This number doesn't seem to correspond to the data that I have to compare it to. Based on the 24 month data for Big Pain, there are 72 pati ... [1]
Deleted: 54
Deleted: %
Deleted: Outcomes
Deleted: ICBG
Deleted: and the morbidities ass ... [2]
Deleted: is

INTRODUCTION

Posterolateral fusion combined with pedicle instrumentation is frequently employed for the treatment of degenerative disease of the lumbosacral spine. Various indications include degenerative disc disease, spondylolisthesis, and instability. The results of instrumented posterolateral fusions in large clinical studies have shown varying rates of fusion and clinical outcomes [1-5]. Traditional sources of grafting material include autograft, obtained locally from the iliac crest or from distal sources, and different types of allograft [2-5].

Previous studies have demonstrated the ability of recombinant human bone morphogenetic protein (rhBMP-2) to achieve a solid fusion [6-8]. Recently prospective randomized human clinical studies demonstrated superior fusion rates and clinical outcomes with rhBMP-2 and a collagen sponge (INFUSE® Bone Graft, Medtronic Sofamor Danek, Memphis, TN) versus autograft when using either cortical bone dowels or threaded interbody cages in anterior lumbar interbody techniques [9,10]. Nonhuman primate studies have demonstrated that rhBMP-2 delivered on an absorbable collagen sponge required additional osteoconductive bulking agents to produce successful posterolateral spine fusion [11-14]. A new formulation using an optimized rhBMP-2 concentration and a compression resistant carrier developed specifically for posterolateral fusions demonstrated excellent results in nonhuman primates [15]. A small, prospective, randomized, clinical investigation also demonstrated excellent posterolateral fusion results for rhBMP-2 combined with biphasic calcium phosphate as compared to iliac crest autograft [16]. Currently, a prospective randomized Food and Drug Administration (FDA) Investigational Device Exemption (IDE) study is ongoing comparing iliac crest bone graft (ICBG) to rhBMP-2 combined with a compression resistant carrier consisting of bovine collagen and tricalcium/hydroxyapatite (rhBMP-2 matrix) for single-level posterolateral fusions. We report the two-year radiographic results and clinical outcomes using rhBMP-2 matrix or iliac crest bone graft (ICBG) in single-level instrumented posterolateral fusions for lumbosacral degenerative disease.

Deleted: and

Deleted: pilot study on humans

Deleted: similar

Deleted: with

Deleted: versus

Deleted: for posterolateral fusions

Deleted: to create a compression resistant matrix

Deleted: is ongoing

MATERIALS AND METHODS

Four hundred sixty-three patients were treated in this multi-center prospective, randomized, FDA-approved IDE study. Sixty-three spine surgeons performed surgery in the study at 29 investigational sites.

Deleted: enrolled

Deleted: nonblinded.

Deleted: Eighty

Deleted: participated

The indications for surgery were symptomatic, single-level lumbosacral degenerative disease from L2/3 to L5/S1 of at least six months' duration that had not responded to nonoperative care. Clinical symptoms were low back pain with or without radicular leg pain. Additional enrollment criteria were a grade 1 or less spondylolisthesis, no previous fusion, and a minimum pre-operative Oswestry Disability Index score of 30. Exclusion criteria included a previous attempt at fusion at the intended surgical level, significant osteoporosis (less than 2 standard deviations below normal on DEXA bone densitometry scan), autoimmune disease, malignancy, infection, pregnancy, or the inability to harvest graft because of a previous surgical procurement.

All patients were treated with a single-level instrumented fusion using CD Horizon® (Medtronic Sofamor Danek, Memphis, TN USA) pedicle screw and rod instrumentation. Patients were randomly assigned to one of two groups: the control group who received autogenous iliac crest bone graft (ICBG) or the investigational group who received rhBMP-2 matrix (AMPLIFY rhBMP-2 Matrix™, Medtronic Sofamor Danek, Memphis, TN, USA). The dose and concentration of rhBMP-2 used in this study is higher (2.0 mg/cc for a total dose of 40 mg) than that of commercially available rhBMP-2, or INFUSE® Bone Graft (Medtronic Sofamor Danek, Memphis, TN, USA), which is 1.5 mg/cc for a total dose of 12 mg per large kit.

A standard open posterior approach was used for both the ICBG and rhBMP-2 matrix groups. Bone graft from the iliac crest in the ICBG group was obtained in a standard open fashion. Was a separate incision used? The bone graft was morselized and placed in the lateral gutters on the decorticated bony surface of the transverse processes and along the pars interarticularis. As required by the protocol, any local bone graft obtained from the decompression was discarded in both groups.

The rhBMP-2 was reconstituted using sterile water into two 5-mL syringes containing 20 mg of rhBMP-2 each. The matrix measuring 4.7cm in length x 3.8cm in width x 1.1cm in thickness was cut lengthwise with a scalpel into two equal pieces (1.9 cm in width) of 10 cc each using a cutting template. The reconstituted rhBMP-2 from each syringe was then uniformly distributed to each piece of the matrix producing a 2 mg/cc concentration of rhBMP-2 in the matrix. The rhBMP-2 matrices were allowed to stand for a minimum of 5 minutes and were implanted within 60 minutes after preparation. In no instance was the matrix of insufficient length to span the transverse processes in a single-level fusion.

Deleted: and

Deleted: 1

Deleted: 2

Deleted: .

Deleted: , 20 mg per side

Formatted: Highlight

Deleted: /

Clinical data were collected preoperatively and postoperatively at 6 weeks, 3 months, 6 months, 12 months, and 24 months. The validated outcome instruments used were the Oswestry Low Back Pain Disability Index (ODI) [17], the Medical Outcomes Study Short Form 36 (SF-36) [18,19], back pain and leg pain scores and, in the ICBG group, graft site pain scores. Patients were asked to rate the frequency and intensity of their pain on a scale of 0 to 10 and the scores were summed to derive a 20-point numerical rating scale. Data on work status, patient satisfaction, and adverse events were also recorded. Results of neurological examinations, which included motor function, sensory function, reflexes, and straight leg raise, were recorded.

Plain radiographs, lateral flexion and extension radiographs, and computed tomography (CT) scans with sagittal and coronal reconstructions were used to evaluate the fusion in both groups at 6, 12, and 24 months after surgery. The CT imaging protocol consisted of 1 millimeter continuous nonoverlapping axial slices that were taken without bone filter. The window and level settings were set to optimize trabecular bone detail (2000/350 on GE Scanners). The field of view was made as small as possible but still encompassed the complete vertebra in between and including the transverse processes.

Fusion success was defined as the presence of bilateral, continuous trabeculated bone connecting the transverse processes, translation of less than or equal to 3 mm and angulation of less than 5° on flexion-extension radiographs, and absence of cracking, as evidenced by radiolucent lines through the fusion mass. The radiographs and computed tomography scans were evaluated by 2 independent radiologists who were blinded to which patient group they were evaluating. A third adjudicate reviewer was used as needed.

The analysis dataset consisted of all patients who were surgically treated. Statistical comparisons were primarily based on the observed and recorded follow-up data. A small number of patients required an additional surgical procedure (removal, revision, or supplemental fixation); their outcomes were recorded as a treatment failure. For other outcome variables, the last observations taken before the additional surgical procedures or interventions were carried forward using the Last Observation Carried Forward technique for all future evaluation periods.

For comparing patients' demographic and preoperative measures, p values for continuous variables were from the analysis of variance, and those for categorical variables were from Fisher's exact test.

Deleted: The rhBMP-2 matrix and ICBG group values were compared using ANOVA for continuous variables and Fisher's exact test for categorical variables for independent samples across each time interval.

Formatted: Justified, Tridient: First line: 36 pt, Line spacing: 1.5 lines

For comparing success or event rates, Fisher's exact test was used for assessing the superiority hypothesis. For comparing continuous outcome measurements such as the Oswestry score, analysis of covariance was used, with the preoperative score as the covariate. For assessing the statistical significance of postoperative improvement in outcome scores from preoperative status within each treatment group, a paired t test was used.

One-sided p values were reported for comparing treatment group differences in most clinical outcomes because the study hypotheses defined in the investigational device exemption protocol for those outcomes were one sided, except for surgery data, adverse events, and additional surgical procedures, as well as for days to return to work, for which two-sided p values were reported.

A p value of less than 0.05 was considered to be statistically significant.

RESULTS

Four hundred ten (90%) of expected subjects were available for assessment at 2 years after surgery: 194 in the ICBG group and 216 in the rhBMP-2 matrix group. Seven patients had died due to causes unrelated to surgery during the two-year follow-up. Randomization resulted in a similar distribution of baseline characteristics in the two study groups as shown in Table 1.

The average surgical time for the ICBG patients was 2.9 hours, which was significantly longer ($P < 0.001$) than the 2.5 hours observed in the rhBMP-2 matrix group (Table 2). The average blood loss was 448.6 mL for the ICBG patients, which was significantly greater ($P < 0.001$) than the 343.1 mL blood loss observed with the rhBMP-2 matrix group. The average volume of bone graft obtained from the iliac crest in the ICBG patients was 36mL. There was no statistically significant difference in length of hospital stay between the two groups. No surgeries were abandoned because of technical problems. There were no unanticipated intraoperative complications related to the fusion procedure.

The ODI scores were similar in both groups over all time intervals (Fig. 1) and showed statistically significant improvement when compared with preoperative scores ($P < 0.001$) in both the ICBG and rhBMP-2 matrix groups at all time intervals (Table 3). The SF-36 Physical Component Summary (PCS) scores were similar in both groups at all time intervals (Fig. 2) and showed statistically significant improvement when compared with preoperative scores ($P < 0.001$) in both the ICBG and rhBMP-2 matrix groups (Table 4).

Deleted: All patients were past the 12-month evaluation point, but 24-month follow-up examinations are ongoing

Deleted: Two hundred eighty-two

Formatted: Highlight

Deleted: 137

Formatted: Highlight

Deleted: 145

Formatted: Highlight

Deleted: 2

Deleted: also

Formatted: Font: Italic

Average back pain scores for the ICBG and rhBMP-2 matrix groups improved significantly from preoperative scores of 15.8 and 15.6 to 7.8 and 7.1 at 24 months, respectively ($P < 0.001$). Both groups showed similar improvements over all time intervals (Fig. 3) with no statistically significant difference in their 24-month average back pain scores ($P = 0.145$). Leg pain scores after surgery in both the ICBG and rhBMP-2 matrix groups improved in a similar manner over all time intervals (Fig. 4). The average improved from 14.0 in both groups, to 6.7 in the ICBG group and 6.2 in the rhBMP-2 matrix group at 24 months ($P < 0.001$). There was no statistically significant difference in 24-month leg pain scores ($P = 0.214$).

Pain resulting from bone harvest in the ICBG group was measured using donor site pain scores. The mean pain score at discharge of 11.3 improved to 7.9 at 6 weeks after surgery and to 6.3 at 3 months postoperatively. There was minimal improvement at subsequent follow-up periods up to 24 months. A large number of patients in the ICBG group (60%) still had persistent donor site pain, with a mean pain score of 5.1, at 24 months after surgery (Fig. 5).

Of the 224 subjects in the ICBG group, 41.1% were working before surgery. At 24 months, 48.4% were able to return to work (Fig. 6). Of the 239 rhBMP-2 matrix group patients, 34.7% were working before surgery. After surgery, 42% of the subjects were working at 24 months.

Using plain radiographs and CT scans, independent radiologists determined fusion according to the IDE protocol-defined analysis, whereby assessment by plain films was considered first. In patients in whom the plain films did not exhibit bridging bone, CT scans were then used to determine the presence of bridging bone. Assessment in this manner showed that statistical differences in fusion success occurred at two time intervals between the two groups. At 6 months, 79.1% of patients in the rhBMP-2 matrix group and 65.3% in the ICBG group achieved fusion success ($P = 0.002$). At 24 months, 95.9% in the rhBMP-2 matrix group had achieved fusion success compared with 89.3% in the ICBG group ($P = 0.014$).

Fine-cut CT scans with sagittal and coronal reconstructions showed that 74.7% of the subjects in the rhBMP-2 matrix group and 56.4% in the ICBG group had evidence of bilateral bridging bone at 6 months ($P < 0.001$). At 12 months, 86.9% of subjects in the rhBMP-2 matrix group and 71.3% in the ICBG group had evidence of bilateral bridging bone ($P < 0.001$). At 24 months, the rate was 94.8% in the rhBMP-2 group compared with 83.8% in the ICBG group ($P = 0.001$) (Fig. 7).

Deleted: Back
Deleted: 8.1
Deleted: 7.1...7. ... [3]
Deleted: 8
Deleted: 8
Formatted: Font: Italic
Deleted: They
Deleted: 7.4...7.1 ... [4]
Formatted: Font: Italic
Deleted: 54...5.0 ... [5]
Deleted: 137
Formatted: Highlight
Deleted: Of those
Deleted: 48.5
Deleted: at 24 months ...145 ... [6]
Formatted: Highlight
Deleted: 40.7
Deleted: returned to work
Deleted: considereded...87.5 ... [7]
Deleted: 87.4
Deleted: 82.5
Deleted: 82.4
Deleted: at 12 months ...199 ... [8]
Deleted: 94.9...86.8 ... [9]
Deleted: 23
Deleted: 0.074
Formatted: Highlight
Deleted: 4
Formatted ... [10]
Deleted: 93.6
Deleted: 82.6
Formatted ... [11]
Formatted ... [12]
Deleted: 024

A new AE table has been added that corresponds to the IDE submission. Unfortunately, we could not verify the original table included since the categories are not those used in the IDE.

Also a second surgery table has been added as well that you may wish to incorporate.

DISCUSSION

The guiding principle for the surgical treatment of painful or unstable lumbosacral degenerative spinal disease remains the ability to achieve a solid fusion. Although autologous ICBG is the gold standard, the morbidity associated with graft harvest has led surgeons to seek viable alternatives, such as allografts, ceramics, and various types of autologous growth factors [20-24]. These graft substitutes have demonstrated great variability in achieving fusion with the greatest success achieved when used in addition to the iliac crest bone graft and not as an alternative to iliac crest bone graft. Additionally, they present their own unique problems including decreased success of fusion [25], limited availability, and the potential for rejection or immunologic reaction [21, 22].

The development of osteoinductive bone grafting options has resulted in the clinical availability of recombinant human bone morphogenetic protein (rhBMP-2 and rhBMP-7) for spinal fusion [26]. These naturally occurring bone proteins stimulate bone healing via a cascade mechanism that results in the differentiation of primitive mesenchymal cells and preosteoblasts into osteoblasts that promote bone formation and, ultimately, healing [Wozney et al.]. The effectiveness of rhBMP-2 in achieving a solid interbody fusion has been demonstrated in numerous experimental animal studies [6-8]. Subsequently, clinical trials have demonstrated similar fusion rates and clinical outcomes when ICBG was compared with rhBMP-2 combined with a collagen sponge carrier (INFUSE® Bone Graft) and a lordotic threaded interbody cage (LT-CAGE®) [9]. As a result of these findings, the FDA approved the use of rhBMP-2 as an iliac crest bone graft replacement for lumbar interbody fusion in 2002.

A recent randomized human pilot study evaluated a new rhBMP-2 formulation consisting of a 2 mg/cc concentration combined with biphasic calcium phosphate granules versus autograft in achieving a successful posterolateral fusion [16]. The study demonstrated a 40% fusion rate in the autograft group versus a 100% fusion rate with the rhBMP-2 matrix group when evaluated by

Deleted: The most common complication possibly related to the surgery was infection of various types at different sites (Table 5). There was a higher incidence of superficial wound infections in the ICBG group. There was no difference in the incidence of deep wound infections, wound drainage or development of wound hematoma. Sixteen patients in the ICBG group complained of continued pain from the bone graft donor site that required active treatment. One patient developed a donor site infection. No adverse events were observed that could be directly attributable to the use of rhBMP-2 matrix.

Formatted: Highlight

Formatted: Highlight

Formatted: Highlight

Deleted: osteoconductive

Deleted: biologics

Deleted: spine

radiographs and CT scans. ODI and SF-36 outcome measures demonstrated significant but similar improvement in both groups at the end of the study. Although the authors cited several deficiencies—most notably the lack of a 24-month follow-up on all subjects—the study presented evidence of the feasibility of rhBMP-2 in achieving a successful radiographically confirmed fusion in humans.

As part of an ongoing FDA-regulated IDE study, rhBMP-2 is now being evaluated for use in single-level posterolateral fusions combined with pedicle screw and rod instrumentation. We reviewed our two-year clinical outcomes and fusion rates based on CT scans in subjects. We used a specifically designed carrier that combines tricalcium phosphate and hydroxyapatite granules with a collagen matrix. This combination provides significant resistance to compression by the musculature when placed in the lateral gutters while providing a high binding affinity for rhBMP-2 and suitable resorption profile to optimize bone formation. It is also important to emphasize that in this study we used a higher concentration of rhBMP-2 (2.0 mg/cc versus 1.5 mg/cc) than was used in previous clinical studies with an absorbable collagen sponge carrier.

Although local bone graft is rarely discarded in clinical practice, the quality and quantity of local bone grafts are highly variable. In this study, local bone graft was discarded in both groups to allow for a direct comparison of the fusion rates of rhBMP-2 matrix to ICBG without local bone graft as a confounding variable.

Perioperative measures indicated improvements in operative time and blood loss, which were significantly less in the rhBMP-2 matrix group than in the ICBG group. The length of hospital stay was the same for both groups. Because of the nature of adverse event reporting in FDA-regulated trials, most patients experienced an adverse event over the two-year course of the study. There were no statistical differences in adverse events with the exception of iliac crest graft-related complications which occurred in 17 (7.4%) of control patients.

An equally important measure of the success of a fusion procedure, beyond the radiographic evidence of fusion, is how the patient feels and functions after surgery. The use of validated patient-based clinical outcome measures such as the Oswestry Disability Index and the SF-36 provide a self-assessment of the patient's functional improvement rather than the clinician's perception [17]. Most of the improvement in ODI scores and SF-36 PCS occurred within the first three months after surgery, in both groups. This improvement was maintained through the subsequent follow-up periods up to 24 months. The improvement in PCS at 24

Deleted: strong

Deleted: efficacy

Deleted: The incidence of deep wound infections, wound drainage, or development of wound hematomas was similar in both groups. There was a higher incidence of superficial wound infections in the ICBG group possibly because of the need for marked retraction to allow access to the iliac crest through the same incision for bone graft harvest.

Formatted: Highlight

months in both groups was well above the 5.41 point threshold in the literature for clinically significant improvement [27]. The decrease in ODI scores at 24 months in both groups was greater than 25 points, which is also above that necessary to demonstrate treatment efficacy [28, 29].

Most of the improvement in back pain and leg pain scores was noted within the first 6 weeks after surgery, and was maintained throughout the entire follow-up period of 24 months. The 8.4-point average decrease in back pain in the rhBMP-2 matrix group and 8.1-point average decrease in the ICBG group indicates a clinically significant diminution in back pain after surgery. The 7.3-point average decrease in leg pain in the rhBMP-2 matrix group and 6.6-point average decrease in the ICBG group indicates a clinically significant diminution in leg pain after surgery.

The rates of fusion in previously published articles vary widely from 60% to 98%. This may be due to the use of plain radiographs with flexion-extension views which are known to be inaccurate with error rates estimated from 20 to 40% [30-32]. When fusion success was determined using the IDE-protocol-defined criteria, the rhBMP-2 matrix group had significantly higher fusion success rates compared to the ICBG group at 6 and 24 months postoperatively. Using thin-cut CT scans, bilateral bridging bone was reported by the independent blinded radiologists significantly more often in the rhBMP-2 matrix group than in the ICBG group at all 3 time points. At the 24-month follow-up period, there were twice as many patients in the ICBG group with established nonunions. Similarly, there were twice as many non-elective surgical procedures to remove hardware in the ICBG group. In a separate study derived from a subset of this patient population, rhBMP-2 matrix produced a more robust fusion mass than ICBG as judged from CT scans alone [20]. The use of fine-cut CT scans with sagittal and coronal reconstructions may increase the ability to demonstrate the robustness of the fusion and the presence of bilateral confluent bridging bone.

Consider including discussion about Herkowitz observations that short-term follow-up did not result in being able to correlate fusions success with clinical outcomes; however, long-term follow-up did result in a correlation between the two. Perhaps longer-term follow-up will of this series will be able to detect to differences since statistical differences in fusion success was detected.

Formatted: Highlight
Formatted: Highlight
Formatted: Highlight
Deleted: smaller differences
Deleted: in
Deleted: than
Deleted: its
Deleted: At the 24-month follow-up period, there were
Formatted: Highlight
Deleted:
Deleted: twice
Deleted: twice
Deleted: as many patients in the ICBG group with established nonunions.

CONCLUSION

This study demonstrates that, for patients with a single-level degenerative disease, an instrumented posterolateral fusion with ICBG and rhBMP-2 matrix provides excellent clinical improvement and exhibits similar clinical outcomes 2 years after surgery. The rhBMP-2 matrix group demonstrated significantly decreased intraoperative blood loss and decreased operative time relative to the ICBG group. The rhBMP-2 matrix demonstrated an improved fusion success rate when compared with the ICBG group at 24 months. There were no significant differences in complications between the two groups with the exception of graft harvesting related complications which were avoided with the use of rhBMP-2 matrix.. In conclusion, rhBMP-2 matrix decreases operative time and blood loss with earlier higher fusion rates and similar clinical outcomes as ICBG and can eliminate the need for harvesting iliac crest bone in successful posterolateral lumbar fusion surgery.

Please acknowledge all principle investigators from all sites.

Deleted: tian

Formatted: Highlight

A new demographics table has been provided.

Table 2. Surgical Data

Variable	rhBMP-2 matrix Group	ICBG Group	P-value
Operative time	2.5	2.9	<0.001
Blood loss	343.1	448.6	<0.001
Hospital stay	4.1	4.0	0.609

Table 3. Mean Improvement from Preoperative Score in Oswestry Disability Index Score at Each Follow-up Interval.

Follow-Up Interval	rhBMP-2 matrix	ICBG	P-value
6 weeks	12.9	13.9	0.530
3 months	22.1	21.2	0.127
6 months	26.0	24.5	0.100
12 months	26.9	25.6	0.119
24 months	26.7	25.5	0.111

Statistically significant improvement from the pre-operative status was noted in both groups at all time intervals (P<0.001).

Table 4. Mean Improvement from Preoperative Score in SF-36 Physical Component Summary Score at Each Follow-Up Interval.

Follow-Up Interval	rhBMP-2 matrix/ ICBG	P-value

Deleted: Table 1. Patient Demographic Data¶ [13]
Formatted: Highlight
Deleted: Change
Formatted Table
Deleted: 580
Deleted: 610
Deleted: 24.4
Formatted: Highlight
Deleted: 382
Formatted: Highlight
Deleted: 25.4
Formatted: Highlight
Deleted: 453
Deleted: 27.2
Deleted: 25.6
Formatted: Highlight
Deleted: 582
Deleted: Change
Formatted Table

6 weeks	3.8	4.5	0.733
3 months	9.5	8.8	0.122
6 months	12.9	11.0	0.020
12 months	13.7	11.7	0.020
24 months	13.2	12.3	0.175

Statistically significant improvement from the pre-operative status was noted in both groups at all the intervals (P<0.001).

Deleted: 378
Deleted: 465
Deleted: 10.9
Deleted: 073
Deleted: 070
Formatted: Highlight
Deleted: 9
Formatted: Highlight
Formatted: Highlight
Deleted: 12.7
Formatted: Highlight
Formatted: Highlight
Deleted: 8
Formatted: Highlight
Deleted: 990
Formatted: Highlight

A new adverse event table has been provided.

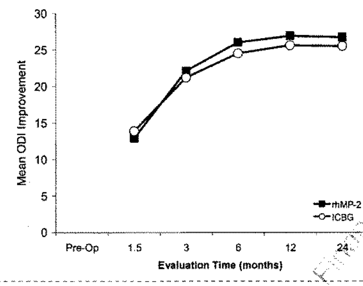


Figure 1. Comparison of mean improvement in Oswestry Disability Index scores in the ICBG and rhBMP-2 matrix groups at each follow-up interval

Comment [sk2]: See attachment for amended Table 5. I have also included a separate table for second surgeries.

Deleted: Table 5. Complications (events during 24-month follow-up period.)¶
Complication ... [14]

Formatted: Highlight

Formatted: Highlight

Deleted: ¶
¶
Page Break

Consider including Mean ODI instead of improvement since the chart already provides improvement?

Formatted: Highlight

Deleted: ¶

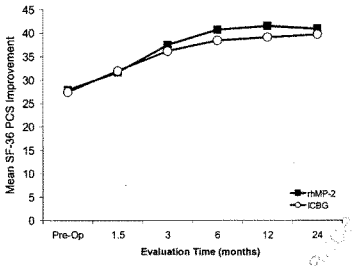
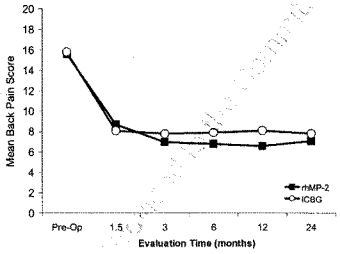


Figure 2. Comparison of SF-36 Physical Component Summary scores in the ICBG and rhBMP-2 matrix groups.

Unable to check numbers used to generate chart. Please ensure they are correct.

Formatted: Highlight



15

Figure 3. Comparison of mean back pain scores in the ICBG and rhBMP-2 matrix groups.

Unable to check numbers used to generate chart. Please ensure they are correct.

Formatted: Highlight

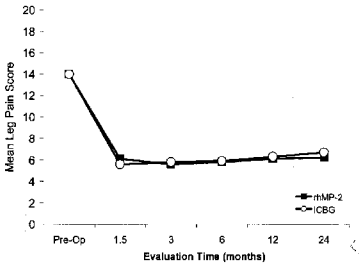


Figure 4. Comparison of mean leg pain scores in the ICBG and rhBMP-2 matrix groups.

Unable to check numbers used to generate chart. Please ensure they are correct.

Formatted: Highlight

Formatted: Body Text 2, Left

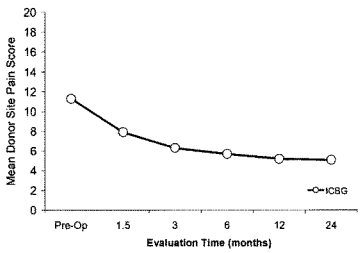
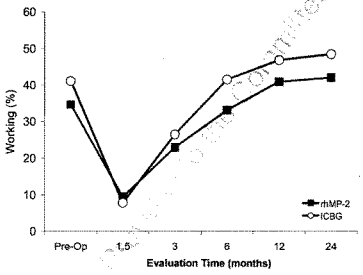


Figure 5. Mean donor site pain scores in the ICBG group.

Unable to check numbers used to generate chart. Please ensure they are correct.

Formatted: Highlight



17

Figure 6. Percentage of subjects working in the ICBG and rhBMP-2 matrix groups.

Unable to check numbers used to generate chart. Please ensure they are correct.

Formatted: Highlight

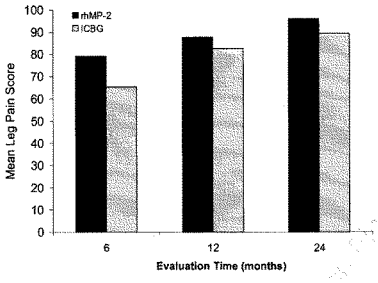


Figure 7. Percentage of subjects with bilateral confluent bridging bone reported by independent radiologists as observed on fine-cut CT scans with reconstructions for the ICBG and rhBMP-2 matrix groups. Differences between groups was statistically significant at all time points.

X-axis title is wrong.

Formatted: Highlight

Unable to check numbers used to generate chart. Please ensure they are correct.

Please insert p values on the chart.

Fusion success table?

Formatted: Highlight

REFERENCES

1. Bono CM, Lee CK. Critical analysis of trends in fusion for degenerative disc disease over the past 20 years: influence of technique on fusion rate and clinical outcome. Spine 2004;29:455-63.

2. An HS, Lynch K, Toth J. Prospective comparison of autograft vs. allograft for adult posterolateral lumbar spine fusion: differences among freeze-dried, frozen, and mixed grafts. J Spinal Disord 1995;8:131-5.

3. Dawson EG, Lotysch M 3rd, Urist MR. Intertransverse process lumbar arthrodesis with autogenous bone graft. Clin Orthop 1981;154:90-6.

4. Dimar J, Glassman S, Burkus JK, Carreon L. A comparison of prospective clincial outcome measures for anterior vs. posterior single-level spine fusion. IMAST Program July 2004

5. Jorgenson SS, Lowe TG, France J, Sabin J. A prospective analysis of autograft versus allograft in posterolateral lumbar fusion in the same patient. A minimum of 1-year follow-up in 144 patients. Spine 1994;19:2048-53.

6. Sandhu HS, Toth JM, Diwan AD, et al. Histological evaluation of the efficacy of rhBMP-2 compared with autograft bone in sheep spinal anterior interbody fusion. Spine 2002;27:567-75.

7. Boden SD, Martin GJ Jr, Horton WC, et al. Laparoscopic anterior spinal arthrodesis with rhBMP-2 in a titanium interbody threaded cage. J Spinal Disord 1998;11:95-101.

8. Hecht BP, Fischgrund JS, Herkowitz HN, et al. The use of recombinant human bone morphogenetic protein-2)rhBMP-2) to promote spinal fusion in a nonjuman primate anterior interbody fusion model. Spine 1999;24:629-36.

9. Burkus JK, Heim SE, Gornet MF, Zdeblick TA: Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-CAGE lumbar tapered fusion device. J Spinal Disord Tech 2003;16:113-22

10. Burkus JK, Sandhu HS, Gornet MF, Longley MC. Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery. J Bone Joint Surg Am. 2005;87:1205-12.

11. Martin JG Jr, Boden SD, Marone MA, Marone MA, Moskovitz PA. Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: important lessons learned regarding dose, carrier, and safety. J Spinal Disord 1999;12:179-86.

12. Barnes B, Boden SD, Louis-Ugbo J, et al. Lower dose of rhBMP-2 achieves spine fusion when combined with an osteoconductive bulking agent in non-human primates. Spine 2005;30:1127-33.

13. Akamaru T, Suh D, Boden SD, et al. Simple carrier matrix modifications can enhance delivery of recombinant human bone morphogenetic protein-2 for posterolateral spine fusion. Spine 2003;28:429-34.

14. Suh DY, Boden SD, Louis-Ugbo J, et al. Delivery of recombinant human bone morphogenetic protein-2 using a compression-resistant matrix in posterolateral spine fusion in the rabbit and in the non-human primate. Spine. 2002;27:353-60.

15. Boden SD, Martin GJ Jr, Morone MA, et al. Posterolateral lumbar intertransverse process spine arthrodesis with recombinant human bone morphogenetic protein 2/hydroxyapatite-tricalcium phosphate after laminectomy in the nonhuman primate. Spine. 1999;24:1179-85.

16. Boden SD, Kang J, Harvinder S, Heller JG. Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial: 2002 Volvo Award in clinical studies. Spine. 2002;27:2662-73.

17. Fairbank JC, Couper J, Davies JB, O'Brien JP. The Oswestry low back pain disability questionnaire. Physiotherapy 1980; 66:271-3.

18. Ware JE Jr, Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;306:473-83.

19. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994;32:40-66.

20. Glassman SD, Dimar JR, Carreon LY, et al. Initial fusion rates with recombinant human bone morphogenetic protein-2/compression resistant matrix and a hydroxyapatite and tricalcium phosphate/collagen carrier in posterolateral spinal fusion. Spine 2005;30;1694-98.

20

21. Boden SD. Overview of the biology of lumbar spine fusion and principles for selecting a bone graft substitute. Spine 2002;27(16S):S26-S31.

22. Ludwig SC, Kowalski JM and Boden SD. Osteoinductive bone graft substitutes. Eur Spine J 2000; 9(Suppl 1):S119-S125.

23. Lind M, Bunger C. Factors stimulating bone formation. Eur Spine J 2000;9(Suppl 1):S102-S109.

24. Vaccaro AR, Sharon AD, Tuan RS, et al. The use of biologic materials in spinal fusion. Orthopedics 2001;24:191-197.

25. Carreon LY, Glassman SD, Anekstein Y, Puno RM. Platelet gel (AGF) fails to increase fusion rates in instrumented posterolateral fusions. Spine. 2005;30:E243-6.

26. Urist MR: Bone: formation by autoinduction. Science. 1965;150:893-9

27. Ware JE, Kosinski M, Keller SK. SF-36® Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: The Health Institute, 1994.

28. Fairbank JCT, Pynsent PB: The Oswestry Disability Index. Spine 2000;25:2940-53.

29. Walsh TL, Hanscom B, Lurie JD, Weinstein JN. Is a condition-specific instrument for patients with low back pain/leg symptoms really necessary? The responsiveness of the Oswestry Disability index, MODEMS and the SF-36. Spine 2003;28:607-15.

30. Blumenthal SL, Gill K. Can lumbar spine radiographs accurately determine fusion in postoperative patients? Correlation of routine radiographs with a second surgical look at lumbar fusions. Spine. 1993;18:1186-9.

31.Brodsky AE, Kovalsky ES, Kahlil MA. Correlation of radiologic assessment of lumbar spine fusions with surgical exploration. Spine. 1991;16(6 Suppl):S261-5.

32. Kant AP, Daum WJ, Dean SM, Uchida T. Evaluation of lumbar spine fusion. Plain radiographs versus direct surgical exploration and observation. Spine 1995;20:2313-7.

Wozney JM. The bone morphogenetic protein family and osteogenesis [review]. Mol Reprod Dev 1992; 32:160-167

Page 2: [1] Comment [sk1] **kepess1** **10/24/2007 3:19:00 PM**
This number doesn't seem to correspond to the data that I have to compare it to. Based on the 24 month data for Hip Pain, there are 72 patients that reported a score of zero, which corresponds to roughly 32% of the 224 control subjects.

Page 2: [2] Deleted **peckhs1** **10/3/2007 12:47:00 PM**
and the morbidities associated with

Page 7: [3] Deleted **kepess1** **10/24/2007 3:07:00 PM**
7.1

Page 7: [3] Deleted **kepess1** **10/24/2007 3:07:00 PM**
7.

Page 7: [4] Deleted **LeahCarreon** **9/21/2007 10:08:00 AM**
7.4

Page 7: [4] Deleted **LeahCarreon** **9/21/2007 10:08:00 AM**
7.1

Page 7: [5] Deleted **LeahCarreon** **9/21/2007 10:08:00 AM**
54

Page 7: [5] Deleted **LeahCarreon** **9/21/2007 10:09:00 AM**
5.0

Page 7: [6] Deleted **bearcj1** **11/14/2007 1:29:00 PM**
at 24 months

Page 7: [6] Deleted **bearcj1** **11/14/2007 1:30:00 PM**
145

Page 7: [7] Deleted **bearcj1** **11/14/2007 1:31:00 PM**
considereded

Page 7: [7] Deleted **bearcj1** **11/14/2007 1:33:00 PM**
87.5

Page 7: [8] Deleted **bearcj1** **11/14/2007 1:34:00 PM**
at 12 months

Page 7: [8] Deleted **bearcj1** **11/14/2007 1:33:00 PM**
199

Page 7: [9] Deleted **LeahCarreon** **9/21/2007 10:09:00 AM**
94.9

Page 7: [9] Deleted **LeahCarreon** **9/21/2007 10:10:00 AM**
86.8

Table 1. Patient Demographic Data

	rhBMP-2 matrix Group	ICBG Group
Age (years)	53.2	52.3
Sex (% male)	45.2	42.4
Workers' Compensation (%)	11.3	12.5
Smoker (%)	26.4	26.3

Table 5. Complications (events during 24-month follow-up period.)[sk1]

Complication	rhBMP-2 matrix Group	ICBG Group
Wound drainage	5	6
Wound infections	16	23
Wound hematoma	1	0

Epidural hematoma	2	0
Malignancy*	7	2
Anemia	25	32
UTI	5	4
Infection (other sites)	25	19
Infection (total)	46	46
Second surgeries	20	37
Revisions	2	3
Removals	12	26
Supplemental fixations	6	8
Dural tear	14	17
Renal stones	6	6
Pulmonary	14	12
Ileus	8	3
Technical complications	5	5
Malposition	4	2
Displacement/loosening	1	3
Death	3	4
Donor site complaints	0	17
Donor site infection	0	1

*Cancer types in the rhBMP-2 matrix group were follicular, squamous cell, laryngeal, pancreatic, prostate, lung, and basal cell; in the ICBG group, cancer types were non-Hodgkin's lymphoma, and colon.

From: Hatcher, Brian, PhD.
Sent: Friday, February 29, 2008 02:58:17 PM
To: Ken Burkus [redacted]
CC: Bearcroft, Julie, PhD; Beals, Neil; Carol Binns [redacted]; Carol Binns [redacted]
Subject: INFUSE 6yr data paper

Attachments: Long-term outcomes of BMP-LT CAGE.EDITS.doc; Table 5 Clinical Outcomes.doc; Table 6 SF-36 Outcomes.doc; Table 7 AE's.doc; Editor_Reviewer Comments 02-04-2008.doc

Hello Dr. Burkus,
I hope that you are doing well. I had a chance to make many of the edits that we discussed when you were here on Monday. I wanted to go ahead and get you the paper so that you could begin taking a look at it and make any additional changes.

Below are a couple comments from the reviewers that need further attention. I have put some of my thoughts down in red in response to these comments, but would be interested in getting your feedback.

- Page 17, line 7-9: This is a highly speculative statement based on a study of a different clinical entity treated with a different surgical technique. The referenced study really does not support this assertion. "In particular, the high rate of segmental arthrodesis may serve to provide long-term maintenance of these significant improvements in clinical outcomes[32]." This reviewer's comment refers to the reference of PLF studies showing a correlation between fusion success and clinical outcomes long term. In the current study, the high rate of arthrodesis does not allow for an analysis to be performed to look at the correlation between fusion success and clinical outcomes. The referenced study, albeit in a different indication, provides evidence and sets a precedence that suggests the importance of fusion on long term improvements in clinical outcomes and success.
- The authors' mention that outcomes were measured at six weeks, and three, six, twelve, twenty-four, forty-eight, and seventy-two months. However, the authors' have mostly reported on outcomes at 72 months. From looking at their results, it seems that outcomes improve within the first year and then plateau. Can the authors comment on these observations? Data from preoperative to 72 months is presented in the tables. The results section focuses on the long term outcomes, as this is the focus of this paper and the 24 month data has been presented/described in detail elsewhere. This study shows that significant improvements in clinical outcomes are achieved by 6 weeks. Many of the outcomes plateau by around 12 months, as stated by this reviewer. This may be due to the initial benefits of the surgical procedure. Additionally, this may suggest the importance of a successful fusion in serving to provide long term support and contribute to the improvements achieved in clinical outcomes.

- On similar lines to my previous comment, it is confusing to present "combined" results of laproscopic and open surgery. It is difficult to draw inferences from the combined results when the authors have appropriately reported outcomes of laproscopic and open procedures separately. I suggest that the "combined" category be removed. The results section has been modified to focus on the outcomes seen in the open and laparoscopic groups. The combined group data is included in the tables and figures. The intent of combining the data sets is to present data on fusion rates and clinical outcomes with rhBMP-2/ACS and the LT Cage irrespective of surgical approach (open versus laparoscopic).
- Is it possible for the authors to elaborate more on what, for instance, a 9.3 points (page 10, line 23) improvement on the back pain scores means for the benefit of our clinical audience? This is an important issue that comes up frequently when dealing with scales. It is often difficult for readers to translate these scores in terms of functional/clinical improvement.

Also attached are the reviewers comments with initial responses.

Please let me know if you have additional comments. We have until April 4 to respond.
Brian

Brian Hatcher, Ph.D.
Technology Manager, Biologics
Medtronic
Spinal and Biologics
1800 Pyramid Place
Memphis, TN 38132
O: [redacted]
M: [redacted]
F: [redacted]

Long-Term Outcomes of Anterior Lumbar Interbody Fusion Using Interbody Fusion Cages and rhBMP-2

Deleted: 2/29/20082/20/2008

ABSTRACT

Background: Twenty-four month outcomes have been reported in patients with degenerative lumbar disc disease who were treated with stand-alone anterior lumbar interbody fusion using dual tapered interbody fusion cages and recombinant human bone morphogenetic protein-2 (rhBMP-2). This report represents an update of the clinical and radiographic results of this treatment at six years.

Methods: Patients enrolled in two prospective, multi-center FDA-approved investigational device exemption (IDE) studies were followed out to 6 years to determine radiographic and clinical outcomes. A total of 146 patients with single-level degenerative disc disease with up to grade 1 spondylolisthesis were treated with an open or a laparoscopic surgical procedure and completed the 6 year follow-up. The patients received recombinant human bone morphogenetic protein-2 on an absorbable collagen sponge with lumbar fusion cage implants. Outcomes were determined using well-established clinical outcome measurements and radiographic assessments.

Results: At six years, patients treated with rhBMP-2 and stand-alone fusion cages showed high rates of fusion and low rates of additional surgery. Radiographic evidence of fusion was documented in 98.5% of patients, and the second surgery rate between 2 and 6 years was 3.7%. Significant improvements in Oswestry Disability Index scores, SF-36® Health Survey Physical Component Summary scores, and back and leg pain scores were achieved by six weeks in both the open and laparoscopic groups, and were sustained at six years. By six

Deleted: We performed an integrated analysis of the six-year follow-up data from two prospective clinical studies in which 146 patients with single-level degenerative disc disease with up to grade 1 spondylolisthesis were treated with an open or a laparoscopic surgical procedure.

Deleted: 2/29/20082/20/2008

months, a higher percentage of patients were working than were working preoperatively, and this improvement was sustained at six years. .

Deleted: There was a trend toward greater improvement in Oswestry Disability Index, back pain, and SF-36 Physical Component Summary scores in the laparoscopic group than in the open group.

Conclusions: The use of dual tapered threaded fusion cages and rhBMP-2 on an absorbable collagen sponge facilitates and maintains intervertebral spinal fusion, improved clinical outcomes, and reduction of pain after anterior lumbar interbody fusion in patients with degenerative lumbar disc disease.

Deleted: Systematic review of Level I randomized controlled trials.

Level of Evidence: Level II: Prospective Cohort Study

Deleted: 2/29/20082/29/2008

INTRODUCTION

Discogenic low back pain results, in part, from abnormal intersegmental load patterns and movement within a degenerative disc[1]. Clinically painful discs have been shown to display specific patterns of altered stresses in the anulus and vertebral end plates, reflecting abnormal loading[2]. Lumbar interbody fusion can eliminate abnormal stress patterns associated with degenerative disc disease and normalize stress distribution patterns[3,4]. Threaded interbody fusion cages stabilize the spinal motion segment and provide a mechanical environment that optimizes fusion[5]. New bone formation in and around the cages increases the contact area and decreases the magnitude of abnormal load in the fused segment.

Deleted: adjacent vertebrae

Various bone grafts have been used in an effort to enhance bone formation within the interverterbal disc space. Recombinant human bone morphogenetic protein-2 (rhBMP-2) is an osteoinductive growth factor that stimulates pleuripotential cells to form bone. In animal and human studies, rhBMP-2 has been shown to be capable of inducing new bone formation[6,7]. At twenty-four month follow up in randomized clinical trials, the use of rhBMP-2 as an iliac crest bone graft (ICBG) replacement has been shown to increase rates of interbody fusion in patients undergoing anterior lumbar interbody fusion (ALIF), and its use has been associated with decreased pain and improved clinical outcomes[8-10]. When used in combination with the LT-CAGE® Device (Medtronic Sofamor Danek, Memphis, TN), rhBMP-2 caused patients to achieve significantly higher fusion rates than patients treated with ICBG (94.4% vs. 89.4%; p =

Deleted: 2/29/20082/20/2008

0.022)[11]. Additional studies of rhBMP-2 on an absorbable collagen sponge in patients undergoing lumbar interbody fusion have shown similar rates of fusion success[8-10,12-19].

The current study was undertaken to validate the long term safety and efficacy of using stand-alone interbody fusion cages and rhBMP-2/ACS as an iliac crest bone graft replacement. Patients in both the open and laparoscopic IDE trials were prospectively followed in this FDA regulated postapproval study to determine fusion rates and clinical outcomes at 6 years, and to compare them to the outcomes seen at 2 years[9, 10].

Deleted: Our purpose was to investigate the postapproval long-term clinical and radiographic outcomes in those investigational patients enrolled in the initial FDA trials using stand-alone interbody fusion cages and rhBMP-2 as an iliac crest bone graft replacement. Patients who received rhBMP-2 on an absorbable collagen sponge were followed for a period of six years to determine the long-term efficacy of its use as a replacement to ICBG.¶

MATERIALS AND METHODS

Two prospective, multi-center FDA-approved investigational device exemption (IDE) studies of patients undergoing treatment for single-level lumbar degenerative disc disease were conducted, utilizing a similar fusion technique through two different surgical approaches[9,20]. All patients were entered into these studies between 1997 and 1999 and were treated with INFUSE® Bone Graft and the LT-CAGE® Device (Medtronic Sofamor Danek, Memphis, TN). These studies used the identical inclusion-exclusion criteria; however, the laparoscopic cohort was a nonrandomized, single-arm study whereas the patients in the open study were randomized to receive either recombinant human bone morphogenetic protein on an absorbable collagen sponge (rhBMP-2/ACS) or iliac crest bone graft (ICBG). In this prospective study, patients enrolled in both the open and laparoscopic studies were followed out to 6 years to determine the long term

Deleted: Our analysis combines data from the patients who were treated with INFUSE® Bone Graft and the LT-CAGE® Device (Medtronic Sofamor Danek, Memphis, TN) in the two FDA IDE trials.

radiographic and clinical outcomes. These two studies were conducted to evaluate the efficacy of rhBMP-2/ACS as a replacement to ICBG and to support PMA approval, and were not designed to directly compare the open and laparoscopic surgical approaches. Internal review board (IRB) approval was completed at all study sites, and informed consent was obtained for all patients enrolled in the follow-up studies.

Inclusion-Exclusion Criteria

At the time of surgery, all patients were between the ages of 19 and 70 years and had symptomatic degenerative disc disease at the L4-L5 or L5-S1 levels (Table 1). All had had low back pain for at least six months before their surgery that was recalcitrant to nonoperative treatment modalities, such as physical therapy, bed rest, and anti-inflammatory medications. Patients were included in the study if their plain radiographic findings documented single-level disc disease, and they had undergone at least one additional confirmatory neuroradiographic study, such as MRI, CT-enhanced myelography, or discography. All patients were considered candidates for a single-level stand-alone anterior lumbar interbody fusion (ALIF). Patients were excluded from the study if they had spinal conditions other than single-level symptomatic degenerative disc disease or greater than Grade 1 spondylolisthesis. Other exclusion criteria were symptomatic disc disease at a level other than the L4-L5 or L5-S1, obesity (more than 40% above ideal body weight), or a medical condition that required medication, such as steroids or nonsteroidal anti-inflammatory medications, that could interfere with fusion.

Deleted: 2/29/20083/20/2008

Patient Follow-Up

There were 277 total patients enrolled in the open (143 patients) and laparoscopic (134 patients) groups in the initial FDA IDE studies. Of the thirty-one initial sites, twenty-three elected to participate in the long-term follow-up. As a result of second surgery failures and nonparticipating sites, fifty-five patients were excluded from this study leaving a total of 222 patients who were eligible for the FDA IDE postapproval follow-up assessments (109 in the open- and 110 in the laparoscopic-surgery arms). One hundred forty-six patients completed the seventy-two-month follow-up assessments (Table 2). This subgroup of patients was examined to determine the clinical outcome measures and fusion status at each time point from the preoperative examination to the seventy-two month follow-up examination after surgery.

Deleted: eight

Deleted: 19

Comment [h1]: Insert patient accountability table and use this in place of the current Table 2.

Surgical Procedures

Patients underwent an ALIF procedure using either an open[9] or a laparoscopic approach[20]. In the open group, transperitoneal or retroperitoneal approaches to the lumbosacral spine were used; in the laparoscopic group, all approaches were transperitoneal. Patients in both surgical groups had two LT-CAGE Devices implanted anteriorly at either the L4-L5 or L5-S1 lumbar interspace.

RhBMP-2 on the absorbable collagen sponge was used exclusively as an ICBG replacement[9,20]. No autogenous grafts and no local host-bone reamings were used. The rhBMP-2 was reconstituted to a concentration of 1.5 mg/mL and allowed to bind to the collagen sponge for a minimum of fifteen minutes, which

Deleted: using sterile water and applied to the appropriate number of collagen sponges. The rhBMP-2 was

Deleted: 2/29/20082/20/2008

Deleted: The rhBMP-2-soaked sponges were placed into the central portion of each LT-CAGE Device. No additional rhBMP-2-bound sponges were placed outside of the fusion cages.

resulted in 95% of the protein being bound to the sponge[21]. The total dose of rhBMP-2 ranged from 4.2 to 8 mg and was determined by matching the volume of the prepared collagen sponge to the internal volume of the fusion cage.

The results from the studies using the two surgical approaches were pooled and analyzed independently to better define the effects of surgical approach in surgical parameters, hospital stay, and the long-term clinical and radiographic outcomes.

Clinical Outcome Measures

Clinical outcome measures, the Oswestry Disability Index (ODI)[22], the MOS 36-item Short-Form health survey (SF-36) questionnaire[23,24], back and leg pain scores, and return-to-work status, were self administered preoperatively and at six weeks, three, six, twelve, twenty-four, forty-eight, and seventy-two months. Back and leg pain scores were determined using a 20-point scale (10 points frequency and 10 points intensity).

Radiographic Assessment

Radiographs (lateral, A/P, and flexion/extension) and thin cut CT scans with sagittal and coronal reconstructions were used to assess the presence of continuous trabecular bone formation between the vertebral bodies and to evaluate fusion[9,10]. Two independent, blinded radiologists interpreted radiographs and CT scans to assess fusion, with a third radiologist available for adjudication. Fusion was defined as bridging bone connecting the adjacent vertebral bodies either through the implants or around the implants, less than 5° of angular motion, less than or equal to 3 mm of translation, and an absence of radiolucent

Deleted: was assessed using radiographs and computed tomography (CT) scans

Deleted: 2/29/2008 2/20/2008

lines around more than 50% of either implant. Second surgery failures were classified as a failed fusion[9]. Fusion was assessed at six, twelve, twenty-four, forty-eight, and seventy-two months, and was considered successful only if all criteria were achieved.

Additional Surgical Procedures

Secondary surgical procedures performed subsequent to the index operation were classified as revisions, removals, supplemental fixations, or reoperations. Second surgeries that occurred as a result of adjacent level disease, but involved the index level, were classified as second surgery failures. A survivorship analysis was used to determine the percentage of patients who were classified as second surgery failures, taking into account all available patients at each follow-up time point.

Deleted: A revision surgery was defined as any procedure that adjusts or modifies the original implant configuration; a removal was defined as a procedure that removes one or more components of the original implant and replaces it with a different type of implant; supplemental fixation was defined as a procedure in which additional spinal devices not approved as part of the protocol are placed; and reoperation was defined as any surgical procedure at the treated level that does not remove, modify, or add any components, for example, a posterior foraminotomy.

Adverse Events

Adverse events were studied and classified as to their severity and relationship with the implants and with surgical procedures.

Statistical Analysis

For assessing the statistical significance of postoperative improvement in outcome scores from preoperative values within each treatment group, a paired *t* test was used. For statistical comparisons of demographic differences between the open and laparoscopic treatment groups, analysis of variance (ANOVA) was used for continuous variables, and Fisher's exact test was used for categorical data.

Deleted: 2/29/20082/20/2008

RESULTS

Patient Follow-Up

One hundred forty-six patients (68 in the laparoscopic group and 78 in the open group) completed the six-year follow-up. The overall follow-up rate was 52.7% (146/277), and the follow-up rate for available patients at six years was 65.8% (146/222). This subset of patients had the demographic characteristics and clinical outcomes prior to 24 months similar to those previously reported for the entire patient population[5,10].

Deleted: 6.7

Deleted: 19

Deleted: A comparison of this subgroup of patients with the entire patient population prior to twenty-four months indicated similar clinical outcomes between the groups, suggesting that this group of patients serves as a representative subset of the

Deleted: two prospective

Deleted: study

Demographic data were compiled for the patients included in the analysis (Table 3). The open and laparoscopic surgical groups were not randomized relative to each other; however, the patients' demographic characteristics and prognostic factors in these 2 groups were similar except for the patient's sex and alcohol use.

Surgical Data

Surgical, hospitalization, and clinical outcomes were analyzed for each surgical technique and the outcomes were combined. The laparoscopic group spent an average of 18 minutes longer under anesthesia and lost an average of 7.3 mL more blood than the open group (Table 4). However, the laparoscopic group left the hospital an average of 1.7 days earlier than the open group.

Clinical Outcomes

Oswestry Disability Scores

ODI scores improved significantly in all groups from the preoperative scores by 6 weeks, and these improvements were maintained out to 6 years

Deleted: 2/29/20082/20/2008

(p<0.001, Table 5 and Figure 1). For the open group, ODI scores improved an average of 32.8 points and 27.7 points at 48 and 72 months, respectively, from a preoperative score of 53.8. For the laparoscopic group, ODI scores improved an average of 34.4 points and 34.3 points at 48 and 72 months, respectively, from a preoperative score of 49.8. These improvements were similar to those seen at 24 months (31.0 points and 32.6 points for the open and laparoscopic groups, respectively).

Deleted: The Oswestry Disability Index (ODI) Questionnaire measures the level of pain and disability associated with various activities. ODI scores improved significantly from preoperative values by six weeks, and these improvements were maintained at six years (p < 0.001). For the combined group, ODI scores improved an average of 33.6 points and 31.0 points at forty-eight and seventy-two months, respectively, from a preoperative score of 52.0. These improvements were similar to those observed at twenty-four months (31.7 points). There was a trend towards slightly greater improvements in ODI scores in the laparoscopic group when compared with those in the open group at seventy-two months (Fig. 1).

Back Pain

Back pain scores improved significantly in all groups from the preoperative scores by 6 weeks, and these improvements were maintained out to 6 years (p<0.001, Table 5). For the open group, back pain scores improved an average of 7.7 points and 6.9 points at 48 and 72 months, respectively, from a preoperative score of 15.3. For the laparoscopic group, back pain scores improved an average of 10.6 points and 10.2 points at 48 and 72 months, respectively, from a preoperative score of 15.6. These improvements were similar to those seen at 24 months (8.7 points and 10.1 points for the open and laparoscopic groups, respectively).

Deleted: Back pain scores improved significantly from preoperative values by six weeks, and these improvements were maintained at six years (p < 0.001). For the combined group, back pain scores improved an average of 9.3 points and 8.6 points at forty-eight and seventy-two months, respectively. These improvements were similar to those observed at twenty-four months (9.3 points). There was a trend towards slightly greater improvements in back pain scores in the laparoscopic group when compared with the open group at forty-eight and seventy-two months (Fig. 2).

Leg Pain

Leg pain scores improved significantly in all groups from the preoperative scores by 6 weeks, and these improvements were maintained out to 6 years (p<0.001, Table 5). For the open group, leg pain scores improved an average of 7.0 points and 6.8 points at 48 and 72 months, respectively, from a preoperative score of 13.4. For the laparoscopic group, leg pain scores improved an average

Deleted: 2/29/2008 2/20/2008

of 5.8 points and 6.6 points at 48 and 72 months, respectively, from a preoperative score of 9.6. These improvements were similar to those seen at 24 months (7.3 points and 5.2 points for the open and laparoscopic groups, respectively).

SF-36

SF-36 PCS scores improved significantly in all groups from the preoperative scores by 6 weeks, and these improvements were maintained out to 6 years ($p<0.001$, Table 5). For the open group, SF-36 PCS scores improved an average of 15.3 points and 12.4 points at 48 and 72 months, respectively, from a preoperative score of 27.1. For the laparoscopic group, SF-36 PCS scores improved an average of 19.1 points and 17.8 points at 48 and 72 months, respectively, from a preoperative score of 28.7. These improvements were similar to those seen at 24 months (16.3 points and 17.5 points for the open and laparoscopic groups, respectively).

For both the open and laparoscopic groups, all SF-36 outcomes except for general health perception and role emotional improved significantly from the preoperative values at 72 months ($p<0.001$, Table 6). All outcomes in the laparoscopic group were maintained between 24 and 72 months ($p>0.05$), however certain outcomes in the open group declined slightly between 24 and 72 months ($p<0.05$, Table 5).

Radiographic Outcomes

At seventy-two months, 130 (89.0%, 130/146) patients had complete radiographic follow-up examinations (Fig. 2 A-D). At forty-eight and seventy-two

Deleted: Leg pain scores improved significantly from preoperative values by six weeks, and these improvements were maintained at six years ($p < 0.001$). For the combined group, leg pain scores improved an average of 6.4 points and 6.7 points at forty-eight and seventy-two months, respectively. These improvements were similar to those observed at twenty-four months (6.4 points). The improvement from the preoperative score at seventy-two months was similar in the laparoscopic and open groups (Fig. 3).¶

Deleted: The SF-36 measures specific health concepts related to physical functioning, social functioning, and health perceptions. For the combined group, Physical Component Summary (PCS) scores improved an average of 17.3 points and 15.1 points at forty-eight and seventy-two months, respectively. These improvements were similar to those observed at 24 months (16.1 points). There was a trend towards slightly greater improvement in SF-36 PCS scores in the laparoscopic group than in the open group at forty-eight and seventy-two months (Fig. 4).

Deleted: 5

Deleted: 2/29/20082/20/2008

Deleted: 6

months, 97.9% (92/94) and 98.5% (128/130) of patients had radiographic evidence of fusion (Fig. 3). The high rates of fusion seen at these later time points were similar to the rates of arthrodesis seen at six, twelve, and twenty-four months. Fusion rates were similar between the open and laparoscopic groups.

Second Surgery Failures

There were a total of twenty-five second surgery failures over the six-year follow-up period: sixteen in the open group and nine in the laparoscopic group. There were twenty-three supplemental fixations, one removal, and one revision. Reasons for second surgeries (implant positioning, migration or loosening, nonunion, suspected nonunion, subsidence, stenosis, radiculopathy, adjacent segment degeneration, and post laminectomy syndrome) were reported by the enrolling surgeon. Second surgery failures occurred between five days and sixty-two months after surgery.

Deleted: pending nonunions

Adjusting for the patients available at each follow-up interval by a time-to-event analysis, the overall second surgery failure rate was 10.4% (13.7% in the open group and 7.1% in the laparoscopic group) (Fig. 4). Eighteen of the twenty-five second surgeries occurred before 2 years, and the second surgery failure rate during this time period was 6.7% for the combined group (6.4% open and 7.1% laparoscopic)[9,10]. The remaining 7 second surgeries occurred between two and six years, and the rate of second surgery failure for the combined group during this time was 3.7% (7.3% open and 0% laparoscopic). All 7 failures were supplemental fixations, and investigators reported suspected nonunion (n=2), back pain (n=2), stenosis (n=2) and post laminectomy syndrome (n=1) as the

Deleted: 7

Deleted: 2/29/20082/20/2008

causes for reoperation. Three of the second surgeries involved only the index level, and the remaining 4 included both the index and adjacent level.

Return-to-Work Status

At forty-eight and seventy-two months, more patients were working than were working before surgery (69.2%;72/104 and 68.1%; 94/138 at forty-eight and seventy-two months, respectively, compared with 52.1% preoperatively). The percentage of patients working at the later time points was similar to that at twenty-four months (70.3%) (Fig. 5). By six months, approximately 90% of the patients who were working preoperatively had returned to work, and this was maintained though the seventy-two-month time point.

Deleted: 5

Adverse Events

Relevant adverse events included anatomical/technical difficulty, malpositioned implants, implant displacement/loosening, and subsidence (Table 7). All AE's within these categories occurred prior to 2 years. Anatomical/technical difficulty was observed to only occur in the laparoscopic surgical group, and all 9 events occurred during the operative period. Seven of these events resulted in a conversion to open or posterior surgery. Subsidence occurred in a total of 7 patients (6 open and 1 lap), with all events occurring within the first 6 months. Of the 24 patients with AE's listed in Table 7, 7 patients had a second surgical procedure.

Deleted: No unanticipated adverse events related to the use of rhBMP-2/ACS occurred during the course of the study. Because the ICBG control group was not followed during the twenty-four- and seventy-two-month time frame, no analysis of adverse events between the investigational and control group could be completed.

DISCUSSION

Results from prospective studies of the LT-CAGE Device have shown a trend towards more rapid fusion with INFUSE Bone Graft and improved clinical

Deleted: 2/29/20082/20/2008

outcomes when compared with patients who received autograft ICBG[11]. These improved outcomes are related, in part, to the successful combination of the surgical approach, the advanced cage designs, the avoidance of bone graft harvesting morbidity, and the high rate of successful interbody fusion. This study represents the longest follow-up, to date, of patients undergoing spine fusion with INFUSE Bone Graft[9,20]. In patients with six years of follow-up, observed radiographic fusion rates were high, rates of second surgery were low, and improvements in clinical outcomes were maintained.

Other studies have reported the long-term radiographic and clinical results of lumbar interbody fusion[25-30]. Kuslich et al. reported four-year results from a study enrolling 947 patients who received Bagby and Kuslich (BAK) cages and ICBG[29]. However, only 20.7% (196/947) of patients completed the four-year follow-up,. Fusion success allowed for up to 7° of angulation on flexion-extension films, and did not include CT scans. At four years, the authors reported an overall fusion success of 98% and a repeat surgery rate of 8.7%. Pain scores were maintained out to four years.

Deleted: which included both anterior (n = 122) and posterior (n = 74) approaches and single-level (n = 116) and two-level (n = 80) fusions

Deleted: no thin cut

Deleted: with reconstructed images were obtained to assess fusion

In a similar study, investigators evaluated clinical and radiographic outcomes following ALIF with stand-alone BAK cages implanted by a single author[28]. Patients underwent single-level (n = 40) or two-level (n = 6) ALIF with BAK cages and autograft, allograft, or a combination of both. Thirty-three of forty-six patients (71.7%) reached a mean follow-up of fifty-five months (range, thirty-six to sixty-five months). The authors reported an overall nonunion rate of 30%

Deleted: 2/29/20082/20/2008

and a revision rate of 22%. Mean ODI score at final follow-up was 41, with only 42% of patients having an ODI less than or equal to 40. ,

Deleted: The fusion rates and improvement in ODI scores at four and six years in patients treated with INFUSE Bone Graft and the LT CAGE Device indicate an improvement relative to this published report.

Brantigan and co-workers also investigated the long-term results of instrumented posterior lumbar interbody fusion (PLIF) [26]. The initial study enrolled 110 patients with degenerative disc disease at six centers. Thirty-three patients selected from two centers completed the ten-year follow-up (30%). Radiographic evidence of fusion, as defined by bridging bone and the absence of radiolucencies was reported in 96.7% of the patients at ten years. At two years, elective removal of pedicle screws indicated that 90% (104/115) of the examined levels were fused. Clinical outcomes were determined using a twenty-point Prolo scale. Preoperatively, 76% of patients had a rating of good or fair. At ten years, 87.8% (29/33) of patients had a rating of excellent, good or fair and achieved clinical success. In our study, 79% (109/138) of patients treated with INFUSE Bone Graft had an ODI improvement of greater than fifteen points at six years.

Deleted: A clinical success was defined as a patient with an excellent, good, or fair outcome and a minimum of a three-point improvement.

Martin et al. compared reoperation rates from the early '90s with those of the late '90s in a study involving approximately 26,000 patients undergoing primary lumbar surgery[31]. For patients whose primary procedure was a fusion (19.1%), these authors found a general overall reoperation rate of 14% at four years, and for patients whose primary diagnosis was herniated disc or degenerative disc disease (90.9%), the reoperation rate was approximately 15%. For patients treated with INFUSE Bone Graft and the LT CAGE Device, the secondary surgery failure rate of 9% at four years and 10% at six years compares favorably with overall failure rates cited for the 1990s.

An observation in the current study was that patients treated by the laparoscopic surgical technique trended to have shortened hospital stay, better Oswestry Low Back Pain Disability Questionnaire scores, improved scores on the SF-36 Health Survey, reduced low back pain, and fewer reoperations when compared with the group treated with open surgery at 6 years ($p>0.05$). There are potential benefits of the laparoscopic surgical approach, such as less muscle damage and tissue retraction, shorter hospital stay, and a quicker return to normal activities, that may have accounted for or contributed to this trend. This study was not designed to compare the open and laparoscopic surgical approaches, however, and there are likely a number of confounding factors that may have contributed to this observation. Patients in the open and laparoscopic surgery groups were not randomized to each other and were enrolled in 2 separate studies. There were preoperative differences in patient's demographics, including sex and alcohol use. Additionally, more patients in the open group had substantial changes in their ODI scores between twenty-four and seventy-two months, which may have contributed bias (eighteen patients in the open group had an ODI increase of 20 points or more, compared with only one patient in the laparoscopic group). Review of case report forms for patients in the open group revealed the occurrence of falls, motor vehicle accidents, adjacent level disease, and a high percentage of patients with a BMI of greater than twenty-five, which may have contributed to the slight differences in clinical outcomes. Importantly, the mean improvement scores for both groups in Oswestry pain scores, PCS scores, and back and leg pain scores were

Deleted: 2/29/20082/20/2008

Deleted: Patients treated by the laparoscopic surgical technique in the current study trended to have shortened hospital stay, better Oswestry Low Back Pain Disability Questionnaire scores, improved scores on the SF-36 Health Survey, reduced low back pain, and fewer reoperations when compared with the group treated with open surgery. There are potential benefits of the laparoscopic surgical approach, such as less muscle damage and tissue retraction, shorter hospital stay, and a quicker return to normal activities, that may have accounted for or contributed to this trend. Preoperative differences in patient demographics, including sex and alcohol use, also may have contributed, in part, to these differences. Additionally, more patients in the open group had substantial changes in their ODI scores between twenty-four and seventy-two months, which may have contributed bias (eighteen patients in the open group had an ODI increase of 20 points or more, compared with only one patient in the laparoscopic group). Review of case report forms for patients in the open group revealed the occurrence of falls, motor vehicle accidents, adjacent level disease, and a high percentage of patients with a BMI of greater than twenty-five, which may have contributed to the slight differences in clinical outcomes. Finally, the lack of randomization between the open and laparoscopic groups makes it difficult to draw definitive conclusions as to the etiology or clinical significance of this difference. Importantly, the mean improvement scores for both groups in Oswestry pain scores, PCS scores, and back and leg pain scores were significantly improved from preoperative measurements and were maintained between the twenty-four- and seventy-two-month follow-up period.

Comment [h2]: Should we include a comment along the lines of "Whether or not the difference in these outcomes between the open and laparoscopic groups is of clinical significance is a point of debate, as the minimally important clinical difference reported in the literature is variable (refs)." Otherwise, we can specifically address the reviewers comment on this point in the cover letter.

 Deleted: 2/29/20082/20/2008

significantly improved from preoperative measurements and were maintained between the twenty-four- and seventy-two-month follow-up period.

A comparison of three outcome parameters, fusion status, operative time, and hospital stay, show an improvement in care for treatment of degenerative disc disease in the lumbar spine with an advancement in therapy options[5]. Additionally, twenty-four month data comparing INFUSE Bone Graft with ICBG has shown superior rates of fusion and clinical outcomes in patients treated with rhBMP-2[11]. The improvement in functional outcomes is maintained at six years after treatment with rhBMP-2 and is also reflected in the high rates of employment in both the open and laparoscopic groups. In particular, the high rate of segmental arthrodesis may serve to provide long-term maintenance of these significant improvements in clinical outcomes[32].

The use of rhBMP-2 on an absorbable collagen-soaked sponge is an effective method of facilitating anterior intervertebral spinal fusion using a stand-alone interbody fusion device. In this long-term study, treatment with INFUSE Bone Graft and threaded titanium cages was shown to lead to high rates of fusion that were maintained at six years after surgery, and significant improvements in clinical outcome measures were maintained. These results further support the use of rhBMP-2 as a replacement for autograft in lumbar interbody fusion.

Deleted: 2/29/2008 2/20/2008

REFERENCES

1. Adams MA, Roughley PJ. What is intervertebral disc degeneration, and what causes it? Spine. 2006;31:2151-61.

2. Videman T, Nurminen M. The occurrence of anular tears and their relation to lifetime back pain history: a cadaveric study using barium sulfate discography. Spine. 2004;29:2668-76.

3. Kumar N, Judith MR, Kumar A, Mishra V, Robert MC. Analysis of stress distribution in lumbar interbody fusion. Spine. 2005;30:1731-5.

4. Palm WJ 4th, Rosenberg WS, Keaveny TM. Load transfer mechanisms in cylindrical interbody cage constructs. Spine. 2002;27:2101-7.

5. Burkus JK. Stand-alone anterior lumbar interbody fusion constructs: effect of interbody design, bone graft and bone morphogenetic protein on clinical and radiographic outcomes. In: Lewandrowski K, Yaszemski MJ, White AA, Trantolo DJ, Wise, DL, eds. *Advances in Spinal Fusion: Clinical Applications of Basic Science, Molecular Biology, Biomechanics, and Engineering.* New York, NY: Marcel Dekker; 2003:69-84.

6. Boden SD, Martin GJ Jr, Horton WC, Truss TL, Sandhu HS. Laparoscopic anterior spinal arthrodesis with rhBMP-2 in a titanium interbody threaded cage. J Spinal Disord. 1998;11:95-101.

7. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine. 1999;24:629-36.

8. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine. 2000;25:376-81.

9. Burkus JK, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. J Spinal Disord Tech. 2002;15:337-49.

10. Burkus JK, Sandhu HS, Gornet MF, Longley MC. Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery. J Bone Joint Surg Am. 2005;87:1205-12.

11. Burkus JK, Heim SE, Gornet MF, Zdeblick TA. Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-CAGE lumbar tapered fusion device. J Spinal Disord Tech. 2003;16:113-22.

12. Anand N, Hamilton JF, Perri B, Miraliakbar H, Goldstein T. Cantilever TLIF with structural allograft and RhBMP2 for correction and maintenance of segmental sagittal lordosis: long-term clinical, radiographic, and functional outcome. Spine. 2006;31:E748-53.

13. Kuklo TR, Rosner MK, Polly DW Jr. Computerized tomography evaluation of a resorbable implant after transforaminal lumbar interbody fusion. Neurosurg Focus. 2004;16:E10.

14. Lanman TH, Hopkins TJ. Lumbar interbody fusion after treatment with recombinant human bone morphogenetic protein-2 added to poly(L-lactide-co-D,L-lactide) bioresorbable implants. Neurosurg Focus. 2004;16:E9.

15. Mummaneni PV, Pan J, Haid RW, Rodts GE. Contribution of recombinant human bone morphogenetic protein-2 to the rapid creation of interbody fusion when used in transforaminal lumbar interbody fusion: a preliminary report. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2004. J Neurosurg Spine. 2004;1:19-23.

16. Potter BK, Freedman BA, Verwiebe EG, Hall JM, Polly DW Jr, Kuklo TR. Transforaminal lumbar interbody fusion: clinical and radiographic results and complications in 100 consecutive patients. J Spinal Disord Tech. 2005;18:337-46.

17. Schwender JD, Holly LT, Rouben DP, Foley KT. Minimally invasive transforaminal lumbar interbody fusion (TLIF): technical feasibility and initial results. J Spinal Disord Tech. 2005;18 SupplS1-6.

18. Slosar PJ, Josey R, Reynolds J. Accelerating lumbar fusions by combining rhBMP-2 with allograft bone: a prospective analysis of interbody fusion rates and clinical outcomes. Spine J. 2007;7:301-7.

19. Villavicencio AT, Burneikiene S, Nelson EL, Bulsara KR, Favors M, Thramann J. Safety of transforaminal lumbar interbody fusion and intervertebral recombinant human bone morphogenetic protein-2. J Neurosurg Spine. 2005;3:436-43.

20. Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2: a prospective study of clinical and radiographic outcomes. Spine. 2001;26:2751-6.

21. Hsu HP, Zanella JM, Peckham SM, Spector M. Comparing ectopic bone growth induced by rhBMP-2 on an absorbable collagen sponge in rat and rabbit models. J Orthop Res. 2006;24:1660-9.

22. Fairbank JC, Couper J, Davies JB, O'Brien JP, The Oswestry low back pain disability questionnaire. Physiotherapy. 1980;66:271-3.

23. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994; 32:40-66.

24. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473-83.

25. Bagby G. The Bagby and Kuslich (BAK) method of lumbar interbody fusion. Spine. 1999;24:1857.

26. Brantigan JW, Neidre A, Toohey JS. The Lumbar I/F Cage for posterior lumbar interbody fusion with the variable screw placement system: 10-year results of a Food and Drug Administration clinical trial. Spine J. 2004; 4:681-8.

27. Brantigan JW, Steffee AD, Lewis ML, Quinn LM, Persenaire JM. Lumbar interbody fusion using the Brantigan I/F cage for posterior lumbar interbody fusion and the variable pedicle screw placement system: two-year results from a Food and Drug Administration investigational device exemption clinical trial. Spine. 2000;25:1437-46.

28. Button G, Gupta M, Barrett C, Cammack P, Benson D. Three- to six-year follow-up of stand-alone BAK cages implanted by a single surgeon. Spine J. 2005;5:155-60.

29. Kuslich SD, Danielson G, Dowdle JD, Sherman J, Fredrickson B, Yuan H, Griffith SL. Four-year follow-up results of lumbar spine arthrodesis using the Bagby and Kuslich lumbar fusion cage. Spine. 2000;25:2656-62.

30. Kuslich SD, Ulstrom CL, Griffith SL, Ahern JW, Dowdle JD. The Bagby and Kuslich method of lumbar interbody fusion. History, techniques, and 2-year follow-up results of a United States prospective, multicenter trial. Spine. 1998;23:1267-78; discussion 1279.

31. Martin BI, Mirza SK, Comstock BA, Gray DT, Kreuter W, Deyo RA. Are lumbar spine reoperation rates falling with greater use of fusion surgery and new surgical technology? Spine. 2007;32:2119-26.

32. Kornblum MB, Fischgrund JS, Herkowitz HN, Abraham DA, Berkower DL, Ditkoff JS. Degenerative lumbar spondylolisthesis with spinal stenosis: a prospective long-term study comparing fusion and pseudarthrosis. Spine. 2004;29:726-33; discussion 733-4.

Deleted: 2/29/20082/20/2008

LEGEND OF FIGURES

Figure 1: Comparison of improvement in Oswestry Disability Index scores.

Figure 2: A, Preoperative lateral radiograph in a study patient shows disc space narrowing at L5-S1, posterior radial osteophyte formation and retrolisthesis of L5 on S1 The L4-L5 disc has a normal height, physiologic segmental lordosis, and no radial osteophytes.

B, At six weeks after surgery, the lateral radiograph shows in this patient shows placement of the dual paired interbody fusion cages in the L5-S1 disc space. Physiologic disc space height and normal sagittal contours have been restored at L5-S1.

C, At seventy-two months, this lateral radiograph shows new bone formation spanning the L5-S1 disc space anterior to the cages. There has been no subsidence of the cages. Disc space height and sagittal contours have been maintained from those seen on earlier radiographic studies. The L4-L5 disc shows no radiographic evidence of adjacent segment degeneration.

D, At seventy-two months after surgery, this sagittal computed tomography scan shows continuous trabecular bone formation through the interbody fusion cage spanning the L5-S1 interspace.

Figure 3: Comparison of radiographic fusion success.

Figure 4: Comparison of second surgery failures.

Figure 5: Comparison of return-to-work status.

Deleted: Figure 2: Comparison of improvement in back pain scores.¶
Figure 3: Comparison of improvement in leg pain scores.¶
Figure 4: Comparison of improvement in SF-36 Physical Component Summary scores.¶

Deleted: 5

Deleted: 6

Deleted: 7

Deleted: 8

Table 5: Clinical outcomes scores.

Clinical Outcome Measure	Preoperative	1 yr	2 yr	4 yr	6 yr
ODI*					
Open	53.8 (13.5)	22.7 (16.9)	22.8 (18.7)	20.6 (19.2)	25.8 (19.3)
Laparoscopic	49.8 (10.4)	17.0 (17.7)	17.6 (20.1)	14.3 (18.2)	15.5 (18.9)
Combined	52.0 (12.3)	20.1 (17.5)	20.5 (19.4)	17.2 (18.9)	20.7 (19.7)
Back Pain*					
Open	15.3 (3.9)	7.0 (5.7)	6.6 (6.0	7.4 (6.5)	8.4 (6.3)
Laparoscopic	15.6 (3.6)	5.8 (5.8)	5.6 (6.1)	4.9 (5.6)	5.4 (5.9)
Combined	15.4 (3.7)	6.4 (5.8)	6.1 (6.1)	6.0 (6.1)	6.9 (6.3)
Leg Pain*					
Open	13.4 (5.0)	5.9 (6.2)	6.1 (6.2)	6.1 (6.3)	6.6 (6.4)
Laparoscopic	9.6 (6.5)	4.2 (5.5)	4.4 (5.7)	3.5 (5.6)	3.1 (4.6)
Combined	11.6 (6.0)	5.1 (5.9)	5.3 (6.0)	4.7 (6.0)	4.8 (5.9)
SF-36 PCS*					
Open	27.1 (5.7)	42.6 (11.0)	43.5 (11.9)	41.9 (12.8)	39.7 (12.6)
Laparoscopic	28.7 (6.1)	45.5 (11.4)	45.4 (12.3)	47.5 (11.9)	46.5 (11.6)
Combined	27.9 (5.9)	44.0 (11.3)	44.4 (12.1)	44.9 (12.6)	43.1 (12.6)

*Clinical outcomes measures improved significantly from preoperative values by 6 weeks, and these improvements were maintained at each time point out to 6 years ($p<0.001$). Outcomes at 48 and 72 months were not significantly different from the outcomes at 24 months.

Table 6: Mean (SD) change in SF-36 scores from preoperative to 72-month follow-up.

	Open	Laparoscopic	Combined
PCS	12.4 (12.6)†	17.8 (10.2)	15.1 (11.7)†
MCS	4.9 (13.2)	7.3 (10.2)	6.1 (11.8)
Physical Function	31.5 (30.4)†	42.8 (26.8)	37.0 (29.1)†
Role Physical	50.7 (46.2)	64.3 (43.0)	57.4 (45.0)
Pain Index	34.8 (27.6)†	43.9 (25.8)	39.3 (27.0)
General Health Perception	-8.3 (27.0)*, †	5.0 (17.3)	-1.7 (23.6)*, †
Social Function	29.8 (31.7) †	41.2 (27.7)	35.4 (30.2)
Mental Health	15.8 (23.5)	16.4 (20.1)	16.1 (21.8)
Role Emotional	10.1 (52.5)*, †	26.0 (40.7)	18.0 (47.5)
Vitality	18.8 (24.6) †	27.1 (23.0)	22.9 (24.1)

*All scores improved significantly from preoperative values at 72 months except for general health perception and role emotional (p≤0.019).
†Changes in SF-36 scores from 24 months to 72 months were statistically significant (p<0.05)

Table 7: Patients who had adverse events occurring prior to 2 years and between 2 and 6 years.

AE	Events ≤ 2 years		Events > 2 years (2<t≤6yrs)	
	Open (n=143)	Lap (n=134)	Open (n=78)	Lap (n=68)
Anatomical/Technical Difficulty	0	9	0	0
Malpositioned Implant	1	4 (2)	0	0
Implant Displacement/Loosening	2 (1)	2	0	0
Subsidence	6 (4)	1	0	0

*The number in parenthesis represents the number of patients within the AE category who had a second surgical procedure.

----- Original Message -----
From: "The Journal of Bone and Joint Surgery" <[redacted]>
To: <jkb[redacted]>
Sent: Monday, February 04, 2008 12:40 PM
Subject: Revise Manuscript

February 4, 2008 12:39:14
John Kenneth Burkus, MD

Dear Dr. Burkus:
Your manuscript entitled, "Long-Term Outcomes of Anterior Lumbar Interbody Fusion Using Interbody Fusion Cages and rhBMP-2," number JBJS-D-07-01485, has been reviewed by Consultant Reviewers to The Journal. There was considerable interest in your manuscript. However, our Consultant Reviewers did have questions and concerns that need to be addressed before further consideration can be given to your manuscript. These are listed below.

I hope that you are able to address these concerns in a revised manuscript accompanied by a cover letter outlining your point-by-point response to each concern. Please resubmit to The Journal within 60 days so that a final decision can be made with regard to publication. The due date for revision will be Apr 4 2008 12:00:00:000AM.

Sincerely,
Charles R. Clark, MD
Deputy Editor

Reviewer #1:

The authors present 72-month follow-up of a subset of two different studies. Both were prospective. The open surgical approach included randomization of treatment (BMP or control: autologous bone). The second study of laparoscopic surgery had no control group. Unhappily, the authors did not follow the controlled patients. This is not really a level I study. Of the 277 original patients they report 146, but all centers did not participate, reducing the number of "eligible patients." Sixteen of the 146 did not have radiographic follow-up. The authors spoke of trends but did not report p-values. Broad sweeping statements were made throughout. The manuscript is not suitable for publication in its current form.

- Page 2, line 16ff: Qualitative terms such as "high" and "low" are used. Please provide numbers. Fusion rates and second surgery rates are provided in the following sentence.

- Page 3, lines 1-2: Is this statistically significant? This statement has been removed from the abstract and this analysis (open compared to laparoscopic) is addressed in the discussion (pursuant to other comments made by the reviewers on this type of comparison and the intent of the study).

- Page 3, line 9: Given study designs and lack of control is this truly level 1 evidence? This study includes 2 prospective IDE studies. The first study was a randomized controlled trial comparing rhBMP-2/ACS to ICBG in lumbar interbody fusion procedures with the LT Cage via an open surgical approach (Level I). The second study was a prospective single arm study investigating rhBMP-2/ACS with the LT Cage via a laparoscopic surgical approach (Level II). The 6 year follow-up of these patients was part of an FDA regulated postapproval study. Therefore, this study is a prospective cohort study and meets the Journals guidelines of a Level II study.

- Page 4, line 10: "Adjacent vertebrae" is confusing. I suggest changing to "motion segment" or "fused segment." This has been changed to fused segment.

- Page 6, lines 16-18: Give the number of patients in each subgroup, the total number of patients in each of the surgical groups is presented in the results section. Additionally, a table on patient follow-up and accountability has been added to the manuscript.

- Page 9, lines 18-21: Please give supporting data. Provided a reference the pivotal and superiority papers where this data on the entire 277 patients is presented.

- Page 9, line 23: This statement is confusing as written. Presumably, they mean that patients were not randomized to the open or laparoscopic approach (coming from different studies). Changed the sentence to read: The open and laparoscopic surgical groups were not randomized relative to each other; however, the patients' demographic characteristics and prognostic factors in

these 2 groups were similar except for the patient's sex and alcohol use.

- **Page 10, lines 17-19: Here and elsewhere they speak of trends but provide no p-values. Nor do the authors indicate whether this is a clinically relevant difference in outcome. This is true throughout the results section.** This point has been stated by many of the reviewers. The results section has been modified to present the outcomes of the open and laparoscopic groups. As the intent of this study was not to directly compare these procedures, the focus on this has been removed from the results. A portion of the discussion has been devoted to this type of comparison as suggested by another reviewer. Whether or not the difference in these outcomes between the open and laparoscopic groups is of clinical significance is a point of debate, as the minimally important clinical difference reported in the literature is variable. FDA criteria stipulate a 15 point improvement in ODI is needed to achieve success for a given patient. When comparing between groups, Fairbank has referenced that a 4 point difference in mean ODI score is the minimum difference between groups that is clinically significant.

- **Page 17, line 7-9: This is a highly speculative statement based on a study of a different clinical entity treated with a different surgical technique. The referenced study really does not support this assertion.** In the current study, the high rate of arthrodesis does not allow for an analysis to be performed to look at the correlation between fusion success and clinical outcomes. The referenced study, albeit in a different indication, provides evidence and sets a precedence that suggests the importance of fusion on long term improvements in clinical outcomes and success.

- **Page 17, line 12: Is this really long-term? I would call it short to medium.** The length of f/u reported here is longer than 2 of the 3 studies referenced in the discussion. When compared to other studies on spine fusion, 72 months appears to constitute long term.

- **Page 17, lines 15-16: Perhaps, but the authors did not provide any follow-up on the controlled patients.** While control patients were not followed out to 6 years, they were followed out to 2 years in the open group. This 2 year f/u established the efficacy of rhBMP-2/ACS as a replacement to ICBG. The fact that outcomes were maintained out to 6 years further supports the use of this technology as a suitable bone graft in the absence of any autograft bone.

- **Pages 23-24, figures 1-4 and figure 8: It would be useful to have the p-values indicated each time point or at least indicate which time points (if and) there was a statistical significant difference between the subgroups.** The clinical outcomes have been summarized in a single Table. The comparison between open and lap groups has been removed from the results section and addressed in a portion of the discussion.

- Table 5: Are there any statistical significant differences? The 24-month data was said to be similar but are not presented. Were there any statistical differences between 24 and 72 months? A statistical analysis comparing 72 month outcomes with those at 24 months has been performed and provided in the results section and in Table 5.

Reviewer #2:

- This is not a systematic review, and is not Level one evidence. This is an original study that presents long term data derived from two separate FDA IDE trials investigating the LT CAGE device with rhBMP-2/ACS for ALIF. One study was a RCT and the other was a prospective cohort. Based on my review and the per cent follow up, I would consider this Level III evidence. It does, however, provide useful long-term data. See above response to Reviewer 1 presenting rational for Level II.

- Fusion Analysis: Please document what plain films were taken. Were the XRs and CTs reviewed independently, and by whom (radiologist or spine surgeon)? This has been added in the radiographic section of the methods.

ODI

- Page 10, Line 12: ODI scores for which group, and what were the values? Numeric values are not presented in the figure. Page 10, Line 14: Were these results statistically significant? Page 10, Lines 11-19: This section should be rewritten, or a table should be included, that clearly denotes numeric values along with the appropriate statistical analysis. As written, it is too vague. The results section has been rewritten to present the clinical outcomes for the open and lap groups, along with statistical data. A single table that gives numerical values for ODI, SF-36 PCS, and back and leg pain scores has been included, and the corresponding figures have been deleted. Comparison of the open and lap groups has been removed from the results section and a portion of the discussion is devoted to this comparison. This is also in line with additional comments from this and other reviewers.

BACK PAIN

- Page 10, Lines 21-22: To which group are you referring to, the open or lap? This has been addressed as described in the ODI question above.

- Pages 10 and 11: Again, as in the above comments on the ODI section, the data should be presented numerically for all groups, either in text or table format, along with the statistical results. Same.

LEG PAIN

- Refer to comments on ODI and BACK PAIN, as they apply here as well. Same

RADIOGRAPHIC OUTCOMES

- Page 12, Lines 4-9: Please provide the per cent follow-up for the radiographic analysis. Also, were both plain films AND CT's obtained at terminal follow-up as implied in the methods section? This should be clear to the reader. Added to results (89%, 130/146) and methods (criteria to assess fusion, also referenced open and lap 24 month studies)

SECOND SURGERY FAILURES

- Page 12, Line 12 - Page 12, Line 3: The precise reasons for the "early" and "late" secondary surgeries need to be documented. Of particular interest to me would be the secondary surgery for pseudoarthrosis, and its final radiographic result (i.e. fusion or no fusion). An important point for the reader would be to provide information that would indicate the best method for treatment of pseudoarthrosis following LT cage fusion. What were the clinical results of these failures and subsequent revision? It is far too vague as written, and one can not discern any useful information about this important outcome measure. Additional information on second surgery failures has been provided in the results section. Between 2 and 6 years, there were 2 patients who had a second surgery because of a suspected nonunion. Both of these patients received supplemental fixation. After a patient was classified as a second surgery failure, they were not carried forward in the database. Therefore, it is not known what the result of the 2nd surgery was on a patient's clinical outcomes.

- Please define "pending non-union"? This is defined as a patient who has a suspected pseudarthrosis. The term to describe a pending non-union has been changed to suspected nonunion in the results section.

- Also, were the patients that had secondary surgery included in the fusion analysis. I presume they were not, but this should be clarified. Patients who had a second surgery were classified as a fusion failure during the time point at which the second surgery occurred. Second surgery failures were not carried forward to additional time points for fusion assessment.

ADVERSE EVENTS

- Page 13, Lines 11-15: What about adverse events related to the LT cages? With this large initial cohort of patients, it is difficult to understand how there are no AE's. Why then would implant migration be listed as a reason for reoperation? This needs to be clarified. Given the evidence already published, one would expect that there would be no identifiable AE's with the use of BMP/ACS. Additional information related to AEs has been added to this section of the manuscript and Table 7 also provides additional information on this topic.

Reviewer #3:

The authors followed patients with degenerative disc disease who were previously enrolled in clinical trials to study the efficacy of interbody fusion cages and rhBMP-2. They describe outcomes at six years of follow-up in these patients. My detailed comments are as under:

Abstract

- This is essentially an observational cohort study of participants recruited from previous clinical trials on interbody fusion cages and rhBMP-2. The current study is interesting in that it describes long-term follow-up outcomes in this cohort but is not a comparison of two surgical techniques or treatments. This is not a systematic review of a Level-1 evidence study, as noted in the abstract, since that term is misleading. The level of evidence for an observational cohort study would be more appropriate for this manuscript. See above comments related to the level of evidence for this study.

Introduction

- The authors should present a more clear rationale for the current study in the introduction. Why did they follow-up patients for six years after two year outcomes had already been reported earlier? A clear rational describing the purpose and design of this study has been provided in the introduction and methods section. This study was an FDA regulated, prospective post approval study conducted to further validate the safety and efficacy of rhBMP-2/ACS and to provide long term data on fusion success and clinical outcomes in lumbar interbody fusion.

Methods

- Page 6, line 2: Bed rest is mentioned as non-operative treatment modality for low back pain. This is not the current standard of care. Enrollment for the open and laparoscopic studies occurred between 1997-1999, at which time the protocol defined bed rest as a nonoperative means of treatment.

- I suggest that the authors present a diagram which represents the case inclusion/exclusion schema with number of patients leading to their final patient population of 146 patients. A table showing the number of patients treated and patient accountability over the 6-year follow-up has been added to the paper.

- Please provide a reference for criteria used in this study to describe "fusion". Fusion criteria are defined in the methods section and a reference to the reports on the 2 year outcomes for these 2 IDE studies is also provided.

- Although this is clear by the end of the manuscript, it needs to be mentioned upfront that patients undergoing laproscopic surgery received interbody fusion cages with rhBMP-2. A statement clarifying this has been added to the methods.

Results

- The authors' mention that outcomes were measured at six weeks, and three, six, twelve, twenty-four, forty-eight, and seventy-two months. However, the authors' have mostly reported on outcomes at 72 months. From looking at their results, it seems that outcomes improve within the first year and then plateau. Can the authors comment on these observations? Data from preoperative to 72 months is presented in the tables. The results section focuses on the long term outcomes, as this is the focus of this paper and the 24 month data has been presented/described in detail elsewhere. This study shows that significant improvements in clinical outcomes are achieved by 6 weeks. Many of the outcomes plateau by around 12 months, as stated by this reviewer. This may be due to the initial benefits of the surgical procedure. Additionally, this may suggest the importance of a successful fusion in serving to provide long term support and contribute to the improvements achieved in clinical outcomes.

- The authors' have appropriately reported separately on outcomes of the open and laproscopic group. However, results on the comparison of these two groups gets confusing since this was not the objective of the study. To compare open versus laproscopic techniques, the authors have to go beyond simple ANOVA tests which do not control for potential confounders. In my judgement, results of the two techniques should be presented separately (as they are) but it is misleading to make statistical inferences about comparison of the two groups. The discussion presented towards the end of the manuscript on why the laproscopic group had shorter length of stay, better Oswestry Low Back Pain Disability Questionnaire scores, and improved scores on SF-36 is appropriate and helpful. But I would clearly state that the objective of this study is not to compare the outcomes of the two groups. The objective of the current study is described in both the introduction and methods section to clearly address the point raised in the above comment. Additionally the comparison between the open and laparoscopic groups has been removed from the results section, and a portion of the discussion is devoted to this comparison.

- On similar lines to my previous comment, it is confusing to present "combined" results of laproscopic and open surgery. It is difficult to draw inferences from the combined results when the authors have appropriately reported outcomes of laproscopic and open procedures separately. I suggest that the "combined" category be removed. The results section has been modified to focus on the outcomes seen in the open and laparoscopic groups. The combined group data is included in the tables and figures. The intent of combining the data sets is to present data on fusion rates and clinical outcomes with rhBMP-2/ACS and the LT Cage irrespective of surgical approach (open versus laparoscopic).

- In the results section (page 9, line 19), authors report on comparison of patient population in the current study with the entire patient population prior to twenty-four months. They have compared clinical outcomes between the groups and suggested that the populations were similar. I suggest that the authors,

instead, compare baseline demographic and clinical characteristics of patients included in the current study with only patients who were not included in the current study (and were in the base population for the two year study) to draw an inference that the two populations were similar. We have modified the results section to say that this subset of patients had the demographic characteristics and clinical outcomes prior to 24 months similar to those previously reported for the whole study, and have provided the references for this. Thus, the patient populations are similar. We did not present the comparisons of demographic data in this subset of patients with the rest, because it would make the flow of the presentation and discussion awkward and it would also digress from the main discussion of the long-term results.

Discussion

* Is it possible for the authors to elaborate more on what, for instance, a 9.3 points (page 10, line 23) improvement on the back pain scores means for the benefit of our clinical audience? This is an important issue that comes up frequently when dealing with scales. It is often difficult for readers to translate these scores in terms of functional/clinical improvement.

- Some of the discussion on previous studies in this area can be abbreviated. This section has been edited to address this point.

Tables/Figures

- I also suggest that the authors report actual baseline and follow-up scores for their outcome measures in both table 5 and the graphs. It is difficult to gauge what the change in scores means unless readers have a baseline score to look at. The mean values for the clinical outcomes have been summarized and are presented in a single table along with the standard deviation.

- There are too many graphs. The authors' can condense some of this data into a single table. The majority of the graphs reporting on the clinical outcomes have been removed and a single table providing ODI, SF-36 PCS, and back pain and leg pain scores has been included.

- Methodology Editor: I would simply add that the authors need to provide 95% CI when they present proportions. Additional statistical data has been added to the manuscript, table and figures. Standard deviations are presented along with mean values.

From:	Hatcher, Brian, PhD.
Sent:	Friday, February 29, 2008 03:21:53 PM
To:	Ma, Guorong; Norman, Dawn; Barnett-Myers, Sharon
CC:	Zhu, Youjun; Newbill, Cathy; Desrochers, Debbie; Bearcroft, Julie, PhD; Peckham, Steve, Ph.D.; Vollmar, Tommy
Subject:	INFUSE 6yr data paper
Attachments:	Long-term outcomes of BMP-LT CAGE.EDITS.doc; Figure 1 ODI Improvement Values.doc; Table 5 Clinical Outcomes.doc; Table 6 SF-36 Outcomes.doc; Table 7 AE's.doc

Hello Publication Committee,
Please find attached an updated draft to the INFUSE/LT Cage 6 year data paper. We received comments back from the reviewers at JBJS and have attempted to address all of their points in this revision. Thanks to all of you for helping me to gather and analyze the information needed to do this.

Please review this paper and provide me with any additional comments by next Friday, March 7 at 5pm.
Thanks
Brian

Additional tables not included in the original submission:

Brian Hatcher, Ph.D.
Technology Manager, Biologics
Medtronic
Spinal and Biologics
1800 Pyramid Place
Memphis, TN 38132
O: [redacted]
M: [redacted]
F: [redacted]

Long-Term Outcomes of Anterior Lumbar Interbody Fusion Using Interbody Fusion Cages and rhBMP-2

Deleted: 2/29/20082/20/2008

ABSTRACT

Background: Twenty-four month outcomes have been reported in patients with degenerative lumbar disc disease who were treated with stand-alone anterior lumbar interbody fusion using dual tapered interbody fusion cages and recombinant human bone morphogenetic protein-2 (rhBMP-2). This report represents an update of the clinical and radiographic results of this treatment at six years.

Methods: Patients enrolled in two prospective, multi-center FDA-approved investigational device exemption (IDE) studies were followed out to 6 years to determine radiographic and clinical outcomes. A total of 146 patients with single-level degenerative disc disease with up to grade 1 spondylolisthesis were treated with an open or a laparoscopic surgical procedure and completed the 6 year follow-up. The patients received recombinant human bone morphogenetic protein-2 on an absorbable collagen sponge with lumbar fusion cage implants. Outcomes were determined using well-established clinical outcome measurements and radiographic assessments.

Results: At six years, patients treated with rhBMP-2 and stand-alone fusion cages showed high rates of fusion and low rates of additional surgery. Radiographic evidence of fusion was documented in 98.5% of patients, and the second surgery rate between 2 and 6 years was 3.7%. Significant improvements in Oswestry Disability Index scores, SF-36® Health Survey Physical Component Summary scores, and back and leg pain scores were achieved by six weeks in both the open and laparoscopic groups, and were sustained at six years. By six

Deleted: We performed an integrated analysis of the six-year follow-up data from two prospective clinical studies in which 146 patients with single-level degenerative disc disease with up to grade 1 spondylolisthesis were treated with an open or a laparoscopic surgical procedure.

Deleted: 2/29/2008 2/20/2008

months, a higher percentage of patients were working than were working preoperatively, and this improvement was sustained at six years. ,

Deleted: There was a trend toward greater improvement in Oswestry Disability Index, back pain, and SF-36 Physical Component Summary scores in the laparoscopic group than in the open group.

Conclusions: The use of dual tapered threaded fusion cages and rhBMP-2 on an absorbable collagen sponge facilitates and maintains intervertebral spinal fusion, improved clinical outcomes, and reduction of pain after anterior lumbar interbody fusion in patients with degenerative lumbar disc disease.

Deleted: Systematic review of Level I randomized controlled trials.

Level of Evidence: Level II: Prospective Cohort Study

Deleted: 2/29/20082/20/2008

INTRODUCTION

Discogenic low back pain results, in part, from abnormal intersegmental load patterns and movement within a degenerative disc[1]. Clinically painful discs have been shown to display specific patterns of altered stresses in the anulus and vertebral end plates, reflecting abnormal loading[2]. Lumbar interbody fusion can eliminate abnormal stress patterns associated with degenerative disc disease and normalize stress distribution patterns[3,4]. Threaded interbody fusion cages stabilize the spinal motion segment and provide a mechanical environment that optimizes fusion[5]. New bone formation in and around the cages increases the contact area and decreases the magnitude of abnormal load in the fused segment.

Deleted: adjacent vertebrae

Various bone grafts have been used in an effort to enhance bone formation within the interverterbal disc space. Recombinant human bone morphogenetic protein-2 (rhBMP-2) is an osteoinductive growth factor that stimulates pleuripotential cells to form bone. In animal and human studies, rhBMP-2 has been shown to be capable of inducing new bone formation[6,7]. At twenty-four month follow up in randomized clinical trials, the use of rhBMP-2 as an iliac crest bone graft (ICBG) replacement has been shown to increase rates of interbody fusion in patients undergoing anterior lumbar interbody fusion (ALIF), and its use has been associated with decreased pain and improved clinical outcomes[8-10]. When used in combination with the LT-CAGE® Device (Medtronic Sofamor Danek, Memphis, TN), rhBMP-2 caused patients to achieve significantly higher fusion rates than patients treated with ICBG (94.4% vs. 89.4%; p =

Deleted: 2/29/20082/20/2008

0.022)[11]. Additional studies of rhBMP-2 on an absorbable collagen sponge in patients undergoing lumbar interbody fusion have shown similar rates of fusion success[8-10,12-19].

The current study was undertaken to validate the long term safety and efficacy of using stand-alone interbody fusion cages and rhBMP-2/ACS as an iliac crest bone graft replacement. Patients in both the open and laparoscopic IDE trials were prospectively followed in this FDA regulated postapproval study to determine fusion rates and clinical outcomes at 6 years, and to compare them to the outcomes seen at 2 years[9, 10].

Deleted: Our purpose was to investigate the postapproval long-term clinical and radiographic outcomes in those investigational patients enrolled in the initial FDA trials using stand-alone interbody fusion cages and rhBMP-2 as an iliac crest bone graft replacement. Patients who received rhBMP-2 on an absorbable collagen sponge were followed for a period of six years to determine the long-term efficacy of its use as a replacement to ICBG.¶

MATERIALS AND METHODS

Two prospective, multi-center FDA-approved investigational device exemption (IDE) studies of patients undergoing treatment for single-level lumbar degenerative disc disease were conducted, utilizing a similar fusion technique through two different surgical approaches[9,20]. All patients were entered into these studies between 1997 and 1999 and were treated with INFUSE® Bone Graft and the LT-CAGE® Device (Medtronic Sofamor Danek, Memphis, TN). These studies used the identical inclusion-exclusion criteria; however, the laparoscopic cohort was a nonrandomized, single-arm study whereas the patients in the open study were randomized to receive either recombinant human bone morphogenetic protein on an absorbable collagen sponge (rhBMP-2/ACS) or iliac crest bone graft (ICBG). In this prospective study, patients enrolled in both the open and laparoscopic studies were followed out to 6 years to determine the long term

Deleted: Our analysis combines data from the patients who were treated with INFUSE® Bone Graft and the LT-CAGE® Device (Medtronic Sofamor Danek, Memphis, TN) in the two FDA IDE trials.

Deleted: 2/29/20082/29/2008

radiographic and clinical outcomes. These two studies were conducted to evaluate the efficacy of rhBMP-2/ACS as a replacement to ICBG and to support PMA approval, and were not designed to directly compare the open and laparoscopic surgical approaches. Internal review board (IRB) approval was completed at all study sites, and informed consent was obtained for all patients enrolled in the follow-up studies.

Inclusion-Exclusion Criteria

At the time of surgery, all patients were between the ages of 19 and 70 years and had symptomatic degenerative disc disease at the L4-L5 or L5-S1 levels (Table 1). All had had low back pain for at least six months before their surgery that was recalcitrant to nonoperative treatment modalities, such as physical therapy, bed rest, and anti-inflammatory medications. Patients were included in the study if their plain radiographic findings documented single-level disc disease, and they had undergone at least one additional confirmatory neuroradiographic study, such as MRI, CT-enhanced myelography, or discography. All patients were considered candidates for a single-level stand-alone anterior lumbar interbody fusion (ALIF). Patients were excluded from the study if they had spinal conditions other than single-level symptomatic degenerative disc disease or greater than Grade 1 spondylolisthesis. Other exclusion criteria were symptomatic disc disease at a level other than the L4-L5 or L5-S1, obesity (more than 40% above ideal body weight), or a medical condition that required medication, such as steroids or nonsteroidal anti-inflammatory medications, that could interfere with fusion.

Deleted: 2/29/20082/20/2008

Patient Follow-Up

There were 277 total patients enrolled in the open (143 patients) and laparoscopic (134 patients) groups in the initial FDA IDE studies. Of the thirty-one initial sites, twenty-three elected to participate in the long-term follow-up. As a result of second surgery failures and nonparticipating sites, fifty-five patients were excluded from this study leaving a total of 222 patients who were eligible for the FDA IDE postapproval follow-up assessments (109 in the open- and 110 in the laparoscopic-surgery arms). One hundred forty-six patients completed the seventy-two-month follow-up assessments (Table 2). This subgroup of patients was examined to determine the clinical outcome measures and fusion status at each time point from the preoperative examination to the seventy-two month follow-up examination after surgery.

Deleted: eight

Deleted: 19

Comment [b1]: Insert patient accountability table and use this in place of the current Table 2.

Surgical Procedures

Patients underwent an ALIF procedure using either an open[9] or a laparoscopic approach[20]. In the open group, transperitoneal or retroperitoneal approaches to the lumbosacral spine were used; in the laparoscopic group, all approaches were transperitoneal. Patients in both surgical groups had two LT-CAGE Devices implanted anteriorly at either the L4-L5 or L5-S1 lumbar interspace.

RhBMP-2 on the absorbable collagen sponge was used exclusively as an ICBG replacement[9,20]. No autogenous grafts and no local host-bone reamings were used. The rhBMP-2 was reconstituted to a concentration of 1.5 mg/mL and allowed to bind to the collagen sponge for a minimum of fifteen minutes, which

Deleted: using sterile water and applied to the appropriate number of collagen sponges. The rhBMP-2 was

Deleted: 2/29/20082/20/2008

Deleted: The rhBMP-2-soaked sponges were placed into the central portion of each LT-CAGE Device. No additional rhBMP-2-bound sponges were placed outside of the fusion cages.

resulted in 95% of the protein being bound to the sponge[21]. The total dose of rhBMP-2 ranged from 4.2 to 8 mg and was determined by matching the volume of the prepared collagen sponge to the internal volume of the fusion cage.

The results from the studies using the two surgical approaches were pooled and analyzed independently to better define the effects of surgical approach in surgical parameters, hospital stay, and the long-term clinical and radiographic outcomes.

Clinical Outcome Measures

Clinical outcome measures, the Oswestry Disability Index (ODI)[22], the MOS 36-item Short-Form health survey (SF-36) questionnaire[23,24], back and leg pain scores, and return-to-work status, were self administered preoperatively and at six weeks, three, six, twelve, twenty-four, forty-eight, and seventy-two months. Back and leg pain scores were determined using a 20-point scale (10 points frequency and 10 points intensity).

Radiographic Assessment

Radiographs (lateral, A/P, and flexion/extension) and thin cut CT scans with sagittal and coronal reconstructions were used to assess the presence of continuous trabecular bone formation between the vertebral bodies and to evaluate fusion[9,10]. Two independent, blinded radiologists interpreted radiographs and CT scans to assess fusion, with a third radiologist available for adjudication. Fusion was defined as bridging bone connecting the adjacent vertebral bodies either through the implants or around the implants, less than 5° of angular motion, less than or equal to 3 mm of translation, and an absence of radiolucent

Deleted: was assessed using radiographs and computed tomography (CT) scans

Deleted: 2/29/20082/20/2008

lines around more than 50% of either implant. Second surgery failures were classified as a failed fusion[9]. Fusion was assessed at six, twelve, twenty-four, forty-eight, and seventy-two months, and was considered successful only if all criteria were achieved.

Additional Surgical Procedures

Secondary surgical procedures performed subsequent to the index operation were classified as revisions, removals, supplemental fixations, or reoperations. Second surgeries that occurred as a result of adjacent level disease, but involved the index level, were classified as second surgery failures. A survivorship analysis was used to determine the percentage of patients who were classified as second surgery failures, taking into account all available patients at each follow-up time point.

Deleted: A revision surgery was defined as any procedure that adjusts or modifies the original implant configuration; a removal was defined as a procedure that removes one or more components of the original implant and replaces it with a different type of implant; supplemental fixation was defined as a procedure in which additional spinal devices not approved as part of the protocol are placed; and reoperation was defined as any surgical procedure at the treated level that does not remove, modify, or add any components, for example, a posterior foraminotomy.

Adverse Events

Adverse events were studied and classified as to their severity and relationship with the implants and with surgical procedures.

Statistical Analysis

For assessing the statistical significance of postoperative improvement in outcome scores from preoperative values within each treatment group, a paired *t* test was used. For statistical comparisons of demographic differences between the open and laparoscopic treatment groups, analysis of variance (ANOVA) was used for continuous variables, and Fisher's exact test was used for categorical data.

Deleted: 2/29/20082/20/2008

RESULTS

Patient Follow-Up

One hundred forty-six patients (68 in the laparoscopic group and 78 in the open group) completed the six-year follow-up. The overall follow-up rate was 52.7% (146/277), and the follow-up rate for available patients at six years was 65.8% (146/222). This subset of patients had the demographic characteristics and clinical outcomes prior to 24 months similar to those previously reported for the entire patient population[9,10].

Deleted: 6.7

Deleted: 19

Deleted: A comparison of this subgroup of patients with the entire patient population prior to twenty-four months indicated similar clinical outcomes between the groups, suggesting that this group of patients serves as a representative subset of the

Deleted: two prospective

Deleted: study

Demographic data were compiled for the patients included in the analysis (Table 3). The open and laparoscopic surgical groups were not randomized relative to each other; however, the patients' demographic characteristics and prognostic factors in these 2 groups were similar except for the patient's sex and alcohol use.

Surgical Data

Surgical, hospitalization, and clinical outcomes were analyzed for each surgical technique and the outcomes were combined. The laparoscopic group spent an average of 18 minutes longer under anesthesia and lost an average of 7.3 mL more blood than the open group (Table 4). However, the laparoscopic group left the hospital an average of 1.7 days earlier than the open group.

Clinical Outcomes

Oswestry Disability Scores

ODI scores improved significantly in all groups from the preoperative scores by 6 weeks, and these improvements were maintained out to 6 years

Deleted: 2/29/20082/20/2008

(p<0.001, Table 5 and Figure 1). For the open group, ODI scores improved an average of 32.8 points and 27.7 points at 48 and 72 months, respectively, from a preoperative score of 53.8. For the laparoscopic group, ODI scores improved an average of 34.4 points and 34.3 points at 48 and 72 months, respectively, from a preoperative score of 49.8. These improvements were similar to those seen at 24 months (31.0 points and 32.6 points for the open and laparoscopic groups, respectively).

Deleted: The Oswestry Disability Index (ODI) Questionnaire measures the level of pain and disability associated with various activities. ODI scores improved significantly from preoperative values by six weeks, and these improvements were maintained at six years (p < 0.001). For the combined group, ODI scores improved an average of 33.6 points and 31.0 points at forty-eight and seventy-two months, respectively, from a preoperative score of 52.0. These improvements were similar to those observed at twenty-four months (31.7 points). There was a trend towards slightly greater improvements in ODI scores in the laparoscopic group when compared with those in the open group at seventy-two months (Fig. 1).

Back Pain

Back pain scores improved significantly in all groups from the preoperative scores by 6 weeks, and these improvements were maintained out to 6 years (p<0.001, Table 5). For the open group, back pain scores improved an average of 7.7 points and 6.9 points at 48 and 72 months, respectively, from a preoperative score of 15.3. For the laparoscopic group, back pain scores improved an average of 10.6 points and 10.2 points at 48 and 72 months, respectively, from a preoperative score of 15.6. These improvements were similar to those seen at 24 months (8.7 points and 10.1 points for the open and laparoscopic groups, respectively).

Deleted: Back pain scores improved significantly from preoperative values by six weeks, and these improvements were maintained at six years (p < 0.001). For the combined group, back pain scores improved an average of 9.3 points and 8.6 points at forty-eight and seventy-two months, respectively. These improvements were similar to those observed at twenty-four months (9.3 points). There was a trend towards slightly greater improvements in back pain scores in the laparoscopic group when compared with the open group at forty-eight and seventy-two months (Fig. 2).

Leg Pain

Leg pain scores improved significantly in all groups from the preoperative scores by 6 weeks, and these improvements were maintained out to 6 years (p<0.001, Table 5). For the open group, leg pain scores improved an average of 7.0 points and 6.8 points at 48 and 72 months, respectively, from a preoperative score of 13.4. For the laparoscopic group, leg pain scores improved an average

Deleted: 2/29/20082/20/2008

of 5.8 points and 6.6 points at 48 and 72 months, respectively, from a preoperative score of 9.6. These improvements were similar to those seen at 24 months (7.3 points and 5.2 points for the open and laparoscopic groups, respectively).

SF-36

SF-36 PCS scores improved significantly in all groups from the preoperative scores by 6 weeks, and these improvements were maintained out to 6 years (p<0.001, Table 5). For the open group, SF-36 PCS scores improved an average of 15.3 points and 12.4 points at 48 and 72 months, respectively, from a preoperative score of 27.1. For the laparoscopic group, SF-36 PCS scores improved an average of 19.1 points and 17.8 points at 48 and 72 months, respectively, from a preoperative score of 28.7. These improvements were similar to those seen at 24 months (16.3 points and 17.5 points for the open and laparoscopic groups, respectively).

For both the open and laparoscopic groups, all SF-36 outcomes except for general health perception and role emotional improved significantly from the preoperative values at 72 months (p<0.001, Table 6). All outcomes in the laparoscopic group were maintained between 24 and 72 months (p>0.05), however certain outcomes in the open group declined slightly between 24 and 72 months (p<0.05, Table 5).

Radiographic Outcomes

At seventy-two months, 130 (89.0%, 130/146) patients had complete radiographic follow-up examinations (Fig. 2 A-D). At forty-eight and seventy-two

Deleted: Leg pain scores improved significantly from preoperative values by six weeks, and these improvements were maintained at six years (p < 0.001). For the combined group, leg pain scores improved an average of 6.4 points and 6.7 points at forty-eight and seventy-two months, respectively. These improvements were similar to those observed at twenty-four months (6.4 points). The improvement from the preoperative score at seventy-two months was similar in the laparoscopic and open groups (Fig. 3).¶

Deleted: The SF-36 measures specific health concepts related to physical functioning, social functioning, and health perceptions. For the combined group, Physical Component Summary (PCS) scores improved an average of 17.3 points and 15.1 points at forty-eight and seventy-two months, respectively. These improvements were similar to those observed at 24 months (16.1 points). There was a trend towards slightly greater improvement in SF-36 PCS scores in the laparoscopic group than in the open group at forty-eight and seventy-two months (Fig. 4).

Deleted: 5

Deleted: 2/29/20082/20/2008

months, 97.9% (92/94) and 98.5% (128/130) of patients had radiographic evidence of fusion (Fig. 3). The high rates of fusion seen at these later time points were similar to the rates of arthrodesis seen at six, twelve, and twenty-four months. Fusion rates were similar between the open and laparoscopic groups.

Deleted: 6

Second Surgery Failures

There were a total of twenty-five second surgery failures over the six-year follow-up period: sixteen in the open group and nine in the laparoscopic group. There were twenty-three supplemental fixations, one removal, and one revision. Reasons for second surgeries (implant positioning, migration or loosening, nonunion, suspected nonunion, subsidence, stenosis, radiculopathy, adjacent segment degeneration, and post laminectomy syndrome) were reported by the enrolling surgeon. Second surgery failures occurred between five days and sixty-two months after surgery.

Deleted: pending nonunions

Adjusting for the patients available at each follow-up interval by a time-to-event analysis, the overall second surgery failure rate was 10.4% (13.7% in the open group and 7.1% in the laparoscopic group) (Fig. 4). Eighteen of the twenty-five second surgeries occurred before 2 years, and the second surgery failure rate during this time period was 6.7% for the combined group (6.4% open and 7.1% laparoscopic)[9,10]. The remaining 7 second surgeries occurred between two and six years, and the rate of second surgery failure for the combined group during this time was 3.7% (7.3% open and 0% laparoscopic). All 7 failures were supplemental fixations, and investigators reported suspected nonunion (n=2), back pain (n=2), stenosis (n=2) and post laminectomy syndrome (n=1) as the

Deleted: 7

Deleted: 2/29/20082/20/2008

causes for reoperation. Three of the second surgeries involved only the index level, and the remaining 4 included both the index and adjacent level.

Return-to-Work Status

At forty-eight and seventy-two months, more patients were working than were working before surgery (69.2%;72/104 and 68.1%; 94/138 at forty-eight and seventy-two months, respectively, compared with 52.1% preoperatively). The percentage of patients working at the later time points was similar to that at twenty-four months (70.3%) (Fig. 5). By six months, approximately 90% of the patients who were working preoperatively had returned to work, and this was maintained though the seventy-two-month time point.

Deleted: 8

Adverse Events

Relevant adverse events included anatomical/technical difficulty, malpositioned implants, implant displacement/loosening, and subsidence (Table 7). All AE's within these categories occurred prior to 2 years. Anatomical/technical difficulty was observed to only occur in the laparoscopic surgical group, and all 9 events occurred during the operative period. Seven of these events resulted in a conversion to open or posterior surgery. Subsidence occurred in a total of 7 patients (6 open and 1 lap), with all events occurring within the first 6 months. Of the 24 patients with AE's listed in Table 7, 7 patients had a second surgical procedure.

Deleted: No unanticipated adverse events related to the use of rhBMP-2/ACS occurred during the course of the study. Because the ICBG control group was not followed during the twenty-four- and seventy-two-month time frame, no analysis of adverse events between the investigational and control group could be completed.

DISCUSSION

Results from prospective studies of the LT-CAGE Device have shown a trend towards more rapid fusion with INFUSE Bone Graft and improved clinical

Deleted: 2/29/20082/26/2008

outcomes when compared with patients who received autograft ICBG[11]. These improved outcomes are related, in part, to the successful combination of the surgical approach, the advanced cage designs, the avoidance of bone graft harvesting morbidity, and the high rate of successful interbody fusion. This study represents the longest follow-up, to date, of patients undergoing spine fusion with INFUSE Bone Graft[9,20]. In patients with six years of follow-up, observed radiographic fusion rates were high, rates of second surgery were low, and improvements in clinical outcomes were maintained.

Other studies have reported the long-term radiographic and clinical results of lumbar interbody fusion[25-30]. Kuslich et al. reported four-year results from a study enrolling 947 patients who received Bagby and Kuslich (BAK) cages and ICBG[29]. However, only 20.7% (196/947) of patients completed the four-year follow-up. Fusion success allowed for up to 7° of angulation on flexion-extension films, and did not include CT scans. At four years, the authors reported an overall fusion success of 98% and a repeat surgery rate of 8.7%. Pain scores were maintained out to four years.

Deleted: which included both anterior (n = 122) and posterior (n = 74) approaches and single-level (n = 116) and two-level (n = 80) fusions

Deleted: no thin cut

Deleted: with reconstructed images were obtained to assess fusion

In a similar study, investigators evaluated clinical and radiographic outcomes following ALIF with stand-alone BAK cages implanted by a single author[28]. Patients underwent single-level (n = 40) or two-level (n = 6) ALIF with BAK cages and autograft, allograft, or a combination of both. Thirty-three of forty-six patients (71.7%) reached a mean follow-up of fifty-five months (range, thirty-six to sixty-five months). The authors reported an overall nonunion rate of 30%

Deleted: 2/29/20082/28/2008

and a revision rate of 22%. Mean ODI score at final follow-up was 41, with only 42% of patients having an ODI less than or equal to 40. ,

Deleted: The fusion rates and improvement in ODI scores at four and six years in patients treated with INFUSE Bone Graft and the LT CAGE Device indicate an improvement relative to this published report.

Brantigan and co-workers also investigated the long-term results of instrumented posterior lumbar interbody fusion (PLIF) [26]. The initial study enrolled 110 patients with degenerative disc disease at six centers. Thirty-three patients selected from two centers completed the ten-year follow-up (30%). Radiographic evidence of fusion, as defined by bridging bone and the absence of radiolucencies was reported in 96.7% of the patients at ten years. At two years, elective removal of pedicle screws indicated that 90% (104/115) of the examined levels were fused. Clinical outcomes were determined using a twenty-point Prolo scale. Preoperatively, 76% of patients had a rating of good or fair. At ten years, 87.8% (29/33) of patients had a rating of excellent, good or fair and achieved clinical success. In our study, 79% (109/138) of patients treated with INFUSE Bone Graft had an ODI improvement of greater than fifteen points at six years.

Deleted: A clinical success was defined as a patient with an excellent, good, or fair outcome and a minimum of a three-point improvement.

Martin et al. compared reoperation rates from the early '90s with those of the late '90s in a study involving approximately 25,000 patients undergoing primary lumbar surgery[31]. For patients whose primary procedure was a fusion (19.1%), these authors found a general overall reoperation rate of 14% at four years, and for patients whose primary diagnosis was herniated disc or degenerative disc disease (90.9%), the reoperation rate was approximately 15%. For patients treated with INFUSE Bone Graft and the LT CAGE Device, the secondary surgery failure rate of 9% at four years and 10% at six years compares favorably with overall failure rates cited for the 1990s.

An observation in the current study was that patients treated by the laparoscopic surgical technique trended to have shortened hospital stay, better Oswestry Low Back Pain Disability Questionnaire scores, improved scores on the SF-36 Health Survey, reduced low back pain, and fewer reoperations when compared with the group treated with open surgery at 6 years ($p>0.05$). There are potential benefits of the laparoscopic surgical approach, such as less muscle damage and tissue retraction, shorter hospital stay, and a quicker return to normal activities, that may have accounted for or contributed to this trend. This study was not designed to compare the open and laparoscopic surgical approaches, however, and there are likely a number of confounding factors that may have contributed to this observation. Patients in the open and laparoscopic surgery groups were not randomized to each other and were enrolled in 2 separate studies. There were preoperative differences in patient's demographics, including sex and alcohol use. Additionally, more patients in the open group had substantial changes in their ODI scores between twenty-four and seventy-two months, which may have contributed bias (eighteen patients in the open group had an ODI increase of 20 points or more, compared with only one patient in the laparoscopic group). Review of case report forms for patients in the open group revealed the occurrence of falls, motor vehicle accidents, adjacent level disease, and a high percentage of patients with a BMI of greater than twenty-five, which may have contributed to the slight differences in clinical outcomes. Importantly, the mean improvement scores for both groups in Oswestry pain scores, PCS scores, and back and leg pain scores were

Deleted: 2/29/20082/20/2008

Deleted: Patients treated by the laparoscopic surgical technique in the current study trended to have shortened hospital stay, better Oswestry Low Back Pain Disability Questionnaire scores, improved scores on the SF-36 Health Survey, reduced low back pain, and fewer reoperations when compared with the group treated with open surgery. There are potential benefits of the laparoscopic surgical approach, such as less muscle damage and tissue retraction, shorter hospital stay, and a quicker return to normal activities, that may have accounted for or contributed to this trend. Preoperative differences in patient demographics, including sex and alcohol use, also may have contributed, in part, to these differences. Additionally, more patients in the open group had substantial changes in their ODI scores between twenty-four and seventy-two months, which may have contributed bias (eighteen patients in the open group had an ODI increase of 20 points or more, compared with only one patient in the laparoscopic group). Review of case report forms for patients in the open group revealed the occurrence of falls, motor vehicle accidents, adjacent level disease, and a high percentage of patients with a BMI of greater than twenty-five, which may have contributed to the slight differences in clinical outcomes. Finally, the lack of randomization between the open and laparoscopic groups makes it difficult to draw definitive conclusions as to the etiology or clinical significance of this difference. Importantly, the mean improvement scores for both groups in Oswestry pain scores, PCS scores, and back and leg pain scores were significantly improved from preoperative measurements and were maintained between the twenty-four- and seventy-two-month follow-up period.

Comment [h2]: Should we include a comment along the lines of "Whether or not the difference in these outcomes between the open and laparoscopic groups is of clinical significance is a point of debate, as the minimally important clinical difference reported in the literature is variable (refs)." Otherwise, we can specifically address the reviewers comment on this point in the cover letter.

significantly improved from preoperative measurements and were maintained between the twenty-four- and seventy-two-month follow-up period.

A comparison of three outcome parameters, fusion status, operative time, and hospital stay, show an improvement in care for treatment of degenerative disc disease in the lumbar spine with an advancement in therapy options[5]. Additionally, twenty-four month data comparing INFUSE Bone Graft with ICBG has shown superior rates of fusion and clinical outcomes in patients treated with rhBMP-2[11]. The improvement in functional outcomes is maintained at six years after treatment with rhBMP-2 and is also reflected in the high rates of employment in both the open and laparoscopic groups. In particular, the high rate of segmental arthrodesis may serve to provide long-term maintenance of these significant improvements in clinical outcomes[32].

The use of rhBMP-2 on an absorbable collagen-soaked sponge is an effective method of facilitating anterior intervertebral spinal fusion using a stand-alone interbody fusion device. In this long-term study, treatment with INFUSE Bone Graft and threaded titanium cages was shown to lead to high rates of fusion that were maintained at six years after surgery, and significant improvements in clinical outcome measures were maintained. These results further support the use of rhBMP-2 as a replacement for autograft in lumbar interbody fusion.

REFERENCES

1. Adams MA, Roughley PJ. What is intervertebral disc degeneration, and what causes it? Spine. 2006;31:2151-61.

2. Videman T, Nurminen M. The occurrence of anular tears and their relation to lifetime back pain history: a cadaveric study using barium sulfate discography. Spine. 2004;29:2668-76.

3. Kumar N, Judith MR, Kumar A, Mishra V, Robert MC. Analysis of stress distribution in lumbar interbody fusion. Spine. 2005;30:1731-5.

4. Palm WJ 4th, Rosenberg WS, Keaveny TM. Load transfer mechanisms in cylindrical interbody cage constructs. Spine. 2002;27:2101-7.

5. Burkus JK. Stand-alone anterior lumbar interbody fusion constructs: effect of interbody design, bone graft and bone morphogenetic protein on clinical and radiographic outcomes. In: Lewandrowski K, Yaszemski MJ, White AA, Trantolo DJ, Wise, DL, eds. *Advances in Spinal Fusion: Clinical Applications of Basic Science, Molecular Biology, Biomechanics, and Engineering.* New York, NY: Marcel Dekker; 2003:69-84.

6. Boden SD, Martin GJ Jr, Horton WC, Truss TL, Sandhu HS. Laparoscopic anterior spinal arthrodesis with rhBMP-2 in a titanium interbody threaded cage. J Spinal Disord. 1998;11:95-101.

7. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine. 1999;24:629-36.

Deleted: 2/29/20082/20/2008

8. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine. 2000;25:376-81.

9. Burkus JK, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. J Spinal Disord Tech. 2002;15:337-49.

10. Burkus JK, Sandhu HS, Gornet MF, Longley MC. Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery. J Bone Joint Surg Am. 2005;87:1205-12.

11. Burkus JK, Heim SE, Gornet MF, Zdeblick TA. Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-CAGE lumbar tapered fusion device. J Spinal Disord Tech. 2003;16:113-22.

12. Anand N, Hamilton JF, Perri B, Miraliakbar H, Goldstein T. Cantilever TLIF with structural allograft and RhBMP2 for correction and maintenance of segmental sagittal lordosis: long-term clinical, radiographic, and functional outcome. Spine. 2006;31:E748-53.

13. Kuklo TR, Rosner MK, Polly DW Jr. Computerized tomography evaluation of a resorbable implant after transforaminal lumbar interbody fusion. Neurosurg Focus. 2004;16:E10.

14. Lanman TH, Hopkins TJ. Lumbar interbody fusion after treatment with recombinant human bone morphogenetic protein-2 added to poly(L-lactide-co-D,L-lactide) bioresorbable implants. Neurosurg Focus. 2004;16:E9.

Deleted: 2/29/20082/20/2008

15. Mummaneni PV, Pan J, Haid RW, Rodts GE. Contribution of recombinant human bone morphogenetic protein-2 to the rapid creation of interbody fusion when used in transforaminal lumbar interbody fusion: a preliminary report. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2004. J Neurosurg Spine. 2004;1:19-23.

16. Potter BK, Freedman BA, Verwiebe EG, Hall JM, Polly DW Jr, Kuklo TR. Transforaminal lumbar interbody fusion: clinical and radiographic results and complications in 100 consecutive patients. J Spinal Disord Tech. 2005;18:337-46.

17. Schwender JD, Holly LT, Rouben DP, Foley KT. Minimally invasive transforaminal lumbar interbody fusion (TLIF): technical feasibility and initial results. J Spinal Disord Tech. 2005;18 SuppIS1-6.

18. Slosar PJ, Josey R, Reynolds J. Accelerating lumbar fusions by combining rhBMP-2 with allograft bone: a prospective analysis of interbody fusion rates and clinical outcomes. Spine J. 2007;7:301-7.

19. Villavicencio AT, Burneikiene S, Nelson EL, Bulsara KR, Favors M, Thramann J. Safety of transforaminal lumbar interbody fusion and intervertebral recombinant human bone morphogenetic protein-2. J Neurosurg Spine. 2005;3:436-43.

20. Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2: a prospective study of clinical and radiographic outcomes. Spine. 2001;26:2751-6.

21. Hsu HP, Zanella JM, Peckham SM, Spector M. Comparing ectopic bone growth induced by rhBMP-2 on an absorbable collagen sponge in rat and rabbit models. J Orthop Res. 2006;24:1660-9.

22. Fairbank JC, Couper J, Davies JB, O'Brien JP, The Oswestry low back pain disability questionnaire. Physiotherapy. 1980;66:271-3.

23. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994; 32:40-66.

24. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473-83.

25. Bagby G. The Bagby and Kuslich (BAK) method of lumbar interbody fusion. Spine. 1999;24:1857.

26. Brantigan JW, Neidre A, Toohey JS. The Lumbar I/F Cage for posterior lumbar interbody fusion with the variable screw placement system: 10-year results of a Food and Drug Administration clinical trial. Spine J. 2004; 4:681-8.

27. Brantigan JW, Steffee AD, Lewis ML, Quinn LM, Persenaire JM. Lumbar interbody fusion using the Brantigan I/F cage for posterior lumbar interbody fusion and the variable pedicle screw placement system: two-year results from a Food and Drug Administration investigational device exemption clinical trial. Spine. 2000;25:1437-46.

28. Button G, Gupta M, Barrett C, Cammack P, Benson D. Three- to six-year follow-up of stand-alone BAK cages implanted by a single surgeon. Spine J. 2005;5:155-60.

29. Kuslich SD, Danielson G, Dowdle JD, Sherman J, Fredrickson B, Yuan H, Griffith SL. Four-year follow-up results of lumbar spine arthrodesis using the Bagby and Kuslich lumbar fusion cage. Spine. 2000;25:2656-62.

30. Kuslich SD, Ulstrom CL, Griffith SL, Ahern JW, Dowdle JD. The Bagby and Kuslich method of lumbar interbody fusion. History, techniques, and 2-year follow-up results of a United States prospective, multicenter trial. Spine. 1998;23:1267-78; discussion 1279.

31. Martin BI, Mirza SK, Comstock BA, Gray DT, Kreuter W, Deyo RA. Are lumbar spine reoperation rates falling with greater use of fusion surgery and new surgical technology? Spine. 2007;32:2119-26.

32. Kornblum MB, Fischgrund JS, Herkowitz HN, Abraham DA, Berkower DL, Ditkoff JS. Degenerative lumbar spondylolisthesis with spinal stenosis: a prospective long-term study comparing fusion and pseudarthrosis. Spine. 2004;29:726-33; discussion 733-4.

Deleted: 2/29/20082/20/2008

LEGEND OF FIGURES

Figure 1: Comparison of improvement in Oswestry Disability Index scores.

Figure 2: A, Preoperative lateral radiograph in a study patient shows disc space narrowing at L5-S1, posterior radial osteophyte formation and retrolisthesis of L5 on S1 The L4-L5 disc has a normal height, physiologic segmental lordosis, and no radial osteophytes.

B, At six weeks after surgery, the lateral radiograph shows in this patient shows placement of the dual paired interbody fusion cages in the L5-S1 disc space. Physiologic disc space height and normal sagittal contours have been restored at L5-S1.

C, At seventy-two months, this lateral radiograph shows new bone formation spanning the L5-S1 disc space anterior to the cages. There has been no subsidence of the cages. Disc space height and sagittal contours have been maintained from those seen on earlier radiographic studies. The L4-L5 disc shows no radiographic evidence of adjacent segment degeneration.

D, At seventy-two months after surgery, this sagittal computed tomography scan shows continuous trabecular bone formation through the interbody fusion cage spanning the L5-S1 interspace.

Figure 3: Comparison of radiographic fusion success.

Figure 4: Comparison of second surgery failures.

Figure 5: Comparison of return-to-work status.

Deleted: Figure 2: Comparison of improvement in back pain scores.¶
Figure 3: Comparison of improvement in leg pain scores.¶
Figure 4: Comparison of improvement in SF-36 Physical Component Summary scores.¶

Deleted: 5

Deleted: 6

Deleted: 7

Deleted: 8

Figure 1: Improvement in ODI scores

Time	Open	Lap	Combined
1.5	13.6	16.5	14.9
3	23.4	24.7	24.0
6	27.4	29.0	28.1
12	31.2	32.4	31.7
24	31.0	32.6	31.7
48	32.8	34.4	33.6
72	27.7	34.3	31

Table 5: Clinical outcomes scores.

Clinical Outcome Measure	Preoperative	1 yr	2 yr	4 yr	6 yr
ODI*					
Open	53.8 (13.5)	22.7 (16.9)	22.8 (18.7)	20.6 (19.2)	25.8 (19.3)
Laparoscopic	49.8 (10.4)	17.0 (17.7)	17.6 (20.1)	14.3 (18.2)	15.5 (18.9)
Combined	52.0 (12.3)	20.1 (17.5)	20.5 (19.4)	17.2 (18.9)	20.7 (19.7)
Back Pain*					
Open	15.3 (3.9)	7.0 (5.7)	6.6 (6.0	7.4 (6.5)	8.4 (6.3)
Laparoscopic	15.6 (3.6)	5.8 (5.8)	5.6 (6.1)	4.9 (5.6)	5.4 (5.9)
Combined	15.4 (3.7)	6.4 (5.8)	6.1 (6.1)	6.0 (6.1)	6.9 (6.3)
Leg Pain*					
Open	13.4 (5.0)	5.9 (6.2)	6.1 (6.2)	6.1 (6.3)	6.6 (6.4)
Laparoscopic	9.6 (6.5)	4.2 (5.5)	4.4 (5.7)	3.5 (5.6)	3.1 (4.6)
Combined	11.6 (6.0)	5.1 (5.9)	5.3 (6.0)	4.7 (6.0)	4.8 (5.9)
SF-36 PCS*					
Open	27.1 (5.7)	42.6 (11.0)	43.5 (11.9)	41.9 (12.8)	39.7 (12.6)
Laparoscopic	28.7 (6.1)	45.5 (11.4)	45.4 (12.3)	47.5 (11.9)	46.5 (11.6)
Combined	27.9 (5.9)	44.0 (11.3)	44.4 (12.1)	44.9 (12.6)	43.1 (12.6)

*Clinical outcomes measures improved significantly from preoperative values by 6 weeks, and these improvements were maintained at each time point out to 6 years ($p<0.001$). Outcomes at 48 and 72 months were not significantly different from the outcomes at 24 months.

Table 6: Mean (SD) change in SF-36 scores from preoperative to 72-month follow-up.

	Open	Laparoscopic	Combined
PCS	12.4 (12.6)†	17.8 (10.2)	15.1 (11.7)†
MCS	4.9 (13.2)	7.3 (10.2)	6.1 (11.8)
Physical Function	31.5 (30.4)†	42.8 (26.8)	37.0 (29.1)†
Role Physical	50.7 (46.2)	64.3 (43.0)	57.4 (45.0)
Pain Index	34.8 (27.6)†	43.9 (25.8)	39.3 (27.0)
General Health Perception	-8.3 (27.0)*, †	5.0 (17.3)	-1.7 (23.6)*, †
Social Function	29.8 (31.7) †	41.2 (27.7)	35.4 (30.2)
Mental Health	15.8 (23.5)	16.4 (20.1)	16.1 (21.8)
Role Emotional	10.1 (52.5)*, †	26.0 (40.7)	18.0 (47.5)
Vitality	18.8 (24.6) †	27.1 (23.0)	22.9 (24.1)

*All scores improved significantly from preoperative values at 72 months except for general health perception and role emotional (p≤0.019).
†Changes in SF-36 scores from 24 months to 72 months were statistically significant (p<0.05)

Table 7: Patients who had adverse events occurring prior to 2 years and between 2 and 6 years.

AE	Events ≤ 2 years		Events > 2 years (2<t<6yrs)	
	Open (n=143)	Lap (n=134)	Open (n=78)	Lap (n=68)
Anatomical/Technical Difficulty	0	9	0	0
Malpositioned Implant	1	4 (2)	0	0
Implant Displacement/Loosening	2 (1)	2	0	0
Subsidence	6 (4)	1	0	0

*The number in parenthesis represents the number of patients within the AE category who had a second surgical procedure.

From: Bearcroft, Julie, PhD
Sent: Monday, March 3, 2008 05:34:29 PM
To: Desrochers, Debbie; Hatcher, Brian, PhD.; Ma, Guorong; Norman, Dawn; Barnett-Myers, Sharon
CC: Zhu, Youjun; Newbill, Cathy; Peckham, Steve, Ph.D.; Vollmar, Tommy
Subject: RE: INFUSE 6yr data paper

Attachments: Editor_Reviewer Comments 02-04-2008.doc

Brian is out of town but attached is the reviewer comments with draft responses that was prepared last week before he left out of town on vacation. The black is the original commentary.

Hope that helps,
julie

From: Desrochers, Debbie
Sent: Monday, March 03, 2008 9:14 AM
To: Hatcher, Brian, PhD.; Ma, Guorong; Norman, Dawn; Barnett-Myers, Sharon
Cc: Zhu, Youjun; Newbill, Cathy; Bearcroft, Julie, PhD; Peckham, Steve, Ph.D.; Vollmar, Tommy
Subject: RE: INFUSE 6yr data paper

Can we get a copy of the comments from the reviewers?
Debbie

From: Hatcher, Brian, PhD.
Sent: Friday, February 29, 2008 3:22 PM
To: Ma, Guorong; Norman, Dawn; Barnett-Myers, Sharon
Cc: Zhu, Youjun; Newbill, Cathy; Desrochers, Debbie; Bearcroft, Julie, PhD; Peckham, Steve, Ph.D.; Vollmar, Tommy
Subject: INFUSE 6yr data paper

Hello Publication Committee,
Please find attached an updated draft to the INFUSE/LT Cage 6 year data paper. We received comments back from the reviewers at JBJS and have attempted to address all of their points in this revision. Thanks to all of you for helping me to gather and analyze the information needed to do this.

Please review this paper and provide me with any additional comments by next Friday, March 7 at 5pm.
Thanks
Brian

<< File: Long-term outcomes of BMP-LT CAGE.EDITS.doc >>
Additional tables not included in the original submission:

<< File: Figure 1 ODI Improvement Values.doc >> << File: Table 5 Clinical Outcomes.doc >> << File: Table 6 SF-36 Outcomes.doc >> << File: Table 7 AE's.doc >>

Brian Hatcher, Ph.D.
Technology Manager, Biologics
Medtronic
Spinal and Biologics
1800 Pyramid Place
Memphis, TN 38132
O: [redacted]
M: [redacted]
F: [redacted]

----- Original Message -----
From: "The Journal of Bone and Joint Surgery" <[redacted]>
To: <jk[redacted]>
Sent: Monday, February 04, 2008 12:40 PM
Subject: Revise Manuscript

February 4, 2008 12:39:14
John Kenneth Burkus, MD

Dear Dr. Burkus:
Your manuscript entitled, "Long-Term Outcomes of Anterior Lumbar Interbody Fusion Using Interbody Fusion Cages and rhBMP-2," number JBJS-D-07-01485, has been reviewed by Consultant Reviewers to The Journal. There was considerable interest in your manuscript. However, our Consultant Reviewers did have questions and concerns that need to be addressed before further consideration can be given to your manuscript. These are listed below.

I hope that you are able to address these concerns in a revised manuscript accompanied by a cover letter outlining your point-by-point response to each concern. Please resubmit to The Journal within 60 days so that a final decision can be made with regard to publication. The due date for revision will be Apr 4 2008 12:00:00:000AM.

Sincerely,
Charles R. Clark, MD
Deputy Editor

Reviewer #1:

The authors present 72-month follow-up of a subset of two different studies. Both were prospective. The open surgical approach included randomization of treatment (BMP or control: autologous bone). The second study of laparoscopic surgery had no control group. Unhappily, the authors did not follow the controlled patients. This is not really a level I study. Of the 277 original patients they report 146, but all centers did not participate, reducing the number of "eligible patients." Sixteen of the 146 did not have radiographic follow-up. The authors spoke of trends but did not report p-values. Broad sweeping statements were made throughout. The manuscript is not suitable for publication in its current form.

- Page 2, line 16ff: Qualitative terms such as "high" and "low" are used. Please provide numbers. Fusion rates and second surgery rates are provided in the following sentence.

- Page 3, lines 1-2: Is this statistically significant? This statement has been removed from the abstract and this analysis (open compared to laparoscopic) is addressed in the discussion (pursuant to other comments made by the reviewers on this type of comparison and the intent of the study).

- Page 3, line 9: Given study designs and lack of control is this truly level 1 evidence? This study includes 2 prospective IDE studies. The first study was a randomized controlled trial comparing rhBMP-2/ACS to ICBG in lumbar interbody fusion procedures with the LT Cage via an open surgical approach (Level I). The second study was a prospective single arm study investigating rhBMP-2/ACS with the LT Cage via a laparoscopic surgical approach (Level II). The 6 year follow-up of these patients was part of an FDA regulated postapproval study. Therefore, this study is a prospective cohort study and meets the Journals guidelines of a Level II study.

- Page 4, line 10: "Adjacent vertebrae" is confusing. I suggest changing to "motion segment" or "fused segment." This has been changed to fused segment.

- Page 6, lines 16-18: Give the number of patients in each subgroup. The total number of patients in each of the surgical groups is presented in the results section. Additionally, a table on patient follow-up and accountability has been added to the manuscript.

- Page 9, lines 18-21: Please give supporting data. Provided a reference the pivotal and superiority papers where this data on the entire 277 patients is presented.

- Page 9, line 23: This statement is confusing as written. Presumably, they mean that patients were not randomized to the open or laparoscopic approach (coming from different studies). Changed the sentence to read: The open and laparoscopic surgical groups were not randomized relative to each other; however, the patients' demographic characteristics and prognostic factors in

these 2 groups were similar except for the patient's sex and alcohol use.

- **Page 10, lines 17-19: Here and elsewhere they speak of trends but provide no p-values. Nor do the authors indicate whether this is a clinically relevant difference in outcome. This is true throughout the results section.** This point has been stated by many of the reviewers. The results section has been modified to present the outcomes of the open and laparoscopic groups. As the intent of this study was not to directly compare these procedures, the focus on this has been removed from the results. A portion of the discussion has been devoted to this type of comparison as suggested by another reviewer. Whether or not the difference in these outcomes between the open and laparoscopic groups is of clinical significance is a point of debate, as the minimally important clinical difference reported in the literature is variable. FDA criteria stipulate a 15 point improvement in ODI is needed to achieve success for a given patient. When comparing between groups, Fairbank has referenced that a 4 point difference in mean ODI score is the minimum difference between groups that is clinically significant.

- **Page 17, line 7-9: This is a highly speculative statement based on a study of a different clinical entity treated with a different surgical technique. The referenced study really does not support this assertion.** In the current study, the high rate of arthrodesis does not allow for an analysis to be performed to look at the correlation between fusion success and clinical outcomes. The referenced study, albeit in a different indication, provides evidence and sets a precedence that suggests the importance of fusion on long term improvements in clinical outcomes and success.

- **Page 17, line 12: Is this really long-term? I would call it short to medium.** The length of f/u reported here is longer than 2 of the 3 studies referenced in the discussion. When compared to other studies on spine fusion, 72 months appears to constitute long term.

- **Page 17, lines 15-16: Perhaps, but the authors did not provide any follow-up on the controlled patients.** While control patients were not followed out to 6 years, they were followed out to 2 years in the open group. This 2 year f/u established the efficacy of rhBMP-2/ACS as a replacement to ICBG. The fact that outcomes were maintained out to 6 years further supports the use of this technology as a suitable bone graft in the absence of any autograft bone.

- **Pages 23-24, figures 1-4 and figure 8: It would be useful to have the p-values indicated each time point or at least indicate which time points (if and) there was a statistical significant difference between the subgroups.** The clinical outcomes have been summarized in a single Table. The comparison between open and lap groups has been removed from the results section and addressed in a portion of the discussion.

- Table 5: Are there any statistical significant differences? The 24-month data was said to be similar but are not presented. Were there any statistical differences between 24 and 72 months? A statistical analysis comparing 72 month outcomes with those at 24 months has been performed and provided in the results section and in Table 5.

Reviewer #2:

- This is not a systematic review, and is not Level one evidence. This is an original study that presents long term data derived from two separate FDA IDE trials investigating the LT CAGE device with rhBMP-2/ACS for ALIF. One study was a RCT and the other was a prospective cohort. Based on my review and the per cent follow up, I would consider this Level III evidence. It does, however, provide useful long-term data. See above response to Reviewer 1 presenting rational for Level II.

- Fusion Analysis: Please document what plain films were taken. Were the XRs and CTs reviewed independently, and by whom (radiologist or spine surgeon)? This has been added in the radiographic section of the methods.

ODI

- Page 10, Line 12: ODI scores for which group, and what were the values? Numeric values are not presented in the figure. Page 10, Line 14: Were these results statistically significant? Page 10, Lines 11-19: This section should be rewritten, or a table should be included, that clearly denotes numeric values along with the appropriate statistical analysis. As written, it is too vague. The results section has been rewritten to present the clinical outcomes for the open and lap groups along with statistical data. A single Table that gives numerical values for ODI, SF-36 PCS, and back and leg pain scores has been included, and the corresponding figures have been deleted. Comparison of the open and lap groups has been removed from the results section and a portion of the discussion is devoted to this comparison. This is also in line with additional comments from this and other reviewers.

BACK PAIN

- Page 10, Lines 21-22: To which group are you referring to, the open or lap? This has been addressed as described in the ODI question above.

- Pages 10 and 11: Again, as in the above comments on the ODI section, the data should be presented numerically for all groups, either in text or table format, along with the statistical results. Same.

LEG PAIN

- Refer to comments on ODI and BACK PAIN, as they apply here as well. Same

RADIOGRAPHIC OUTCOMES

- Page 12, Lines 4-9: Please provide the per cent follow-up for the radiographic analysis. Also, were both plain films AND CT's obtained at terminal follow-up as implied in the methods section? This should be clear to the reader. Added to results (89%, 130/146)and methods (criteria to assess fusion, also referenced open and lap 24 month studies)

SECOND SURGERY FAILURES

- Page 12, Line 12 - Page 12, Line 3: The precise reasons for the "early" and "late" secondary surgeries need to be documented. Of particular interest to me would be the secondary surgery for pseudoarthrosis, and its final radiographic result (i.e. fusion or no fusion). An important point for the reader would be to provide information that would indicate the best method for treatment of pseudoarthrosis following LT cage fusion. What were the clinical results of these failures and subsequent revision? It is far too vague as written, and one can not discern any useful information about this important outcome measure. Additional information on second surgery failures has been provided in the results section. Between 2 and 6 years, there were 2 patients who had a second surgery because of a suspected nonunion. Both of these patients received supplemental fixation. After a patient was classified as a second surgery failure, they were not carried forward in the database. Therefore, it is not known what the result of the 2nd surgery was on a patient's clinical outcomes.

- Please define "pending non-union"? This is defined as a patient who has a suspected pseudarthrosis. The term to describe a pending non-union has been changed to suspected nonunion in the results section.

- Also, were the patients that had secondary surgery included in the fusion analysis. I presume they were not, but this should be clarified. Patients who had a second surgery were classified as a fusion failure during the time point at which the second surgery occurred. Second surgery failures were not carried forward to additional time points for fusion assessment.

ADVERSE EVENTS

- Page 13, Lines 11-15: What about adverse events related to the LT cages? With this large initial cohort of patients, it is difficult to understand how there are no AE's. Why then would implant migration be listed as a reason for reoperation? This needs to be clarified. Given the evidence already published, one would expect that there would be no identifiable AE's with the use of BMP/ACS. Additional information related to AEs has been added to this section of the manuscript and Table 7 also provides additional information on this topic.

Reviewer #3:

The authors followed patients with degenerative disc disease who were previously enrolled in clinical trials to study the efficacy of interbody fusion cages and rhBMP-2. They describe outcomes at six years of follow-up in these patients. My detailed comments are as under:

Abstract

- This is essentially an observational cohort study of participants recruited from previous clinical trials on interbody fusion cages and rhBMP-2. The current study is interesting in that it describes long-term follow-up outcomes in this cohort but is not a comparison of two surgical techniques or treatments. This is not a systematic review of a Level-1 evidence study, as noted in the abstract, since that term is misleading. The level of evidence for an observational cohort study would be more appropriate for this manuscript. See above comments related to the level of evidence for this study.

Introduction

- The authors should present a more clear rationale for the current study in the introduction. Why did they follow-up patients for six years after two year outcomes had already been reported earlier? A clear rational describing the purpose and design of this study has been provided in the introduction and methods section. This study was an FDA regulated, prospective post approval study conducted to further validate the safety and efficacy of rhBMP-2/ACS and to provide long term data on fusion success and clinical outcomes in lumbar interbody fusion.

Methods

- Page 6, line 2: Bed rest is mentioned as non-operative treatment modality for low back pain. This is not the current standard of care. Enrollment for the open and laparoscopic studies occurred between 1997-1999, at which time the protocol defined bed rest as a nonoperative means of treatment.

- I suggest that the authors present a diagram which represents the case inclusion/exclusion schema with number of patients leading to their final patient population of 146 patients. A table showing the number of patients treated and patient accountability over the 6-year follow-up has been added to the paper.

- Please provide a reference for criteria used in this study to describe "fusion". Fusion criteria are defined in the methods section and a reference to the reports on the 2 year outcomes for these 2 IDE studies is also provided.

- Although this is clear by the end of the manuscript, it needs to be mentioned upfront that patients undergoing laproscopic surgery received interbody fusion cages with rhBMP-2. A statement clarifying this has been added to the methods.

Results

- The authors' mention that outcomes were measured at six weeks, and three, six, twelve, twenty-four, forty-eight, and seventy-two months. However, the authors' have mostly reported on outcomes at 72 months. From looking at their results, it seems that outcomes improve within the first year and then plateau. Can the authors comment on these observations? Data from preoperative to 72 months is presented in the tables. The results section focuses on the long term outcomes, as this is the focus of this paper and the 24 month data has been presented/described in detail elsewhere. This study shows that significant improvements in clinical outcomes are achieved by 6 weeks. Many of the outcomes plateau by around 12 months, as stated by this reviewer. This may be due to the initial benefits of the surgical procedure. Additionally, this may suggest the importance of a successful fusion in serving to provide long term support and contribute to the improvements achieved in clinical outcomes.

- The authors' have appropriately reported separately on outcomes of the open and laproscopic group. However, results on the comparison of these two groups gets confusing since this was not the objective of the study. To compare open versus laproscopic techniques, the authors have to go beyond simple ANOVA tests which do not control for potential confounders. In my judgement, results of the two techniques should be presented separately (as they are) but it is misleading to make statistical inferences about comparison of the two groups. The discussion presented towards the end of the manuscript on why the laproscopic group had shorter length of stay, better Oswestry Low Back Pain Disability Questionnaire scores, and improved scores on SF-36 is appropriate and helpful. But I would clearly state that the objective of this study is not to compare the outcomes of the two groups. The objective of the current study is described in both the introduction and methods section to clearly address the point raised in the above comment. Additionally the comparison between the open and laparoscopic groups has been removed from the results section, and a portion of the discussion is devoted to this comparison.

- On similar lines to my previous comment, it is confusing to present "combined" results of laproscopic and open surgery. It is difficult to draw inferences from the combined results when the authors have appropriately reported outcomes of laproscopic and open procedures separately. I suggest that the "combined" category be removed. The results section has been modified to focus on the outcomes seen in the open and laparoscopic groups. The combined group data is included in the tables and figures. The intent of combining the data sets is to present data on fusion rates and clinical outcomes with rhBMP-2/ACS and the LT Cage irrespective of surgical approach (open versus laparoscopic).

- In the results section (page 9, line 19), authors report on comparison of patient population in the current study with the entire patient population prior to twenty-four months. They have compared clinical outcomes between the groups and suggested that the populations were similar. I suggest that the authors,

instead, compare baseline demographic and clinical characteristics of patients included in the current study with only patients who were not included in the current study (and were in the base population for the two year study) to draw an inference that the two populations were similar. We have modified the results section to say that this subset of patients had the demographic characteristics and clinical outcomes prior to 24 months similar to those previously reported for the whole study, and have provided the references for this. Thus, the patient populations are similar. We did not present the comparisons of demographic data in this subset of patients with the rest, because it would make the flow of the presentation and discussion awkward and it would also digress from the main discussion of the long-term results.

Discussion

* Is it possible for the authors to elaborate more on what, for instance, a 9.3 points (page 10, line 23) improvement on the back pain scores means for the benefit of our clinical audience? This is an important issue that comes up frequently when dealing with scales. It is often difficult for readers to translate these scores in terms of functional/clinical improvement.

- Some of the discussion on previous studies in this area can be abbreviated. This section has been edited to address this point.

Tables/Figures

- I also suggest that the authors report actual baseline and follow-up scores for their outcome measures in both table 5 and the graphs. It is difficult to gauge what the change in scores means unless readers have a baseline score to look at. The mean values for the clinical outcomes have been summarized and are presented in a single table along with the standard deviation.

- There are too many graphs. The authors' can condense some of this data into a single table. The majority of the graphs reporting on the clinical outcomes have been removed and a single table providing ODI, SF-36 PCS, and back pain and leg pain scores has been included.

- Methodology Editor: I would simply add that the authors need to provide 95% CI when they present proportions. Additional statistical data has been added to the manuscript, table and figures. Standard deviations are presented along with mean values.

From: Hatcher, Brian, PhD.
Sent: Friday, May 23, 2008 02:38:34 PM
To: Ken Burkus [redacted]
CC: Carol Binns [redacted] ; Bearcroft, Julie, PhD
Subject: INFUSE 6 year data manuscript

Attachments: Table I.doc; Long-term outcomes of BMP-LT CAGE.resubmit.3.doc; Reviewers comments 05-13-2008.doc

Hello Dr. Burkus,
Please find attached some edits to the 6 year data paper. Most of the reviewer's comments have been addressed by updating the paper with the relevant data that Guorong's group pulled together. Others were addressed by adding comments to the letter responding to the reviewers. For example, there was a question raised about the potential impact of alcohol use. I am really not sure the basis for this question, but when you analyze the potential impact of alcohol use on fusion success and clinical outcomes, there is no effect. I don't know if it sufficient to address this point in the cover letter, or if the paper will have to be updated. One challenge is that the paper is currently too long, and adding more info will only lengthen it.

Also, in response to the request to shorten the paper, I inserted some comments where we may be able to trim the length. I also made some edits that shortened the paper but did not change any of the messages. Dr. Burkus, I think that this is an area where your guidance would be helpful. Right now the paper is about 3 pages over the suggested length.

The deadline for resubmission is June 12.
Please let me know if you have any questions about the added info, or if you need anything further from me.
Thanks for all of your hard work on this paper. Hopefully this is the last round!

Brian

Brian Hatcher, Ph.D.
Technology Manager, Biologics
Medtronic
Spinal and Biologics
1800 Pyramid Place
Memphis, TN 38132
O: [redacted]
M: [redacted]
F: [redacted]

Table I. Patient inclusion-exclusion criteria.

Inclusion Criteria	Exclusion Criteria
≥ 18 yrs old	Spinal conditions other than DDD
Single-level symptomatic DDD	DDD at disc space levels other than L4-L5 or L5-S1
≤ Grade 1 spondylolisthesis	Previous anterior fusion at involved level
Disabling back pain and/or leg pain	Obesity (>40% above ideal weight)
for greater than 6 months	Active bacterial infection
unresolved by nonoperative	Medical condition requiring medication that could
treatment	interfere with fusion (e.g. steroids or NSAIDS)
One additional confirmatory	
neuroradiographic study, such as	
MRI, CT-enhanced myelography, or	
discography	

DDD = degenerative disc disease; NSAID = nonsteroidal anti-inflammatory medication

1 Six Year Outcomes of Anterior Lumbar Interbody Fusion Using Interbody Fusion Cages
2 and Recombinant Human Bone Morphogenetic Protein - 2

Deleted: Long-Term

Deleted: RhBMP-2

Deleted: 5/23/20085/21/2008

ABSTRACT

Background: Twenty-four month outcomes have been reported in patients with degenerative lumbar disc disease who were treated with stand-alone anterior lumbar interbody fusion using dual tapered interbody fusion cages and recombinant human bone morphogenetic protein-2 (rhBMP-2). This report represents an update of the clinical and radiographic results of this treatment at six years.

Methods: Patients enrolled in two prospective, multicenter FDA-approved investigational device exemption (IDE) studies (n=277) were followed for 6 years to determine radiographic and clinical outcomes. One hundred forty-six patients with single-level degenerative disc disease with up to grade 1 spondylolisthesis were treated with an open or a laparoscopic surgical procedure and completed the six-year follow-up. The patients received recombinant human bone morphogenetic protein-2 on an absorbable collagen sponge with lumbar fusion cage implants. Outcomes were determined using well-established clinical outcome measurements (ODI, SF-36, back and leg pain scores) and radiographic assessments.

Results: At six years, patients treated with rhBMP-2 and stand-alone fusion cages showed high rates of fusion and low rates of additional surgery. Radiographic evidence of fusion was documented in 98.5% of patients, and the second-surgery rate between two and six years was 3.7%. Significant improvements in Oswestry Disability Index scores, SF-36® Health Survey Physical Component Summary scores, and back and leg pain scores were

Deleted: 5/23/20085/21/2008

achieved by six weeks in both the open and laparoscopic groups, and were sustained at six years. By six months, a higher percentage of patients were working than were working preoperatively (57.1% vs. 48.7%), and this improvement was sustained at six years.

Conclusions: The use of dual tapered threaded fusion cages and rhBMP-2 on an absorbable collagen sponge facilitates and maintains intervertebral spinal fusion, improved clinical outcomes, and reduction of pain after anterior lumbar interbody fusion in patients with degenerative lumbar disc disease.

Level of Evidence: Level III: Prospective cohort study with <80% follow-up

Deleted: 5/23/20085/21/2008

INTRODUCTION

Discogenic low back pain results, in part, from abnormal intersegmental load patterns and movement within a degenerative disc[1]. Clinically painful discs have been shown to display specific patterns of altered stresses in the anulus and vertebral end plates, reflecting abnormal loading[2]. Lumbar interbody fusion can eliminate abnormal stress patterns associated with degenerative disc disease and normalize stress distribution patterns[3,4]. Threaded interbody fusion cages stabilize the spinal motion segment and provide a mechanical environment that optimizes fusion[5]. New bone formation in and around the cages increases the contact area and decreases the magnitude of abnormal load in the fused segment.

Comment [h1]: Could this paragraph be shortened without deleting the message?

Recombinant human bone morphogenetic protein-2 (rhBMP-2) is an osteoinductive growth factor that stimulates pleuripotential cells to form bone. In animal and human studies, rhBMP-2 on an absorbable collagen sponge (rhBMP-2/ACS) has been shown to be capable of inducing new bone formation[6,7]. At twenty-four month follow up in randomized clinical trials, the use of rhBMP-2 as an iliac crest bone graft (ICBG) replacement has been shown to increase rates of interbody fusion in patients undergoing anterior lumbar interbody fusion (ALIF), and its use has been associated with decreased pain and improved clinical outcomes[8-10]. When used in combination with the LT-CAGE® Device, rhBMP-2/ACS resulted in significantly higher fusion rates than ICBG (94.4% vs. 89.4%; p = 0.022)[11]. Additional studies of rhBMP-2 on an absorbable collagen sponge in

Deleted: Various bone grafts have been used in an effort to enhance bone formation within the interverterbal disc space.

Deleted: (Medtronic Sofamor Danek, Memphis, TN)

Deleted: caused patients to achieve

Deleted: patients treated with

patients undergoing lumbar interbody fusion have shown similar rates of fusion success[8-10,12-19].

The current study was undertaken to validate the long-term safety and efficacy of using stand-alone interbody fusion cages and rhBMP-2/ACS as an iliac crest bone graft replacement. Patients in this FDA-regulated postapproval study were prospectively followed to determine fusion rates and clinical outcomes at six years, and to compare them with outcomes at two years[9,10].

MATERIALS AND METHODS

Two prospective, multicenter FDA-approved investigational device exemption (IDE) studies of patients undergoing treatment for single-level lumbar degenerative disc disease were conducted, utilizing a similar fusion technique through two different surgical approaches[9,20]. All patients were entered into these studies between 1997 and 1999 and were treated with INFUSE® Bone Graft and the LT-CAGE® Device (Medtronic Sofamor Danek, Memphis, TN). These studies used the identical inclusion-exclusion criteria (Table I); however, the laparoscopic cohort was a nonrandomized, single-arm study whereas the patients in the open study were randomized to receive either rhBMP-2/ACS or ICBG. The two studies were conducted to evaluate the efficacy of rhBMP-2/ACS as a replacement for ICBG and to support PMA approval, and were not designed to compare the open and laparoscopic surgical approaches directly. In this prospective study, patients were followed for six years to determine their long-term radiographic and clinical

Deleted: 5/23/20085/21/2008

Deleted: In both the open and laparoscopic IDE trials were followed prospectively

Deleted: the

Deleted: found

Deleted: recombinant human bone morphogenetic protein on an absorbable collagen sponge (

Deleted:)

Deleted: iliac crest bone graft (

Deleted:)

Deleted: enrolled in the open and laparoscopic studies

outcomes. Internal review board (IRB) approval was completed, and informed consent was obtained for all patients enrolled in the follow-up studies.

Patient Follow-Up

There were 277 total patients enrolled in the initial FDA IDE studies (143 in the open- and 134 in the laparoscopic-surgery arms). Of the thirty-one initial sites, twenty-three elected to participate in the long-term follow-up. As a result of second surgery failures and nonparticipating sites, fifty-five patients were excluded from this study leaving a total of 222 patients who were eligible for the FDA IDE postapproval follow-up assessments (109 in the open- and 110 in the laparoscopic-surgery arms). One hundred forty-six patients completed the seventy-two-month follow-up assessments (Table II). This subgroup of patients was examined to determine the clinical outcome measures and fusion status at each time point.

Surgical Procedures

Patients underwent an ALIF procedure using either an open[9] or a laparoscopic approach[20], and had two LT-CAGE Devices implanted at either the L4-L5 or L5-S1 lumbar interspace.

rhBMP-2/ACS was used exclusively as an ICBG replacement[9,20]. The rhBMP-2 was reconstituted to a concentration of 1.5 mg/mL and bound to the ACS for a minimum of fifteen minutes, which resulted in 95% of the protein being bound to the sponge[21]. The total dose of rhBMP-2 ranged from 4.2 to 8 mg and was determined by matching the volume of the prepared collagen sponge to the internal volume of the fusion cage.

Deleted: 5/23/20085/21/2008

Deleted: These two studies were conducted to evaluate the efficacy of rhBMP-2/ACS as a replacement for ICBG and to support PMA approval. They were not designed to compare the open and laparoscopic surgical approaches directly.

Deleted: at all study sites

Deleted: ***Inclusion-Exclusion Criteria*** . At the time of surgery, all patients were between the ages of 19 and 70 years and had symptomatic degenerative disc disease at the L4-L5 or L5-S1 levels (Table I). All had had low back pain for at least six months before their surgery that was recalcitrant to nonoperative treatment modalities, such as physical therapy, bed rest, and anti-inflammatory medications. Patients were included in the study if their plain radiographic findings documented single-level disc disease, and they had undergone at least one additional confirmatory neuroradiographic study, such as MRI, CT-enhanced myelography, or discography. All patients were considered candidates for a single-level stand-alone anterior lumbar interbody fusion (ALIF). Patients were excluded from the study if they had spinal conditions other than single-level symptomatic degenerative disc disease or greater than Grade 1 spondylolisthesis. Other exclusion criteria were symptomatic disc disease at a level other than the L4-L5 or L5-S1, obesity (more than 40% above ideal body weight), or a medical condition that required medication, such as steroids or [11]

Deleted: in the open (143 patients) and laparoscopic (134 patients) groups

Deleted: from the preoperative examination to the seventy-two month follow-up examination after surgery

Deleted: .

Deleted: In the open group, transperitoneal or retroperitoneal approaches to the lumbosacral spine were used; in the laparoscopic group, all approaches were transperitoneal [21]

Deleted:

Deleted: anteriorly

Deleted: RhBMP-2 on the absorbable collagen sponge

Deleted: No autogenous grafts and no local host-bone reamings were used.

Deleted: 5/23/2008 5/21/2008

The results from the studies using the two surgical approaches were pooled and analyzed independently to better define the effects of surgical approach in surgical parameters, hospital stay, and the long-term clinical and radiographic outcomes.

Clinical Outcome Measures

Clinical outcome measures, the Oswestry Disability Index (ODI)[22], the MOS 36-item Short-Form health survey (SF-36) questionnaire[23,24], back and leg pain scores, and return-to-work status, were self administered preoperatively and at six weeks, three, six, twelve, twenty-four, forty-eight, and seventy-two months. Back and leg pain scores were determined using a 20-point scale (10 points frequency and 10 points intensity). Although it is difficult to draw an exact correlation between functional improvement and quantitative changes in a pain score, the scale is designed such that a reduction in the pain score by half corresponds to a patient's experiencing half as much pain.

Radiographic Assessment

Radiographs (lateral, anteroposterior, and flexion/extension) and thin cut computed tomography scans with sagittal and coronal reconstructions were used to assess the presence of continuous trabecular bone formation between the vertebral bodies and to evaluate fusion[9,10]. Two independent blinded radiologists interpreted radiographs and CT scans to assess fusion, with a third radiologist available for adjudication. Fusion was defined as bridging bone connecting the adjacent vertebral bodies either through the implants or around the implants, less than 5° of angular motion, less than or equal to 3 mm of translation, and an

Deleted: 5/23/20083/21/2008

absence of radiolucent lines around more than 50% of either implant. Second surgery failures were classified as a failed fusion[9]. Fusion was assessed at six, twelve, twenty-four, forty-eight, and seventy-two months, and was considered successful only if all criteria were achieved.

Additional Surgical Procedures

Secondary surgical procedures performed subsequent to the index operation were classified as revisions, removals, supplemental fixations, or reoperations. Second surgeries that occurred as a result of adjacent level disease, but involved the index level, were classified as second surgery failures. A survivorship analysis was used to determine the percentage of patients who were classified as second surgery failures, taking into account all available patients at each follow-up time point.

Adverse Events

Adverse events were studied and classified as to their severity and relationship with the implants and with surgical procedures.

Statistical Analysis

For assessing the statistical significance of postoperative improvement in outcome scores from preoperative values within each treatment group, a paired *t* test was used. For statistical comparisons of demographic differences between the open and laparoscopic treatment groups, analysis of variance (ANOVA) was used for continuous variables, and Fisher's exact test was used for categorical data.

Deleted: 5/23/20085/21/2008

RESULTS

Patient Follow-Up

One hundred forty-six patients (68 in the laparoscopic group and 78 in the open group) completed the six-year follow-up. The overall follow-up rate was 52.7% (146/277), and the follow-up rate for available patients at six years was 65.8% (146/222). This subset of patients had demographic characteristics and clinical outcomes prior to twenty-four months similar to those previously reported for the entire patient population[9,10].

Demographic data were compiled for the patients included in the analysis (Table III). The open and laparoscopic surgical groups were not randomized relative to each other; however, the patients' demographic characteristics and prognostic factors in these two groups were similar except for the patient's sex and alcohol use.

Surgical Data

The laparoscopic group spent an average of eighteen minutes longer under anesthesia, lost an average of 7.3 mL more blood, and left the hospital an average of 1.7 days earlier than the open group (Table IV).

Deleted: Surgical, hospitalization, and clinical outcomes were analyzed for each surgical technique, and the outcomes were combined.

Deleted: and

Deleted: However, the laparoscopic group left the hospital an average of 1.7 days earlier than the open group.

Clinical Outcomes

Oswestry Disability Index

By six weeks, ODI scores improved significantly from preoperative scores in both groups and in their combined data, and these improvements were maintained at six years ($p<0.001$, Table V and Fig. 1). For the open group, ODI scores improved an average of 32.8 points and 27.7 points at forty-eight and

Deleted: 5/23/20085/21/2008

seventy-two months, respectively, from a preoperative score of 53.8. For the laparoscopic group, ODI scores improved an average of 34.4 points and 34.3 points at forty-eight and seventy-two months, respectively, from a preoperative score of 49.8. These improvements were similar to those seen at twenty-four months (31.0 points and 32.6 points for the open and laparoscopic groups, respectively).

Back Pain

By six weeks, back pain scores improved significantly from preoperative values in both groups and in their combined data, and these improvements were maintained at six years ($p<0.001$, Table V). For the open group, back pain scores improved an average of 7.7 points and 6.9 points at forty-eight and seventy-two months, respectively, from a preoperative score of 15.3. For the laparoscopic group, back pain scores improved an average of 10.6 points and 10.2 points at forty-eight and seventy-two months, respectively, from a preoperative score of 15.6. These improvements were similar to those seen at twenty-four months (8.7 points and 10.1 points for the open and laparoscopic groups, respectively).

Deleted: Back and leg pain scores are scored on a 20-point scale, which comprises an intensity component (0-10 points) and frequency component (0-10 points). Although it is difficult to draw an exact correlation between functional improvement and quantitative changes in a pain score, the scale is designed such that a reduction in the pain score by half corresponds to a patient's experiencing half as much pain.

Leg Pain

By six weeks, leg pain scores improved significantly from preoperative values in both groups and in their combined data, and these improvements were maintained at six years ($p<0.001$, Table V). For the open group, leg pain scores improved an average of 7.0 points and 6.8 points at forty-eight and seventy-two months, respectively, from a preoperative score of 13.4. For the laparoscopic group, leg pain scores improved an average of 5.8 points and 6.6 points at forty-

Deleted: 5/23/20085/21/2008

eight and seventy-two months, respectively, from a preoperative score of 9.6. These improvements were similar to those seen at twenty-four months (7.3 points and 5.2 points for the open and laparoscopic groups, respectively).

SF-36

By six weeks, SF-36 PCS scores improved significantly in both groups from preoperative scores, and these improvements were maintained at six years ($p<0.001$, Table V). For the open group, SF-36 PCS scores improved an average of 15.3 points and 12.4 points at forty-eight and seventy-two months, respectively, from a preoperative score of 27.1. For the laparoscopic group, SF-36 PCS scores improved an average of 19.1 points and 17.8 points at forty-eight and seventy-two months, respectively, from a preoperative score of 28.7. These improvements were similar to those seen at twenty-four months (16.3 points and 17.5 points for the open and laparoscopic groups, respectively). Additional SF-36 outcomes are presented in Table VI.

Radiographic Outcomes

At seventy-two months, 130 patients had complete radiographic follow-up examinations (89.0% of available patients (130/146), and 46.9% of all patients enrolled in both the open and laparoscopic groups (130/277); Fig. 2 A-D). At forty-eight and seventy-two months, 97.9% (92/94) and 98.5% (128/130) of patients had radiographic evidence of fusion (Fig. 3). The high rates of fusion seen at these later time points were similar to the rates of arthrodesis seen at six,

Deleted: For both the open and laparoscopic groups, all SF-36 outcomes except for general health perception and role emotional improved significantly from the preoperative values at seventy-two months ($p<0.001$, Table VI). All outcomes in the laparoscopic group were maintained between twenty-four and seventy-two months ($p>0.05$); however certain outcomes in the open group declined slightly between twenty-four and seventy-two months ($p<0.05$, Table VI).

Deleted: (89.0%, 130/146)

Deleted: (

 Deleted: 5/23/20085/21/2008

twelve, and twenty-four months. Fusion rates were similar between the open and laparoscopic groups.

Second Surgery Failures

There were a total of twenty-five second surgery failures over the six-year follow-up period: sixteen in the open group and nine in the laparoscopic group. There were twenty-three supplemental fixations, one removal, and one revision. Reasons for second surgeries (implant positioning, migration or loosening, nonunion, suspected nonunion, subsidence, stenosis, radiculopathy, adjacent segment degeneration, and post laminectomy syndrome) were reported by the enrolling surgeon. Second surgery failures occurred between five days and sixty-two months after surgery.

Adjusting for the patients available at each follow-up interval by a time-to-event analysis, the overall second surgery failure rate was 10.4% (13.7% in the open group and 7.1% in the laparoscopic group) (Fig. 4). Eighteen of the twenty-five second surgeries occurred before two years, and the second surgery failure rate during this time period was 6.7% for the combined group (6.4% open and 7.1% laparoscopic)[9,10]. The remaining seven second surgeries occurred between two and six years, and the rate of second surgery failure for the combined group during this time was 3.7% (7.3% open and 0% laparoscopic). All seven of the failures were supplemental fixations, and investigators reported suspected nonunion (N = 2), back pain (N = 2), stenosis (N = 2) and post laminectomy syndrome (N = 1) as the causes for reoperation. Three of the second surgeries

Deleted: 5/23/2008 5/21/2008

involved only the index level, and the remaining four included both the index and adjacent level.

Return-to-Work Status

At forty-eight and seventy-two months, more patients were working than were working before surgery (69.2%; 72/104 and 68.1%; 94/138 at forty-eight and seventy-two months, respectively, compared with 52.1% preoperatively). The percentage of patients working at the later time points was similar to that at twenty-four months (70.3%) (Fig. 5). By six months, approximately 90% of the patients who were working preoperatively had returned to work, and this rate was maintained though the seventy-two-month time point.

Adverse Events

Relevant adverse events are shown in Table VII, and all adverse events within these categories occurred prior to two-year follow-up. Anatomical/technical difficulty was observed to occur during the operative period and only in the laparoscopic surgical group. Seven of the nine events resulted in a conversion to an open anterior (N = 5) or instrumented posterolateral (N = 2) fusion procedure. Subsidence occurred in seven patients, with all events occurring within the first six months. Of the twenty-four patients listed in Table VII, seven patients had a second surgical procedure.

Comment [h2]: Most of the text deleted from this section is presented in Table VII.

Deleted: included anatomical/technical difficulty, malpositioned implants, implant displacement/loosening, and subsidence (

Deleted:)

Deleted: . A

Deleted: , and all nine events occurred during the operative period

Deleted: se

Deleted: (six open and one laparoscopic)

DISCUSSION

This study represents the longest follow-up, to date, of patients undergoing spine fusion with INFUSE Bone Graft[9-20]. In patients with six years of

Deleted: Results from prospective studies of the LT-CAGE Device have shown a trend toward more rapid fusion with INFUSE Bone Graft and improved clinical outcomes when compared with patients who received autograft ICBG[1]. These improved outcomes are related, in part, to the successful combination of the surgical approach, the advanced cage designs, the avoidance of bone graft harvesting morbidity, and the high rate of successful interbody fusion.

Deleted: 5/23/20085/21/2008

follow-up, observed radiographic fusion rates were high, rates of second surgery were low, and improvements in clinical outcomes were maintained.

Other studies have reported the long-term radiographic and clinical results of lumbar interbody fusion[25-30]. Kuslich et al. reported four-year results from a study enrolling 947 patients who received Bagby and Kuslich (BAK) cages and ICBG[28]. However, only 20.7% (196/947) of patients completed the four-year follow-up. Fusion success allowed for up to 7° of angulation on flexion-extension films, and did not include CT scans. At four years, the authors reported a fusion success of 98%, a repeat surgery rate of 8.7%, and maintenance of pain scores.

Comment [h3]: We may be able to cut down on the length by removing the description of how fusion was defined in these studies. I am hesitant to delete this though, as this may be part of the reason these fusion rates are as high as they are.

Deleted: n overall

Deleted: and

Deleted: Pain scores were maintained out to four years.

In a similar study, investigators evaluated clinical and radiographic outcomes following ALIF with stand-alone BAK cages implanted by a single author[28]. Patients underwent single-level (n = 40) or two-level (n = 6) ALIF with BAK cages and autograft, allograft, or both. Thirty-three of forty-six patients (71.7%) reached a mean follow-up of fifty-five months. The authors reported an overall nonunion rate of 30% and a revision rate of 22%. Mean ODI score at final follow-up was 41, with 42% of patients having an ODI less than or equal to 40.

Deleted: a combination of

Deleted: (range, thirty-six to sixty-five months)

Deleted: only

Brantigan and co-workers also investigated the long-term results of instrumented posterior lumbar interbody fusion (PLIF) [26]. The initial study enrolled 110 patients with degenerative disc disease; thirty-three patients completed the ten-year follow-up (30%). Radiographic evidence of fusion, as defined by bridging bone and the absence of radiolucencies was reported in 96.7% of the patients at ten years. At two years, elective removal of pedicle screws indicated that 90% (104/115) of the examined levels were fused.

Deleted: at six centers. T

Deleted: selected from two centers

Deleted: 5/23/20085/21/2008

Deleted: Clinical outcomes were determined using a twenty-point Prolo scale.

Preoperatively, 76% of patients had a rating of good or fair, using a twenty-point Prolo scale. At ten years, 87.8% (29/33) of patients had a rating of excellent, good or fair and achieved clinical success. In our study, 79% (109/138) of patients treated with INFUSE Bone Graft had an ODI improvement of greater than fifteen points at six years.

Deleted: compared

Deleted: from the early '90s with those of the late '90s in a study involving

Martin et al. assessed reoperation rates in approximately 25,000 patients undergoing primary lumbar surgery[31]. For patients whose primary procedure was a fusion (19.1%), these authors found a general overall reoperation rate of 14% at four years, and for patients whose primary diagnosis was herniated disc or degenerative disc disease (90.9%), the reoperation rate was approximately 15%. For patients treated with INFUSE Bone Graft and the LT CAGE Device, the secondary surgery failure rate of 9% at four years and 10% at six years compares favorably with overall failure rates cited for the 1990s.

Comment [b4]: This section was requested on the 1st review, so I'm not sure that we can cut this down much.

An observation in the current study was that patients treated by the laparoscopic surgical technique trended to have shortened hospital stay, better Oswestry Low Back Pain Disability Index scores, improved scores on the SF-36 Health Survey, reduced low back pain, and fewer reoperations when compared with the group treated with open surgery at six years ($p>0.05$). There are potential benefits of the laparoscopic surgical approach, such as less muscle damage and tissue retraction, shorter hospital stay, and a quicker return to normal activities, that may have accounted for or contributed to this trend. This study was not designed to compare the open and laparoscopic surgical approaches, however, and there are likely a number of confounding factors that

Deleted: 5/23/20085/21/2008

may have contributed to this observation. Patients in the open and laparoscopic surgery groups were not randomized to each other and were enrolled in two separate studies. There were preoperative differences in patient demographics, such as sex and alcohol use. Additionally, more patients in the open group had substantial changes in their ODI scores between twenty-four and seventy-two months, which may have contributed bias (eighteen patients in the open group had an ODI increase of 20 points or more, compared with only one patient in the laparoscopic group). Importantly, the mean scores for both groups in Oswestry pain scores, PCS scores, and back and leg pain scores were significantly improved from preoperative measurements and were maintained between the twenty-four- and seventy-two-month follow-up period. Whether the difference in these outcomes between the open and laparoscopic groups is of clinical significance is a point of debate, as the minimally important clinical difference reported in the literature is variable[22].

Deleted: Review of case report forms for patients in the open group revealed the occurrence of falls, motor vehicle accidents, adjacent level disease, and a high percentage of patients with a BMI of greater than twenty-five, which may have contributed to the slight differences in clinical outcomes.

Weaknesses of this study include an overall follow-up rate of 52.7%, which has the potential to introduce bias and impact the long term results. Additionally, the study did not follow ICBG patients, and therefore, a comparison to the control can not be performed.

A comparison of three outcome parameters, fusion status, operative time, and hospital stay, show an improvement in care for treatment of degenerative disc disease in the lumbar spine with an advancement in therapy options[5]. Additionally, twenty-four month data comparing INFUSE Bone Graft with ICBG has shown superior rates of fusion and clinical outcomes in patients treated with

Comment [h5]: This may be a paragraph that could be shortened or perhaps removed.

rhBMP-2[11]. The improvement in functional outcomes is maintained at six years after treatment with rhBMP-2 and is also reflected in the high rates of employment in both the open and laparoscopic groups. In particular, the high rate of segmental arthrodesis may serve to provide long-term maintenance of these significant improvements in clinical outcomes[32].

The use of rhBMP-2 on an absorbable collagen-soaked sponge is an effective method of facilitating anterior intervertebral spinal fusion using a stand-alone interbody fusion device. In this long-term study, treatment with INFUSE Bone Graft and threaded titanium cages was shown to lead to high rates of fusion that were maintained at six years after surgery, and significant improvements in clinical outcome measures were maintained. These results further support the use of rhBMP-2 as a replacement for autograft in lumbar interbody fusion.

Deleted: 5/23/20085/21/2008

REFERENCES

1. Adams MA, Roughley PJ. What is intervertebral disc degeneration, and what causes it? Spine. 2006;31:2151-61.
2. Videman T, Nurminen M. The occurrence of anular tears and their relation to lifetime back pain history: a cadaveric study using barium sulfate discography. Spine. 2004;29:2668-76.
3. Kumar N, Judith MR, Kumar A, Mishra V, Robert MC. Analysis of stress distribution in lumbar interbody fusion. Spine. 2005;30:1731-5.
4. Palm WJ 4th, Rosenberg WS, Keaveny TM. Load transfer mechanisms in cylindrical interbody cage constructs. Spine. 2002;27:2101-7.
5. Burkus JK. Stand-alone anterior lumbar interbody fusion constructs: effect of interbody design, bone graft and bone morphogenetic protein on clinical and radiographic outcomes. In: Lewandrowski K, Yaszemski MJ, White AA, Trantolo DJ, Wise, DL, eds. *Advances in Spinal Fusion: Clinical Applications of Basic Science, Molecular Biology, Biomechanics, and Engineering.* New York, NY: Marcel Dekker; 2003:69-84.
6. Boden SD, Martin GJ Jr, Horton WC, Truss TL, Sandhu HS. Laparoscopic anterior spinal arthrodesis with rhBMP-2 in a titanium interbody threaded cage. J Spinal Disord. 1998;11:95-101.
7. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine. 1999;24:629-36.

8. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine. 2000;25:376-81.

9. Burkus JK, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. J Spinal Disord Tech. 2002;15:337-49.

10. Burkus JK, Sandhu HS, Gornet MF, Longley MC. Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery. J Bone Joint Surg Am. 2005;87:1205-12.

11. Burkus JK, Heim SE, Gornet MF, Zdeblick TA. Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-CAGE lumbar tapered fusion device. J Spinal Disord Tech. 2003;16:113-22.

12. Anand N, Hamilton JF, Perri B, Miraliakbar H, Goldstein T. Cantilever TLIF with structural allograft and RhBMP2 for correction and maintenance of segmental sagittal lordosis: long-term clinical, radiographic, and functional outcome. Spine. 2006;31:E748-53.

13. Kuklo TR, Rosner MK, Polly DW Jr. Computerized tomography evaluation of a resorbable implant after transforaminal lumbar interbody fusion. Neurosurg Focus. 2004;16:E10.

14. Lanman TH, Hopkins TJ. Lumbar interbody fusion after treatment with recombinant human bone morphogenetic protein-2 added to poly(L-lactide-co-D,L-lactide) bioresorbable implants. Neurosurg Focus. 2004;16:E9.

15. Mummaneni PV, Pan J, Haid RW, Rodts GE. Contribution of recombinant human bone morphogenetic protein-2 to the rapid creation of interbody fusion when used in transforaminal lumbar interbody fusion: a preliminary report. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2004. J Neurosurg Spine. 2004;1:19-23.

16. Potter BK, Freedman BA, Verwiebe EG, Hall JM, Polly DW Jr, Kuklo TR. Transforaminal lumbar interbody fusion: clinical and radiographic results and complications in 100 consecutive patients. J Spinal Disord Tech. 2005;18:337-46.

17. Schwender JD, Holly LT, Rouben DP, Foley KT. Minimally invasive transforaminal lumbar interbody fusion (TLIF): technical feasibility and initial results. J Spinal Disord Tech. 2005;18 SuppIS1-6.

18. Slosar PJ, Josey R, Reynolds J. Accelerating lumbar fusions by combining rhBMP-2 with allograft bone: a prospective analysis of interbody fusion rates and clinical outcomes. Spine J. 2007;7:301-7.

19. Villavicencio AT, Burneikiene S, Nelson EL, Bulsara KR, Favors M, Thramann J. Safety of transforaminal lumbar interbody fusion and intervertebral recombinant human bone morphogenetic protein-2. J Neurosurg Spine. 2005;3:436-43.

20. Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2: a prospective study of clinical and radiographic outcomes. Spine. 2001;26:2751-6.

Deleted: 5/23/20085/21/2008

21. Hsu HP, Zanella JM, Peckham SM, Spector M. Comparing ectopic bone growth induced by rhBMP-2 on an absorbable collagen sponge in rat and rabbit models. J Orthop Res. 2006;24:1660-9.

22. Fairbank JC, Couper J, Davies JB, O'Brien JP, The Oswestry low back pain disability questionnaire. Physiotherapy. 1980;66:271-3.

23. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994; 32:40-66.

24. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473-83.

25. Bagby G. The Bagby and Kuslich (BAK) method of lumbar interbody fusion. Spine. 1999;24:1857.

26. Brantigan JW, Neidre A, Toohey JS. The Lumbar I/F Cage for posterior lumbar interbody fusion with the variable screw placement system: 10-year results of a Food and Drug Administration clinical trial. Spine J. 2004; 4:681-8.

27. Brantigan JW, Steffee AD, Lewis ML, Quinn LM, Persenaire JM. Lumbar interbody fusion using the Brantigan I/F cage for posterior lumbar interbody fusion and the variable pedicle screw placement system: two-year results from a Food and Drug Administration investigational device exemption clinical trial. Spine. 2000;25:1437-46.

28. Button G, Gupta M, Barrett C, Cammack P, Benson D. Three- to six-year follow-up of stand-alone BAK cages implanted by a single surgeon. Spine J. 2005;5:155-60.

29. Kuslich SD, Danielson G, Dowdle JD, Sherman J, Fredrickson B, Yuan H, Griffith SL. Four-year follow-up results of lumbar spine arthrodesis using the Bagby and Kuslich lumbar fusion cage. Spine. 2000;25:2656-62.

30. Kuslich SD, Ulstrom CL, Griffith SL, Ahern JW, Dowdle JD. The Bagby and Kuslich method of lumbar interbody fusion. History, techniques, and 2-year follow-up results of a United States prospective, multicenter trial. Spine. 1998;23:1267-78; discussion 1279.

31. Martin BI, Mirza SK, Comstock BA, Gray DT, Kreuter W, Deyo RA. Are lumbar spine reoperation rates falling with greater use of fusion surgery and new surgical technology? Spine. 2007;32:2119-26.

32. Kornblum MB, Fischgrund JS, Herkowitz HN, Abraham DA, Berkower DL, Ditkoff JS. Degenerative lumbar spondylolisthesis with spinal stenosis: a prospective long-term study comparing fusion and pseudarthrosis. Spine. 2004;29:726-33; discussion 733-4.

Deleted: 5/23/20085/21/2008

LEGEND OF FIGURES

Figure 1: Comparison of improvement in Oswestry Disability Index scores.

Figure 2: A, Preoperative lateral radiograph in a study patient shows disc space narrowing at L5-S1, posterior radial osteophyte formation and retrolisthesis of L5 on S1 The L4-L5 disc has a normal height, physiologic segmental lordosis, and no radial osteophytes.

B, At six weeks after surgery, the lateral radiograph shows in this patient shows placement of the dual paired interbody fusion cages in the L5-S1 disc space. Physiologic disc space height and normal sagittal contours have been restored at L5-S1.

C, At seventy-two months, this lateral radiograph shows new bone formation spanning the L5-S1 disc space anterior to the cages. There has been no subsidence of the cages. Disc space height and sagittal contours have been maintained from those seen on earlier radiographic studies. The L4-L5 disc shows no radiographic evidence of adjacent segment degeneration.

D, At seventy-two months after surgery, this sagittal computed tomography scan shows continuous trabecular bone formation through the interbody fusion cage spanning the L5-S1 interspace.

Figure 3: Comparison of radiographic fusion success.

Figure 4: Comparison of second surgery failures.

Figure 5: Comparison of return-to-work status.

Page 6: [1] Deleted hatchb1 5/21/2008 4:21:00 PM

Inclusion-Exclusion Criteria

At the time of surgery, all patients were between the ages of 19 and 70 years and had symptomatic degenerative disc disease at the L4-L5 or L5-S1 levels (Table I). All had had low back pain for at least six months before their surgery that was recalcitrant to nonoperative treatment modalities, such as physical therapy, bed rest, and anti-inflammatory medications. Patients were included in the study if their plain radiographic findings documented single-level disc disease, and they had undergone at least one additional confirmatory neuroradiographic study, such as MRI, CT-enhanced myelography, or discography. All patients were considered candidates for a single-level stand-alone anterior lumbar interbody fusion (ALIF). Patients were excluded from the study if they had spinal conditions other than single-level symptomatic degenerative disc disease or greater than Grade 1 spondylolisthesis. Other exclusion criteria were symptomatic disc disease at a level other than the L4-L5 or L5-S1, obesity (more than 40% above ideal body weight), or a medical condition that required medication, such as steroids or nonsteroidal anti-inflammatory medications, that could interfere with fusion.

Page 6: [2] Deleted hatchb1 5/22/2008 3:35:00 PM

In the open group, transperitoneal or retroperitoneal approaches to the lumbosacral spine were used; in the laparoscopic group, all approaches were transperitoneal. Patients in both surgical groups

----- Original Message -----
From: "The Journal of Bone and Joint Surgery" [redacted]>
To: <jk[redacted]>
Sent: Tuesday, May 13, 2008 1:12 PM
Subject: Revise Manuscript

May 13 2008 1:09:12
RE: "Long-Term Outcomes of Anterior Lumbar Interbody Fusion Using Interbody Fusion Cages and rhBMP-2," number JBJS-D-07-01485R1

Dear Ken:

First of all, I want to thank you and your co-authors for the obviously considerable effort you have expended with regard to revision of your manuscript. Indeed, it is much improved, however, important concerns remain. Nonetheless, a decision has been made to provisionally accept your manuscript for publication provided you are able to adequately address the additional concerns which have been identified. Foremost are the concerns identified by Reviewer #1 with respect to the fact that you had a 46% drop out rate and you have no control group. Indeed, our statistician believed that these statistical analysis was appropriate, however, Reviewer #1's concerns need to be addressed at least through adequate discussion.

In addition, I believe your manuscript is much too long for the message it conveys. A typical manuscript is ten pages in length with a one page Introduction and three pages each of Materials and Methods, Results, and Discussion. Please make every attempt to make your manuscript much more concise and get as close as possible to the above recommendations. Lastly, in your title, you should spell out what you mean by rhBMP-2. I believe you are referring to recombinant bone morphogenic protein.

I believe all these concerns are relatively straightforward and should be readily addressable by you and your co-authors, hence I look forward to your prompt reply. Note that when your manuscript returns, I will be the only one reviewing it, and hence I anticipate a much quicker turn around. The due date for revision will be Jun 12 2008 12:00:00:000AM.

I certainly appreciate your cooperation in this important editorial process.

Sincerely yours,

Chuck

Charles R. Clark, MD
Deputy Editor for Adult Reconstruction and Spine

CRC/ps

Reviewer #1:
The authors present a revised manuscript of 72-month follow-up of a subset of 2 different study groups. Both were prospective though only one of the two had a control group. Several reviewers commented that this was not a level I study. One reviewer felt that it was a level III and the authors downgraded it to level II. This may be optimistic on their part. Given the lack of control group and a high percentage patients of lost to follow-up, a case could be made for as low as level IV. Only 53% of the original patients receiving the rhBMP were followed. This improves slightly to 66% if one considers only the "participating" centers (which could introduce bias). Even fewer patients (130) had radiographic follow-up. This reviewer still has reservations about the manuscript but if the editor disagrees I recommend that it by reviewed by the Journal's statistical consultant. The strength of the study is 6-year follow-up of a particular application of rhBMP-2. Weakness include lack of control group, only 53 % follow-up, and gaps in radiographic and other data points.

- Title, line 1: One can debate the definition of "long-term" or other qualitative designations. Change the title. Simply state "Six-year" or "72-months outcomes." Let the reader weigh the importance and relative length of the follow-up. Changed the title to read 6 years.

- Page 2, methods: Indicate the denominator, i.e. the total number of original patients receiving rhBMP and the number in the "participating" centers. The total number of patients enrolled in the open and lap groups was added to the abstract.

- Page 2, lines 14-15: This is a vague statement. The measures used to evaluate clinical outcomes have been added.

- Page 3, lines 1-2: Give the numbers. The number of patients working has been added.

- Page 3, line 9: Level IV or maybe level III (at best). Level III

- Page 10, line 2: Define alcohol use. What impact if any did this have? On the preoperative questionnaire, patients where asked whether or not they used alcohol. This was a Y/N question. Alcohol consumption was not captured at the post operative follow-up visits. A statistical analysis showed that alcohol use did not impact fusion success or clinical outcomes (Dr. Burkus and Carol, does this need to be added into the paper or is it sufficient to address it in a letter back to the editor?).

- Page 12, line 12-18: How often did the third radiologist adjudicate disagreements? Agreement between the 1st and second reviewers occurred 94.3% - 100% of the time (Carol, can this point be made in the Figure caption to help with the length restriction?).

- Page 15, line 22: Why is the denominator 138 rather than 146? In this study, there were 146 patients with outcome data at 72 months. These 146 patients did not necessarily have complete

outcome data for all measures assessed. Therefore, the denominator for the different outcome measures varies.

- Table 1: Is this table necessary? It seems to simply restate the information found in the methodology section. The section in the Methods discussing the inclusion exclusion criteria was deleted and this information is presented only in Table 1. This also helps address the length requirement raised by the editor.

Reviewer #2:
The revisions made greatly improved the strength of this manuscript.

- The in the radiographic outcomes section, the authors noted that "At seventy-two months, 130 (89.0%, 130/146) patients had complete radiographic follow-up examinations (Fig. 2 A-D). At forty-eight and seventy-two months, 97.9% 15 (92/94) and 98.5% (128/130) of patients had radiographic evidence of fusion (Fig. 3)." This represents follow-up of 130 of the original 222 patients, or 58% radiographic follow-up. This needs to be clear in the manuscript. Information about follow-up rates relative to available patients and total enrolled patients has been added to the results section.

- My only remaining concern is the designation as Level II Evidence. While the study design represents Level II Evidence, having only 65% f/u at 6 years requires a redesignation to Level III Evidence. This is a good study, and I understand that achieving 80% or more f/u at 6 years is extremely difficult. However, that does not change the fact that follow-up on ~76 patients, or ~35% of the original cohort, is unavailable. It is unclear what happened to this subset of patients. While I personally think this is a reliabe operation with very good outcomes, it is nonetheless important to emphasize the lack of follow-up in this subset and its potential implication on the conclusion the LT Cage fusion results in sustained and statistically significant improvements in clinical outcomes. The same emphasis should be brought out on the discussion of fusion rates. Changed to Level III. Weaknesses of the study have been added to the discussion.

Reviewer #3:
The authors have satisfactorily responded to my comments.

From: Hatcher, Brian, PhD.
Sent: Wednesday, October 8, 2008 03:12:59 PM
To: Carol Binns[redacted]; Ken Burkus[redacted]; Bearcroft, Julie, PhD
Subject: 6 year data paper

Attachments: Editor's Comments and Response 09-22-08.doc

Carol
Please find attached the remaining information needed to respond to JBJS regarding fusion and second surgeries. Most of this centers around a worst case scenario for fusion. Carrying forward all second surgery failures that were the result of a pseudo results in a fusion rate of 90.8%. Commentary on this type of analysis and the associated issues, as well as on the differences between second surgery failures and radiographic failures has been added. Some of the key points that will need to be added are pasted below for review. Dr. Burkus, are you ok with this?

Please let me know if you have any questions.
Brian

Radiographic Outcomes
At forty-eight and seventy-two months, 97.9% (92 of 94) and 98.5% (128 of 130) of patients included in this analysis had radiographic evidence of fusion (Fig. 3). The high rates of fusion seen at these later time points were similar to the rates of arthrodesis seen at six, twelve, and twenty-four months. Fusion rates were similar between the open and laparoscopic group

In an effort to determine a worst case scenario for fusion success, all second surgery failures due to pseudarthrosis were carried forward for the entire 277 patients enrolled in the IDE studies. This analysis introduces bias and results in artificially low fusion rates in this cohort, as all the failures regardless of participation in the post-approval study are carried forward. This report includes only the subset of patients with greater than 2 years of follow-up and thus fusion successes from non-participating patients/sites are not counted in the calculations. In this analysis, fusion rates at 48 and 72 months would be 88.5% (92/104) and 90.8% (128/141), respectfully.

Second Surgery Failures
In order to better determine the overall failure rate for the procedure, any second surgery that occurred during the 6 years of follow-up was reported. This included all 277 patients enrolled in the IDE studies, as well as the 146 who were followed out to 6 years. There were a total of twenty-five second surgery failures over the six-year follow-up period: sixteen in the open group and nine in the laparoscopic group…

Brian Hatcher, Ph.D.

Technology Manager, Biologics
Medtronic
Spinal and Biologics
1800 Pyramid Place
Memphis, TN 38132
O: [redacted]
M: [redacted]
F: [redacted]

----- Original Message -----
From: "The Journal of Bone and Joint Surgery" <[redacted]>
To: <[redacted]>
Sent: Wednesday, September 10, 2008 10:21 AM
Subject: Revise Manuscript

September 10, 2008 10:19:41

John Kenneth Burkus, MD

RE: "Six-Year Outcomes of Anterior Lumbar Interbody Arthrodesis Using Interbody Fusion Cages and Recombinant Human Bone Morphogenetic Protein-2,"
number JBJS-D-07-01485R5.

Dear Ken:

Thank you for your response to the previous concerns which had been identified. Indeed, you have responded to some of the concerns, but still issues remain particularly with regard to your fusion rate as well as providing the rationale which you presented in your reply letter regarding the fact that not all of the sites were involved in the six-year follow-up and this information needs to be presented in the text. The specifics of these concerns are included in the comments below.

The following concerns refer to the numbers I have placed in the right hand column of the partially edited copy of your manuscript. As always, your revised manuscript should be accompanied by a cover letter noting how you have addressed each of these concerns. Please note that no further decision has been made regarding the acceptance of your manuscript pending your satisfactory response to these concerns.

1) Please specify in your Abstract the number of patients with six-year radiographic follow-up.

One hundred forty-six patients completed the six-year follow-up, **and 130 patients had complete radiographic follow-up at six-years.**

2) Please provide the numbers which correspond to these percents in parentheses as previously requested.

Fusion after arthrodesis was documented at a rate of 98.5% **(128/130)** at six years. The second-surgery rate prior to two years was 6.7% **(n=18)**, and the rate from two years to six years was 3.7% **(n=7)**.

This statement in the abstract referred only to the open surgery group: "By six months, a higher percentage of patients were working than were working preoperatively (57.1% versus. 48.7%), and this improvement was sustained at six years."
It has been edited to reflect the entire patient population (open and laparoscopic groups), and include the number of patients:
"By six months, a higher percentage of patients were working than were working preoperatively (62.5%; 90/144 versus. 52.1%; 76/146), and this improvement was sustained at six years (68.1%; 94/138)."

Carol, in the results section update At forty-eight and seventy-two months, more patients were working than were working before surgery (69.2%; 72 of 104 and 68.1%; 94 of 138 at forty-eight and seventy-two months, respectively, compared with **52.1%; 76 of 146** preoperatively).

3) I, and Dr. Heckman, still believes that your data is misleading. Excluding secondary surgery failures artificially increases your fusion rate. If you insist upon describing your fusion rate at 98.5% you should also, at the very least, describe a worst care scenario in which the secondary surgery failures are included in your denominator. Indeed, any problem leading to failure should be included in a fusion rate, therefore, you should at the very least have a worst case scenario which would indeed show a lower fusion rate.

4) You need to include the information in the text as you provided in your reply letter, stating why all of the sites were not included in the six-year follow-up to prevent any misunderstanding on the part of the readers.

REPLACE

"There were 277 total patients enrolled in the initial FDA IDE studies: 143 in the open-surgery and 134 in the laparoscopic-surgery arms. Of the thirty-one initial sites, twenty-three elected to participate in the long-term follow-up. Additionally, patients who were classified as a second surgery failure (secondary lumbar surgical procedures performed subsequent to the index operation that involved the index level regardless of the radiographic findings) prior to two years were not assessed for clinical and radiographic outcomes in this long-term follow-up study. As a result of second surgery failures and nonparticipating sites, fifty-five patients were excluded from this study leaving a total of 222 patients who were eligible for the FDA IDE postapproval follow-up assessments (109 in the open- and 110 in the laparoscopic-surgery arms). One hundred forty-six patients completed the seventy-two-month follow-up assessments (Table I). This subgroup of patients was examined to determine the clinical outcome measures and fusion status at each time point."

WITH

"There were 277 total patients enrolled in thirty-one sites in the initial FDA IDE studies: 143 in the open-surgery and 134 in the laparoscopic-surgery arms. As a condition of market approval, the FDA requested that a post- approval study be conducted to obtain 6 years of postoperative data from a statistically justified number of patients. All investigational sites received protocols and were invited, but not required, to participate in the 6 year follow-up post-approval study. Of the thirty-one initial sites, twenty-three elected to participate in the long-term follow-up. Seven sites declined participation, and one site was not eligible for inclusion in the post-approval study. Additionally, patients who were classified as a second surgery failure (secondary lumbar surgical procedures performed subsequent to the index operation that involved the index level regardless of the radiographic findings) prior to two years were not followed out to 6 years and were excluded from this study.

As a result of second surgery failures prior to 2 years and nonparticipating sites, fifty-five patients were excluded from this

study, leaving 222 patients who were eligible for the FDA IDE postapproval follow-up assessments (109 in the open- and 110 in the laparoscopic-surgery arms). One hundred forty-six patients completed the seventy-two-month follow-up assessments, which exceeded the FDA required minimum of 119. A flow chart of patient accountability is shown in Table 1. This subgroup of patients was examined to determine the clinical outcome measures and fusion status at each time point, and to evaluate clinical and radiographic outcomes between two and six years."

5) Consistent with concern #3, if these are indeed "failed fusions" how could they possibly be excluded from the fusion rate? This is why I and Dr. Heckman believe your fusion rate is misleading and this must be corrected before we can publish this in The Journal.

Second surgery failures and fusion failures were defined as two separate outcome measures. Only those second surgery failures that were due to pseudarthrosis or suspected pseudarthrosis were classified as a fusion failure. This was not clearly defined in the methods, so this section has been updated to better explain this.

REPLACE:
"Secondary lumbar surgical procedures (second surgery failures) performed subsequent to the index operation regardless of the radiographic findings were classified as a failed fusion[4]."

WITH:
"Secondary lumbar surgical procedures performed subsequent to the index operation because of a suspected nonunion, regardless of the radiographic findings, were classified as second surgery failures and fusion failures[4]. Second surgeries performed for reasons other that pseudarthrosis were defined as second surgery failures only, as these reasons were independent of bone formation and fusion (e.g. adjacent segment degeneration)."

6) Once again, you need to present the worst case scenario analysis as described above.

The manuscript has been updated to include this. Additional text discussing the methods and an explanation of this analysis has also been added.
Carol - see notes below for manuscript updates.

7) Once again, you need to present the worst case scenario as describe above.

The manuscript has been updated to include this. Additional text discussing the methods and an explanation of this analysis has also been added.
Carol - see notes below for manuscript updates.

8) Please provide the number of patients who had this evaluation in each of the circled groups at each follow-up interval so that the reader clearly understands the number of patients who had a specific outcome measure at a specific interval.

See table below.

It is important that you present a clear and accurate report of your findings to the readers which is not misleading. Therefore, I certainly ask your patience and understanding in addressing these very important concerns.

I certainly appreciate your cooperation in this important editorial process. The due date for revision will be Oct 10 2008 12:00:00:000AM.

Sincerely yours,

Chuck

Charles R. Clark, MD
Deputy Editor for Adult Reconstruction and Spine

Second Surgery Info:
Methods:
Replace
"Secondary lumbar surgical procedures (second surgery failures) performed subsequent to the index operation regardless of the radiographic findings were classified as a failed fusion[4]."

With
"Secondary surgical procedures performed subsequent to the original operation because of a suspected nonunion, regardless of the radiographic findings, were classified as second surgery failures and fusion failures[4]. Second surgeries performed for reasons other than pseudarthrosis were defined as second surgery failures only, as these reasons were independent of bone formation and fusion.

Results:
Update radiographic outcomes and second surgery failure paragraphs:

Radiographic Outcomes
At forty-eight and seventy-two months, 97.9% (92 of 94) and 98.5% (128 of 130) of patients included in this analysis had radiographic evidence of fusion (Fig. 3). The high rates of fusion seen at these later time points were similar to the rates of arthrodesis seen at six, twelve, and twenty-four months. Fusion rates were similar between the open and laparoscopic group

In an effort to determine a worst case scenario for fusion success, all second surgery failures due to pseudarthrosis were carried forward for the entire 277 patients enrolled in the IDE studies. This analysis introduces bias and results in artificially low fusion rates in this cohort, as all the failures regardless of participation in the post-approval study are carried forward. This report includes only the subset of patients with greater than 2 years of follow-up and thus fusion successes from non-participating patients/sites are not counted in the calculations. In this analysis, fusion rates at 48 and 72 months would be 88.5% (92/104) and 90.8% (128/141), respectfully.

Second Surgery Failures
In order to better determine the overall failure rate for the procedure, any second surgery that occurred during the 6 years of follow-up was reported. This included all 277 patients enrolled in the IDE studies, as well as the 146 who were followed out to 6 years. There were a total of twenty-five second surgery failures over the six-year follow-up period: sixteen in the open group and nine in the laparoscopic group…

Discussion:
In our study, 79% of patients treated with INFUSE Bone Graft had an Oswestry Disability Index improvement of greater than fifteen points at six years. Radiographic fusion success at six years was 98.5% for the patients included in this analysis, and 90.8% in a worst case analysis. Over the 6 year follow-up, the second surgery failure rate for the procedure was 10.4%.

Table V: Clinical Outcomes Scores

Clinical Outcome Measure	Preoperative	1 yr	2 yr	4 yr	6 yr
ODI*†					
Open	53.8 (13.5)	22.7 (16.9)	22.8 (18.7)	20.6 (19.2)	25.8 (19.3)
	N=78	N=75	N=77	N=48	N=70
Laparoscopic	49.8 (10.4)	17.0 (17.7)	17.6 (20.1)	14.3 (18.2)	15.5 (18.9)
	N=68	N=66	N=61	N=55	N=68
Combined	52.0 (12.3)	20.1 (17.5)	20.5 (19.4)	17.2 (18.9)	20.7 (19.7)
	N=146	N=141	N=138	103	N=138
Back Pain*					
Open	15.3 (3.9)	7.0 (5.7)	6.6 (6.0)	7.4 (6.5)	8.4 (6.3)
	N=78	N=74	N=77	N=47	N=69
Laparoscopic	15.6 (3.6)	5.8 (5.8)	5.6 (6.1)	4.9 (5.6)	5.4 (5.9)
	N=68	N=66	N=61	N=55	N=68
Combined	15.4 (3.7)	6.4 (5.8)	6.1 (6.1)	6.0 (6.1)	6.9 (6.3)
	N=146	N=140	N=138	N=102	N=137
Leg Pain*					
Open	13.4 (5.0)	5.9 (6.2)	6.1 (6.2)	6.1 (6.3)	6.6 (6.4)
	N=78	N=74	N=77	N=47	N=69
Laparoscopic	9.6 (6.5)	4.2 (5.5)	4.4 (5.7)	3.5 (5.6)	3.1 (4.6)
	N=68	N=66	N=61	N=55	N=67
Combined	11.6 (6.0)	5.1 (5.9)	5.3 (6.0)	4.7 (6.0)	4.8 (5.9)
	N=146	N=140	N=138	N=102	N=136
SF-36 PCS*					

Open	27.1 (5.7)	42.6 (11.0)	43.5 (11.9)	41.9 (12.8)	39.7 (12.6)
	N=77	N=76	N=77	N=48	N=70
Laparoscopic	28.7 (6.1)	45.5 (11.4)	45.4 (12.3)	47.5 (11.9)	46.5 (11.6)
	N=68	N=66	N=60	N=55	N=68
Combined	27.9 (5.9)	44.0 (11.3)	44.4 (12.1)	44.9 (12.6)	43.1 (12.6)
	N=145	n=142	N=137	N=103	N=138

From: Michael DeMane
Sent: Tuesday, March 26, 2002 12:17:35 AM
To: Bailey Lipscomb; Tara Hood
CC: Rick Treharne; Jon Serbousek
BCC: Jim McDermid
Subject: FW: CONFIDENTIAL

Attachments: Burkus paper comments 3-25-02.doc; Table 5 - 3-25-02.doc

You guys (gals) are awesome. Thanks for making the difference. It is clearly appreciated by Ken and on behalf of the rest of MSD I'd like to throw in my thanks as well. Effort like this is the difference between MSD and the also rans. Thanks!

-----Original Message-----
From: JKE[redacted]
Sent: Monday, March 25, 2002 7:34 PM
To: Mike DeMane
Subject: CONFIDENTIAL

Mike,

This is typical of the type of response that I get from Bailey Lipsomb and Tara Hood and everyone in the Regulatory Department at MSD.

Let me set the stage.

This morning at 6AM, I was in my office in Columbus. On my secretary's desk, I found an unopened envelope from SPINE with the responses from the reviewers to the Bone Dowel/BMP manuscript.

At 7:30 AM, I went over with Lynn Sanders the information that I needed. Lynn faxed the SPINE editor's queries to Memphis and to Bailey and Tara.

At 7:45 AM, I had to leave for a clinic in Albany, Georgia.

At 5:30 PM, I returned to my office in Columbus. ON MY DESK WERE HARD COPIES OF TARA'S RESPONSES to the SPINE editors. I opened the follow-up email when I got home.

It is very hard to keep up with the Research and Regulatory Department that you have assembled at MSD. I am trying.

With the help and encouragement from all at MSD, the final version of the manuscript will be on its way by end of the week.

I can take credit for only a small fraction of the work that has gone into this paper.

With great respect,

Ken Burkus

----- Original Message -----
From: "Tara Hood" [redacted]>
To: "'Ken Burkus, MD'" [redacted]>; "J. Kenneth Burkus" [redacted]>
Cc: "'Lynn Sanders'" [redacted]>; "Bailey Lipscomb" [redacted]
Sent: Monday, March 25, 2002 4:25 PM
Subject: BMP/Bone Dowel Manuscript

> Dr. Burkus,
> Enclosed is some information to hopefully assist in responding to Spine's
> comments. We tried to go through and address all of the questions possible.
> There was one question on excluding "facet syndrome" that I was a little
> unclear on. This is not specifically mentioned in the inclusion/exclusion
> criteria and I was not exactly sure on what they were trying to get at.
> Please let me know if there is information we can provide to help you
> address this question. I am also faxing this information to you and I am
> including the operative report from the investigational patient who had a
> supplemental fixation after 24 months.
> Thank you for all of your work on this project. Please just let me know if
> we can be of further help or if you need additional information.
> Thanks,
> Tara
>
> <<Burkus paper comments 3-25-02.doc>> <<Table 5 - 3-25-02.doc>>
>

Reviewer #2
Methods

Inclusion/Exclusion-

(Point 1)
Discogenic pain: patient "has degenerative disc disease as noted by back pain of discogenic origin, with or without leg pain, with degeneration of the disc confirmed by patient history (e.g., pain [leg, back, or symptoms in the sciatic nerve distribution], functional deficit and/or neurological deficit) and radiographic studies (e.g., CT, MRI, X-Ray, etc.) to include one or more of the following:

a) Instability (angulation ≥ 5° and/or translation ≥ 4mm)
b) osteophyte formation;
c) decreased disc height;
d) thickening of ligamentous tissue;
e) disc herniation; and/or
f) facet joint degeneration."

This inclusion criteria did not require patients to have discography, even though some were probably performed.

(Point 2)
As stated in the above inclusion criteria, the back pain experienced by the patient can be with or without leg pain or with or without sciatica. The specification is simply that there be back pain present and the preoperative Oswestry (low back pain disability index) score be ≥ 35.

(Point 3)
Facet syndrome - ??

(Point 4)
NSAIDS – The exclusion criteria ask that a patient that requires NSAIDS for known problems be excluded from the study. "Has a condition which requires postoperative medications that interfere with fusion, such as steroids or nonsteroidal anti-inflammatory drugs (this does not include low dose aspirin for prophylactic anticoagulation)." If a patient undergoes surgery as part of the clinical trial, the postopertive regimen asks that prolonged use of NSAIDS is avoided.

(Point 5)
Preoperative conservative treatment – Inclusion criteria – "Has not responded to non-operative treatment (e.g., bed rest, physical therapy, medications, spinal injections, manipulation, and/or TENS) for a period of 6 months."

Results

Preoperative Leg Pain – Investigational – 12.8; Control – 14.6
(*P* value= 0.2291 [comparing treatment groups]) I don't think you will need to include this on the table. After you move the *p*-values as indicated below, I think it will help clear things. You could just indicate in your response that they are not statistically different.
On Tables 4, 5, & 7 – it may help to clear some of the confusion if you move the *P* value** into another column. These *P* values are comparing the postop change from preop between the two treatment groups and do not really belong under either treatment group. (I have attached an example Table 5 to this e-mail/fax).

Fusion Rate – fusion is defined as bridging bone, no motion (<5° angulation, <3mm translation), and absence of radiolucent lines around more than 50% of either implant.
The other factor that plays into fusion are 2nd surgeries for 'non-union.' If a patient has a 2nd surgery, e.g. supplemental fixation, at the involved level and it is reported to be due to pseudoarthrosis by the investigator, that patient is called a fusion failure from that time forward. We do not go back and call them a fusion failure at previous visits. At previous visits they met the protocol required elements of radiographic fusion and probably would again at the time of the 2nd surgery. The pseudoarthrosis diagnosis may have been in response to pain.

In the control group, there were patients who were felt to be radiographically fused at 12 months, and then later at 24 months, they were felt to be radiographically not fused. This was due to the radiolucent line criteria. The patients had bridging bone and no motion at 12 & 24 months; however, at 12 months radiolucent lines were not evident, where at 24 months they were. This is very likely due to the nature of the control implant. The dowels were packed solid with autograft bone and lucencies may not have been evident early on. Due to the nature of rhBMP-2/ACS, you do not have this issue early postop.

Reviewer #3

Radiographic determination of fusion – please see above comments addressing Reviewer #2 comments.

"Facet Joint Motion at 36 months" – there are several points to address on this patient:
#1 – this patient had had a previous failed posterior fusion at the involved level prior to study entry.

#2 – the operative report from the 2nd "pseudoarthrosis" surgery stated that the level "was extremely stable and contained only micro-motion noted after the facet joints were debrided" (I have faxed you a copy of this operative report to review)
#3 – the patient was a smoker preoperative, but had quit approximately 1 month prior to the study surgery. The patient resumed smoking postoperatively.

Table 5. Leg Pain Outcomes **QQ AU:Does "Std" stand for standard deviation?XQQ**

Period	Variable	Investigational n = 24	Control n = 22	P value**
Preoperative	n	24	22	
	Mean	12.8	14.6	
	Std	5.7	4.5	
6 Weeks	n	24	21	
	Mean	7.0	8.8	
	Std	5.9	5.9	
Improvement from Preoperative	Mean	-5.8	-5.6	0.933
	P value*	0.001	0.001	
3 Months	n	24	21	
	Mean	6.2	8.3	
	Std	4.4	5.8	
Improvement from Preoperative	Mean	-6.7	-6.4	0.874
	P value*	<0.001	<0.001	
6 Months	n	24	20	
	Mean	5.0	6.1	
	Std	4.7	4.4	
Improvement from Preoperative	Mean	-7.9	-8.7	0.654
	P value*	<0.001	<0.001	
12 Months	N	24	19	
	Mean	5.5	8.1	
	Std	5.5	6.1	
Improvement from Preoperative	Mean	-7.3	-6.8	0.818
	P value*	<0.001	0.001	
24 Months	n	24	17	
	Mean	6.3	11.5	
	Std	6.0	6.3	
Improvement from Preoperative	Mean	-6.5	-3.5	0.142
	P value*	<0.001	0.023	

**P* values for change from preoperative in each group are from paired tests.
***P* values for difference between the treatment groups are from analysis of variance.

From: Bearcroft, Julie, PhD
Sent: Tuesday, June 27, 2006 07:19:45 AM
To: JDIMAR[redacted] LCarreor[redacted]
CC: Ma, Guorong; Hatcher, Brian
Subject: Hibb's Award manuscript

Attachments: 2YrBMP-CRMSRS2006_06-07-06v2_MSD.doc

John and Leah -

Thank you for developing this draft manuscript for the Hibb's award.

Guorong and I have gone through this very carefully and made some suggestions. I know the document looks bad but track changes with multiple individuals makes it difficult. You can turn off the track changes temporarily to make it easier to read and follow.

I made some alternative suggestions to the citations in the introduction to better support your comments as well as add in a little more detail to the background story. I don't know if you are restricted on words so I apologize if I made this too long.

Of course, we carefully combed through all the numbers in the manuscript to update them. We are still in the process of verifying the AEs (highlighted in yellow) as you have written them. It appears that you have grouped them differently and therefore, it makes it difficult for us to verify them. I don't think grouping them differently is an issue as long as we can trace how these numbers compare to the PMA. I do like having a more detailed section related to AEs in the manuscript as this has been a criticism of past papers on INFUSE.

And finally, I did edit the fusion methodology and results sections. I know this is confusing and perhaps the document will make more sense now. We have to be very careful not to report the CT bridging bone as fusion success. This is only one of the parameters monitored that was considered as fusion success was determined per the IDE protocol. (The confusing thing is that some surgeons may consider it on its own but in our protocol, we did not.) If you have questions, I will be happy to discuss this with you live time.

I did not send this to Carol yet as I thought you may wish to review it first. Unfortunately, I will not have access to email after today. I am on vacation this week. Right now, I am in Boston with access but Wednesday, I head to upstate NY to visit my husband's children and family. I won't have easy access (if at all) there. Even my cell phone coverage will be spotty there, but please call me and suggest convenient times for me to call you back if you wish to talk. Otherwise, I will return to the office on Wed the 5th.

Thanks and happy 4th,

julie

A large-scale, level 1, clinical and radiographic analysis of an optimized rhBMP-2 formulation as an autograft replacement in posterolateral lumbar spine fusion

John R. Dimar II, MD*, Steven D. Glassman, MD*, J. Kenneth Burkus, MD†, Philip W. Pryor‡, MD, James W. Hardacker. MD‡, Scott D. Boden, MD§

*Spine Institute for Special Surgery, Louisville, KY; †The Hughston Clinic, Columbus, GA; ‡The Spine Institute, Carmel, IN; § Emory Spine Center, Emory University School of Medicine, Atlanta, GA

Purpose: To determine the feasibility of using a new recombinant human bone morphogenetic protein-2 formulation utilizing a new compression resistant matrix (rhBMP-2 matrix) as an iliac crest bone graft (ICBG) substitute in patients undergoing posterolateral fusion.

Methods: In this ongoing prospective study, 463 patients with symptomatic single-level degenerative disc disease with ≤ Grade 1 spondylolisthesis were treated with decompression and instrumented single-level posterolateral fusion through an open midline approach. Patients were randomly assigned to either the rhBMP-2 matrix (AMPLIFY™, Medtronic Sofamor Danek) group (239 patients) or the ICBG group (224 patients). ODI, SF-36, and back and leg pain scores were determined preoperatively and at 1.5, 3, 6, 12 and 24 months postoperatively. Two independent radiologists reviewed radiographs and CT scans taken at 6, 12, and 24 months postoperatively. Fusion was defined as the presence of bilateral, continuous trabeculated bone connecting the transverse processes, translation of ≤3 mm and angulation of <5° on flexion-extension radiographs, and absence of cracking as evidenced by radiolucent lines completely through the fusion mass.

Results: No significant differences in demographics existed between the groups. The mean operative time in the rhBMP-2 group (2.5 hours) was less than in the ICBG group (2.9 hours) (p<0.001). Average blood loss in the rhBMP-2 group was 343.1 ml compared with 448.6 ml in the ICBG group (p<0.001). Average hospital stay was similar in both groups. No differences existed between groups in adverse events except cumulative nonunion rate reported by the investigators was higher in the ICBG group (7.1%;16 patients) (p=.042) than in the rhBMP-2 group (2.5%; 6 patients). Based on fine-cut CT Scans with coronal and sagittal reconstructions, at 12 months, 86.9% of patients in the rhBMP-2 group and 71.3% in the ICBG group had evidence of bilateral bridging bone (p<0.001). At 24 months, 93.6% in the rhBMP-2 group had bilateral bridging bone compared with 82.6% in the ICBG group (p=0.024). Both groups showed similar improvements in clinical outcomes and reduced pain. At 24 months, 54% of the ICBG group reported enduring donor site pain.

Conclusions: The use of rhBMP-2 can eliminate the need for harvesting iliac crest bone in successful posterolateral lumbar fusions.

Deleted: with
Deleted: rhBMP-2/CRM
Deleted: rhBMP-2/CRM
Deleted: and
Deleted: Mean
Deleted: lower
Deleted: in the rhBMP-2 group (2.5%; 6 patients)
Deleted: in the ICBG group (7.1%;16 patients) (p=.042)
Deleted: fusion
Deleted: were fused
Deleted:

INTRODUCTION

Posterolateral fusion combined with pedicle instrumentation is frequently employed for the treatment of degenerative disease of the lumbosacral spine. Various indications include degenerative disc disease, spondylolisthesis, and instability. The results of instrumented posterolateral fusions in large clinical studies have shown varying rates of fusion and clinical outcomes [1-6]. Traditional sources of grafting material include autograft obtained locally from the iliac crest or from distal sources and different types of allograft [3-6].

Previous studies have demonstrated the ability of recombinant human bone morphogenetic protein (rhBMP-2) to achieve a solid fusion [7-9]. Recently, prospective randomized human clinical studies demonstrated superior fusion rates and clinical outcomes with rhBMP-2 and a collagen sponge (INFUSE® Bone Graft) versus autograft when using either cortical bone dowels or threaded interbody cages in anterior lumbar interbody techniques [10-11]. Nonhuman primate studies have demonstrated that rhBMP-2/ACS required additional osteoconductive bulking agents in order to achieve successful posterolateral spine fusion (11A-11C). A new formulation using an optimized rhBMP-2 concentration and a compression resistant carrier developed specifically for posterolateral fusions demonstrated excellent results in nonhuman primates (11D). A small pilot study on humans demonstrated similar results with rhBMP-2 combined with biphasic calcium phosphate versus iliac crest autograft for posterolateral fusions [12]. Currently, a prospective randomized FDA IDE study comparing iliac crest bone graft (ICBG) to rhBMP-2 combined with a carrier consisting of bovine collagen and tricalcium/hydroxyapatite to create a compression resistant matrix for single-level posterolateral fusions is ongoing. The purpose of our report is to present the two year radiographic results and clinical outcomes using rhBMP-2 matrix or ICBG in single-level instrumented fusions for lumbosacral degenerative disease.

MATERIAL AND METHODS

There were 463 patients enrolled in a multi-center prospective, randomized, nonblinded, FDA IDE study. There were 29 participating investigational sites with 83 spine surgeons. All of the patients were treated with a single-level instrumented fusion using CD Horizon® (I need to make this match the IDE and will provide proper language ASAP.) (Medtronic Sofamor Danek, Memphis, TN USA) pedicle screw and rod instrumentation. Exclusion criteria included a previous attempt at fusion at the intended surgical level, significant osteoporosis (less than 2 SD below normal on DEXA), autoimmune disease, malignancy, pregnancy, or the inability to harvest graft due to previous surgical procurement. Patients were randomly assigned to one of two groups: the control group received autogenous iliac crest bone graft (ICBG) and the investigational group received rhBMP-2 matrix (Medtronic Sofamor Danek, Memphis, TN, USA). The dose and concentration of rhBMP-2 used in this study is higher (2.0mg/cc for a total dose of 40mg, 20mg per side) than that of commercially available INFUSE® Bone Graft (1.5mg/cc for a total dose of 12mg per large kit).

The indications for surgery were symptomatic, single-level lumbosacral degenerative disease from L2/3 to L5/S1 of at least six months duration that had not responded to conservative care. The clinical symptoms included low back pain with or without radicular leg pain. Additional enrollment criteria were a Grade I or less spondylolisthesis and no previous fusion.

Deleted: equivalent
Deleted: Infuse
Formatted: Superscript
Deleted: (
Deleted: Compression
Deleted: , CRM)
Deleted: /CRM
Deleted: 476
Deleted: MS
Deleted: is this accurate?
Deleted: /CRM
Deleted: Infuse
Deleted: 6
Deleted: , 8 mg per side
Deleted: .
Deleted: , or both
Deleted: , although degenerative disease adjacent to a previous fusion was acceptable

A standard open posterior approach was used for both the ICBG and rhBMP-2 matrix groups. Local bone graft obtained during the decompression was discarded. Bone graft from the iliac crest in the ICBG group was obtained in a standard open fashion. The bone graft was morselized and placed in the lateral gutters on the decorticated bony surface of the transverse processes and along the pars interarticularis.

The rhBMP-2 was reconstituted using sterile water into two 5 ml syringes containing 20mg of rhBMP-2. The matrix was cut lengthwise with a scalpel into two equal pieces using a cutting template. The reconstituted rhBMP-2 from each syringe was then uniformly distributed to each piece of the matrix and allowed to stand for a minimum of five minutes. The rhBMP-2 matrices were all implanted within 60 minutes following preparation. In no instance was the matrix of insufficient length to span the transverse processes in a single-level fusion. As required by the protocol, any local bone graft obtained from the decompression was discarded in the rhBMP-2 matrix group.

Clinical data were collected preoperatively and post operatively at six weeks, 3 months, 6 months, 12months, and 24 months. The validated outcome instruments employed included the Oswestry Low Back Pain Disability Index (ODI), the Short Form 36 (SF-36). Back pain, leg pain, and donor graft site pain in the control group were also monitored. Patients were asked to rate the frequency and intensity of their pain on a scale of 0 to 10 and the scores were summed to derive a 20 point numerical rating scale. Data on work status, patient satisfaction, and adverse events were also recorded. Neurological examination including motor function, sensory function, reflexes, and straight leg raise were recorded.

Plain radiographs, lateral flexion and extension radiographs, and CT Scans with sagittal and coronal reconstruction were used to evaluate the fusion in both groups post operatively at 6, 12, and 24 months. The CT imaging protocol consisted of one millimeter continuous non-overlapping axial slices that were taken without bone filter. The window and level settings were set to optimize trabecular bone detail (2000/350 on GE Scanners). The field of view was made as small as possible but still encompassed the complete vertebra in between and including the transverse processes. The radiographs and CT scans were evaluated by two independent radiologists who were blinded to which patient group they were evaluating (is this true?).

The rhBMP-2 matrix and ICBG group values were compared using ANOVA for continuous variables and Fisher's exact test for categorical variables for independent samples across each time interval.

RESULTS

All the patients were past the 12-month evaluation point, but the 24-month follow-ups are ongoing. There were 282 subjects available for assessment at two years postoperatively, 137 in the ICBG group and 145 in the rhBMP-2 matrix group. Randomization resulted in a similar distribution of baseline characteristics in the two study groups as shown in Table 1.

The average surgical time for the control patients was 2.9 hours which was significantly longer ($p<0.001$) than the 2.5 hours observed in the rhBMP-2 matrix group (Table 2). The average blood loss was 448.6 ml for the control patients which was also significantly greater ($p<0.001$) than the 343.1 ml blood loss observed with the rhBMP-2 matrix group. There was no statistically significant difference in length of hospital stay between the two groups. No surgeries were abandoned due to technical problems. There were no unanticipated intra-operative complications related to the fusion procedure.

4

Deleted: /CRM
Deleted: CRM
Deleted: /CRM
Deleted: /CRM sponges
Deleted: sponge
Deleted: /CRM
Deleted: was
Deleted: post operatively
Deleted:
Deleted: , b
Deleted: and
Deleted: scores
Deleted: the Oswestry Low Back Pain Disability Index (ODI),
Deleted: , back pain and leg pain scores
Deleted: Scans
Deleted: as
Deleted: as
Deleted: /CRM
Deleted: initial review
Deleted: /CRM
Deleted: that might be independently related to the study outcomes
Deleted: e
Deleted: rhBMP-2/CRM
Deleted: ce
Deleted: s
Deleted: ce
Deleted: rhBMP-2/CRM

The ODI scores were similar in both groups over all time intervals (Figure 2) and showed statistically significant improvement compared to pre-operative scores in both the ICBG and rhBMP-2 matrix groups Table 4 [Comments: p-values showing significant improvement for within groups are not shown, but p-values comparing between the groups are shown, which are not significant. I would not show those between groups.]. The SF-36 physical component summary (PCS) scores were similar in both groups at all time intervals (Figure 1) and showed statistically significant improvement compared to pre-operative scores in both the ICBG and rhBMP-2 matrix groups Table 3 [Comments: p-values showing significant improvement for within groups are not shown, but p-values comparing between the groups are shown, which are not significant. I would not show those between groups.].

The back pain scores for the ICBG and rhBMP-2 matrix groups improved significantly from pre operative scores of 15.8 and 15.6 to 8.1 and 7.8 at 24 months, respectively. Both groups showed similar improvements over all time intervals (Figure 3) with no statistically significant difference in their 24 month back pain scores. The leg pain scores following surgery demonstrated that both the ICBG and rhBMP-2 matrix groups improved in a similar manner over all time intervals (Figure 4). Leg pain scores improved from 14.0 in both groups, to 7.4 in the ICBG group and 7.1 in the rhBMP-2 matrix group at 24 months. There was no statistically significant difference in their 24 month leg pain scores.

Pain resulting from iliac crest harvest was measured using donor site pain scores. These were collected only from the ICBG group. The mean donor site score after discharge was 11.3, which improved to 7.9 six weeks after surgery. There was minimal improvement on subsequent follow-up periods up to 24 months. A large number of patients in the ICBG group (54%) still had persistent donor site pain with a mean pain score of 5.0 at 24 months after surgery (Figure 5).

41.1% of subjects in the ICBG group were working prior to surgery and 48.5% were able to return to work at 24 months (Figure 6). 34.7% of the subjects in the rhBMP-2 matrix group were working prior to surgery as compared to 40.7% at 24 months postoperatively.

All plain films and CT scans were read by the independent radiologists. Fusion success was determined by the IDE protocol-defined analysis whereby assessment per plain films were considered first. In cases where the plain films did not exhibit bridging bone, CT scans were then considered and used for bridging bone determination. Assessment in this manner showed that 87.4% of patients in the rhBMP-2 group and 82.4% in the ICBG group achieved fusion success (p=.199) at 12 months. At 24 months, 94.9% in the rhBMP-2 matrix group achieved fusion success compared with 86.8% in the ICBG group (p=.074). Fine-cut CT scans with sagittal and coronal reconstructions showed that 74.4% of the subjects in the rhBMP-2 matrix group and 56.4% in the ICBG group had evidence of bilateral bridging bone at 6 months (p<0.001). At 12 months, 86.9% of subjects in the rhBMP-2 matrix group and 71.3% in the ICBG group had evidence of bilateral bridging bone (p<0.001) At 24 months, the rate was 93.6% in the rhBMP-2 group compared to 82.6% in the ICBG group (p=0.024)(Figure 7).

The most common complication which may have been related to the surgery were infections of various types at different sites. There was a higher incidence of superficial wound infections in the ICBG group. There was no difference in the incidence of deep wound infections, wound drainage or development of wound hematoma. Sixteen patients in the ICBG group complained of continued pain from the bone graft donor site that

Formatted: Highlight
Deleted: (PCS)
Deleted: rhBMP-2/CRM
Formatted: Highlight
Deleted: ,
Deleted: The ODI scores were s ... [1]
Deleted: rhBMP-2/CRM
Deleted: and
Deleted: rhBMP-2/CRM
Deleted: rhBMP-2/CRM
Deleted: hip
Deleted: hip pain
Deleted: Patients
Deleted: hip
Deleted: rhBMP-2/CRM
Deleted: , and
Deleted: 16
Deleted: returned to work
Deleted: T
Deleted: fusion
Deleted: fusion
Deleted: fusion success
Deleted: missingin fusion [1su ... [2]
Deleted: P
Deleted: plain radiographs and CTs]
Formatted: Font: Not Bold
Deleted: at 12 months
Deleted: had evidence of fusion
Deleted: 2
Deleted: rhBMP-2/CRM
Deleted: were fused
Deleted: 37
Deleted: Scans
Deleted: rhBMP-2/CRM
Deleted: fusion
Deleted: rhBMP-2/CRM
Deleted: fusion
Deleted: of
Deleted: were fused
Deleted: of
Deleted: There were twice as m ... [3]
Deleted: ¶
Formatted: Indent: First line: 36 pt
Formatted: Highlight

required active treatment. One patient developed a donor site infection. No adverse events were observed that could be directly attributable to the use of rhBMP-2 matrix.

Deleted: rhBMP-2/CRM

DISCUSSION

The guiding principle for the surgical treatment of painful or unstable lumbosacral degenerative spinal disease remains the ability to achieve a solid fusion. Although autologous ICBG is the gold standard, the morbidity associated with graft harvest has led surgeons to seek viable alternatives, such as allografts, ceramics, and various types of growth factors [16-20]. These graft substitutes have demonstrated great variability in achieving fusion with the best success achieved when used in addition to iliac crest bone graft and not as an alternative to iliac crest bone graft. Additionally, they present their own unique problems including decreased success of fusion [21], limited availability, and the potential for rejection or immunologic reaction [17, 18].

The development of osteoinductive biologics has resulted in the clinical availability of recombinant human bone morphogenetic protein (rhBMP-2 and rhBMP-7) for spinal fusion [22]. These naturally occurring bone proteins stimulate bone healing via a cascade mechanism that results in the differentiation of primitive mesenchymal cells and preosteoblasts into osteoblasts that promote bone formation and ultimately, healing [23]. The effectiveness of rhBMP-2 in achieving a solid interbody fusion has been demonstrated in numerous experimental animal studies [7-9]. Subsequently, clinical trials have demonstrated similar fusion rates and clinical outcomes when ICBG was compared to rhBMP-2 combined with a collagen sponge carrier (INFUSE® Bone Graft) and a lordotic threaded interbody cage (LT-cage) [10, 11]. As a result of these findings the FDA approved the use of rhBMP-2 as a iliac crest bone graft replacement for lumbar interbody fusions in 2002.

Deleted: tissue
Deleted: appear to
Deleted: de
Deleted: 24
Deleted: Infuse
Deleted: bone graft substitute
Deleted: anterior

A recent randomized human pilot study evaluated rhBMP-2 combined with biphasic calcium phosphate granules versus autograft in achieving a successful posterolateral fusion [11F]. The study demonstrated a 40% fusion rate in the autograft group versus a 100% fusion rate with the investigational group when evaluated by radiographs and CT scans. Oswestry and SF-36 outcome measures demonstrated significant but similar improvement of all groups at the end of the study. Although the authors sited several deficiencies, most notably the lack of a 24 month follow-up on all the subjects, the study presented strong evidence of the efficacy of rhBMP-2 in achieving a successful radiographically confirmed fusion in humans.

Deleted: posterior
Deleted: 10

As part of an ongoing FDA regulated IDE study, rhBMP-2 is now being evaluated for use in single-level posterolateral fusions combined with pedicle screw/rod instrumentation. This report reviews our two-year clinical outcomes and fusion rates based on CT scans. This study utilizes a specifically designed carrier, that combines tricalcium phosphate and hydroxyapatite granules with a collagen matrix. This combination provides significant resistance to compression when placed in the lateral gutters. It is also important to emphasize that this study uses a higher concentration of rhBMP-2 (2.0mg/cc vs 1.5mg/cc) when compared to the concentration utilized in previous clinical studies with an absorbable collagen sponge carrier.

Deleted: two
Deleted: for 282 subjects

Comment [LYC1]: Pre-clinical studies have shown that the concentration per carrier is more critical than the actual amount of BMP)

Although local bone graft is rarely discarded in clinical practice, the quality and quantity of local bone grafts are highly variable. In this study, local bone graft was discarded in both groups to allow for a direct comparison of the fusion rates of rhBMP-2 matrix to ICBG without local bone graft as a confounding variable.

Deleted: ml
Deleted: ml
Deleted: rhBMP-2/CRM

Perioperative measures indicate improvements in operative time and blood loss, which were significantly less in the rhBMP-2 matrix group as compared to the ICBG group. The length of hospital stay was the same for both groups. The incidence of deep wound infections, wound drainage or development of wound hematoma was similar in both groups. There was a higher incidence of superficial wound infections in the ICBG group which may be due to the need for significant retraction to access the iliac crest through the same incision for bone graft harvest.

An equally important measure of the success of a fusion procedure, beyond the radiographic evidence of fusion, is how the patient feels and functions after surgery. The use of validated patient-based clinical outcome measures such as the Oswestry Disability Index and the SF-36 provide a self-assessment of the patient's functional improvement rather than the clinician's perception [13]. Most of the improvement in ODI scores and SF-36 PCS occurred within the first three months after surgery, in both groups. This improvement was maintained through the subsequent follow-up periods up to 24 months. The improvement in PCS at 24 months in both groups was well above the 5.41 point threshold in the literature for clinically significant improvement [26? check reference?]. The average decrease in ODI scores at 24 months in both groups was greater than 25 points [comments: I think the 15-point value refers to patient-based meaningful improvement. The group-based value would be 4-5 points], which is also above that necessary to demonstrate treatment efficacy [27].

Most of the improvement in back pain and leg pain scores was noted within the first six weeks after surgery, and was maintained throughout the entire follow-up period. The 6.9 point decrease in back pain in the rhBMP-2 matrix group and 7.7 in the ICBG group indicates a clinically significant diminution in back pain following surgery. The 7.9 point decrease in leg pain in the rhBMP-2 matrix group and 8.4 in the ICBG group indicates a clinically significant diminution in leg pain following surgery.

The rates of fusion in previously published articles vary widely from 60% to 98%. This may be due to the use of plain radiographs with flexion extension views which are known to be inaccurate with error rates estimated from 20 to 40% [citation?]. When fusion success was determined using the IDE protocol-defined criteria, the rhBMP-2 matrix group had smaller differences in fusion success rates as compared with the ICBG group. Using thin-cut CT scans, bilateral bridging bone was reported by the independent, blinded radiologists significantly more often in the rhBMP-2 matrix group as compared to the ICBG group at all three time points. [include statement referencing Steve Glassman's work (SPINE 2005) on the quality of fusion? Perhaps – In a separate study derived from a subset of this patient population, it was reported that rhBMP-2 matrix produced a more robust fusion mass as compared to iliac crest bone graft as judged from CT scans alone.] This suggests that the use of fine-cut CT scans with sagittal and coronal reconstructions may increase its ability to demonstrate the robustness of the fusion and the presence of bilateral confluent bridging bone. At the 24 month follow-up period, there were twice as many patients in the ICBG group with established nonunions [what is the source for this comment? Is this the adverse event nonunion rate? I would move this statement earlier in the discussion, perhaps with the adverse events above, to help end on a strong note.].

CONCLUSION

Deleted: The results of this study demonstrate significant improvement of the ODI, SF-36,

Deleted: ODI,

Deleted: leg and back pain scores in both groups over all time intervals. There were differences in

Deleted: /CRM

Deleted: all

Deleted: 25

Deleted: 15

Formatted: Highlight

Deleted: 26,

Deleted: rhBMP-2/CRM

Deleted: rhBMP-2/CRM

Deleted: rates of fusion in previously published articles varies

Deleted: form

Deleted: 1

Deleted: and CT Scans

Deleted: assessed

Deleted: that use plain radiographs and CTs

Deleted: rhBMP-2/CRM

Deleted: both groups

Deleted: similar

Deleted: without radiolucencies or clefts within the fusion mass

Formatted: Highlight

Deleted: and these rates were higher than that observed when fine-cut CT Scans were used. [Comments: if just plain radiographs are used, the fusion rates would be lower than those just from CTs. The IDE fusion rates use both for determining bridging bone.] Subjects in the ICBG group demonstrated lower fusion rates over all time intervals compared to the rhBMP-2/CRM group when fine-cut CT Scans with reconstructions were used to assess fusions.

Deleted: T

Deleted: the accuracy by which fusions are assessed by

Formatted: Highlight

Deleted: The incidence of deep wound infections, wound drainage or development of wound hematoma was similar in both groups. There was a higher incidence of superficial wound infections in the ICBG group which may be due to the need for significant retraction to access the iliac crest through the same incision for bone graft harvest.

This study demonstrates that, for patients with a single-level degenerative disease, an instrumented posterolateral fusion with ICBG and rhBMP-2 matrix provide excellent clinical improvement and exhibit similar clinical outcomes two years after surgery. The rhBMP-2 matrix group demonstrated significantly decreased intraoperative blood loss and decreased operative time when compared to the ICBG group. The rhBMP-2 matrix demonstrated an improved fusion success rate when compared to the ICBG group at 24 months. There were no significant differences in complications between the two groups. In conclusion, rhBMP-2 matrix demonstrated similar clinical outcomes and increased fusion rates when compared to ICBG for a single-level instrumented posterolateral fusion.

Deleted: rhBMP-2/CRM

Deleted: rhBMP-2/CRM

Deleted:

Deleted: rhBMP-2/CRM

Deleted: rhBMP-2/CRM

8

Table 1. Patient Demographic Data

	rhBMP-2 matrix	ICBG
Age (years)	53.2	52.3
Gender (%Male)	45.2	42.4
Workmen's Comp (%)	11.3	12.5
Smoker (%)	26.4	26.3

Table 2. Surgical data

	rhBMP-2 matrix	ICBG	p=value
OR Time	2.5	2.9	<0.001
EBL	343.1	448.6	<0.001
Hospital Stay	4.1	4.0	0.609

Table 3. Mean change in SF-36 PCS compared to pre-operatively on each follow-up period

Mean Change in SF-36 PCS	rhBMP-2 matrix	ICBG	p=value
6 weeks	3.8	4.5	0.378
3 months	9.5	8.8	0.465
6 months	12.9	10.9	0.073
12 months	13.7	11.6	0.070
24 months	12.7	12.8	0.990

Table 4. Mean Improvement in ODI compared to pre-operatively on each follow-up period

Mean Improvement in ODI	rhBMP-2 matrix	ICBG	p=value
6 weeks	12.9	13.9	0.580
3 months	22.1	21.2	0.810
6 months	26.0	24.4	0.382
12 months	26.9	25.4	0.452
24 months	27.2	25.6	0.582

Deleted: rhBMP-2/CRM
Deleted: 9
Deleted: rhBMP-2/CRM
Deleted: 4
Deleted: rhBMP-2/CRM
Deleted: 9
Deleted: 7
Deleted: 1
Deleted: 3
Deleted: change
Deleted: Change
Deleted: rhBMP-2/CRM
Deleted: 5
Deleted: 5.8
Deleted: 2

Table 5. Complications

	rhBMP-2 matrix	ICBG
Wound Drainage	4	3
Superficial Infection	5	15
Deep Infection	5	5
Wound Hematoma	1	0
Epidural Hematoma	2	0
Malignancy*	7	4
Anemia	26	29
UTI	8	9
Infection (Other sites)	27	19
Infection (Total)	46	48
Nonunion	11	22
AIF	6	10
PSF	0	6
Symptomatic	2	5
Asymptomatic	3	1
Dural Tear	14	18
Adjacent Level Degeneration	3	7
Surgical	2	5
Nonsurgical	1	2
Renal Stones	7	4
Pulmonary	17	9
Ileus	10	4
Technical Problems	9	6
Death	3	4
Donor Site Complaints	0	16
Donor Site Infection	0	2

*Cancer types in the rhBMP-2 matrix group include Follicular, Squamous Cell, Laryngeal, Pancreatic, Prostate, Lung and Basal Cell; in the ICBG group types include NonHodgkin's Lymphoma, Breast, Colon and an Unknown Primary

Formatted: Highlight
Deleted: rhBMP-2/CRM

Deleted: rhBMP-2/CRM

FIGURES

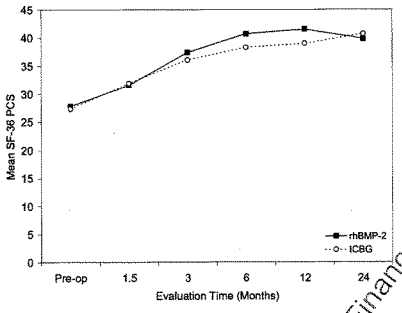


Figure 1. Comparison of SF-36 PCS in the ICBG and rhBMP-2 matrix groups.

Deleted: rhBMP-2/CRM

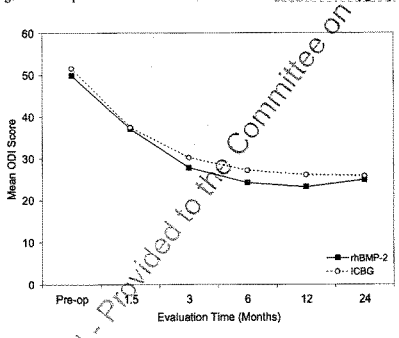


Figure 2. Comparison of ODI in the ICBG and rhBMP-2 matrix groups. I would recommend substituting the plot showing average improvement here rather than average scores. I think it will be more compelling to surgeons and payers alike.

Deleted: rhBMP-2/CRM

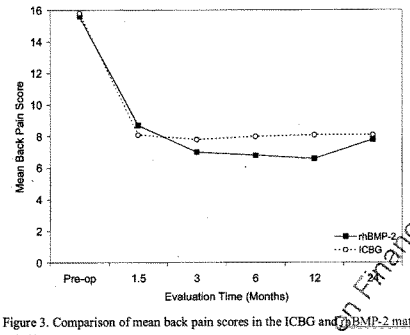


Figure 3. Comparison of mean back pain scores in the ICBG and rhBMP-2 matrix groups.

Deleted: rhBMP-2/CRM

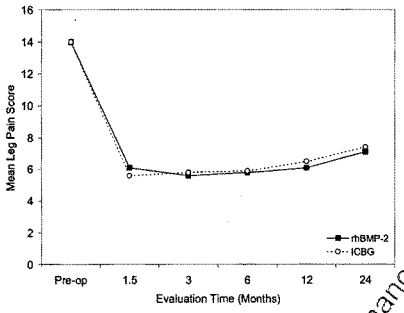


Figure 4. Comparison of mean leg pain scores in the ICBG and rhBMP-2/matrix groups. Deleted: rhBMP-2/CRM

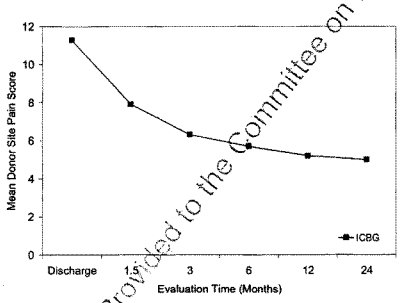


Figure 5. Mean donor site pain scores in the ICBG group. Deleted: hip

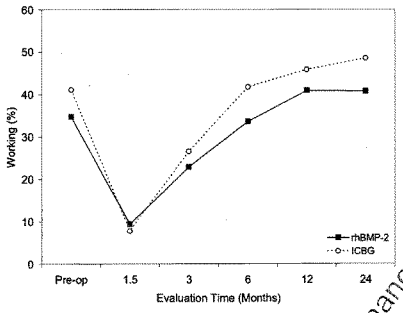


Figure 6. Percentage of subjects working in the ICBG and rhBMP-2 matrix groups.

Deleted: rhBMP-2/CRM

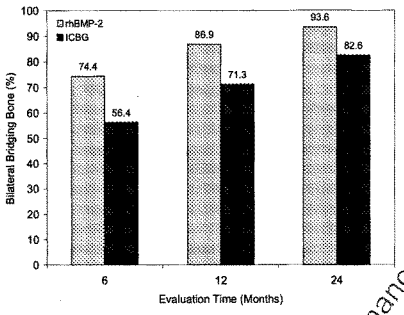


Figure 7. Percentage of subjects with bilateral confluent bridging bone reported by independent radiologists as observed on fine-cut CT scans with reconstructions for the ICBG and rhBMP-2 matrix groups.

Deleted: Scans
Deleted: rhBMP-2/ICRM

REFERENCES

1. Bono CM, Lee CK: Critical Analysis of Trends in Fusion for Degenerative Disc Disease Over the Past 20 Years. Spine. Feb 15;29(4):455-63.

2. An HS, Lynch K, Toth J: Prospective Compatison of Autograft vs. Allograft for Adult Posterolateral Lumbar Spine Fusion: Differences Among Freeze-Dried, Frozen, and Mixed Grafts. J Spinal Disord. Apr;8(2):131-5, 1995

3. An HS, Lynch K, Toth J: Prospective Compatison of Autograft vs. Allograft for Adult Posterolateral Lumbar Spine Fusion: Differences Among Freeze-Dried, Frozen, and Mixed Grafts. J Spinal Disord. Apr;8(2):131-5, 1995

4. Dawson EG, Lotysch M 3rd, Urist MR: Intertransverse Process Lumbar Arthrodesis with Autogenous Bone Graft. Clin Orthop Jan-Feb;(154):90-6,1981

5. Dimar, Glassman, Burkus, Carreon: A Comparison of Prospective Clincial Outcome Measures for Anterior vs. Posterior Single-level Spine Fusion. IMAST Program July 2004

6. Jorgenson SS, Lowe TG, France J, Sabin J: A prospective analysis of autograft versus allograft in posterolateral lumbar fusion in the same patient. A minimum of 1 – year follow-up in 144 patients. Spine Sep 15;19(18):2048-53, 1994

7. consider using this citation instead: Sandhu HS, Toth JM, Diwan AD, Seim HB III, Kanim LEA, Kabo JM, Turner AS "Histological evaluation of the efficacy of rhBMP-2 compared with autogenic bone in sheep spinal anterior interbody fusion" *Spine*. 27 (6): 567 – 575, 2002
Rather than
Martin GJ Jr, Boden SD, Marone MA, Moskovitz PA: Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: important lessons learned regarding dose, carrier, and safety. J Spinal Disord. Jun;12(3):179-86, 1999

8. Boden SD, Martin GJ Jr., Horton WC, Truss TL, Sandhu HS "Laparoscopic anterior spinal arthrodesis with rhBMP-2 in a titanium interbody threaded cage" *J Spinal Disorders*. 11 (2): 95 – 101, 1998

9. consider using this citation as an alternate: Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A "The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model" *Spine*. 24 (7): 629 – 636, 1999
Rather than
Boden SD, Schimandle JH, Hutton WC, Chen MI: 1995 Volvo Award in Basic Science. The Use of an Osteoinductive Growth Factor for Lumbar Spine Fusion. Part I: Biology of Spinal Fusion. Spine 15; 20(24):2626-32, 1995

10. Burkus JK, et al. "Is INFUSE Bone Graft superior to iliac crest bone graft? ...." J Spinal Disord Tech, 2003

11. Burkus JK, Dorchak JD, Sanders DL,: Radiographic Assessment of Interbody Fusion Using Recombinant Human Bone Morphogenetic Protein Type 2. Spine 15; 8(4):372-7, 2003

11A Martin GJ Jr., Boden SD, Morone MA, Moskovitz PA "Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: Important lessons learned regarding dose, carrier, and safety" *J Spinal Disorders*. 12 (3): 179 – 186, 1999

Deleted: 8. Yoon ST, Park JS, Kim KS, Li J, Attallah-Wasif ES, Hutton WC, Boden SD: ISLS Prize Winner: LMP-1 Upregulates Intervertebral Disc Cell Production of Proteoglycans and BMPs in Vitro and in Vivo. Spine 29(23):2603-11, 2004¶

Deleted: Gornet MF, Dickman CA, Zdeblick TA: Anterior Lumbar Interbody Fusion Using rhBMP-2 with Tapered Interbody Cages.

Deleted: 15(5):337-49

Deleted: 2002

Formatted: Normal, Justified, Space After: 12 pt, Keep lines together

11B Barnes B, Boden SB, Louis-Ugbo J, Tomak PR, Park J, Park M, Minamide A "Lower dose of rhBMP-2 achieves spine fusion when combined with an osteoconductive bulking agent in non-human primates" *Spine*, 30 (10): 1127-1133, 2005

11C Akamaru T, Suh D, Boden SD, Kim H-S, Minamide A, Louis-Ugbo J "Simple carrier matrix modifications can enhance delivery of recombinant human bone morphogenetic protein-2 for posterolateral spine fusion" *Spine*, 28 (5): 429 – 434, 2003

11 D Suh DY, Boden SD, Louis-Ugbo J, Mayr M, Murakami H, Kim HS, Minamide A, Hutton WC "Delivery of recombinant human bone morphogenetic protein – 2 using a compression-resistant matrix in posterolateral spine fusion in the rabbit and in the non-human primate" *Spine*, 27 (4): 353 – 360, 2002

11E Boden SD, Martin GJ Jr., Marone MA, Ugbo JL, Moskovitz PA "Posterolateral lumbar intertransverse process arthrodesis with recombinant human bone morphogenetic protein 2 / hydroxyapatite – tricalcium phosphate after laminectomy in the nonhuman primate" *Spine*, 24 (12): 1179 – 1185, 1999

11F Boden SD, Kang J, Sandhu H, Heller JG "Use of rhBMP-2 to achieve posterolateral lumbar spine fusion in humans: A prospective and randomized clinical pilot trial" *Spine*, 27 (23): 2662 – 2673, 2002

12. Boden SD, Kang J, Harvinder S, Heller JG: Use of Recombinant Human Bone Morphogenetic Protein-2 to Achieve Posterolateral Lumbar Spine. Spine. Dec 1;27(23):2662-73, 2002

13. Ware JE Jr, Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. Jun;30(6):473-83, 1992

14. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD: The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. Jan;32(1):40-66, 1994

15. Fairbank JC, Couper J, Davies JB, O'Brien JP: The Oswestry low back pain disability questionnaire. Physiotherapy. Aug;66(8):271-3, 1980

16. Glassman SD, Dimar JR, Carreon LY, Campbell MJ, Johnson JR and Puno RM. Initial fusion rates with rh-BMP-2 and HA-TCP/Collagen carrier in posterolateral fusion. In Publication.

17. Boden SD. Overview of the biology of lumbar spine fusion and principles for selecting a bone graft substitute. Spine, 2002; 27(16S):S26-S31.

18. Ludwig SC, Kowalski JM and Boden SD. Osteoinductive bone graft substitutes. Eur Spine J, 2000; 9(Suppl 1):S119-S125.

19. Lind M and Bunger C. Factors stimulating bone formation. Eur Spine J, 2000; 9(Suppl 1):S102-S109.

21. Vaccaro AR, Sharon AD, Tuan RS, Kang JD, An HS, et al. The use of biologic materials in spinal fusion. Orthopedics. 2001; 24(2):191-197.

22. Carreon LY, Glassman SD, Anekstein Y, Puno RM. Platelet gel (AGF) fails to increase fusion rates in instrumented posterolateral fusions. Spine. 2005 May 1;30(9):E243-6.

23. Urist MR: Bone: formation by autoinduction. Science. 1965 Nov 12;150(698):893-9

24. Martin GJ Jr, Boden SD, Marone MA, Marone MA, Moskovitz PA: Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: important lessons learned regarding dose, carrier, and safety. J Spinal Disord. Jun;12(3):179-86, 1999

25. Suh DY, Boden SD, Louis-Ugbo J, Mayr M, Murakami H, Kim HS, Minamide A, Hutton WC. Delivery of recombinant human bone morphogenetic protein-2 using a

compression-resistant matrix in posterolateral spine fusion in the rabbit and in the non-human primate. Spine. 2002 Feb 15;27(4):353-60.
26. Ware JE, Kosinski M, Keller SK. SF-36® Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: The Health Institute, 1994.
27. Fairbank JCT, Pynsent PB: The Oswestry Disability Index. SPINE 2000;25(22):2940-2953.
28. Walsh TL, Hanscom B, Lurie JD, Weinstein JN: Is a condition-specific instrument for patients with low back pain/leg symptoms really necessary? The responsiveness of the Oswestry Disability index, MODEMS and the SF-36. Spine 2003 Mar 15;28(6):607-15.

Page 5: [1] Deleted bearcj1 6/26/2006 5:50:00 AM

The ODI scores were similar in both groups over all time intervals (Figure 2) and showed statistically significant improvement compared to pre-operative scores in both the ICBG and rhBMP-2/CRM groups Table 4 [Comments: p-values showing significant improvement for within groups are not shown, but p-values comparing between the groups are shown, which are not significant. I would not show those between groups.] [I would change the order ODI and PCS]

Page 5: [2] Deleted bearcj1 6/27/2006 8:53:00 AM

missingin fusion [I suggest to delete this sentence. It is still not accurate.][which utilized both

Page 5: [3] Deleted bearcj1 6/26/2006 6:08:00 AM

There were twice as many nonunions in the ICBG group compared to the rhBMP-2/CRM group.

From: Hatcher, Brian
Sent: Friday, August 31, 2007 01:59:20 PM
To: J. Kenneth Burkus [redacted]
CC: Bearcroft, Julie, PhD
Subject: INFUSE/LT long term manuscript

Attachments: BMP.LT.Cage.72.months.Draft 08-07-07.doc; Spine J 2007 Brantigan 10yr fu.pdf; Spine 2000 Kuslich 4 yr BAK fu.pdf; Spine J 2005 Button BAK 3-6yr fu.pdf; Long term follow up studies.doc; E Spin J 1996 Christensen Fusion and Outcomes.pdf; Fishgrund 1997.htm; Fischgrund long term SPINE 2004.pdf

Hello Dr. Burkus,
Please see an updated draft of the long term manuscript. I have included some additional comments in red font. I think a couple of areas that still need to be adressed are the significance of the 6 yr data with Infuse, how this relates to other long term studies, the benefits of a fusion as it relates to long term outcomes, and the comparison between the open and lap groups. I have started to expand on this somewhat in the discussion section, but it could certainly use your input. Additionally, please include any other commentary that you think is relevant to this study.

Here are the papers that report on long term follow up from other IB studies for your reference.

Here are the papers that discuss the relationship between fusion and clinical outcomes. I thought it may be worth discussing in the manuscript the long term benefits of a fusion (see comments within manuscript). These papers may provide supporting background data for this.

Thanks for continuing to build on this important study. Look forward to seeing your comments.
Brian

Brian Hatcher, Ph.D.
Technology Manager, Biologics
Medtronic
Spinal and Biologics
1800 Pyramid Place
Memphis, TN 38132
O: [redacted]
M: [redacted]

F: [redacted]

Me ic Confident

Long -Term Follow-up of Patients Treated with Stand Alone Anterior Lumbar Interbody Fusion and Recombinant Human Bone Morphogenetic Protein-2

J. Kenneth Burkus, M.D.*

Matthew F. Gornet MD†

Thomas A. Zdeblick MD§

* Staff Physician, Spine Service, The Hughston Clinic, P.C.; [redacted]

†Staff Physician, Missouri Bone and Joint Institute, St. Louis, Missouri

§Chairman, Department of Orthopedics and Rehabilitation, University of Wisconsin, Madison, Wisconsin

FDA device/drug status: Approved for this indication.

Statement of Financial Relationship: The authors are consultants and clinical investigators for the company distributing the device studied.

Address correspondence and reprint requests to: J. K. Burkus, M.D., The Hughston Clinic, [redacted]

ABSTRACT

Background: Stand alone anterior lumbar interbody fusion using paired threaded tapered interbody fusion cages and recombinant human bone morphogenetic protein-2 (rhBMP-2) on an absorbable collagen sponge (ACS) has been reported with 24-month outcomes. Longer clinical and radiographic follow-up is needed to verify the sustained improvements in outcomes in the surgical treatment of degenerative lumbar disc disease.

Methods: An integrated analysis of two prospective studies of patients who received lumbar fusion cage implants by either a laparoscopic or an open surgical method using rhBMP-2 with 6 year follow up was performed. A total of 146 patients treated for single-level degenerative disc disease with up to grade 1 spondylolisthesis were studied and their clinical and radiographic outcomes were determined using well-established clinical outcome measurements and radiographic assessments.

Results: Patients treated with rhBMP-2 and stand-alone fusion cages showed high rates of fusion at 48 and 72 months and low rates of additional surgery. Additionally, sustained improvements in clinical outcomes as measured by average Oswestry Disability Index scores (ODI), SF-36® Health Survey Physical Component Summary scores, Back Pain and Leg Pain scores and work status were observed out to 6 years. There was a trend towards greater improvement in ODI, back pain scores, and SF-36 PCS in the laparoscopic group compared to the open group.

Conclusions: The use of dual tapered threaded fusion cages and rhBMP-2 on a collagen based sponge facilitates and maintains anterior intervertebral spinal fusion and sustained improvements in clinical outcomes and reduction of pain following anterior lumbar interbody fusion of degenerative lumbar disc disease.

Keywords: Anterior lumbar interbody fusion, INFUSE Bone Graft, bone morphogenetic protein, fusion cage, degenerative disc disease, lumbar spine

INTRODUCTION

Anterior lumbar interbody fusion (ALIF) is an effective treatment for patients with single level symptomatic degenerative lumbar disc disease. In ALIF surgery, the use of threaded interbody fusion devices, such as titanium cages and allograft dowels, enhance the stability of the spinal motion segment and help to promote higher rates of intervertebral fusion. At 24 months in randomized ALIF clinical trials, the use of recombinant human bone morphogenetic protein-2 (rhBMP-2) as a bone graft replacement has been shown to increase rates of interbody fusion by promoting osteoinduction, and its use has been associated with decreased pain and improved clinical outcomes [1-4]. When used in combination with the LT CAGE® Device, patients treated with rhBMP-2 had significantly higher fusion rates than patients treated with ICBG (94.4% vs. 89.4%; p=0.022) [3]. Additional studies with rhBMP-2/ACS in lumbar interbody fusion have also shown similar rates of fusion success [1, 2, 4-12].

INFUSE® Bone Graft with the LT-CAGE® Device was approved by the U.S. Food and Drug Administration in 2002 for treatment of degenerative lumbar disc disease and up to grade I spondylolisthesis through an anterior interbody spinal fusion procedure. The surgical technique and indications for implanting the LT-CAGE Lumbar Tapered Fusion Device (Medtronic Sofamor Danek, Memphis, Tennessee) and reports of outcome measurements in patients in whom it has been implanted have already been reported [2, 3]. The purpose of our analysis was to investigate the post-approval long term clinical and radiographic outcomes in those investigational patients enrolled in these initial FDA trials using stand alone interbody fusion cages and rhBMP-2 as a bone graft replacement. Patients who received INFUSE® Bone Graft were followed for a period of 6 years to determine the long term efficacy as a replacement to ICBG.

METHODS

Two prospective, multi-center FDA-approved IDE studies of patients who were undergoing treatment for single level lumbar degenerative disc disease were conducted utilizing a similar fusion technique through two different surgical approaches. All patents were entered into these studies between 1997 and 1999. Our analysis combines data from the patients who received treatment with the INFUSE® Bone Graft/LT-CAGE® Device in the two FDA IDE trials (Table 1). These studies used the identical inclusion-exclusion criteria (Table 2); however, the laparoscopic cohort was a single-arm study whereas patients in the open study were randomized to rhBMP-2/ACS or ICBG.

Inclusion Exclusion Criteria

At the time of surgery, all patients were between the ages of 19 and 70 years and had symptomatic degenerative disc disease at the L4-L5 or L5-S1 levels. All had low back pain for at least 6 months before their surgery that was recalcitrant to nonoperative treatment modalities, such as physical therapy, bed rest, and anti-inflammatory medications. Patients were included in the study if their plain radiographic findings documented single-level disc disease, and they had undergone at least one additional confirmatory neuroradiographic study, such as MRI, CT-enhanced myelography, or discography. All patients were considered candidates for a single-level stand-alone anterior lumbar interbody fusion.

Patients were excluded from the study if they had spinal conditions other than single-level symptomatic degenerative disc disease or Grade 0 or 1 spondylolisthesis. Other exclusion criteria were symptomatic disc disease at a level other than the L4-L5 or L5-S1 disc space levels, obesity (more than 40% above ideal body weight), or a medical

condition that required medication, such as steroids or nonsteroidal anti-inflammatory medications, that could interfere with fusion.

Patient Accountability and Demographics

There were 277 patients enrolled in both the open (143 patients) and laparoscopic (134 patients) groups in the initial FDA IDE studies. A total of 23 out of the 31 initial sites participated in the long term follow up. As a result of second surgery failures and non participating sites, a total of 219 patients (109 in the open arm and 110 in the laparoscopic arm) were eligible for the post-approval follow-ups. A total of 146 patients completed the 72-month follow-ups. This subgroup of patients who successfully completed the 72 month follow up was evaluated to determine the clinical outcome measures and fusion status at each time point (preoperative through 72 months).

Demographic data were compiled for the patients included in the analysis (Table 3). The two prospective study groups were not randomized; however, the patients' demographic characteristics and prognostic factors were similar except for sex and alcohol use.

Surgical Procedures

Patients underwent an ALIF procedure using either an open or a laparoscopic approach. Patients in the open group were enrolled in a prospective randomized clinical trial and patients in the laparoscopic group were enrolled in a prospective nonrandomized clinical trial. In the open group, either transperitoneal or retroperitoneal approaches to the lumbosacral spine were utilized; in the laparoscopic group, all approaches were transperitoneal. Patients had two LT-CAGE devices implanted anteriorly at one lumbar level.

rhBMP-2 on an absorbable collagen sponge was used exclusively as a bone graft replacement. No autogenous grafts and no local host bone reamings were used. The method of use of rhBMP-2 has been reviewed. The genetically engineered the rhBMP-2 component (Wyeth BioPharma, Cambridge, MA) and the absorbable collagen sponge component (Integra LifeSciences, Plainsboro, NJ) are distributed commercially under the trade name INFUSE® Bone Graft (Medtronic Sofamor Danek, Memphis, TN). The rhBMP-2 was reconstituted to a concentration of 1.5mg/ml using sterile water and applied to the appropriate number of absorbable collagen sponges (ACS). The rhBMP-2 was allowed to bind to the ACS for a minimum of 15 minutes, which results in 95% of the protein being bound to the sponge [13]. The rhBMP-2 soaked sponges were placed into the central portion of each LT-CAGE. No additional rhBMP-2-bound sponges were placed outside of the fusion cages. The total dose of rhBMP-2 ranged from 4.2 to 12 mg and was determined by matching the volume of the ACS to the internal volume of the LT-CAGE.

The results from the two surgical approaches were pooled and analyzed independently so as to better define the effects of surgical approach in surgical parameters, hospital stay, and the long-term clinical and radiographic outcomes.

Clinical Outcome Measures

Clinical outcome measures, including Oswestry Disability Index, Short Form 36 questionnaire, back and leg pain scores and return to work status were self administered preoperatively and at 1.5, 3, 6, 12, 24, 48, and 72 months. Back and leg pain scores were determined using a 20 point scale (10 points frequency and 10 points intensity).

Radiographic Assessment

The presence of continuous trabecular bone formation between the vertebral bodies was assessed using radiographs and computed tomography (CT) scans. Fusion was defined as bridging bone connecting the adjacent vertebral bodies either through the implants or around the implants, less than 5° of angular motion, less than or equal to 3 mm of translation, and an absence of radiolucent lines around more than 50% of either implant. Fusion was assessed at 6, 12, 24, 48, and 72 months, and was considered successful only if all four criteria were achieved.

Additional Surgical Procedures

Secondary surgical procedures performed subsequent to the index operation were classified as revisions, removals, supplemental fixations, or reoperations. A revision surgery was defined as any procedure that adjusts or modifies the original implant configuration; a removal was defined as a procedure that removes one or more components of the original implant replacing with different type of implant; supplemental fixation was defined as a procedure that additional spinal devices not approved as part of the protocol are placed; and re-operation was defined as any surgical procedure at the treated level that does not remove, modify, or add any components, for example a posterior foraminotomy. A survivorship analysis was used to determine the percentage of patients who were second surgery failures.

Adverse Events

Adverse events were studied and classified as to their severity and relationship with the implants and with surgical procedures.

RESULTS

Patient Accountability

A total of 146 patients (68 in the laparoscopic surgical group and 78 in the open surgical group) completed the 6 year follow up. The overall follow up rate was 52.7% (146/277), and the follow up rate for available patients at 6 years was 66.7% (146/219). A comparison of this subgroup of patients with the entire patient population prior to 24 months indicated similar clinical outcomes between the groups.

Surgical Data

Surgical, hospitalization and clinical outcomes were analyzed for each surgical technique and the outcomes were combined. Analysis of surgical and hospitalization data for the two surgical treatment groups (Table 4) shows the laparoscopic group spent an average 18 minutes longer under anesthesia and lost an average of 7.3 mL more blood. However, the laparoscopic group, on average, left the hospital 1.7 days earlier than the open group.

Clinical Outcomes

Oswestry Disability Scores: The Oswestry Disability Index (ODI) Questionnaire measures the level of pain and disability associated with various activities. For the combined surgical groups, ODI scores improved an average of 33.6 points and 31.0 points at 48 and 72 months, respectively, from a preoperative score of 52.0. These improvements were similar to those observed at 24 months (31.7 points). There was a trend towards slightly greater improvements in ODI scores in the laparoscopic group compared to the open group at 72 months (Fig 1).

Back Pain: For the combined surgical groups, back pain scores improved an average of 9.3 points and 8.6 points at 48 and 72 months, respectively. These improvements were

similar to those observed at 24 months (9.3 points). There was a trend towards slightly greater improvements in back pain scores in the laparoscopic group compared to the open group and 48 and 72 months (Fig 2).

Leg Pain: For the combined surgical groups, leg pain scores improved an average of 6.4 points and 6.7 points at 48 and 72 months, respectively. These improvements were similar to those observed at 24 months (6.4 points). The improvement from the preoperative score at 72 months was similar in the laparoscopic and open group (Fig 3).

SF-36: The SF-36 measures specific health concepts related to physical functioning, social functioning and health perceptions. For the combined surgical groups, SF-36 PCS scores improved an average of 17.3 points and 15.1 points at 48 and 72 months, respectively. These improvements were similar to those observed at 24 months (16.1 points). There was a trend towards slightly greater improvements in SF-36 PCS scores in the laparoscopic group compared to the open group at 48 and 72 months (Fig 4). Additional SF-36 scores improved significantly from preoperative values ($p<0.05$) and were maintained between 24 and 72 months (Table 5). There was a trend towards greater improvement in SF-36 scores in the open group compared to the laparoscopic group (Figure x).

Radiographic Outcomes: Radiographic fusion success is shown in Figure 5. At 72 months, 130 patients had complete radiographic follow up. At 48 and 72 months, 97.9% and 98.5% of patients had radiographic evidence of fusion. The high rates of fusion seen at these later time points were similar to the rates of arthrodesis seen at 6, 12, and 24 months. Fusion rates were similar between the open and laparoscopic groups.

Second Surgery Failures: There were a total of 25 second surgery failures in the 6 year follow up (16 in the open group and 9 in the laparoscopic group). Adjusting for the patients available at each follow up, the overall second surgery rate was 10.4% (13.7% in the open group and 7.1% in the laparoscopic group, Fig 7).

Return-to-Work Status: At 48 and 72 months, more patients were working than were working preoperatively (69.2% and 68.1% at 48 and 72 months, respectively compared to 52.1% preoperatively). The percentage of patients working at the later time points was similar to what was seen at 24 months (70.3%, Figure 6). By 6 months, approximately 90% of the patients who were working preoperatively had returned to work, and this was maintained though the 72 month time point.

Adverse events: No unanticipated adverse events that were related to the use of rhBMP-2 and the collagen sponge carrier occurred during the course of the study.

DISCUSSION

Discogenic low back pain results, in part, from abnormal intersegmental load patterns and movement within a degenerative disc. Clinically painful discs have been shown to display specific patterns of altered stresses in the annulus and vertebral endplates, reflecting abnormal loading. Lumbar interbody fusion can eliminate abnormal stress patterns associated with degenerative disc disease and normalize stress distribution patterns. Threaded interbody fusion cages stabilize the spinal motion segment and provide a mechanical environment that optimizes fusion. The threaded cages provide a temporary scaffold allowing bone to grow and protect the segment from collapse during the fusion process. However, the fusion cages alone transmit high focal load to the adjacent vertebrae. New bone formation in and around the mesh cage increases the contact area and decreases the magnitude of abnormal load in the adjacent vertebrae. The small weight-bearing surface of the cages is largely dependent on bone formation within and around it to take load and to reestablish normal stresses between the vertebra. A successful bony fusion restores near physiologic stress distribution patterns.

Recombinant human bone morphogenetic protein (rhBMP-2) is an osteoinductive growth factor that stimulates pleuripotential cells to form bone. In animal and human studies, rhBMP-2 has been shown to be capable of inducing new bone formation. Results from prospective, randomized studies of the LT-CAGE Lumbar Tapered Fusion Device have showed a trend towards faster fusion with INFUSE® Bone Graft and improved clinical outcomes when compared with patients who received autograft ICBG. These improved outcomes are related, in part, to the successful

combination of the surgical approach, the advanced cage designs, the avoidance of bone graft harvesting morbidity, and the high rate of successful interbody fusion.

This study represents the longest follow up to date of patients undergoing spine fusion with INFUSE® Bone Graft. In patients followed out to 6 years, it was observed that radiographic fusion rates were high, rates of second surgery were low, and improvements in clinical outcomes were maintained.

Various other studies have reported on the long term radiographic and clinical results following lumbar interbody fusion [14-19]. Kuslich et al. reported on 4 year results from a study enrolling 947 patients who received Bagby and Kuslich (BAK) cages and ICBG [18]. A total of 196 patients completed the 4 year follow up (20.7%), which included anterior (n=122) and posterior (n=74) approaches and single level (n=116) and 2-level (n=80) fusions. Fusion success allowed for up to 7° of angulation on flexion extension films. At 4 years, the authors reported an overall fusion success of 98% and a repeat surgery rate of 8.7%. Pain scores were maintained out to 4 years.

In a similar study, clinical and radiographic outcomes following ALIF with BAK cages implanted by a single author were evaluated [17]. Patients underwent single level (n=40) or 2-level (n=6) ALIF with BAK Cages and autograft, allograft, or a combination of both. A total of 33 out of 46 patients (71.7%) reached a mean follow up of 55 months (range = 36-65 months). The authors reported an overall nonunion rate of 30% and a revision rate of 22%. Mean ODI score at final follow up was 41, with only 42% of patients having an ODI ≤ 40. The fusion rates and improvement in ODI scores at 4 and 6 years in patients treated with INFUSE® Bone Graft and the LT CAGE® Device indicate an improvement relative to this published report.

Brantigan also investigated the long term results following instrumented PLIF. The initial study enrolled a total of 110 patients with degenerative disc disease at 6 centers. A total of 33 patients selected from 2 centers completed the 10 year follow up (30%). Radiographic evidence of fusion, as defined by bridging bone and the absence of radiolucencies was reported in 96.7% of the patients at 10 years. At 2 years, elective removal of pedicle screws indicated that 90% (104/115) of the examined levels were fused. Clinical outcomes, were measured using an extended Prolo scale and a 5 point Likert scale. An excellent or good clinical outcome at was reported in 88% of patients at 10 years. Preoperatively, only 24% of these patients had a poor rating, however. Clinical success was modeled after an expanded Prolo scale and included patients with a rating of excellent, good, or fair. At 10 years, 87.8% (29/33) of patients had achieved clinical success. Preoperatively, 76% of patients met this definition of clinical success, however, resulting in a net change of only 11.8% of patients. In the current study, 79% (109/138) of patients treated with INFUSE Bone Graft had an ODI improvement of greater than 15 points at 6 years.

In the current study, patients treated by the laparoscopic surgical technique trended to have improved outcomes in shortened hospital stay, better Oswestry Low Back Pain Disability Questionnaire scores, Physical Component Scores on the SF-36 Health Survey and reduced low back pain, and fewer reoperations when compared to the open surgically treated group. Preoperatively, there were differences in certain patient demographics including sex and alcohol use that may have contributed in part to these differences. Additionally, 9 patients in the open surgical group had ODI scores increase by more than 30 points between 24 and 72 months, and 18 patients had an ODI increase

of 20 points or more. No patients in the laparoscopic group had their ODI score increase by more than 30 points, and only 1 patient had an ODI score increase by more than 20 points. Case report forms for patients in the open group revealed the occurrence of falls, motor vehicle accidents, and adjacent level disease. Additionally, all patients with a 30 point increase in ODI had a BMI > 25 that may have contributed in part to the increase in ODI scores and the differences seen between the open and laparoscopic groups. The lack of randomization between these groups makes it difficult to draw definitive conclusions as to the specific cause(s) for this difference, however. Importantly, the mean improvement scores for both groups in Oswestry pain scores, PCS scores, and back and leg pain were maintained between the 24 and 72 month follow-up period. These functional improvements are also reflected in the high rates of employment in both groups.

In this long term follow up, the ICBG control patients from the open surgical treatment group were not followed. Therefore, no conclusions can be drawn relative to these patients. Additionally, 146 of 277 total patients (52.7%) and 146 of 219 available patients (66.7%) completed 4 year radiographic and clinical follow up. This subgroup of patients had similar outcomes when compared to the entire patient population prior to 24 months, and thus serves as a representative subgroup of the entire patient population.

The use of rhBMP-2 on an absorbable collagen-soaked sponge (INFUSE® Bone Graft) is an effective method of facilitating anterior intervertebral spinal fusion using a stand-alone interbody fusion device. Fusion success and improved clinical outcomes were maintained through 72 months. INFUSE Bone Graft demonstrates long term efficacy as a replacement to ICBG for lumbar spine fusion.

CONCLUSIONS

This paper reports the clinical and radiographic outcomes from patients treated with INFUSE® Bone Graft and threaded titanium cages with 6 years follow up. rhBMP-2 was shown to lead to high rates of fusion that was maintained out to 6 years. Additionally, improvements in clinical outcome measures, including ODI, SF-36 PCS, and back and leg pain scores were maintained out to 72 months. These results further substantiate the use of rhBMP-2 as a replacement to autograft for lumbar interbody fusion.

REFERENCES

Blumenthal SL, Baker J, Dossett A, Selby DK: The role of anterior lumbar fusion for internal disc disruption. *Spine* 1988;13: 566-9.

Burkus JK, Dorchak JD, Sanders DL. Radiographic assessment of interbody fusion using recombinant human bone morphogenetic protein type-2. Spine 2003 Feb 15;28(4):372-377

Burkus JK. Intervertebral fixation: clinical results with anterior cages. *Orthop Clin North Am* 2002;33: 349-57

Burkus JK. Stand-alone anterior lumbar interbody fusion constructs: effect of interbody design, bone graft and bone morphogenetic protein on clinical and radiographic outcomes. In: Lewandrowski K, Yaszemski MJ, White AA, Trantolo DJ, Wise, DL (eds.) *Advances in Spinal Fusion: Clinical Applications of Basic Science, Molecular Biology, Biomechanics, and Engineering.* New York: Marcel Dekker, Inc.; 2003:69-84

Fairbank JCT, Couper J, Davies JB, O'Brien JP. The Oswestry Low Back Pain Disability Questionnaire. Physiotherapy 1980;66:271-273.

Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2. A prospective study of clinical and radiographic outcomes. Spine 2001;26:2751-6.

Kumar N, Judith MR, Kumar A, Mishra V, Robert MC. Analysis of Stress Distribution in Lumbar Interbody Fusion. Spine 2005; 30:1731-35.

Palm WJ, Rosenberg WS, Keaveny TM. Load Transfer Mechanisms in Cylindrical Interbody Cage Constructs. Spine 2002; 27:1201-07

McHorney CA, Ware JE Jr., Lu RJF, Sherbourne CD. The MOS 36-Item Short-From Health Survey (SF-36), III: tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994;32:40-66

McKay B, Sandhu HS. Use of recombinant human bone morphogenetic protein-2 in spinal fusion applications. Spine 2002;27(16 Suppl 1):S66-85.

McNally DS, Shackleford IM, Goodship AE, et al. In vivo stress measurement can predict pain on discography. *Spine* 1996;21:2580–7.

Newman MH, Grinstead GL: Anterior lumbar interbody fusion for internal disc disruption. *Spine* 17: 831-833, 1992.

Sandhu HS, Kanim LE, Kabo JM, Toth JM, Zeegen EN, Liu D, Delamarter RB, Dawson EG. Effective doses of recombinant human bone morphogenetic protein-2 in experimental spinal fusion. Spine 1996;21:2115-22.

Sandhu HS, Toth JM, Diwan AD, Seim HB, Kanim LE, Kabo JM, Turner AS. Histologic evaluation of the efficacy of rhBMP-2 compared with autograft bone in sheep spinal anterior interbody fusion. Spine 2002;27:567-75.

Sasso RC, Kitchel SH, Dawson EG. A prospective, randomized controlled clinical trial of anterior lumbar interbody fusion using titanium cylindrical threaded fusion device. *Spine* 2004;29:113-22.

Poynton AR, Lane JM. Safety profile for the clinical use of bone morphogenetic proteins in the spine. Spine 2002;27(16 Suppl 1):S40-8.

Urist MR. Bone: formation by autoinduction. Science 1965;150:893-9

Ware JE Jr, Sherbourne CD. The MOS 36-Item Short-From Health Survey (SF-36), I: conceptual framework and item selection. Med Care. 1992;30:473-483.

Table 1. Summary of study groups analyzed.

Surgical approach	Randomized	Prospective	Total Patients	Patients w/ 72 mo f/u
Open	Y	Y	143	78
Laparoscopic	N	Y	134	68

Table 2. Patient inclusion/exclusion criteria

Inclusion Criteria	Exclusion Criteria
▪ ≥ 18 yrs old ▪ Single level symptomatic DDD ▪ ≤ Grade 1 spondylolisthesis ▪ Disabling back pain and/or leg pain for greater than 6 months unresolved by nonoperative treatment	▪ Spinal conditions other than DDD ▪ DDD at disc space levels other than L4-L5 or L5-S1 ▪ Previous anterior fusion at involved level ▪ Obesity (>40% above ideal weight) ▪ Active bacterial infection ▪ Medical condition requiring medication that could interfere with fusion (eg steroids or NSAIDS)

DDD = degenerative disc disease; NSAID = nonsteroidal anti-inflammatory medication

Table 3. Patient demographics.

	Open	Laparoscopic	Combined
Number	78	68	146
Age (yr)	43.1	43.3	43.2
Weight (lbs)	181.1	172.6	177.2
Gender (% male)	56.4	38.2	47.9
Smoking (%)	26.9	27.9	27.4
Worker's Compensation (%)	30.8	25.0	28.1
Unresolved litigation (%)	10.3	10.3	10.3

Table 4. Surgical data

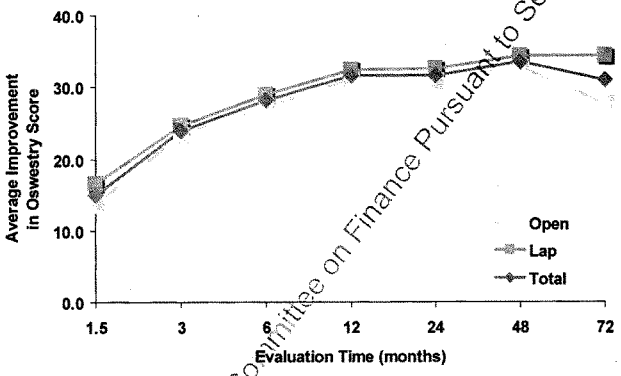
	Open	Laparoscopic	Combined
OR Time (hr)	1.6	1.9	1.8
Blood Loss (ml)	118.7	126.0	122.1
Length of Stay (days)	3.1	1.4	2.3

Table 5: Mean (S.D.) change in SF-36 scores from preoperative to 72 months.

	Open	Laparoscopic	Combined
PCS	12.4 (12.6)	17.8 (10.2)	15.1 (11.7)
MCS	4.9 (13.2)	7.3 (10.2)	6.1 (11.8)
Physical Function	31.5 (30.4)	42.8 (26.8)	37.0 (29.1)
Role Physical	50.7 (46.2)	64.3 (43.0)	57.4 (45.0)
Pain Index	34.8 (27.6)	43.9 (25.8)	39.3 (27.0)
General Health Perception	-8.3 (27.0)	5.0 (17.3)	-1.7 (23.6)
Social Function	29.8 (31.7)	41.2 (27.7)	35.4 (30.2)
Mental Health	15.8 (23.5)	16.4 (20.1)	16.1 (21.8)
Role Emotional	10.1 (52.5)	26.0 (40.7)	18.0 (47.5)
Vitality	18.8 (24.6)	27.1 (23.0)	22.9 (24.1)

Note: Changes in SF-36 scores from preoperative to 24 months were similar between groups.

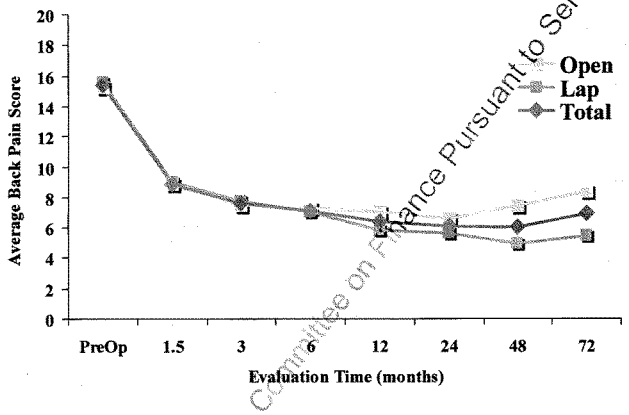
Figure 1: Improvement in Oswestry Disability Index.



Long Term LT CAGE/InFUSE Outcomes
JK Burkus, MF Gornet, TA Zdeblick

26

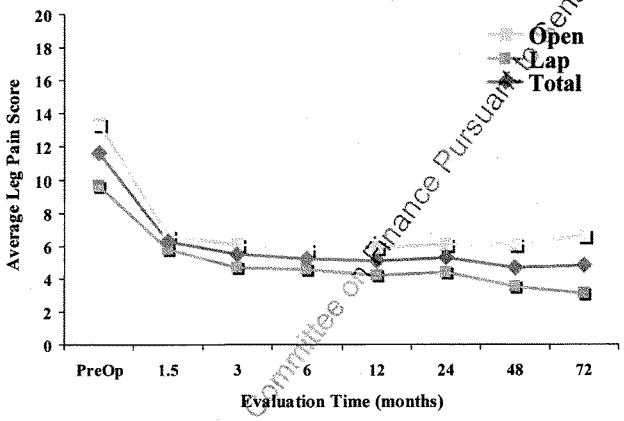
Figure 2: Back pain scores.



Long Term LT CAGE/InFUSE Outcomes
JK Burkus, MF Gornet, TA Zdeblick

27

Figure 3: Leg pain scores.



Long Term LT CAGE/InFUSE Outcomes
JK Burkus, MF Gornet, TA Zdeblick

28

Figure 4: SF-36 PCS.

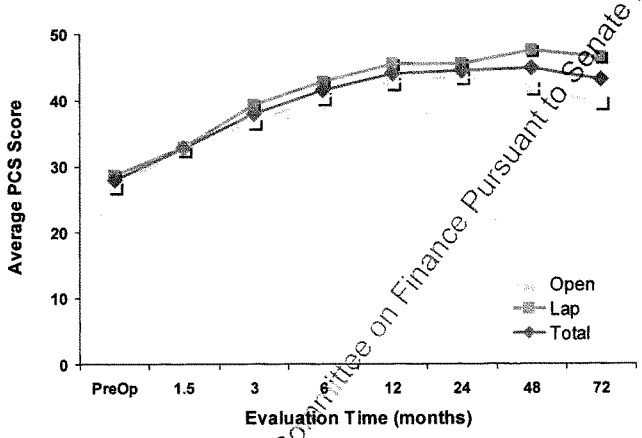
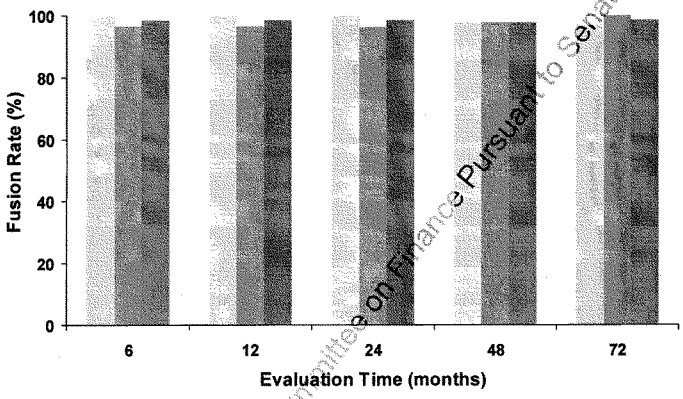


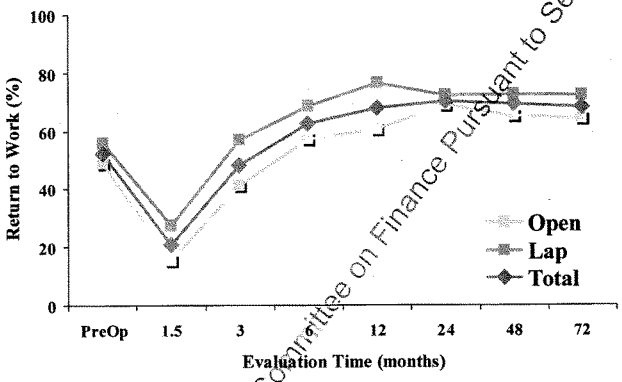
Figure 5: Radiographic fusion success.



Long Term LT CAGE/InFUSE Outcomes
JK Burkus, MF Gornet, TA Zdeblick

30

Figure 6: Return to work status.



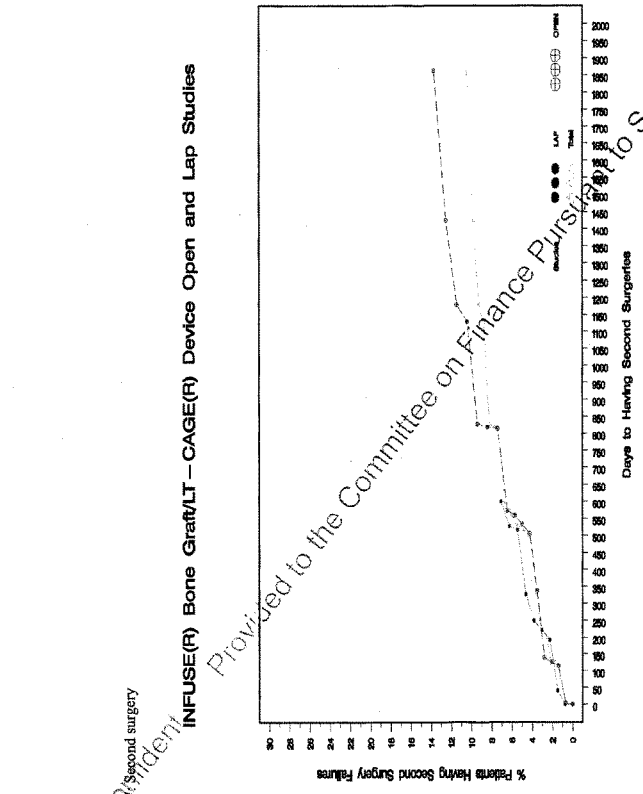
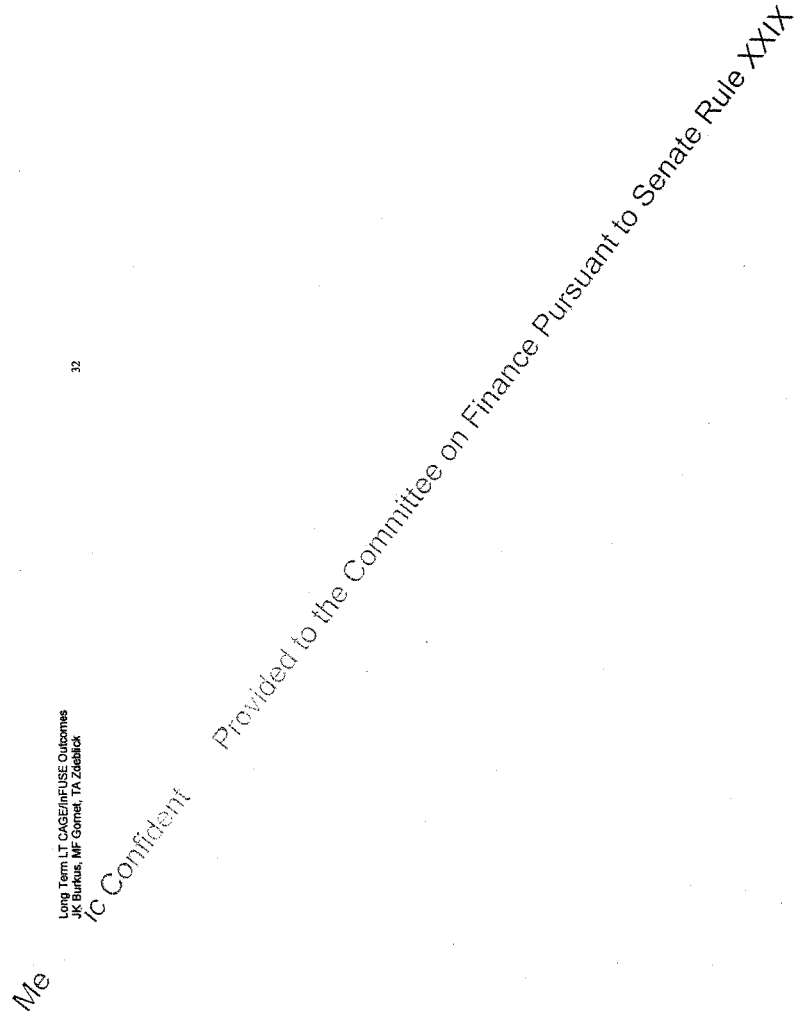


Figure 7: Second surgery failures.


Me
Long Term LT CAGE/inFUSE Outcomes
JK Burkus, MF Gornet, TA Zdeblick
/c Confident
Provided to the Committee on Finance Pursuant to Senate Rule XXIX

1. Boden, S.D., et al., *The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report.* Spine, 2000. **25**(3): p. 376-81.
2. Burkus, J.K., et al., *Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages.* J Spinal Disord Tech, 2002. **15**(5): p. 337-49.
3. Burkus, J.K., et al., *Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-CAGE lumbar tapered fusion device.* J Spinal Disord Tech, 2003. **16**(2): p. 113-22.
4. Burkus, J.K., et al., *Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery.* J Bone Joint Surg Am, 2005. **87**(6): p. 1205-12.
5. Anand, N., et al., *Cantilever TLIF with structural allograft and RhBMP2 for correction and maintenance of segmental sagittal lordosis: long-term clinical, radiographic, and functional outcome.* Spine, 2006. **31**(20): p. E748-53.
6. Kuklo, T.R., M.K. Rosner, and D.W. Polly, Jr., *Computerized tomography evaluation of a resorbable implant after transforaminal lumbar interbody fusion.* Neurosurg Focus, 2004. **16**(3): p. E10.
7. Lanman, T.H. and T.J. Hopkins, *Lumbar interbody fusion after treatment with recombinant human bone morphogenetic protein-2 added to poly(L-lactide-co-D,L-lactide) bioresorbable implants.* Neurosurg Focus, 2004. **16**(3): p. E9.
8. Mummaneni, P.V., et al., *Contribution of recombinant human bone morphogenetic protein-2 to the rapid creation of interbody fusion when used in transforaminal lumbar interbody fusion: a preliminary report. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2004.* J Neurosurg Spine, 2004. **1**(1): p. 19-23.
9. Potter, B.K., et al., *Transforaminal lumbar interbody fusion: clinical and radiographic results and complications in 100 consecutive patients.* J Spinal Disord Tech, 2005. **18**(4): p. 337-46.
10. Schwender, J.D., et al., *Minimally invasive transforaminal lumbar interbody fusion (TLIF): technical feasibility and initial results.* J Spinal Disord Tech, 2005. **18 Suppl**: p. S1-6.
11. Slosar, P.J., R. Josey, and J. Reynolds, *Accelerating lumbar fusions by combining rhBMP-2 with allograft bone: a prospective analysis of interbody fusion rates and clinical outcomes.* Spine J, 2007. **7**(3): p. 301-7.
12. Villavicencio, A.T., et al., *Safety of transforaminal lumbar interbody fusion and interveriebral recombinant human bone morphogenetic protein-2.* J Neurosurg Spine, 2005. **3**(6): p. 436-43.
13. Hsu, H.P., et al., *Comparing ectopic bone growth induced by rhBMP-2 on an absorbable collagen sponge in rat and rabbit models.* J Orthop Res, 2006. **24**(8): p. 1660-9.
14. Bagby, G., *The Bagby and Kuslich (BAK) method of lumbar interbody fusion.* Spine, 1999. **24**(17): p. 1857.
15. Brantigan, J.W., A. Neidre, and J.S. Toohey, *The Lumbar I/F Cage for posterior lumbar interbody fusion with the variable screw placement system: 10-year*

results of a Food and Drug Administration clinical trial. Spine J, 2004. **4**(6): p. 681-8.
16. Brantigan, J.W., et al., *Lumbar interbody fusion using the Brantigan I/F cage for posterior lumbar interbody fusion and the variable pedicle screw placement system: two-year results from a Food and Drug Administration investigational device exemption clinical trial.* Spine, 2000. **25**(11): p. 1437-46.
17. Button, G., et al., *Three- to six-year follow-up of stand-alone BAK cages implanted by a single surgeon.* Spine J, 2005. **5**(2): p. 155-60.
18. Kuslich, S.D., et al., *Four-year follow-up results of lumbar spine arthrodesis using the Bagby and Kuslich lumbar fusion cage.* Spine, 2000. **25**(20): p. 2656-62.
19. Kuslich, S.D., et al., *The Bagby and Kuslich method of lumbar interbody fusion. History, techniques, and 2-year follow-up results of a United States prospective, multicenter trial.* Spine, 1998. **23**(11): p. 1267-78; discussion 1279.

From: Ken Burkus[redacted]
Sent: Saturday, January 19, 2008 02:49:26 PM
To: Carol Binns[redacted] ; Hatcher, Brian, PhD.; Bearcroft, Julie, PhD
Subject: Mastergraft BMP Manuscript

Attachments: Infuse MGG Manuscript Response final 2008.doc

Carol, Brian & Julie.

This manuscript is an absolute pleasure to read. It condenses so much information in such a tight format. JBJS is lucky to have this submission.

SEND IT IN WITH BRIAN'S ADDITIONS AND CHANGES.

I made a few small changes highlighted in blue on pages 6 and 7.

Best.
Ken Burkus

Use of rhBMP-2 on an Absorbable Collagen Sponge Combined with an Osteoconductive Bulking Agent in Instrumented Posterolateral Fusion: Clinical and Radiographic Outcomes from a Prospective, Randomized Trial

ABSTRACT

Background: Recombinant human bone morphogenetic protein-2 soaked into an absorbable collagen sponge (rhBMP-2/ACS) has been shown to be a safe and effective replacement for an iliac crest bone graft in anterior lumbar interbody fusions when used with a threaded fusion device. In posterolateral lumbar fusions, rhBMP-2/ACS requires the addition of a bulking agent to provide compression resistance and serve as an osteoconductive scaffold for new bone formation.

Methods: In this prospective, randomized, multicenter pilot study of forty-six patients, we used rhBMP-2/ACS combined with a ceramic granule bulking agent as an alternative to autogenous iliac crest bone graft in instrumented single-level posterolateral lumbar arthrodesis. The investigational group (n = 25) received rhBMP-2/ACS (1.5 mg/cc, 12 mg total dose) combined with 10 cc of ceramic granules. The control group (n = 21) received iliac crest bone graft. Clinical outcomes were assessed using well-established instruments. Radiographs were reviewed for consolidation of fusion.

Results: At all follow-up intervals, there were statistically significant improvements in clinical outcome measures in both treatment groups. There was a trend toward greater improvement in Oswestry Disability Index scores, Short Form-36 scores, and back and leg pain scores in the investigational group than in the control group. By 24 months, 95% of the investigational patients had a radiographically documented fusion compared with 70% of the control patients (p = 0.091).

Deleted: 46

Deleted: ceramic

Deleted: time

Conclusions: This is the first prospective randomized clinical study evaluating rhBMP-2/ACS combined with ceramic granules for posterolateral fusion without iliac crest bone graft. In this study, combining rhBMP-2/ACS with ceramic granules resulted in a higher rate of radiographic fusion success in the investigational group than in the control group who received an iliac crest bone graft. Clinical outcomes in both groups were significantly improved by 6 weeks from preoperative values, and improvements were maintained at 24 months. There was a trend toward greater improvement in the rhBMP-2 group. This combination of an osteoinductive agent with an osteoconductive matrix may be an effective autograft replacement for single-level instrumented posterolateral fusions.

Level of Evidence: Therapeutic Level I

Deleted: and maintained out to 24 months

INTRODUCTION

Recombinant human bone morphogenetic protein-2 combined with an absorbable collagen sponge (rhBMP-2/ACS) has been shown to be a safe and effective replacement for autogenous iliac crest bone graft (ICBG) for anterior lumbar interbody fusion[1]. In a pooled analysis of 679 patients undergoing lumbar interbody fusion, patients treated with rhBMP-2 had significantly higher fusion rates than patients treated with ICBG (94.4% vs. 89.4%; p = 0.022)[2]. These fusion rates with rhBMP-2 in lumbar interbody fusion are consistent with those in other published reports[1-8].

Reported fusion rates from posterolateral interbody fusion procedures using ICBG vary widely from 73% to 95%[9-14], and can depend on numerous factors such as diagnosis and fusion assessment methods. To date, there have been no prospective randomized trials published on the use of rhBMP-2/ACS in posterolateral fusions. When rhBMP-2/ACS was first investigated in nonhuman primate models for its ability to induce posterolateral fusion, it was observed that the absorbable collagen sponge alone did not lead to a robust fusion mass[15]. When the sponge was combined with an osteoconductive bulking agent capable of providing compression resistance and longer-term scaffolding, robust bone formation and high rates of arthrodesis were reported[16,17].

A series of studies were undertaken to determine the optimal ceramic composition for use with rhBMP-2. These studies showed that ceramics high in hydroxyapatite content (60% hydroxyapatite/40% tricalcium phosphate) resulted in fusion masses containing residual ceramic at six months, and ceramics high in

Deleted: , INFUSE® Bone Graft, Medtronic Sofamor Danek, Memphis, TN

Deleted: [1]

Deleted: with rhBMP-2 in lumbar interbody fusion

Deleted: Posterolateral fusion rates achieved with ICBG vary

Deleted: widely in the literature from 73% - 95%[9-14] [1]

Deleted: .

Deleted: may

Deleted: including patient

Deleted: reported

Deleted: INFUSE® Bone Graft

Deleted: the

Deleted: ACS

Deleted: mass[15]

Deleted: ACS

Deleted: longer

Deleted: reported[16]

Deleted: [17]

Deleted:

Deleted: HA

Deleted:

Deleted: HA:TCP

Deleted: 6

biphasic ceramic phosphate (5% hydroxyapatite/95% tricalcium phosphate) led to smaller fusion masses as a result of rapid remodeling[18]. The 15% hydroxyapatite/85% tricalcium phosphate composition (MasterGraft® Ceramics; Medtronic Sofamor Danek, Memphis, TN) has demonstrated an optimal resorption profile and led to high rates of fusion when used as a bulking agent with rhBMP-2/ACS[16-19]. Applying rhBMP-2 to the collagen sponge at 1.5 mg/cc and wrapping it around either 15% hydroxyapatite/85% tricalcium phosphate ceramic granules or compression resistant matrix (CRM) has been shown to reliably induce fusion and lead to ceramic incorporation by six months in nonhuman primates[16,17].

The purpose of this study was to investigate rhBMP-2 on an absorbable collagen sponge combined with the 15% hydroxyapatite/85% tricalcium phosphate ceramic granule as a replacement for an iliac crest bone graft in instrumented posterolateral fusion.

MATERIALS and METHODS

Study Design

Institutional review board approval was obtained and all patients gave their informed consent before participating in this study, conducted at four centers by seven surgeons. Forty-six patients were enrolled in this prospective, randomized, multicenter, FDA-approved, Investigational Device Exemption (IDE) pilot trial between April 2003 and August 2004. Patients who were undergoing treatment for degenerative disc disease were randomly assigned to either the investigational group or to the control group. Randomization was stratified by site

Deleted: β-TCP
Deleted: :
Deleted:
Deleted: HA:TCP
Deleted: remodeling
Deleted: :
Deleted: HA:TCP
Deleted: [16-19]
Deleted: :
Deleted: ACS
Deleted: :
Deleted: HA:TCP
Deleted: primates[16]
Deleted: [17]
Deleted: /ACS
Deleted: :
Deleted: HA:TCP
Deleted: , which was
Deleted: 4
Deleted: 7
Deleted: (INFUSE/MasterGraft™ Posterolateral Revision Device, Medtronic Sofamor Danek, Memphis, TN)
Deleted: (iliac crest bone graft) in a single-level instrumented posterolateral arthrodesis.
Deleted:

with a fixed block size of four. Twenty-five patients in the investigational group received the INFUSE/MasterGraft™ Posterolateral Revision Device (Medtronic Sofamor Danek, Memphis, TN) and 21 patients in the control group received ICBG in a single-level instrumented posterolateral arthrodesis. After consent and randomization, two patients in each group elected not to participate in the study. Preoperatively, all patients met the inclusion criteria of symptomatic, single-level degenerative disc disease in the lumbar spine from L1 through S1. Degenerative lumbar disc disease was confirmed by patient history, objective physical findings, and correlative neuroradiographic studies confirming instability, osteophyte formation, decreased disc height, thickening of ligamentous tissue, disc degeneration or herniation, or facet joint degeneration. The clinical symptoms included low back pain and radicular leg pain. All patients had failed to respond to nonoperative treatment for a minimum of six months. Additional enrollment criteria were a grade I or less spondylolisthesis and no previous surgery at the index level. Patient demographics were similar in the two groups; there were no statistically significant differences ($p < 0.05$) between the demographic profiles (Table 1).

Surgical Technique

Device Preparation

Investigational group patients received INFUSE/MasterGraft™ Posterolateral Revision Devices, implants of rhBMP-2 on an absorbable collagen sponge combined with ceramic granules. A single 3 in x 4 in sponge from a Large II Kit of INFUSE® Bone Graft (Medtronic Sofamor Danek, Memphis, TN)

Deleted: Twenty five
Deleted: were randomized
Deleted: to
Deleted:
Deleted: and/
Deleted: P
Deleted: INFUSE/MasterGraft™ Posterolateral Revision

was sectioned in half into two 2 in x 3 in pieces (Figure 1). RhBMP-2 was reconstituted in the standard fashion at a concentration of 1.5 mg/cc, and 4 mL of solution was applied to each of the two sponge strips. Thus, each patient in the investigational group received 12 mg of rhBMP-2 on 8 cc of the collagen sponge. The ceramic granules used as the bulking agent are a 15:85 blend of hydroxyapatite and tricalcium phosphate (MasterGraft® Granules, Medtronic Sofamor Danek, Memphis, TN). No rhBMP-2 was applied directly to the ceramic. After allowing the rhBMP-2 to bind to the collagen sponge for at least fifteen minutes, 5 cc of the ceramic granules were distributed and rolled within each of the ACS strips.

Surgical Procedure.

Both patient groups underwent an instrumented posterolateral fusion procedure through a standard open midline approach using the CD Horizon® Spinal System (Medtronic Sofamor Danek, Memphis, TN). Posterior decompression of the spinal canal was carried out, as needed. The transverse processes were exposed bilaterally, and their dorsal surfaces were decorticated. The morcellized autogenous iliac crest bone graft or the INFUSE/MasterGraft montage was then placed into the lateral gutters and along the pars interarticularis. Pedicle screws were placed and rods attached. Importantly, all local autograft obtained as a result of the decompression was discarded and not used in either group. No interbody fusion was performed in either group.

Radiographic Analysis

Deleted: INFUSE/MasterGraft™ Posterolateral Revision Device

Deleted: with use of

Deleted: bilaterally

Deleted: morselized

Radiographic assessment of fusion was performed at six, twelve, and twenty-four months after surgery by two independent radiologists who were blinded to the treatment assignment. A third reviewer was available for adjudication. Plain radiographs, lateral flexion and extension radiographic views, and thin-cut computed tomography scans with sagittal and coronal reconstructions were used to evaluate the fusion mass. A successful arthrodesis, as outlined in the IDE fusion criteria, was defined as bridging trabecular bone between the transverse processes, the absence of motion (≤3 mm of translation and <5° of angulation on flexion-extension views), and the absence of radiolucent lines through the fusion mass (Figure 2).

Clinical Outcome Measures

Clinical and functional outcomes were assessed preoperatively and at six weeks and at three, six, twelve, and twenty-four months postoperatively. Clinical outcomes were measured using the Oswestry Disability Index (ODI)[20], the 36-Item Short Form Health Survey® (SF-36)[21], and return-to-work status. Back, leg, and donor site pain scores were determined using numeric rating scales of 0-20 (10 points frequency and 10 points intensity).

Deleted: [14]

Deleted: [15]

Statistical Methods

For statistical comparisons between the treatment groups, analysis of variance (ANOVA) was used for continuous variables, and Fisher's exact test was used for categorical data. For assessing the statistical significance of postoperative improvement in outcome scores from preoperative status within each treatment group, a paired *t*-test was used.

RESULTS

Surgery

Surgical data for the two groups are shown in Table 2. Operating times and hospital stays were similar for the two groups. The investigational group patients showed a trend toward less blood loss. Patients in the control group had a mean graft volume of 42.4 ± 29.9 cc (range, 10-80 cc).

Clinical Follow Up

At twenty-four months, 88% (22/25) of the investigational patients and 86% (18/21) of the control patients were available for follow up. There were two second surgery failures and one death in the investigational group, and two second surgery failures and one patient without a 24-month follow-up examination in the control group.

Clinical outcome measures showed statistically significant improvements over the preoperative scores in both groups, with the investigational group showing trends toward greater improvement than the control group. At twenty-four months, the mean Oswestry score in the investigational group had improved 28.2 points from the preoperative score, compared with 23.0 points for the control group (p = 0.336; Table 3 and Figure 3). With regard to Oswestry scores, 91% (twenty-one of twenty-three) of the investigational patients and 70% (fourteen of twenty) of the control patients achieved a 20% improvement (p = 0.081).

Deleted: 2

Deleted: 1

Deleted: 2

Deleted: 1

Deleted: 24

There was also a trend toward greater improvement in SF-36 scores in the investigational group at twenty-four months, including the Physical Component Summary score (13.0 versus 9.9 points; p = 0.394) and physical function score (36.3 versus 18.5 points, p = 0.034) (Table 4 and Figure 4). At twenty-four months, the mean back pain scores for the investigational group and the iliac crest bone graft group had improved 9.6 and 7.2 points, respectively (p = 0.183) (Table 5 and Figure 5). Similarly, the mean leg pain scores at twenty-four months for the investigational group and the control group had improved 9.3 and 7.2 points, respectively, from preoperative scores (p = 0.347) (Table 6 and Figure 6). In the control-group patients, who were treated with iliac crest bone graft, 70% (14/20) were still experiencing donor site pain at twenty-four months, with a mean pain score of 8.6 (out of a possible score of 20) (Figure 7). Pain scores for donor site pain or for generalized pelvic pain were not obtained in the investigational group of patients.

Fusion Assessment

Deleted: ¶

At each time interval, there was a trend toward greater fusion success in the investigational group. Evidence of fusion, as defined by the stringent IDE fusion criteria, was 22%, 16%, and 25% higher in the investigational group than in the control group at six, twelve, and twenty-four months. At the twenty-four-month follow up, 95% (eighteen of nineteen) of investigational patients had evidence of fusion compared with 70% (fourteen of twenty) of control patients (p = 0.091; Table 7).

Computed tomography scans provide high-resolution detail and a sensitive means of assessing bone formation. In this study, thin-cut axial slices (1-mm) along with coronal and sagittal reconstructions were evaluated to assess the presence of bridging trabecular bone. At six, twelve, and twenty-four months, 90% to 95% of the investigational patients had evidence of bridging bone. At last follow up, 95% of investigational patients and 67% of control patients had bridging trabecular bone ($p = 0.038$; Table 8). Thin-cut CT scan reconstructions demonstrated the progressive formation of bridging bone across the transverse processes and illustrated incorporation and remodeling of the ceramic component (Figure 8).

Additional Surgery or Treatment

Two patients sustained incidental durotomies intraoperatively, which were repaired (one in each group). Two patients developed wound infections at the surgical site, which resolved after antibiotic treatment (one in each of the two groups). One control patient had an infection at the graft site. There were two second surgery failures in the investigational group—a revision procedure one day after the initial surgery due to bilateral malpositioned pedicle screws and a hardware removal at six months. In the control group, there were two revision procedures for pseudarthrosis.

Return to Work

By twenty-four months, 35% (eight of twenty-three) of the patients in the investigational group were working (Figure 9), including all patients who were working before surgery (six of six). In the control group, 30% (six of twenty) of the

Deleted: ¶

Deleted: ¶

patients had returned to work, including six of nine patients who were working before surgery.

Deleted: 67% (

Deleted:) of those

DISCUSSION

In this report, we present the first Level-1 data evaluating rhBMP-2/ACS combined with a 15% hydroxyapatite/85% tricalcium phosphate osteoconductive ceramic bulking agent as a replacement for iliac crest bone graft in instrumented posterolateral fusion. Fusion rates in the investigational group were 16% to 25% higher than in the control group at the follow-up time points examined. Additionally, there were trends toward greater improvements in clinical outcome measures in the patients treated with the rhBMP-2/ACS/ceramic.

Deleted: Level-1

Deleted: 15

Deleted:

Deleted: HA:TCP

Others have investigated the use of rhBMP-2 when combined with local autograft bone as a bulking agent in posterolateral fusion.[9,22] In the first human study investigating rhBMP-2/ACS in posterolateral fusions, Singh et al.[9] reported that the use of rhBMP-2 led to higher fusion rates and better fusion quality than iliac crest bone graft alone. At twelve and twenty-four months, 97% (sixty-eight/seventy) of the levels in the rhBMP-2/ACS patients were graded as fused, compared with 77% (seventeen/twenty-two) of the levels in autograft patients ($p < 0.05$). Additionally, 92% (thirty-six/thirty-nine) of patients treated with rhBMP-2/ACS and autograft had excellent fusion quality, compared with only 27% (three/eleven) of the autograft-alone patients ($p < 0.05$). These published results are consistent with those reported in our study at twenty-four months, in which no autograft bone was added to the rhBMP-2/ACS/ceramic implant.

Deleted: [9,22]

Deleted: [9]

Deleted: alone[9]

Deleted: of

Deleted: 97

In a separate study, Glassman et al.[22] reported on patients who had undergone posterolateral fusion with rhBMP-2/ACS and various bulking agents, such as local bone, MasterGraft® Granules, demineralized bone matrix, allograft, or a combination of local bone with one of the other bulking agents. In this clinical series, which included primary and revision procedures and single-level and multilevel fusions, 93% of the patients had radiographic evidence (computed tomography scans) of fusion at a mean follow up of twenty-seven months. These studies by Singh et al.[9] and Glassman et al.[22] provide further evidence of the efficacy of using rhBMP-2/ACS when combined with local autograft bone or other bulking agents in posterolateral fusion procedures.

In similar studies investigating the ability of OP-1® Putty (Stryker Biotech, Kalamazoo, MI) to induce posterolateral arthrodesis, lower rates of fusion have been reported[23-25]. A kit of OP-1® Putty contains 3.5 mg of OP-1 (rhBMP-7) delivered within a collagen/CMC carrier at 0.88 mg/cc. Clinical studies involving the use of OP-1® Putty have described the use of two kits per level. In uninstrumented posterolateral fusions, OP-1® Putty was shown to lead to fusion in five of ten patients, when used to extend autogenous iliac crest bone graft[25]. When OP-1 Putty was used as a replacement for autograft, eleven of twenty patients achieved a fusion[24]. In instrumented posterolateral fusions, radiographic evidence of fusion was observed in seven of nine OP-1 Putty patients and nine of ten patients treated with local bone and ceramic. During removal of the hardware, surgical exploration indicated that four of seven OP-1® Putty patients

Deleted: (DBM)
Deleted: 16
Deleted: single
Deleted: two
Deleted: in posterolateral fusions
Deleted: 22-24
Deleted: a
Deleted: 50% (5/10) fusion rate
Deleted: graft[24]
Deleted: to
Deleted: a 55%
Deleted: (11/20)
Deleted: rate was reported[23]
Deleted: 77.8%
Deleted: (7/9)
Deleted: OP-1® Putty patients
Deleted: 90% (9/10)
Deleted:
Deleted: 57% (4/7) of

achieved a fusion, compared with seven of nine, patients treated with local bone and ceramic[23].

The ability of biological agents such as rhBMP-2 to induce new bone formation is dependent, in part, on the specific agent used, its concentration and dose, the carrier, and the site of implantation. Nonhuman primate studies established that lower concentrations or doses of rhBMP-2 on the absorbable collagen sponge either failed to induce fusion or showed slightly less bone formation than the 1.5mg/cc concentration[15,26]. When rhBMP-2 was applied to the collagen sponge at 1.5mg/cc and protected from compression in posterolateral fusion, consistently high fusion rates in both nonhuman primate and clinical studies are reported[15-18]. When the carrier for rhBMP-2 was changed to either a compression resistant matrix containing 15% hydroxyapatite/85% tricalcium phophate granules or to biphasic calcium phosphate granules, nonhuman primate studies illustrated that a higher rhBMP-2 concentration was needed to effectively induce posterolateral fusion[17]. In clinical studies, using a 2mg/cc concentration and a 40mg dose of rhBMP-2 on either the compression resistant matrix or biphasic calcium phosphate carriers resulted in fusion rates of 95% at 24 months[10-12,27]. Thus, the selection of an appropriate carrier, concentration and dose for a specific biological agent may vary and should be validated clinically.

In this Level-1 clinical study, rhBMP-2/ACS combined with an osteoconductive ceramic bulking agent was shown to be a replacement for autogenous iliac crest bone graft and to reliably induce fusion in instrumented

Deleted: were fused
Deleted: 78% (7/9) of
Deleted: ceramic[23]
Deleted: ACS
Deleted: concentration[1]
Deleted: Boden J Bone Dis 1995
Deleted: ACS
Deleted: have been
Deleted: 9-12
Deleted:
Deleted: 85 HA:TCP
Deleted:
Deleted: in order
Deleted: fusion[11]
Deleted: CRM
Deleted: BCP
Deleted: 19-21

posterolateral arthrodesis. No local bone or other autogenous bone was used with rhBMP-2/ACS to allow for a reproducible technique to be defined. The investigational montage contained a sufficient concentration and dose of rhBMP-2 on the collagen sponge and provided the necessary volume to establish a successful fusion and served as an autograft replacement. Patients treated with rhBMP-2 had a higher rate of fusion success at twenty-four months than the autograft group, and the morbidity associated with graft harvest was avoided. Outcomes for all patients were significantly improved by six weeks after surgery and were maintained at twenty-four months following surgery. There was a trend toward greater improvement in the investigational rhBMP-2 group in their Oswestry, SF-36, and back and leg pain scores. This combination of an osteoinductive agent with an osteoconductive matrix may be an effective autograft replacement for single level posterolateral instrumented fusions.

Deleted: 95%

Deleted: 24

Deleted: compared with 70% for

Deleted: 24

REFERENCES:

1. Burkus JK, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. J Spinal Disord Tech. 2002;15:337-49.

2. Burkus JK, Heim SE, Gornet MF, Zdeblick TA. Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-CAGE lumbar tapered fusion device. J Spinal Disord Tech. 2003;16:113-22.

3. Anand N, Hamilton JF, Perri B, Miraliakbar H, Goldstein T. Cantilever TLIF with structural allograft and RhBMP2 for correction and maintenance of segmental sagittal lordosis: long-term clinical, radiographic, and functional outcome. Spine. 2006;31:E748-53.

4. Boden SD, Kang J, Sandhu H, Heller JG. Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial: 2002 Volvo Award in clinical studies. Spine. 2002;27:2662-73.

5. Burkus JK, Sandhu HS, Gornet MF, Longley MC. Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery. J Bone Joint Surg Am. 2005;87:1205-12.

6. Haid RW Jr, Branch CL Jr, Alexander JT, Burkus JK. Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages. Spine J. 2004;4:527-38; discussion 538-9.

7. Lanman TH, Hopkins TJ. Lumbar interbody fusion after treatment with recombinant human bone morphogenetic protein-2 added to poly(L-lactide-co-D,L-lactide) bioresorbable implants. Neurosurg Focus. 2004;16:E9.

8. Slosar PJ, Josey R, Reynolds J. Accelerating lumbar fusions by combining rhBMP-2 with allograft bone: a prospective analysis of interbody fusion rates and clinical outcomes. Spine J. 2007;7:301-7.

9. Singh K, Smucker JD, Gill S, Boden SD. Use of recombinant human bone morphogenetic protein-2 as an adjunct in posterolateral lumbar spine fusion: a prospective CT-scan analysis at one and two years. J Spinal Disord Tech. 2006;19:416-23.

10. Dimar JR. Evaluation of rhBMP-2/ceramic matrix as an ICBG replacement in posterolateral fusions: A multicenter, level I clinical study. Paper presented at: 21st Annual Meeting of the North American Spine Society. 2006 September 26-30. Seattle, WA.

11. Dimar JR, Glassman SD, Burkus KJ, Carreon LY. Clinical outcomes and fusion success at 2 years of single-level instrumented posterolateral fusions with recombinant human bone morphogenetic protein-2/compression resistant matrix versus iliac crest bone graft. Spine. 2006;31:2534-9; discussion 2540.

12. Glassman SD, Dimar JR, Burkus K, Hardacker JW, Pryor PW, Boden SD, Carreon LT. The efficacy of rhBMP-2 for posterolateral lumbar fusion in smokers. Spine. 2007;32:1693-8.

Deleted: 9. Martin GJ Jr, Boden SD, Marone MA, Marone MA, Moskovitz PA. Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: important lessons learned regarding dose, carrier, and safety. J Spinal Disord. 1999;12:179-86.¶
10. Akamaru T, Suh D, Boden SD, Kim HS, Minamide A, Louis-Ugbo J. Simple carrier matrix modifications can enhance delivery of recombinant human bone morphogenetic protein-2 for posterolateral spine fusion. Spine. 2003;28:429-34.¶
11. Barnes B, Boden SD, Louis-Ugbo J, Tomak PR, Park JS, Park MS, Minamide A. Lower dose of rhBMP-2 achieves spine fusion when combined with an osteoconductive bulking agent in non-human primates. Spine. 2005;30;10:1127-33.¶
12. Suh DY, Boden SD, Louis-Ugbo J, Mayr M, Murakami H, Kim HS, Minamide A, Hutton WC. Delivery of recombinant human bone morphogenetic protein-2 using a compression-resistant matrix in posterolateral spine fusion in the rabbit and in the non-human primate. Spine. 2002;27:353-60.¶

13. Deguchi M, Rapoff AJ, Zdeblick TA. Posterolateral fusion for isthmic spondylolisthesis in adults: analysis of fusion rate and clinical results. J Spinal Disord. 1998;11:459-64.

14. Senqupta DK, Truumees E, Patel CK, Kazmierczak C, Hughes B, Elders G, Herkowitz HN. Outcome of local bone versus autogenous iliac crest bone graft in the instrumented posterolateral fusion of the lumbar spine. Spine. 2006;31:985-91.

15. Martin GJ Jr, Boden SD, Marone MA, Marone MA, Moskovitz PA. Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: important lessons learned regarding dose, carrier, and safety. J Spinal Disord. 1999;12:179-86.

16. Akamaru T, Suh D, Boden SD, Kim HS, Minamide A, Louis-Ugbo J. Simple carrier matrix modifications can enhance delivery of recombinant human bone morphogenetic protein-2 for posterolateral spine fusion. Spine. 2003;28:429-34.

17. Barnes B, Boden SD, Louis-Ugbo J, Tomak PR, Park JS, Park MS, Minamide A. Lower dose of rhBMP-2 achieves spine fusion when combined with an osteoconductive bulking agent in non-human primates. Spine. 2005;30:10:1127-33.

18. Suh DY, Boden SD, Louis-Ugbo J, Mayr M, Murakami H, Kim HS, Minamide A, Hutton WC. Delivery of recombinant human bone morphogenetic protein-2 using a compression-resistant matrix in posterolateral spine fusion in the rabbit and in the non-human primate. Spine. 2002;27:353-60.

19. Boden SD, Martin GJ Jr, Morone MA, Ugbo JL, Moskovitz PA. Posterolateral lumbar intertransverse process spine arthrodesis with recombinant human bone morphogenetic protein 2/hydroxyapatite-tricalcium phosphate after laminectomy in the nonhuman primate. Spine. 1999;24:1179-85.

20. Fairbank JC, Pynsent PB. The Oswestry Disability Index. Spine. 2000;25;2940-52.

21. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994;32:40-66.

22. Glassman SD, Carreon L, Djurasovic M, Campbell MJ, Puno RM, Johnson JR, Dimar JR. Posterolateral lumbar spine fusion with INFUSE bone graft. Spine J. 2007;7:44-9.

23. Kanayama M, Hashimoto T, Shigenobu K, Yamane S, Bauer TW, Togawa D. A prospective randomized study of posterolateral lumbar fusion using osteogenic protein-1 (OP-1) versus local autograft with ceramic bone substitute: emphasis of surgical exploration and histologic assessment. Spine. 2006;31:1067-74.

24. Vaccaro AR, Anderson DG, Patel D, Fischgrund J, Truumees E, Herkowitz HN, Phillips F, Hilibrand A, Albert TJ, Wetzel T, McCulloch JA. Comparison of OP-1 Putty (rhBMP-7) to iliac crest autograft for posterolateral lumbar arthrodesis: a minimum 2-year follow-up pilot study. Spine 2005;30:2709-16.

25. Vaccaro AR, Patel T, Fischgrund J, Anderson DG, Truumees E, Herkowitz H, Phillips F, Hilibrand A, Albert TJ. A 2-year follow-up pilot study evaluating the

Deleted: 13

Deleted: Marone

Deleted: 14

Deleted: 15

Deleted: 17. Singh K, Smucker JD, Boden SD. Use of recombinant human bone morphogenetic protein-2 as an adjunct in posterolateral lumbar spine fusion: a prospective CT-scan analysis at one and two years. J Spinal Disord Tech. 2006;19:416-23.¶ 18. Dimar JR., Evaluation of rhBMP-2/Ceramic Matrix as an ICBG Replacement in Posterolateral Fusions: A Multicenter, Level I Clinical Study. in North American Spine Society. 2006. Seattle, WA.¶ 19. Dimar JR, Glassman SD, Burkus KJ, Carreon LY. Clinical outcomes and fusion success at 2 years of single-level instrumented posterolateral fusions with recombinant human bone morphogenetic protein-2/compression resistant matrix versus iliac crest bone graft. Spine. 2006;31:2534-9; discussion 2540.¶ 20. Glassman SD, Dimar JR, Carreon LY, Campbell MJ, Puno RM, Johnson JR. Initial fusion rates with recombinant human bone morphogenetic protein-2/compression resistant matrix and a hydroxyapatite and tricalcium phosphate/collagen carrier in posterolateral spinal fusion. Spine. 2005;30:1694-8.¶ 21. Alexander DI., . A New rhbmp-2 Formulation in Posterolateral Lumbar Spine Fusion: A Prospective, Randomized Study. in American Academy of Orthopaedic Surgeons. 2005. Washington, D.C.¶ 22

Deleted: 23

Deleted: 24

safety and efficacy of op-1 putty (rhbmp-7) as an adjunct to iliac crest autograft in posterolateral lumbar fusions. Eur Spine J. 2005;14:623-9.

26. Boden SD, Martin GJ, Horton WC, Truss TL, Sandhu HS. Laparoscopic anterior spinal arthrodesis with rhBMP-2 in a titanium interbody threaded cage. J Spinal Disord. 1998;11:95-101.

27. Alexander DI. A new rhBMP-2 formulation in posterolateral lumbar spine fusion: a prospective, randomized study. Paper presented at: the 72nd Annual Meeting of the American Academy of Orthopaedic Surgeons. 2005 February 23-26. Washington, D.C.

Deleted: 25. Grauer JN, Vaccaro AR, Kato M, Kwon BK, Beiner JM, Patel JC, Hilibrand AS, Chiba K, Albert TJ. Development of a New Zealand white rabbit model of spinal pseudarthrosis repair and evaluation of the potential role of OP-1 to overcome pseudarthrosis. Spine. 2004;29:1405-12.¶
26. Lawrence JP, Waked W, Gillon TJ, White AP, Spock CR, Biswas D, Rosenberger P, Troiano N, Albert TJ, Grauer JN. rhBMP-2 (ACS and CRM Formulations) Overcomes Pseudarthrosis in a New Zealand White Rabbit Posterolateral Fusion Model. Spine. 2007;32:1206-13.¶

Deleted: 27. Glassman SD, Dimar JR, Burkus K, Hardacker JW, Pryor PW, Boden SD, Carreon LT. The efficacy of rhBMP-2 for posterolateral lumbar fusion in smokers. Spine. 2007;32:1693-8.¶
28. Kornblum MB, Fischgrund JS, Herkowitz HN, Abraham DA, Berkower DL, Ditkoff JS. Degenerative lumbar spondylolisthesis with spinal stenosis: a prospective long-term study comparing fusion and pseudarthrosis. Spine. 2004;29:726-33; discussion 733-4.

LEGEND OF FIGURES

Figure 1: Preparation of INFUSE/MasterGraft™ Posterolateral Revision Device. A, RhBMP-2 is applied to the absorbable collagen sponges (ACS) at a concentration of 1.5mg/cc and allowed to bind for a minimum of fifteen minutes. A total of 10 cc of ceramic granules (5 cc per sponge) is added to the sponge. B, The sponge is then wrapped around the ceramic granules. C, The device is then implanted posterolaterally along the pars interarticularis. D, The device is in place.

Figure 2: A, Anteroposterior radiograph at six weeks after surgery shows the ceramic granules (arrows) in place between the L5 transverse processes and the sacral ala. B, Anteroposterior radiograph at twelve months shows resorption of the ceramic granules and bilateral new bone formation (arrows). C, Anteroposterior radiograph at twenty-four months shows bridging trabecular bone (arrows) and complete resorption of the ceramic granules.

Figure 3: Comparison of mean improvement in Oswestry Disability Index scores in the investigational and control groups.

Figure 4: Comparison of mean improvement in SF-36 in the investigational and control groups.

Figure 5: Comparison of back pain scores in the investigational and control groups.

Figure 6: Comparison of leg pain scores in the investigational and control groups.

Figure 7: Donor site pain in control patients.

Figure 8: A, Computed tomography scan immediately after surgery shows ceramic granules (arrows) overlying the transverse processes of L5 and the sacral ala. B, Computed tomography scan at six months shows bridging trabecular bone (arrows) and interspersed ceramic carrier. C, Computed tomography scan at twenty-four months shows broad bridging trabecular bone (arrows) spanning the interspace between L5 and the sacrum with complete removal of the ceramic carrier.

Figure 9: Comparison of return-to-work status in the investigational and control groups.

From: Hatcher, Brian, PhD.
Sent: Tuesday, May 6, 2008 09:04:40 AM
To: Ken Burkus[redacted]
CC: Carol Binn[redacted]; Bearcroft, Julie, PhD
Subject: INFUSE/MasterGraft Manuscript

Attachments: INFUSE-MGG FINAL SUBMISSION.doc; Table 1.doc; Table 2.doc; Table 3.doc; Table 4.doc; Table 5.doc; Table 6.doc; Table 7.doc; Table 8.doc

Hello Dr. Burkus,
Please see the updated manuscript to reflect the additional information requested by the reviewers, and the edits we discussed last week.

- The ICBG data has been removed.
- To address the potential impact of workers comp, litigation, and previous surgery, Guorong performed a statistical analysis adjusting for these factors. As a result, the p values comparing the 2 groups have changed, but the data still indicates similar improvements in clinical outcomes between groups, and in some cases nonsignificant trends towards greater improvement in the investigational group.
- We are still working on the patient accountability flow chart and should have that shortly.
- The primary outcome (overall success) has been added.

The track changes is on, so that you can easily identify the edits.
Please let me know if you have any questions regarding this.
Thanks
Brian

Brian Hatcher, Ph.D.
Technology Manager, Biologics
Medtronic
Spinal and Biologics
1800 Pyramid Place
Memphis, TN 38132
O:[redacted]
M:[redacted]
F:[redacted]

Use of rhBMP-2 on an Absorbable Collagen Sponge Combined with an Osteoconductive Bulking Agent in Instrumented Posterolateral Fusion: Clinical and Radiographic Outcomes from a Prospective, Randomized Trial

Deleted: 5/6/20084/25/2008

ABSTRACT

Background: Recombinant human bone morphogenetic protein-2 soaked into an absorbable collagen sponge (rhBMP-2/ACS) has been shown to be a safe and effective replacement for an iliac crest bone graft in anterior lumbar interbody fusions when used with a threaded fusion device. In posterolateral lumbar fusions, rhBMP-2/ACS requires the addition of a bulking agent to provide compression resistance and serve as an osteoconductive scaffold for new bone formation.

Methods: In this prospective, randomized, multicenter pilot study of forty-six patients, we used rhBMP-2/ACS combined with a ceramic-granule bulking agent as an alternative to autogenous iliac crest bone graft in instrumented single-level posterolateral lumbar arthrodesis. The investigational group (n = 25) received rhBMP-2/ACS (1.5 mg/cc, 12 mg total dose) combined with 10 cc of ceramic granules. The control group (n = 21) received iliac crest bone graft. Clinical outcomes were assessed using well-established instruments. Radiographs were reviewed for consolidation of fusion.

Results: At all follow-up intervals, there were statistically significant improvements in clinical outcome measures in both treatment groups. There was a trend toward greater improvement in Oswestry Disability Index scores, Short Form-36 scores, and back and leg pain scores in the investigational group than in the control group. At twenty-four months, the mean Oswestry score in the investigational group had improved 28.2 points from the preoperative score, compared with 23.0 points for the control group. By 24 months, 95% of the

Deleted: 5/6/20084/25/2008

investigational patients had a radiographically documented fusion compared with 70% of the control patients. The overall success rate was 81% for the investigational group and 55% for the ICBG control group.

Deleted: (p = 0.091)

Conclusions: This is the first prospective randomized clinical study evaluating rhBMP-2/ACS combined with ceramic granules for posterolateral fusion without iliac crest bone graft. In this study, combining rhBMP-2/ACS with ceramic granules resulted in a higher rate of radiographic fusion success in the investigational group than in the control group who received an iliac crest bone graft. Clinical outcomes in both groups were significantly improved by 6 weeks from preoperative values, and improvements were maintained at 24 months. There was a nonsignificant trend toward greater improvement in the rhBMP-2 group. This combination of an osteoinductive agent with an osteoconductive matrix may be an effective autograft replacement for single-level instrumented posterolateral fusions.

Level of Evidence: Therapeutic Level I

INTRODUCTION

Recombinant human bone morphogenetic protein-2 combined with an absorbable collagen sponge (rhBMP-2/ACS) has been shown to be a safe and effective replacement for autogenous iliac crest bone graft (ICBG) for anterior lumbar interbody fusion[1]. In a pooled analysis of 679 patients undergoing lumbar interbody fusion, patients treated with rhBMP-2 had significantly higher fusion rates than patients treated with ICBG (94.4% vs. 89.4%; p = 0.022)[2]. These fusion rates with rhBMP-2 in lumbar interbody fusion are consistent with those in other published reports[1-7].

Reported fusion rates from posterolateral interbody fusion procedures using ICBG vary widely from 73% to 95%[8-13] and can depend on numerous factors such as diagnosis and fusion assessment methods. To date, there have been no prospective randomized trials published on the use of rhBMP-2/ACS in posterolateral fusions. When rhBMP-2/ACS was first investigated in nonhuman primate models for its ability to induce posterolateral fusion, it was observed that the absorbable collagen sponge alone did not lead to a robust fusion mass[14]. When the sponge was combined with an osteoconductive bulking agent capable of providing compression resistance and longer-term scaffolding, robust bone formation and high rates of arthrodesis were reported[15,16].

A series of studies were undertaken to determine the optimal ceramic composition for use with rhBMP-2. These studies showed that ceramics high in hydroxyapatite content (60% hydroxyapatite/40% tricalcium phosphate) resulted in fusion masses containing residual ceramic at six months, and ceramics high in

Deleted: 5/6/20084/25/2008

beta tricalcium phosphate (5% hydroxyapatite/95% tricalcium phosphate) led to smaller fusion masses as a result of rapid remodeling[17,18]. The 15% hydroxyapatite/85% tricalcium phosphate composition (MasterGraft® Ceramics; Medtronic Sofamor Danek, Memphis, TN) has demonstrated an optimal resorption profile and led to high rates of fusion when used as a bulking agent with rhBMP-2/ACS[15-17]. Applying rhBMP-2 to the collagen sponge at 1.5 mg/cc and wrapping it around either 15% hydroxyapatite/85% tricalcium phosphate ceramic granules or compression resistant matrix (CRM) has been shown to reliably induce fusion and to lead to ceramic incorporation by six months in nonhuman primates[15,16].

The purpose of this study was to investigate rhBMP-2 on an absorbable collagen sponge combined with the 15% hydroxyapatite/85% tricalcium phosphate ceramic granule as a replacement for an iliac crest bone graft in instrumented posterolateral fusion.

MATERIALS and METHODS

Study Design

Institutional review board approval was obtained and all patients gave their informed consent before participating in this study conducted at four centers by seven surgeons. Forty-six patients were enrolled in this prospective, randomized, multicenter, FDA-approved, Investigational Device Exemption (IDE) pilot trial between April 2003 and August 2004. Patients who were undergoing treatment for degenerative disc disease were randomly assigned to either the investigational group or to the control group. Randomization was stratified by site

Deleted: 5/6/20084/25/2008

with a fixed block size of four. Twenty-five patients in the investigational group received rhBMP-2/ACS combined with a 15% hydroxyapatite/85% tricalcium phosphate ceramic bulking agent (INFUSE/MasterGraft™, Medtronic Sofamor Danek, Memphis, TN) and 21 patients in the control group received ICBG in a single-level instrumented posterolateral arthrodesis. After consent and randomization, two patients in each group elected not to participate in the study. Preoperatively, all patients met the inclusion criteria of symptomatic, single-level degenerative disc disease at the L1-S1 levels. Degenerative lumbar disc disease was confirmed by patient history, objective physical findings, and correlative neuroradiographic studies confirming instability, osteophyte formation, decreased disc height, thickening of ligamentous tissue, disc degeneration or herniation, or facet joint degeneration. The clinical symptoms included low back pain and radicular leg pain. All patients had failed to respond to nonoperative treatment for a minimum of six months. Additional enrollment criteria were a grade I or less spondylolisthesis and no previous fusion at the index level. Patient demographics were similar in the two groups; there were no statistically significant differences ($p < 0.05$) between the demographic profiles (Table 1).

Surgical Technique

Device Preparation

Investigational group patients received implants of rhBMP-2 on an absorbable collagen sponge combined with ceramic granules. A single 3 in x 4 in sponge from a Large II Kit of INFUSE® Bone Graft (Medtronic Sofamor Danek, Memphis, TN) was sectioned into two 2 in x 3 in pieces (Figure 1). RhBMP-2 was

Deleted: 5/6/20084/25/2008

reconstituted in the standard fashion at a concentration of 1.5 mg/cc, and 4 mL of solution was applied to each of the two sponge strips. Thus, each patient in the investigational group received 12 mg of rhBMP-2 on 8 cc of the collagen sponge. The ceramic granules used as the bulking agent are a blend of 15% hydroxyapatite and 85% tricalcium phosphate (MasterGraft® Granules, Medtronic Sofamor Danek, Memphis, TN). No rhBMP-2 was applied directly to the ceramic. After allowing the rhBMP-2 to bind to the collagen sponge for at least fifteen minutes, 5 cc of the ceramic granules were distributed and rolled within each of the collagen sponge strips.

Surgical Procedure.

Both patient groups underwent an instrumented posterolateral fusion procedure through a standard open midline approach using the CD Horizon® Spinal System (Medtronic Sofamor Danek, Memphis, TN). Posterior decompression of the spinal canal was carried out, as needed. The transverse processes were exposed bilaterally, and their dorsal surfaces were decorticated. The morcellized autogenous iliac crest bone graft or the rhBMP-2/ACS montage was then placed into the lateral gutters and along the pars interarticularis. Pedicle screws were placed and rods attached. Importantly, all local autograft obtained as a result of the decompression was discarded and not used in either group. No interbody fusion was performed in either group.

Radiographic Analysis

Radiographic assessment of fusion was performed at six, twelve, and twenty-four months after surgery by two independent radiologists who were

Deleted: 5/6/20084/25/2008

blinded to the treatment assignment. A third reviewer was available for adjudication. Plain radiographs, lateral flexion and extension radiographic views, and thin-cut computed tomography scans with sagittal and coronal reconstructions were used to evaluate the fusion mass. A successful arthrodesis, as outlined in the IDE fusion criteria, was defined as bridging trabecular bone between the transverse processes, the absence of motion (≤3 mm of translation and <5° of angulation on flexion-extension views), and the absence of radiolucent lines through the fusion mass (Figure 2).

Clinical Outcome Measures

Clinical and functional outcomes were assessed preoperatively and at six weeks and at three, six, twelve, and twenty-four months postoperatively. Clinical outcomes were measured using the Oswestry Disability Index (ODI)[19], the 36-Item Short Form Health Survey® (SF-36)[20], and return-to-work status. Back and leg pain scores were determined using numeric rating scales of 0-20 (10 points frequency and 10 points intensity).

Deleted: , leg, and donor site

Overall Success

The primary outcome of this study was overall success, which was a combination of fusion success, ODI improvement (>15%), the absence of severe device related AE's or second surgery failures, and maintenance or improvement of neurological status.

Statistical Methods

For statistical comparisons between the treatment groups for demographic, preoperative measurements, and surgery data, analysis of

Deleted: 5/6/20084/25/2008

variance (ANOVA) was used for continuous variables, and Fisher's exact test was used for categorical data. For assessing the statistical significance of postoperative improvement in outcome scores from preoperative status within each treatment group, a paired *t*-test was used. To compare clinical and radiographic outcomes between the treatment groups, analysis of covariance (ANCOVA) using either general linear model for continuous responses or logistic model for binary responses was employed for adjusting for potential confounding effects of worker's compensation, litigation, and previous back surgery.

RESULTS

Surgery

Surgical data for the two groups are shown in Table 2. Operating times and hospital stays were similar for the two groups. The investigational group patients showed a trend toward less blood loss. Patients in the control group had a mean graft volume of 42.4 ± 29.9 cc (range, 10-80 cc).

Clinical Follow Up

Deleted: 22/25

Deleted: 18/21

At twenty-four months, 88% (twenty-two of twenty-five) of the investigational patients and 86% (eighteen of twenty-one) of the control patients were available for follow up. There were two second-surgery failures and one death in the investigational group, and two second-surgery failures and one patient without a 24-month follow-up examination in the control group.

Clinical outcome measures showed statistically significant improvements over the preoperative scores in both groups, with the investigational group showing nonsignificant trends toward greater improvement than the control group

following an adjustment for worker's compensation, litigation, and previous back surgery. At twenty-four months, the mean Oswestry score in the investigational group had improved 28.2 points from the preoperative score, compared with 23.0 points for the control group (p = 0.953; Table 3 and Figure 3). With regard to Oswestry scores, 91% (twenty-one of twenty-three) of the investigational patients and 70% (fourteen of twenty) of the control patients achieved a 20% improvement (p = 0.532).

At twenty-four months, the improvements in Physical Component Summary score (13.0 versus 9.9 points; p = 0.927) and physical function score (36.3 versus 18.5 points, p = 0.200) were slightly greater in the investigational group compared to the control group (Table 4 and Figure 4). At twenty-four months, the mean back pain scores for the investigational group and the iliac crest bone graft group had improved 9.6 and 7.2 points, respectively (p = 0.664) (Table 5 and Figure 5). Similarly, the mean leg pain scores at twenty-four months for the investigational group and the control group had improved 9.3 and 7.2 points, respectively, from preoperative scores (p = 0.892) (Table 6 and Figure 6).

Fusion Assessment

At each time interval, there was a trend toward greater fusion success in the investigational group. Evidence of fusion, as defined by the stringent IDE fusion criteria, was 22%, 16%, and 25% higher in the investigational group than in the control group at six, twelve, and twenty-four months. At the twenty-four-month follow up, 95% (eighteen of nineteen) of investigational patients had

Deleted: 5/6/20084/25/2008

Deleted: 336

Deleted: 081

Deleted: There was also a trend toward greater improvement in SF-36 scores in the investigational group a

Deleted: including

Deleted: 394

Deleted: 034

Deleted: 183

Comment [h1]: Need to delete Figure 7 and update remaining Figure #s.

Deleted: 347

Deleted: In the control-group patients, who were treated with iliac crest bone graft, 70% (14/20) were still experiencing donor site pain at twenty-four months, with a mean pain score of 8.6 (out of a possible score of 20) (Figure 7). Pain scores for donor site pain or for generalized pelvic pain were not obtained in the investigational group of patients

Deleted: 5/6/2004/25/2008

evidence of fusion compared with 70% (fourteen of twenty) of control patients (p = 0.174; Table 7).

Deleted: 091

Computed tomography scans provide high-resolution detail and a sensitive means of assessing bone formation. In this study, thin-cut axial slices (1-mm) along with coronal and sagittal reconstructions were evaluated to assess the presence of bridging trabecular bone. At six, twelve, and twenty-four months, 90% to 95% of the investigational patients had evidence of bridging bone. At last follow up, 95% of investigational patients and 67% of control patients had bridging trabecular bone (p = 0.120; Table 8). Thin-cut CT scan reconstructions demonstrated the progressive formation of bridging bone across the transverse processes and illustrated incorporation and remodeling of the ceramic component (Figure 8).

Deleted: 038

Additional Surgery or Treatment

Two patients sustained incidental durotomies intraoperatively, which were repaired (one in each group). Two patients developed wound infections at the surgical site, which resolved after antibiotic treatment (one in each group). One control patient had an infection at the graft site. There were two second surgery failures in the investigational group—a revision procedure one day after the initial surgery due to bilateral malpositioned pedicle screws and a hardware removal at six months. In the control group, there were two revision procedures for pseudarthrosis.

Deleted: 5/6/20084/25/2008

Overall Success

At 2 years the overall success rate was 81% (seventeen of twenty-one) for the rhBMP-2/ACS and ceramic granule group, compared to 55% (eleven of twenty) for the ICBG group (p=0.345). In the investigational group, 95.7% (twenty-two of twenty-three) had an ODI improvement of more than 15%, compared to 75% (fifteen of twenty) ICBG patients (p=0.240).

Return to Work

By twenty-four months, 35% (eight of twenty-three) of the patients in the investigational group were working (Figure 9), including all patients who were working before surgery (six of six). In the control group, 30% (six of twenty) of the patients had returned to work, including six of nine patients who were working before surgery.

DISCUSSION

In this report, we present the first Level-1 data evaluating rhBMP-2/ACS combined with a 15% hydroxyapatite/85% tricalcium phosphate osteoconductive ceramic bulking agent as a replacement for iliac crest bone graft in instrumented posterolateral fusion. Fusion rates in the investigational group were 16% to 25% higher than in the control group at the follow-up time points examined. Additionally, there were nonsignificant trends toward greater improvements in clinical outcome measures in the patients treated with the rhBMP-2/ACS/ceramic following an adjustment for variables that have been shown to impact clinical outcomes (Harris, JAMA 2008; DeBerard, Spine J 2008).

Others have investigated the use of rhBMP-2 when combined with local autograft bone as a bulking agent in posterolateral fusion[8,21]. In the first human study investigating rhBMP-2/ACS in posterolateral fusions, Singh et al.[8] reported that the use of rhBMP-2 led to higher fusion rates and better fusion quality than iliac crest bone graft alone. At twelve and twenty-four months, 97% (sixty-eight/seventy) of the levels in the rhBMP-2/ACS patients were graded as fused, compared with 77% (seventeen/twenty-two) of the levels in autograft patients ($p < 0.05$). Additionally, 92% (thirty-six/thirty-nine) of patients treated with rhBMP-2/ACS and autograft had excellent fusion quality, compared with only 27% (three/eleven) of the autograft-alone patients ($p < 0.05$). These published results are consistent with those reported in our study at twenty-four months, in which no autograft bone was added to the rhBMP-2/ACS/ceramic implant.

In a separate study, Glassman et al.[21] reported on patients who had undergone posterolateral fusion with rhBMP-2/ACS and various bulking agents, such as local bone, MasterGraft® Granules, demineralized bone matrix, allograft, or a combination of local bone with one of the other bulking agents. In this clinical series, which included primary and revision procedures and single-level and multilevel fusions, 93% of the patients had radiographic evidence (computed tomography scans) of fusion at a mean follow up of twenty-seven months. These studies by Singh et al.[8] and Glassman et al.[21] provide further evidence of the efficacy of using rhBMP-2/ACS when combined with local autograft bone in posterolateral fusion procedures.

In similar studies investigating the ability of OP-1® Putty (Stryker Biotech, Kalamazoo, MI) to induce posterolateral arthrodesis, lower rates of fusion have been reported[22-24]. A kit of OP-1® Putty contains 3.5 mg of OP-1 (rhBMP-7) delivered within a collagen/CMC carrier at 0.88 mg/cc. Clinical studies involving the use of OP-1® Putty have described the use of two kits per level. In uninstrumented posterolateral fusions, OP-1® Putty was shown to lead to fusion in five of ten patients when used to extend autogenous iliac crest bone graft[24]. When OP-1 Putty was used as a replacement for autograft, eleven of twenty patients achieved a fusion[23]. In instrumented posterolateral fusions, radiographic evidence of fusion was observed in seven of nine OP-1 Putty patients and nine of ten patients treated with local bone and ceramic. During removal of the hardware, surgical exploration indicated that four of seven OP-1® Putty patients achieved a fusion, compared with seven of nine patients treated with local bone and ceramic[22].

The ability of biological agents such as rhBMP-2 to induce new bone formation is dependent, in part, on the specific agent used, its concentration and dose, the carrier, and the site of implantation. Nonhuman primate studies established that lower concentrations or doses of rhBMP-2 on the absorbable collagen sponge either failed to induce fusion or showed slightly less bone formation than the 1.5mg/cc concentration[14,25]. When rhBMP-2 was applied to the collagen sponge at 1.5mg/cc and protected from compression in posterolateral fusion, consistently high fusion rates in both nonhuman primate and clinical studies are reported[14-17]. When the carrier for rhBMP-2 was changed

Deleted: 5/6/20084/25/2008

to either a compression resistant matrix containing 15% hydroxyapatite/85% tricalcium phosphate granules or to biphasic calcium phosphate granules, nonhuman primate studies illustrated that a higher rhBMP-2 concentration was needed to effectively induce posterolateral fusion[16]. In clinical studies, using a 2mg/cc concentration and a 40mg dose of rhBMP-2 on either the compression resistant matrix or biphasic calcium phosphate carriers resulted in fusion rates of 95% at 24 months[9-11,26,27]. Thus, the selection of an appropriate carrier, concentration and dose for a specific biological agent may vary and should be validated clinically.

In this Level-1 clinical study, rhBMP-2/ACS combined with an osteoconductive ceramic bulking agent was shown to be a replacement for autogenous iliac crest bone graft and to reliably induce fusion in instrumented posterolateral arthrodesis. No local bone or other autogenous bone was used with rhBMP-2/ACS to allow for a reproducible technique to be defined. The investigational montage contained a sufficient concentration and dose of rhBMP-2 on the collagen sponge and provided the necessary volume to establish a successful fusion and served as an autograft replacement. Patients treated with rhBMP-2 had a higher rate of fusion success at twenty-four months than the autograft group, and the morbidity associated with graft harvest was avoided. Outcomes for all patients were significantly improved by six weeks after surgery and were maintained at twenty-four months following surgery. There was a nonsignificant trend toward greater improvement in the investigational rhBMP-2 group in their Oswestry, SF-36, and back and leg pain scores. This combination

of an osteoinductive agent with an osteoconductive matrix may be an effective autograft replacement for single level posterolateral instrumented fusions.

Deleted: 5/6/20084/25/2008

REFERENCES:

1. Burkus JK, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. J Spinal Disord Tech. 2002;15:337-49.

2. Burkus JK, Heim SE, Gornet MF, Zdeblick TA. Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-CAGE lumbar tapered fusion device. J Spinal Disord Tech. 2003;16:113-22.

3. Anand N, Hamilton JF, Perri B, Miraliakbar H, Goldstein T. Cantilever TLIF with structural allograft and RhBMP2 for correction and maintenance of segmental sagittal lordosis: long-term clinical, radiographic, and functional outcome. Spine. 2006;31:E748-53.

4. Burkus JK, Sandhu HS, Gornet MF, Longley MC. Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery. J Bone Joint Surg Am. 2005;87:1205-12.

5. Haid RW Jr, Branch CL Jr, Alexander JT, Burkus JK. Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages. Spine J. 2004;4:527-38; discussion 538-9.

6. Lanman TH, Hopkins TJ. Lumbar interbody fusion after treatment with recombinant human bone morphogenetic protein-2 added to poly(L-lactide-co-D,L-lactide) bioresorbable implants. Neurosurg Focus. 2004;16:E9.

7. Slosar PJ, Josey R, Reynolds J. Accelerating lumbar fusions by combining rhBMP-2 with allograft bone: a prospective analysis of interbody fusion rates and clinical outcomes. Spine J. 2007;7:301-7.

8. Singh K, Smucker JD, Gill S, Boden SD. Use of recombinant human bone morphogenetic protein-2 as an adjunct in posterolateral lumbar spine fusion: a prospective CT-scan analysis at one and two years. J Spinal Disord Tech. 2006;19:416-23.

9. Dimar JR. Evaluation of rhBMP-2/ceramic matrix as an ICBG replacement in posterolateral fusions: A multicenter, level I clinical study. Paper presented at: 21st Annual Meeting of the North American Spine Society. 2006 September 26-30. Seattle, WA.

10. Dimar JR, Glassman SD, Burkus KJ, Carreon LY. Clinical outcomes and fusion success at 2 years of single-level instrumented posterolateral fusions with recombinant human bone morphogenetic protein-2/compression resistant matrix versus iliac crest bone graft. Spine. 2006;31:2534-9; discussion 2540.

11. Glassman SD, Dimar JR, Burkus K, Hardacker JW, Pryor PW, Boden SD, Carreon LT. The efficacy of rhBMP-2 for posterolateral lumbar fusion in smokers. Spine. 2007;32:1693-8.

12. Deguchi M, Rapoff AJ, Zdeblick TA. Posterolateral fusion for isthmic spondylolisthesis in adults: analysis of fusion rate and clinical results. J Spinal Disord. 1998;11:459-64.

13. Sengupta DK, Truumees E, Patel CK, Kazmierczak C, Hughes B, Elders G, Herkowitz HN. Outcome of local bone versus autogenous iliac crest bone graft in the instrumented posterolateral fusion of the lumbar spine. Spine. 2006;31:985-91.

14. Martin GJ Jr, Boden SD, Marone MA, Marone MA, Moskovitz PA. Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: important lessons learned regarding dose, carrier, and safety. J Spinal Disord. 1999;12:179-86.

15. Akamaru T, Suh D, Boden SD, Kim HS, Minamide A, Louis-Ugbo J. Simple carrier matrix modifications can enhance delivery of recombinant human bone morphogenetic protein-2 for posterolateral spine fusion. Spine. 2003;28:429-34.

16. Barnes B, Boden SD, Louis-Ugbo J, Tomak PR, Park JS, Park MS, Minamide A. Lower dose of rhBMP-2 achieves spine fusion when combined with an osteoconductive bulking agent in non-human primates. Spine. 2005;30:10:1127-33.

17. Suh DY, Boden SD, Louis-Ugbo J, Mayr M, Murakami H, Kim HS, Minamide A, Hutton WC. Delivery of recombinant human bone morphogenetic protein-2 using a compression-resistant matrix in posterolateral spine fusion in the rabbit and in the non-human primate. Spine. 2002;27:353-60.

18. Boden SD, Martin GJ Jr, Morone MA, Ugbo JL, Moskovitz PA. Posterolateral lumbar intertransverse process spine arthrodesis with recombinant human bone morphogenetic protein 2/hydroxyapatite-tricalcium phosphate after laminectomy in the nonhuman primate. Spine. 1999;24:1179-85.

19. Fairbank JC, Pynsent PB. The Oswestry Disability Index. Spine. 2000;25:2940-52.

20. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994;32:40-66.

21. Glassman SD, Carreon L, Djurasovic M, Campbell MJ, Puno RM, Johnson JR, Dimar JR. Posterolateral lumbar spine fusion with INFUSE bone graft. Spine J. 2007;7:44-9.

22. Kanayama M, Hashimoto T, Shigenobu K, Yamane S, Bauer TW, Togawa D. A prospective randomized study of posterolateral lumbar fusion using osteogenic protein-1 (OP-1) versus local autograft with ceramic bone substitute: emphasis of surgical exploration and histologic assessment. Spine. 2006;31:1067-74.

23. Vaccaro AR, Anderson DG, Patel D, Fischgrund J, Truumees E, Herkowitz HN, Phillips F, Hilibrand A, Albert TJ, Wetzel T, McCulloch JA. Comparison of OP-1 Putty (rhBMP-7) to iliac crest autograft for posterolateral lumbar arthrodesis: a minimum 2-year follow-up pilot study. Spine 2005;30:2709-16.

24. Vaccaro AR, Patel T, Fischgrund J, Anderson DG, Truumees E, Herkowitz H, Phillips F, Hilibrand A, Albert TJ. A 2-year follow-up pilot study evaluating the safety and efficacy of op-1 putty (rhbmp-7) as an adjunct to iliac crest autograft in posterolateral lumbar fusions. Eur Spine J. 2005;14:623-9.

25. Boden SD, Martin GJ, Horton WC, Truss TL, Sandhu HS. Laparoscopic anterior spinal arthrodesis with rhBMP-2 in a titanium interbody threaded cage. J Spinal Disord. 1998;11:95-101.

26. Alexander DI. A new rhBMP-2 formulation in posterolateral lumbar spine fusion: a prospective, randomized study. Paper presented at: the 72nd Annual Meeting of the American Academy of Orthopaedic Surgeons. 2005 February 23-26. Washington, D.C.

27. Boden SD, Kang J, Sandhu H, Heller JG. Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial: 2002 Volvo Award in clinical studies. Spine. 2002;27:2662-73.

Deleted: 5/6/20084/25/2008

LEGEND OF FIGURES

Figure 1: Preparation of rhBMP-2/ACS with ceramic bulking agent. A, RhBMP-2 is applied to the absorbable collagen sponges (ACS) at a concentration of 1.5mg/cc and allowed to bind for a minimum of fifteen minutes. A total of 10 cc of ceramic granules (5 cc per sponge) is added to the sponge. B, The sponge is then wrapped around the ceramic granules. C, The device is then implanted posterolaterally along the pars interarticularis. D, The device is in place.

Figure 2: A, Anteroposterior radiograph at six weeks after surgery shows the ceramic granules (arrows) in place between the L5 transverse processes and the sacral ala. B, Anteroposterior radiograph at twelve months shows resorption of the ceramic granules and bilateral new bone formation (arrows). C, Anteroposterior radiograph at twenty-four months shows bridging trabecular bone (arrows) and complete resorption of the ceramic granules.

Figure 3: Comparison of mean improvement in Oswestry Disability Index scores in the investigational and control groups.

Figure 4: Comparison of mean improvement in SF-36 in the investigational and control groups.

Figure 5: Comparison of back pain scores in the investigational and control groups.

Figure 6: Comparison of leg pain scores in the investigational and control groups.

Figure 7: Donor site pain in control patients.

Deleted: 5/6/2008 4/25/2008

Figure 8: A, Computed tomography scan immediately after surgery shows ceramic granules (arrows) overlying the transverse processes of L5 and the sacral ala. B, Computed tomography scan at six months shows bridging trabecular bone (arrows) and interspersed ceramic carrier. C, Computed tomography scan at twenty-four months shows broad bridging trabecular bone (arrows) spanning the interspace between L5 and the sacrum with complete removal of the ceramic carrier.

Figure 9: Comparison of return-to-work status in the investigational and control groups.

Table 1: Patient demographic data.

	Investigational Group	Control Group	P Value
No. of patients	25	21	
Average age (yr)	55.9	56.9	0.811
Average weight (kg)	79.8	83.9	0.470
Sex (% male)	40.0	42.9	1.000
Patients receiving Workers' Compensation or with pending litigation (%)	12.0	19.0	0.686
Smokers (%)	24.0	23.8	1.000
Previous Back Surgery (%)	24.0	28.6	0.749

Table 2: Surgical data.

	Investigational Group*	Control Group*	P Value
Operative time (hrs)	2.4 ± 0.7	2.6 ± 0.8	0.415
Estimated blood loss (mL)	329.0 ± 212.3	452.4 ± 210.0	0.055
Length of hospital stay (d)	4.0 ± 1.4	4.1 ± 1.1	0.844

*Values are given as the mean and standard deviation.

Table 3: Oswestry Disability Index scores

Evaluation Period	Investigational Group*	Control Group*	P Value
Preoperative	52.1 ± 13.3	49.7 ± 12.8	0.720
1.5 months	39.0 ± 17.9	37.1 ± 17.0	0.430
3 months	30.0 ± 17.6	30.1 ± 18.4	0.587
6 months	28.7 ± 17.5	30.2 ± 18.6	0.908
12 months	24.1 ± 19.0	27.9 ± 19.9	0.857
24 months	22.8 ± 18.3	26.1 ± 18.6	0.901

*Values are given as the mean and standard deviation.

Table 4: Improvement in SF-36 Health Survey scores at 24 months.

Measure	Investigational Group*	Control Group*	P Value
Physical Component Summary	13.0 ± 11.5	9.9 ± 11.9	0.927
Mental Component Summary	4.7 ± 13.3	-1.6 ± 10.8	0.102
Physical Function	36.3 ± 24.3	18.5 ± 29.1	0.200
Role Physical	37.0 ± 47.0	33.8 ± 47.5	0.648
Pain Index	34.6 ± 21.9	26.8 ± 29.6	0.835
General Health Perception	2.8 ± 23.0	-5.0 ± 20.5	0.305
Social Function	30.4 ± 28.2	21.3 ± 31.2	0.891
Mental Health	10.4 ± 22.8	0.5 ± 23.7	0.145
Role Emotional	23.9 ± 49.4	-1.7 ± 46.5	0.100
Vitality	13.7 ± 22.9	1.0 ± 22.0	0.207

*Values are given as the mean and standard deviation.

Table 5: Improvement in back pain scores.

Evaluation Period	Investigational Group*	Control Group*	P Value
1.5 months	8.0 ± 6.1	7.7 ± 5.9	0.653
3 months	8.0 ± 6.0	8.4 ± 5.7	0.306
6 months	9.1 ± 5.4	7.1 ± 5.4	0.666
12 months	8.8 ± 6.1	7.9 ± 6.2	0.684
24 months	9.6 ± 5.4	7.2 ± 6.5	0.664

*Values are given as the mean and standard deviation.

Table 6: Improvement in leg pain scores.

Evaluation Period	Investigational Group*	Control Group*	P Value
1.5 months	9.4 ± 5.4	7.8 ± 7.8	0.575
3 months	8.8 ± 5.4	8.3 ± 6.0	0.589
6 months	8.8 ± 5.1	7.0 ± 6.8	0.730
12 months	8.4 ± 6.7	7.6 ± 6.7	0.582
24 months	9.3 ± 6.8	7.2 ± 8.1	0.892

*Values are given as the mean and standard deviation.

Table 7: Percentage of patients determined to have a successful fusion defined by the IDE criteria.

Evaluation Period	Investigational Group	Control Group	P Value
6 months	82% (18/22)	60% (12/20)	0.160
12 months	81% (17/21)	65% (13/20)	0.359
24 months	95% (18/19)	70% (14/20)	0.174

Table 8: Percentage of patients who had computed tomographic evidence of bridging trabecular bone.

Evaluation Period	Investigational Group	Control Group	P Value
6 months	91% (20/22)	58% (11/19)	0.032
12 months	90% (17/19)	65% (13/20)	0.184
24 months	95% (19/20)	67% (12/18)	0.120

From: Hatcher, Brian, PhD.
Sent: Wednesday, August 6, 2008 03:39:14 PM
To: Carol Binns [redacted]; Bearcroft, Julie, PhD; Ken Burkus [redacted]
Subject: RE: Edited manuscript

Carol
Here is the response to question 10 regarding specific p values. I had to reword the sentence a bit for accuracy.
Brian

Change this sentence to read: "An observation in our study was that patients treated by the laparoscopic surgical technique trended to have shortened hospital stay (p=0.128), fewer reoperations (p=0.194), and greater improvements in Oswestry Low Back Pain and Disability Index scores (p=0.102), SF-36 PCS scores (p=0.085) and low back pain scores (p=0.598) at 6 years when compared to the open surgical group."

Also, please update the methods section by deleting the word "demographic" on pg 9, line 19.

From: Carol Binns [mailto:[redacted]]
Sent: Wednesday, August 06, 2008 3:25 PM
To: Bearcroft, Julie, PhD; Ken Burkus
Cc: Hatcher, Brian, PhD.
Subject: Re: Edited manuscript

There is no reason we cannot politely rebut individual requests for changes by Dr. Clark. He states, "unless you can convince me otherwise..." If you agree, Dr. Burkus, I can paraphrase Julie's comments in the response to Dr. Clark's comments.

Carol

----- Original Message -----
From: Bearcroft, Julie, PhD
To: Ken Burkus ; Carol Binns
Cc: Hatcher, Brian, PhD.
Sent: Wednesday, August 06, 2008 10:52 AM
Subject: RE: Edited manuscript

Ken -
I would like to suggest that we don't opt to change out the phrase of ICBG replacement with

ICBG substitute. This is FDA language that is reserved for INFUSE and not approved for use with other 'substitutes' such as ceramics and DBMs. Replacement means that it is effective on its own without mixing with ICBG. Substitute does not carry the same regulatory meaning. Subtle issue to most readers but important to maintain consistency.

I have a similar reaction to their desire to strike out 'stand-alone'. Maybe we can compromise by removing it from the body sections of the paper but maintaining it in the intro and conclusion sections. As you know, stand-alone cages have been fraught with inconsistent success in the past. That past is important to remember when trying to place this new information into context and how to apply this knowledge to clinical practice.

We can discuss if this will produce an undue burden on the two of you. I know this has been a long and arduous process to bring this paper to completion. I deeply appreciate your consistent diligence in addressing the ongoing questions from the reviewers. This is an unprecedented behavior on the part of the editorial staff which is puzzling to me.

all the best,
julie

From: Hatcher, Brian, PhD.
Sent: Tuesday, August 05, 2008 7:59 AM
To: Ken Burkus; Carol Binns; Bearcroft, Julie, PhD
Subject: RE: Edited manuscript

I feel like I am missing something.
I agree that most of these are very minor. It is interesting though, because with at least one of these, the reviewers asked for more detail on the last round of edits and are now saying that it is too much (see comment 6 about defining second surgery failures). It looks like they also want some more p values and modifications to the Figures so that the scale is linear. I will gather this information and get it to you guys. Please let me know if you need anything else from me.
Brian

From: Ken Burkus [mailto[redacted]]
Sent: Monday, August 04, 2008 5:04 PM
To: Carol Binns; Hatcher, Brian, PhD.; Bearcroft, Julie, PhD
Subject: Fw: Edited manuscript

These changes look rather simple. Am I missing anything?

Best.
Ken Burkus
----- Original Message -----
From: Editorial
To: [redacted]
Sent: Monday, August 04, 2008 2:39 PM
Subject: Edited manuscript

Dear Dr. Burkus:

Attached is a copy of your manuscript which has been edited by Dr. Clark.

Cathy Griffin | Editorial Department
The Journal of Bone and Joint Surgery
[redacted]
Needham, MA 02492
[redacted] ext. [redacted]

From: McGuinness, Tom
Sent: Saturday, February 28, 2009 03:01:47 PM
To: JK Burkus [redacted]
CC: Bearcroft, Julie, PhD; Hatcher, Brian, PhD.; Martin, Kathy
Subject: RE: Letter to the Editor regarding your JBJS article, "Use of rhBMP-2 in Combination with Structural Cortical Allografts..."

Great to see you at AAOS, Ken. I look forward to continuing to push our couple ideas on the call Brian will coordinate.

I'd like to include both Julie and Brian, but it may have to just be the two of us given both of their vacation schedules (on the beach).

Look forward to it and let's stay in better touch,

Tom

Tom McGuinness
General Manager / VP – Global Biologics Business

Medtronic, Inc. | Spinal & Biologics
[redacted], Memphis, TN 38132
Office – [redacted] | Mobile – [redacted]

From: JK Burkus [mailto:[redacted]
Sent: Thursday, February 26, 2009 5:07 PM
To: Bearcroft, Julie, PhD
Cc: Hatcher, Brian, PhD.; Peckham, Steve, Ph.D.; Beals, Neil; McGuinness, Tom
Subject: Re: Letter to the Editor regarding your JBJS article, "Use of rhBMP-2 in Combination with Structural Cortical Allografts..."

Julie,

Got it.

I am traveling home tomorrow morning from AAOS. I will be working on this over the weekend.

Please pass the salsa. How is Cancun this time of year?

You know you are the BEST.

Ken

----- Original Message -----
From: Bearcroft, Julie, PhD
To: JK Burkus
Cc: Hatcher, Brian, PhD. ; Peckham, Steve, Ph.D. ; Beals, Neil ; McGuinness, Tom
Sent: Thursday, February 26, 2009 1:53 PM
Subject: RE: Letter to the Editor regarding your JBJS article, "Use of rhBMP-2 in Combination with Structural Cortical Allografts..."

Ken

Here are some suggested responses/clarification to make in response to the issues raised in Dr Smoljanovic's letter:
1) There was not change in the amount of INFUSE Bone Graft between the pilot and pivotal phases of this trial. I went back to the IDE document to indeed verify that. However, I went to back to the pilot paper (Spine, 2002) and the pivotal paper (JBJS, 2005) and I discovered that there is a typo in the original pilot paper. It reads that the amount used was 8 - 12 mL but should have been 8 - 12 mg. Thus, when Dr S applied the 1.5 mg/mL concentration, he calculated a higher range of rhBMP-2 than was actually used.

2) Dr S assumed that there was an omission of the radiographic findings reported in Spine (2006) from this JBJS (2005) article. As you know, the radiographic analysis was done in retrospective fashion from films gathered in this IDE reported here. It was conducted in response to other reports with similar observations after the market introduction of INFUSE and completion of the initial FDA study. The advantage of using this data to better understand the possible mechanism and etiology of these defects is that this study was conducted in the context of an IDE trial where the amount of INFUSE was determined prospectively and used consistently throughout the patient series. We know now, in retrospect, one confounding variable in this trial may be the variability in the internal volume of the bone dowels since the central canal was not machined.

3) It was reported at NASS (2007) that overfilling a defect or hyperconcentrating the rhBMP-2 solution resulted in a short-term radiolucency when implanted into the cancellous bone within the distal femur of sheep. The histological evaluation in animals treated in that fashion exhibited an accelerated level of bone turnover whereby, in the early time points, the neighboring bone tissue was observed to be demineralized. Normal healing without any change in the surrounding tissue was observed in defects that were treated appropriately (i.e., not overfilled nor hyperconcentrated). With longer term follow-up, these radiolucent zones, like those reported in Spine 2006, did undergo mineralization and appear to be healing. However, the animal work did not progress to complete healing within the time frame of the study.

4) Meisel's publication that Dr S cites, demonstrates a similar finding in humans. In 16/17 patients, Meisel administered 12 mg of rhBMP-2 equally divided within 2 PEEK Telamon cages. In terms of volume, he delivered 4 cc of INFUSE Bone Graft in each interbody construct with an internal volume ranging from 0.75 to 1.3 cc, depending on their size. (Therefore, even in the case of the one patient where Dr M divided the kit equally between two treated levels, he was still

significantly overfilling the device relative to its internal volume, i.e., 2 cc rhBMP-2/ACS within the construct). In all instances, the cages were overfilled in a similar manner to that evaluated in the sheep study above. Dr M reports that all cases attained a radiographic fusion by 6-month follow-up despite observing the transient resorption surrounding the cage at 3-month time point. (FYI, Meisel cites the sheep study above to help put these findings into perspective.)

5) In response to his question about considering discontinuation of the bone dowel study, it was noted that in the radiographic report (Spine 2006) that there were no differences in fusion, ODI, SF-36 PCS, or re-operations associated with the radiographic appearance of remodeling observed at 6 months. In fact, this publication in JBJS demonstrates that superior outcomes were achievable in some of these parameters when compared to patients treated with iliac crest bone graft.

6) This phenomenon was not observed in the pivotal study for INFUSE Bone Graft in combination with the LT Cage fusion devices and therefore, not mentioned in the original product labeling. However, since these studies mentioned above have been completed, the package insert has been recently updated (2008) to advise surgeons of the risk of inappropriate use described as overfilling a defect or hyperconcentrating the rhBMP-2 solution when preparing the INFUSE Bone Graft.

Sorry it is so long but Dr S raises several questions and cites a wide variety of literature. Unfortunately, he does not appear to be aware of the sheep study and its subsequent impact on the product labeling. Perhaps your response will help to educate him and others who take note of the discussion.

Please let me know if you need further information/details as you work on the response letter to Dr S.

Best regards,
julie

From: JK Burkus [mailto:[redacted]
Sent: Tuesday, February 24, 2009 5:41 PM
To: Bearcroft, Julie, PhD; Hatcher, Brian, PhD.
Subject: Fw: Letter to the Editor regarding your JBJS article, "Use of rhBMP-2 in Combination with Structural Cortical Allografts..."

----- Original Message -----
From: JBJS Letters to the Editor
To: [redacted]
Sent: Tuesday, February 24, 2009 2:24 PM
Subject: Letter to the Editor regarding your JBJS article, "Use of rhBMP-2 in Combination with Structural Cortical Allografts..."

Dear Dr. Burkus;

Your recent article in The Journal of Bone & Joint Surgery has prompted a Letter to the Editor from one of our readers which has been published on The Journal's website: www.ejbjs.org in the Letters to the Editor section. I have attached this letter below.

We invite you to respond to the issues raised and believe that by so doing, you will contribute to the valuable post peer review discussion that should follow the presentation on new knowledge.

To submit a response to this Letter to the Editor, the most direct way is to go to: http://www.ejbjs.org/cgi/eletter-submit/87/6/1205 where you will access the online submission page to write a direct response. As corresponding author, please include the names of all authors that collaborate on your response. By doing so, you are indicating that those authors have approved the text of this response. You or your co-authors need not submit a Conflict of Interest form.

Alternatively, you may access the online submission page by finding your article on www.ejbjs.org and clicking on the, "Letters to the Editor: Submit a response" link on the right-hand side of the page.

Thank you for contributing valuable knowledge to The Journal's readership.

Sincerely,

Robert Poss, M.D. | Deputy Editor for Electronic Media
The Journal of Bone & Joint Surgery
[redacted] Needham, MA 02492
ph [redacted] | [redacted]

The Letter is as follows:

Continuing Questions Regarding Adverse Effects Of Spinal Interbody Fusion Using rhBMP-2/ACS

24 February 2009

Tomislav Smoljanovic, MD, PhD,
Orthopaedic Surgeon & Research Assistant
Department of Orthopaedic Surgery, School of Medicine, Zagreb University, Zagreb, Croatia,

Ivan Bojanic, MD, PhD; Domagoj Delimar, MD, PhD

To the Editor:

In the paper "Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery", Burkus et al. (1) presented clinical and radiographic outcomes in 79 patients who received recombinant human bone morphogenetic protein-2 soaked into an absorbable collagen sponge (rhBMP-2/ACS) in combination with threaded cortical allograft dowels and compared those results with the outcomes in 52 patients who received autograft in a stand alone anterior lumbar interbody fusion (LIF). It was a prospective, randomized, multicenter United States Food and Drug Administration (FDA)-approved investigational device exemption study conducted in two sequential phases. In the pilot phase (2), 46 patients were enrolled at 5 clinical sites, and in the pivotal phase (1), 85 patients were enrolled at 13 clinical sites. The patients were enrolled over a three-year period (May 1998 to March 2001). The study protocols for both phases were identical. Stability and radiolucent lines were assessed on plain radiographs with use of anteroposterior, lateral, and flexion-extension views. In addition, thin-slice (1-mm overlapping) computed tomography (CT) scans with coronal and sagittal plane reconstructions were used to assess bridging bone and allograft incorporation. The radiographs and CT scans were reviewed by two independent radiologists in a blinded fashion to critically assess fusion at 6, 12, and 24 months. A third independent radiologist was used to adjudicate conflicting findings.

However, we believe there are substantial shortcomings in the two studies (1,2). First, the authors did not report any transient resorption of trabecular bone within vertebral bodies after the rhBMP-2/ACS application in the pilot phase (2). Furthermore, they claimed that because of early incorporation of the allograft into the vertebral end plates in the rhBMP/ACS group, radiolucent lines were not seen after surgery in the investigational group, and so the study proceeded to the pivotal phase. However, although large osteolytic cysts were discovered within the vertebral bodies several years later (Figure 10) (3), there was no explanation offered by the authors.

Secondly, although the authors claimed that the study protocols for both phases were identical (1), it was found that the dose of rhBMP-2 used per level of interbody fusion was decreased from 12 - 18 mg in the pilot phase to 8.4 - 12 mg in the pivotal phase (4).

Although the dose of rhBMP-2 was decreased by 30%, 18% of the resorptions occurred among the patients from the rhBMP-2/ACS group at the end of the second phase (1). Our first analysis, performed almost three years ago, revealed that the resorptions occurred in cases when additional rhBMP-2/ACS (other than those placed within the interbody spacers) was placed adjacent to the interbody implant in direct contact with the vertebral endplates (5). Subsequently, a more specific analysis revealed that because of the imperfection of the carrier, i.e. initial burst release of rhBMPs from collagen sponge (6), the size of the contact area between the rhBMP-2/ACS and the trabecular bone of vertebral bodies is the most important factor associated with the incidence of the resorptions (7) (and T. Smoljanovic, et al., unpublished data, 2008). In the studies of Burkus et al. (1,2) the larger contact area was created by placing of an additional rhBMP-2/ACS between the bone dowels, the central portion of which was filled by single rhBMP-2/ACS. Another way of creating the larger contact area between the rhBMP-2/ACS and vertebral endplates in the other studies, which reported the resorptions, was achieved due to the design of the interbody spacers, i.e. by their large

apertures as in case of femoral ring allografts (FRA) or poly-ethyl-ether-ketone (PEEK) cages. To be fair, it should be mentioned that there are several studies in which the larger contact surface between the rhBMP-2/ACS and trabecular bone of vertebral bodies existed, and which had CT control within early follow up, but in which no resorption was reported (T. Smoljanovic, et al., unpublished data, 2008).

We speculated why the authors (2), who did not report resorptions in the pilot phase (3), then presented the CT scans with such large resorptions. One might speculate that there simply was no CT scan without resorptions within early follow up among the patients in the rhBMP-2/ACS group. There are reports in the literature in which the resorptions were found in each case where CT scanning was performed within the early follow up in patients who underwent LIF assisted with rhBMP-2/ACS (8,9), but as only some patients were scanned (usually those who were symptomatic (8)), it was not possible to raise any questions about the incidence of resorptions in the work of Burkus et al. (1,2) until recently when a paper by Meisel et al. (10) was published. Meisel et al. (10) performed CT scanning at 3 months after the surgery in all patients (N=17) who underwent posterior LIF assisted with rhBMP-2/ACS within the PEEK cage and with additional posterior fixation. All those patients, in the words of the authors, were asymptomatic. The resorptions surrounding the PEEK cage were found in 100% of the patients. Although the dose of rhBMP-2 clinically used per level of interbody fusion was found to have no influence on development of the resorptions (T. Smoljanovic, et al., unpublished data, 2008), we should mention that Meisel et al. (10) used from 6 to 12 mg of rhBMP-2 per level.

Finally, we come to clinical consequences of the resorptions. Mentioning fusion assessment outcomes, Burkus et al. (1) stated that in the autograft group, no patient had a fracture or migration or extrusion of the allograft implant. But, the authors did not mention migration or extrusion of the allograft implant (neither subsidence of interbody spacer nor loss of correction) presenting the results of rhBMP-2/ACS group. It was only mentioned that all radiolucent areas had resolved by 24 months after surgery. However, the analysis of reported resorptions revealed that patients in whom the resorptions developed were often faced with spacer subsidence, loss of correction, graft migration and the failure of spinal interbody fusion even with additional stabilization of fused levels (7) (and T. Smoljanovic, et al., unpublished data, 2008). However, there is another study, in which additional stabilization was not used as in the study of Burkus et al. (1,2), and in which observed resorptions had no clinical impact (11).

Although Burkus et al. (1,2) did not report clinical significance of the resorptions, we would like to know whether any of the investigators at the numerous clinical sites at which the patients were enrolled (5 plus 13) in the study over the three-year period (May 1998 to March 2001) considered discontinuing and redesigning the study after the unexpected large vertebral resorptions were observed 6 months after the surgery in their patients. (There are examples where enrollment of patients was stopped immediately after preliminary results of the resorptions become available (12,13), or where the use of rhBMP-2/ACS was abandoned in practice after completion of the studies due to the side effects, high cost, and the availability of a suitable alternative (9,14)). We also question why there was no mention of resorptions among potential adverse effects of the device in the premarket approval application (PMA) of the InFUSE Bone Graft/LT-CAGE Lumbar Tapered Fusion Device to the Center for Devices and Radiological Health (CDHR) of the FDA (15)? We have previously posed these questions and they remain unanswered (3,4,16,17). We hope that this letter will stimulate discussion in the wider medical scientific community to resolve them.

The authors did not receive any outside funding or grants in support of their research for or preparation of this work. Neither they nor a

member of their immediate families received payments or other benefits or a commitment or agreement to provide such benefits from a commercial entity. No commercial entity paid or directed, or agreed to pay or direct, any benefits to any research fund, foundation, division, center, clinical practice, or other charitable or nonprofit organization with which the authors, or a member of their immediate families, are affiliated or associated.

References

1. Burkus JK, Sandhu HS, Gornet MF, Longley MC. Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery. J Bone Joint Surg Am. 2005;87:1205-12.

2. Burkus JK, Transfeldt EE, Kitchel SH, Watkins RG, Balderston RA. Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2. Spine. 2002;27:2396-408.

3. Smoljanovic T, Pecina M. Re: Burkus JK, Transfeldt EE, Kitchel SH, et al. Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2. Spine 2002;27:2396-408. Spine. 2008;33:224.

4. Smoljanovic T, Pecina M. Unexplained decreasing of rhBMP-2 dose. J Bone Joint Surg Am. Electronically published letter. 23rd October 2007. Available from: http://www.ejbjs.org/cgi/eletters/87/6/1205#5117.

5. Smoljanovic T, Grgurevic L, Jelic M, Kreszinger M, Haspl M, Maticic D, Vukicevic S, Pecina M. Regeneration of the skeleton by recombinant human bone morphogenetic proteins. Coll Antropol. 2007;31:923-32.

6. Seeherman H, Wozney JM. Delivery of bone morphogenetic proteins for orthopedic tissue regeneration. Cytokine Growth Factor Rev. 2005;16:329-45.

7. Smoljanovic T, Bicanic G, Bojanic I. Update of comprehensive review of the safety profile of bone morphogenetic protein in spine surgery. Neurosurgery. 2009; In press.

8. Lewandrowski KU, Nanson C, Calderon R. Vertebral osteolysis after posterior interbody lumbar fusion with recombinant human bone morphogenetic protein 2: a report of five cases. Spine J. 2007;7:609-14.

9. Vaidya R, Weir R, Sethi A, Meisterling S, Hakeos W, Wybo CD. Interbody fusion with allograft and rhBMP-2 leads to consistent fusion but early subsidence. J Bone Joint Surg Br. 2007;89:342-5.

10. Meisel HJ, Schnöring M, Hohaus C, Minkus Y, Beier A, Ganey T, Mansmann U. Posterior lumbar interbody fusion using rhBMP-2. Eur Spine J. 2008;17:1735-44.

11. Kuklo TR, Rosner MK, Polly DW Jr. Computerized tomography evaluation of a resorbable implant after transforaminal lumbar interbody fusion. Neurosurg Focus. 2004;16:E10.

12. Laursen M, Hoy K, Hansen ES, Gelineck J, Christensen FB, Bunger CE. Recombinant bone

morphogenetic protein-7 as an intracorporal bone growth stimulator in unstable thoracolumbar burst fractures in humans: preliminary results. Eur Spine J. 1999;8:485-90.

13. Pradhan BB, Bae HW, Dawson EG, Patel VV, Delamarter RB. Graft resorption with the use of bone morphogenetic protein: lessons from anterior lumbar interbody fusion using femoral ring allografts and recombinant human bone morphogenetic protein-2. Spine. 2006;31:E277-84.

14. Vaidya R, Carp J, Sethi A, Bartol S, Craig J, Les CM. Complications of anterior cervical discectomy and fusion using recombinant human bone morphogenetic protein-2. Eur Spine J. 2007;16:1257-65.

15. U.S. Food and Drug Administration, Department of Health and Human Services, Center for Devices and Radiological Health: Infuse Bone Graft /LT-Cage Lumbar Tapered Fusion Device—P000058. Available from: www.fda.gov/cdrh/pdf/P000058.html, Accessed January 12, 2007.

16. Smoljanovic T, Bojanic I, Dapic T. Significance of Early CT Evaluation after the Lumbar Interbody Fusions Assisted with rhBMP-2. Am J Neuroradiol. 2009; In press.

17. Smoljanovic T, Pecina M. Re: Burkus JK, Sandhu HS, Gornet MF. Influence of rhBMP-2 on the healing patterns associated with allograft interbody constructs in comparison with autograft. Spine 2006;31:775-81. Spine. 2008;33:226.

From: Bill Martin
Sent: Friday, July 27, 2001 01:09:01 PM
To: Guorong Ma
CC: Tara Hood; Bailey Lipscomb
Subject: RE: Dr. Burkus's Paper

Guorong,
One additional note : Regarding comment #3-

> 3) The investigational patient (patient 66) who was lost to follow-up after his 12-month evaluation and therefore not included in the discussion had radiolucency that caused fusion failure at 12 months. We would be much more comfortable if this is discussed in the paragraph of Plain Radiographs of the RESULTS section on Page 9.

Discussion of patient #66 was not included in this followup of 42 patients as there was no 24 month followup. Given that the last paragraph on page 6 begins with "Forty-two patients were followed for two years after surgery", the assumption is that the excluded patient does not have to be discussed.

If you disagree please let me know.

I'll have the additional information for you soon.
Thanks!
Bill

> -----Original Message-----
> **From:** Guorong Ma
> **Sent:** Thursday, July 26, 2001 4:51 PM
> **To:** Bill Martin
> **Cc:** Tara Hood; Bailey Lipscomb
> **Subject:** Dr. Burkus's Paper
>
> Bill,
>
> A few comments on the paper:
>
> 1) To facilitate statistical discussions, I suggest to add two tables as attached here.
>
> << File: Bone_Burkus.doc >>
> By using these two tables, we can make some simple statistical comparisons and might show that osteoinduction (bone density increase within cages and bone formation outside of cages) is faster in the BMP group than in the control group. We may say, the differences are statistically significant at least at 6 months.

To complete Table 1, I need original (by patient) bone density data or the following data for each group:
number of patients;
mean of bone density **increase**; and
standard deviation of bone density **increase**.

2) One patient who died (patient 65) was not an investigational patient but a control patient. Thus, only one (1) investigational patient (patient 66) rather than two (2) was lost to follow-up (see bottom of Page 6).

3) The investigational patient (patient 66) who was lost to follow-up after his 12-month evaluation and therefore not included in the discussion had radiolucency that caused fusion failure at 12 months. We would be much more comfortable if this is discussed in the paragraph of Plain Radiographs of the RESULTS section on Page 9.

4) With regard to "bone formation outside of cages", Bailey suggested, the paper needs to emphasize, wherever possible, the location where bone is formed. For example, point out that bone is formed within the interbody space. As you know, the concern is from the extra bone growth in the BMP/PLIF study.

Please let me know if you can be of help.

Guorong

From: Tara Hood
Sent: Friday, July 27, 2001 03:52:24 PM
To: Guorong Ma; Bailey Lipscomb
Subject: FW: Dr. Burkus's Paper

FYI - I have not seen this paper and that is fine, but from looking at these comments it seems as if the numbers are wrong. I am not sure where the data came from, but there are not 42 patients at Burkus' with 24 month follow-up. Maybe this is the planned #, but there cannot be results on that many yet - the 41st patient came in Wednesday and the 42nd patient was scheduled to come in this afternoon. Just wanted to make sure you guys knew that.

Tara

-----Original Message-----
From: Bill Martin
Sent: Friday, July 27, 2001 1:09 PM
To: Guorong Ma
Cc: Tara Hood; Bailey Lipscomb
Subject: RE: Dr. Burkus's Paper

Guorong,
One additional note : Regarding comment #3-

> 3) The investigational patient (patient 66) who was lost to follow-up after his 12-month evaluation and therefore not included in the discussion had radiolucency that caused fusion failure at 12 months. We would be much more comfortable if this is discussed in the paragraph of Plain Radiographs of the RESULTS section on Page 9.

Discussion of patient #66 was not included in this followup of 42 patients as there was no 24 month followup. Given that the last paragraph on page 6 begins with "Forty-two patients were followed for two years after surgery", the assumption is that the excluded patient does not have to be discussed.

If you disagree please let me know.

I'll have the additional information for you soon.
Thanks!
Bill

> -----Original Message-----
> **From:** Guorong Ma
> **Sent:** Thursday, July 26, 2001 4:51 PM
> **To:** Bill Martin
> **Cc:** Tara Hood; Bailey Lipscomb

Subject: Dr. Burkus's Paper

Bill,

A few comments on the paper:

1) To facilitate statistical discussions, I suggest to add two tables as attached here.

<< File: Bone_Burkus.doc >>
By using these two tables, we can make some simple statistical comparisons and might show that osteoinduction (bone density increase within cages and bone formation outside of cages) is faster in the BMP group than in the control group. We may say, the differences are statistically significant at least at 6 months.

To complete Table 1, I need original (by patient) bone density data of the following data for each group:
number of patients;
mean of bone density **increase**; and
standard deviation of bone density **increase**.

2) One patient who died (patient 65) was not an investigational patient but a control patient. Thus, only one (1) investigational patient (patient 66) rather than two (2) was lost to follow-up (see bottom of Page 6).

3) The investigational patient (patient 66) who was lost to follow-up after his 12-month evaluation and therefore not included in the discussion had radiolucency that caused fusion failure at 12 months. We would be much more comfortable if this is discussed in the paragraph of Plain Radiographs of the RESULTS section on Page 9.

4) With regard to "bone formation outside of cages", Bailey suggested, the paper needs to emphasize, wherever possible, the location where bone is formed. For example, point out that bone is formed within the interbody space. As you know, the concern is from the extra bone growth in the BMP/PLIF study.

Please let me know if you can be of help.

Guorong

From: Guorong Ma
Sent: Friday, July 27, 2001 04:21:28 PM
To: Bill Martin
CC: Bailey Lipscomb
Subject: FW: Dr. Burkus's Paper

Attachments: RT_BONE_DENSITY.DOC

Bill,

Please see Tara's comments. The table 2 that I prepared yesterday was derived from the paper.

Based on the bone density data you gave me today, the numbers can not be exactly matched with those cited in the paper. And more importantly there are too many missing data, especially those at 24 months and immediate postop. Here is the summary based on today's bone density data.

I guess the current data are still too rough, although the trend is there.

Thanks,

Guorong

-----Original Message-----
From: Tara Hood
Sent: Friday, July 27, 2001 3:52 PM
To: Guorong Ma; Bailey Lipscomb
Subject: FW: Dr. Burkus's Paper

FYI - I have not seen this paper and that is fine, but from looking at these comments it seems as if the numbers are wrong. I am not sure where the data came from, but there are not 42 patients at Burkus' with 24 month follow-up. Maybe this is the planned #, but there cannot be results on that many yet - the 41st patient came in Wednesday and the 42nd patient was scheduled to come in this afternoon. Just wanted to make sure you guys knew that.

Tara

-----Original Message-----
From: Bill Martin
Sent: Friday, July 27, 2001 1:09 PM
To: Guorong Ma
Cc: Tara Hood; Bailey Lipscomb
Subject: RE: Dr. Burkus's Paper

Guorong,
One additional note : Regarding comment #3-

> 3) The investigational patient (patient 66) who was lost to follow-up after his 12-month evaluation and therefore not included in the discussion had radiolucency that caused fusion failure at 12 months. We would be much more comfortable if this is discussed in the paragraph of Plain Radiographs of the RESULTS section on Page 9.

Discussion of patient #66 was not included in this followup of 42 patients as there was no 24 month followup. Given that the last paragraph on page 6 begins with "Forty-two patients were followed for two years after surgery", the assumption is that the excluded patient does not have to be discussed.

If you disagree please let me know.

I'll have the additional information for you soon.
Thanks!
Bill

> -----Original Message-----
> **From:** Guorong Ma
> **Sent:** Thursday, July 26, 2001 4:51 PM
> **To:** Bill Martin
> **Cc:** Tara Hood; Bailey Lipscomb
> **Subject:** Dr. Burkus's Paper
>
> Bill,
>
> A few comments on the paper:
>
> 1) To facilitate statistical discussions, I suggest to add two tables as attached here.
>
> << File: Bone_Burkus.doc >>
> By using these two tables, we can make some simple statistical comparisons and might show that osteoinduction (bone density increase within cages and bone formation outside of cages) is faster in the BMP group than in the control group. We may say, the differences are statistically significant at least at 6 months.
>
> To complete Table 1, I need original (by patient) bone density data or the following data for each group:
> number of patients;
> mean of bone density **increase**; and
> standard deviation of bone density **increase**.
>
> 2) One patient who died (patient 65) was not an investigational patient but a control patient. Thus, only one (1) investigational patient (patient 66) rather than two (2) was lost to follow-up (see bottom of Page 6).

3) The investigational patient (patient 66) who was lost to follow-up after his 12-month evaluation and therefore not included in the discussion had radiolucency that caused fusion failure at 12 months. We would be much more comfortable if this is discussed in the paragraph of Plain Radiographs of the RESULTS section on Page 9.

4) With regard to "bone formation outside of cages", Bailey suggested, the paper needs to emphasize, wherever possible, the location where bone is formed. For example, point out that bone is formed within the interbody space. As you know, the concern is from the extra bone growth in the BMP/PLIF study.

Please let me know if you can be of help.

Guorong

InFUSE(TM) Bone Graft/LT-CAGE(TM) Device Open Study

Summary of Bone Density Changes at Dr. Burkus Site

Period	Variable	Investigational	Control	p-value**
Immediate Postop	Bone Density (HU)			
	n	15	12	
	Mean	175.4	541.2	
	Std	89.5	103.7	
	Min	94.0	403.0	
	Max	436.5	712.0	

Program (Date): RT_BONE_DENSITY (27JUL01) (15:45) (PAGE 1 OF 4)

* P-values for change from immediate postop in each group are from paired t-test.
** P-values for difference between the treatment groups are from analysis of variance.

InFUSE(TM) Bone Graft/LT-CAGE(TM) Device Open Study

Summary of Bone Density Changes at Dr. Burkus Site

Period	Variable	Investigational	Control	p-value**
6 Months	Bone Density (HU)			
	n	20	18	
	Mean	326.8	575.6	
	Std	132.1	137.7	
	Min	144.0	320.0	
	Max	679.0	811.0	
	Change from Immediate Postop (HU)			
	n	15	11	0.067
	Mean	135.5	42.1	
	Std	145.9	79.3	
	Min	-175	-74.0	
	Max	452.5	189.5	
	p-value *	0.003	0.109	

Program (Date): RT_BONE_DENSITY (27JUL01) (15:45) (PAGE 2 OF 4)

* P-values for change from immediate postop in each group are from paired t-test.
** P-values for difference between the treatment groups are from analysis of variance.

InFUSE(TM) Bone Graft/LT-CAGE(TM) Device Open Study

Summary of Bone Density Changes at Dr. Burkus Site

Period	Variable	Investigational	Control	p-value**
12 Months	Bone Density (HU)			
	n	21	19	
	Mean	434.1	667.6	
	Std	174.3	168.5	
	Min	112.0	329.0	
	Max	796.5	925.0	
	Change from Immediate Postop (HU)			
	n	14	12	0.600
	Mean	225.3	184.5	
	Std	206.4	180.6	
	Min	-257	-168	
	Max	570.0	502.0	
	p-value *	0.001	0.005	

Program (Date): RT_BONE_DENSITY (27JUL01) (15:45) (PAGE 3 OF 4)

* P-values for change from immediate postop in each group are from paired t-test.
** P-values for difference between the treatment groups are from analysis of variance.

InFUSE(TM) Bone Graft/LT-CAGE(TM) Device Open Study

Summary of Bone Density Changes at Dr. Burkus Site

Period	Variable	Investigational	Control	p-value**
24 Months	Bone Density (HU)			
	n	10	7	
	Mean	503.5	693.4	
	Std	125.8	263.3	
	Min	307.0	236.0	
	Max	663.0	980.5	
	Change from Immediate Postop (HU)			
	n	5	3	0.203
	Mean	354.4	141.3	
	Std	110.7	317.5	
	Min	208.5	-221	
	Max	471.0	371.0	
	p-value *	0.002	0.521	

Program (Date): RT_BONE_DENSITY (27JUL01) (15:45) (PAGE 4 OF 4)

* P-values for change from immediate postop in each group are from paired t-test.
** P-values for difference between the treatment groups are from analysis of variance.

From: Bill Martin
Sent: Monday, July 30, 2001 10:45:15 AM
To: Guorong Ma
CC: Bailey Lipscomb
Subject: RE: Dr. Burkus's Paper

Guorong,
THANKS! Looking good. I will talk with Dr. Burkus today to understand if he is expecting more data. Otherwise, I assume that we could use the info you supplied as long as we clean up the wording in the paper to make it more clear.

Do you agree?

-----Original Message-----
From: Guorong Ma
Sent: Friday, July 27, 2001 4:21 PM
To: Bill Martin
Cc: Bailey Lipscomb
Subject: FW: Dr. Burkus's Paper

Bill,

Please see Tara's comments. The table 2 that I prepared yesterday was derived from the paper.

Based on the bone density data you gave me today, the numbers can not be exactly matched with those cited in the paper. And more importantly there are too many missing data, especially those at 24 months and immediate postop. Here is the summary based on today's bone density data.

<< File: RT_BONE_DENSITY.DOC >>

I guess the current data are still too rough, although the trend is there.

Thanks,

Guorong

-----Original Message-----
From: Tara Hood
Sent: Friday, July 27, 2001 3:52 PM
To: Guorong Ma; Bailey Lipscomb
Subject: FW: Dr. Burkus's Paper

FYI - I have not seen this paper and that is fine, but from looking at these comments it seems as if the numbers are wrong. I am not sure where the data came from, but there are not 42 patients at Burkus with 24 month follow-up. Maybe this is the planned #, but there cannot be results on that many yet - the 41st patient came in Wednesday and the 42nd patient was scheduled to come in this afternoon. Just wanted to make sure you guys knew that.

Tara

-----Original Message-----
From: Bill Martin
Sent: Friday, July 27, 2001 1:09 PM
To: Guorong Ma
Cc: Tara Hood; Bailey Lipscomb
Subject: RE: Dr. Burkus's Paper

Guorong,
One additional note : Regarding comment #3-

> 3) The investigational patient (patient 66) who was lost to follow-up after his 12-month evaluation and therefore not included in the discussion had radiolucency that caused fusion failure at 12 months. We would be much more comfortable if this is discussed in the paragraph of Plain Radiographs of the RESULTS section on Page 9.

Discussion of patient #66 was not included in this followup of 42 patients as there was no 24 month followup. Given that the last paragraph on page 6 begins with "Forty-two patients were followed for two years after surgery", the assumption is that the excluded patient does not have to be discussed.

If you disagree please let me know.

I'll have the additional information for you soon.
Thanks!
Bill

> -----Original Message-----
> **From:** Guorong Ma
> **Sent:** Thursday, July 26, 2001 4:51 PM
> **To:** Bill Martin
> **Cc:** Tara Hood; Bailey Lipscomb
> **Subject:** Dr. Burkus's Paper
>
> Bill,
>
> A few comments on the paper:
>
> 1) To facilitate statistical discussions, I suggest to add two tables as attached here.

<< File: Bone_Burkus.doc >>
By using these two tables, we can make some simple statistical comparisons and might show that osteoinduction (bone density increase within cages and bone formation outside of cages) is faster in the BMP group than in the control group. We may say, the differences are statistically significant at least at 6 months.

To complete Table 1, I need original (by patient) bone density data or the following data for each group:

number of patients;
mean of bone density **increase**; and
standard deviation of bone density **increase**.

2) One patient who died (patient 65) was not an investigational patient but a control patient. Thus, only one (1) investigational patient (patient 66) rather than two (2) was lost to follow-up (see bottom of Page 6).

3) The investigational patient (patient 66) who was lost to follow-up after his 12-month evaluation and therefore not included in the discussion had radiolucency that caused fusion failure at 12 months. We would be much more comfortable if this is discussed in the paragraph of Plain Radiographs of the RESULTS section on Page 9.

4) With regard to "bone formation outside of cages", Bailey suggested, the paper needs to emphasize, wherever possible, the location where bone is formed. For example, point out that bone is formed within the interbody space. As you know, the concern is from the extra bone growth in the BMP/PLIF study.

Please let me know if you can be of help.

Guorong

From: Treharne, Rick
Sent: Monday, September 30, 2002 12:22:33 PM
To: Ma, Guorong
Subject: FW: BMP Pooled Data manuscript

Attachments: All BMP Outcomes paper.3.doc; Tables in question.doc

This is Burkus' write-up of the INFUSE integrated analysis. Please review. Note the questions in the tables on the right. If you could answer them for me, I will pass them back to them. Thanks...Rick

-----Original Message-----
From: Ken Burkus [SMTP:[redacted]
Sent: Monday, September 30, 2002 7:08 AM
To: Rick Treharne
Cc: Neil Beals; Julie Bearcroft
Subject: BMP Pooled Data manuscript

Rick,

I have attached two WORD documents.

The first is the revised Integrated Data manuscript.

The second holds the Tables for the paper in which a few questions have been highlighted.

You can reply directly to Carol Binns ([redacted] She is the wonderful lady that gets all the manuscripts out the door at the Hughston Foundation. She has copies of all of the manuscript drafts and has been reformatting the Tables.

I will be spending the day in Albany Georgia at an off site clinic.

Best regards
Ken Burkus

Is InFUSE™ Bone Graft Superior to Autograft Bone? An Integrated Analysis of Clinical Trials Using the LT-CAGE™ Lumbar Tapered Fusion Device

J. Kenneth Burkus, M.D.*

Stephen E. Heim MD#

Matthew F. Gornet MD†

Thomas A. Zdeblick MD§

* Staff Physician, Spine Service, The Hughston Clinic, P.C., [redacted]

Staff Physician, Orthopaedic Associates of DuPage, Warrenville, Illinois

†Staff Physician, Missouri Bone and Joint Institute, St. Louis, Missouri

§Chairman, Department of Orthopedics and Rehabilitation, University of Wisconsin, Madison, Wisconsin

FDA device/drug status: Approved for this indication.

Statement of Financial Relationship: The authors are consultants and clinical investigators for the company distributing the device studied.

Address correspondence and reprint requests to: J. K. Burkus, M.D., The Hughston Clinic, [redacted] Columbus, Georgia 31908-9517

ABSTRACT

Background context: A product containing recombinant bone morphogenetic protein, or rhBMP-2, marketed as InFUSE™ Bone Graft, is now commercially available in the United States. Three multicenter human clinical studies of patients undergoing anterior lumbar fusion have been conducted using this material or autograft and the LT-CAGE™ Lumbar Tapered Fusion device, in which the material was implanted.

Purpose: We hypothesized that InFUSE™ Bone Graft is superior to autograft when used inside an LT-CAGE™ Lumbar Tapered Fusion device in patients undergoing anterior lumbar fusion. We increased the overall sample size by combining several smaller clinical trials to increase the statistical power of the analysis.

Study design/setting: An integrated analysis of prospective studies of patients who received lumbar fusion cage implants by one of two surgical methods using one of two graft materials with a minimum follow-up of 2 years.

Patient Sample: A total of 679 patients from 36 sites were implanted with the LT-CAGE™ Lumbar Tapered Fusion Device for single-level degenerative disc disease with up to grade 1 spondylolisthesis. Of these patients, 277 had their cages implanted with InFUSE™ Bone Graft, and 402 received autograft transferred from the iliac crest.

Outcome Measures: After surgery, fusion was assessed at 6, 12, and 24 months and pain was measured on the Oswestry Disability Index and the SF-36 Pain Index at 3, 6, 12, and 24 months. The surgery-to-return-to-work interval and second surgeries were recorded.

Methods: An integrated analysis of multiple clinical studies was performed using an analysis of covariance to adjust for preoperative variables.

Results: The patients treated with InFUSE™ Bone Graft had statistically superior outcomes with regard to length of surgery, blood loss, hospital stay, reoperation rate, and average time to return to work. Oswestry Disability Index scores and the Physical Component Scores and Pain Index of the SF-36 scale at 3, 6, 12, and 24 months showed statically superior outcomes in the InFUSE™ group. Similarly, fusion rates were statistically superior at 6, 12, and 24 months in the InFUSE™ group.

Conclusions: InFUSE™ Bone Graft should become the new gold standard and should replace autograft bone inside the LT-CAGE™ device in patients undergoing anterior lumbar spinal fusions.

Keywords: Anterior lumbar interbody fusion, InFUSE™ Bone Graft, Bone morphogenetic protein, Fusion cage, Degenerative disc disease, Lumbar spine

INTRODUCTION

The surgical technique and indications for implanting the LT-CAGE™ Lumbar Tapered Fusion Device (Medtronic Sofamor Danek, Memphis, Tennessee) and reports of outcome measurements in patients in whom it has been implanted have been reported in the literature [1-3]. The history, development, and method of use of the protein product, called rhBMP-2 (recombinant human bone morphogenetic protein), used in our study have also been reviewed [4-7], and the prospective, randomized trial that lead to the product's approval by showing equivalency in outcome between the InFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, Tennessee) and autograft was published in 2002 [2]. The advantages to the patient and to the surgeon of not having to create a second surgical site and the complications and pain of iliac crest harvesting have also been reviewed [8].

The purpose of our analysis was to investigate the potential statistical superiority of InFUSE™ Bone Graft to autograft used inside the LT-CAGE™ Lumbar Tapered Fusion Device in surgical parameters, hospital stay, and clinical outcome in single-level spinal fusions. We integrated, or pooled, the results from similar large-scale clinical trials of the same device used for the same indication and measured in the same way to check for statistical superiority. This data came from both published and unpublished studies.

InFUSE™ Bone Graft with the LT-CAGE™ device was approved by the U.S. Food and Drug Administration on July 2, 2002, for treating patients with degenerative disc disease and up to grade I spondylolisthesis using a single-level anterior spinal fusion procedure. The approval was based primarily on the clinical data from a prospective,

randomized, controlled clinical trial that is discussed in detail elsewhere [2]. That study used the INFUSE™ Bone Graft with the LT-CAGE™ Tapered Lumbar Fusion Device in the investigational group patients and compared their results with those of the control group patients who received autograft inside the LT-CAGE™ device in open surgical procedures. Wyeth BioPharma, Cambridge, MA, genetically engineered the rhBMP-2 component. The absorbable collagen sponge component is manufactured by Integra LifeSciences, Plainsboro, NJ. Together, the components are distributed commercially under the trade name InFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, TN). This clinical trial was designed to establish statistical equivalence (noninferiority) between the InFUSE group and autograft group. The fusion success rate in the InFUSE group was 94.5% at 24 months after surgery compared with 88.7% in the autograft group. The probability of noninferiority of InFUSE to autograft was shown to be essentially 100%. The probability of superiority was 90.2%, which, albeit high, did not meet the minimum superiority criterion of 95% predefined in the prospective, randomized protocol. Fusion superiority was not shown because of insufficient sample size and, therefore, insufficient statistical power. This clinical trial was designed with patients' participation to show equivalence. The number of patients enrolled in this study alone was not adequate to demonstrate statistical superiority. The to additional studies were combined in order to assess the statical superiority of InFUSE over the autograft controls.

METHODS

Our analysis combines the two patient data sets from a published randomized trial [2] with those from two additional clinical trials to increase the sample size and statistical power. Two patient data sets involved an open surgical technique through which the LT

CAGE™ Tapered Lumbar Fusion Device was implanted [2]. Two patient data sets involved the laparoscopic implantation of the fusion cage. The third patient data set is from the clinical trial in which InFUSE™ Bone Graft was used with the LT-CAGE™ Tapered Lumbar Fusion Device and implanted laparoscopically. This study used the identical inclusion-exclusion criteria and procedures as the other studies; however, patients in this study were not randomly assigned to treatment groups [3]. A portion of the results of this study has been published [3]. The fourth patient data set was from an earlier clinical trial in which autograft in the LT-CAGE™ device was inserted using a laparoscopic surgical approach. The inclusion-exclusion criteria for these patients were identical to those for the patients in the randomized trial and the other laparoscopic arm of the study with the minor exception of there being no minimum Oswestry low back pain disability score for entry. The results of this study have been published. The four clinical studies are summarized in Table 1. All patents were entered into these studies between 1997 and 1999.

The two treatment factors in these four patient data sets are bone graft type (InFUSE™ Bone Graft or autograft) and the surgical approach (open or laparoscopic). Our goal was to compare and analyze the results in the patients who received InFUSE™ Bone Graft with those in the patients who received autograft. The results from the two surgical approaches are pooled and the effects of surgical approach, if any, such as at early time points, are statistically adjusted so as not to affect the comparison between the graft types. Thus, our analysis compared the results of 277 InFUSE™ Bone Graft patients with 402 autograft patients. All of the 679 patients had degenerative disc disease with up to grade 1 spondylolisthesis. All patients had two LT-CAGE devices implanted anteriorly

at one lumbar level, and all were included in prospective studies using the same outcome measurement tools and methodology of analysis (Figure 1). More than 60 surgeons at 36 different sites enrolled the 679 patients. The author was the surgeon for 45 of these patients, and no single surgeon performed more than 10% of the cases. Hence, the outcomes represent typical results from a wide variety of surgeons with different degrees of experience.

Because the four prospectively studied groups were not randomized, the patients' demographic characteristics and prognostic factors could be different among the groups. Tables 2, 3, and 4 summarize demographic information, preoperative medical condition and medication usage, and preoperative measurements of some clinical endpoints, respectively. Among approximately 20 summarized variables, seven were found to be significantly different between the combined InFUSE group and the combined autograft group. Finding statistical significance in minor changes is the result of the increased statistical power of the study caused by the larger sample size from the combination of the groups.

Statistical Analysis

The seven variables that were found to have statistically significant differences were age, previous back surgery, preoperative non-narcotic medication use, weak-narcotic medication use, muscle relaxant medication use, preoperative low back pain score on the Oswestry Disability Index, and preoperative SF-36 Physical Component Score. Because these seven prognostic factors could potentially affect the clinical outcomes and therefore confound the analysis of a study between the InFUSE and autograft groups, a statistical technique called analysis of covariance (ANCOVA) was

performed. With the use of this statistical methodology, the influences of these prognostic factors are adjusted for and comparisons between the InFUSE and autograft results are made. In essence, this statistical method makes it possible to have both groups start out at the same level statistically for these seven factors before any differences in outcome are examined.

RESULTS

The statistical analysis of operative time, blood loss, and hospital stay for the InFUSE and autograft groups are also shown in Table 5. This analysis reveals superior benefits of the combined InFUSE group compared with the autograft group for all three variables. The InFUSE group spent an average of 0.9 hours (54 minutes) less under anesthesia, lost an average of 66 mL less blood (probably because of the shorter surgery time and not having a second surgery site), and, on average, left the hospital nearly a day (0.9) earlier than the autograft group.

The fusion success rate in the combined InFUSE group was 94.4% (201/213) at 24 months after surgery compared with 89.4% (252/282) in the autograft group (Table 6). This 5 basis point percentage difference was shown to be statistically significant by an analysis of covariance, with an adjusted *p*-value of .022. In short, fusion, the primary goal of performing the original surgery, was found to be statistically superior for the InFUSE patients.

In the combined InFUSE group, from preoperative low back pain scores on the validated Oswestry Disability Index improved significantly over those in the autograft group for all time points—3, 6, 12, and 24 months—in the study (Table 7). The adjusted *p*-values were all highly significant.

The Physical Component and Pain Index scores of SF-36 Health Survey, which measures a patient's physical well being after surgery, are shown in Table 8. As with the Oswestry Disability Index low back pain scores, the results showed the statistical superiority of the combined InFUSE group to the autograft group for all time points after surgery.

Additional surgical events in the study patients are summarized in Table 9. Simple Fisher's exact tests show that the combined InFUSE groups had statistically fewer reoperations than patients who were implanted with autograft (p=.0036). At the two-year time point used in the study, the revision rate in InFUSE patients approached statistical superiority (p=.0631).

Although the difference was not statistically significant, 103 (74.6%) of the InFUSE patients who were working before surgery, returned to work after surgery compared with 109 (64.9%) patients in the autograft group. Again although not statistically significant, 49 (35.3%) of the InFUSE patients who were not working before surgery returned to work after surgery compared with 73 (31.3%) of the autograft patients. The difference that was found to be statistically significant was the time it took for the patients to return to work. A summary of time-to-event type analysis of return to work is contained in Table 10. The statistical comparison between the InFUSE and autograft groups was adjusted by the preoperative work status, the seven prognostic covariates, and the surgical approach. For the 334 patients who are known to have gone back to work after surgery, the average number of days to return to work was 54.5 days shorter for the LT-CAGE patients implanted with InFUSE Bone Graft. This finding was highly significant in favor of the InFUSE patients (adjusted p-value=.0156).

DISCUSSION

Surgeons have long sought to find the best way to fuse two bones. Although allograft bone has been used with some degree of success, transplanting living bone from one part of the body to another has become the "gold standard" by which all other procedures are measured [8]. Finding a substitute for human tissue has also been a noble goal of researchers for decades, and finding a bone graft substitute to replace autogenous bone seemed at times an impossible task. What material could researchers develop that would be better than a naturally occurring material?

Since the discovery of bone morphogenetic proteins (BMP) by Dr. Marshall Urist in 1965 [9], his dream, and those of many others, was to have BMP available in operating rooms as a safe and effective replacement for autograft. In July 2002, his dream became a reality in the United States with the FDA approval of BMP-2, a recombinant version of one of the family of BMPs. His goal, and the goal of other researchers like him, was for the substitute to be equal to autograft so harvesting of autograft bone from other parts of the body would no longer be necessary. Preclinical studies [5,6,10-14] have indicated the possibility that osteoinductive protein-containing materials may be superior to autograft in some applications and for some outcome measurements. Wozney [7] suggests that BMP can result in direct intramembranous ossification because in some animal models direct bone formation is observed after administration of the protein. Because chips of transferred autogenous graft may need to be resorbed or be remodeled before fusing and BMP-formed bone does not, this feature may explain why some animal studies had superior results with BMP-containing grafts when compared with autograft. However, the question remains: Can any recombinant BMP on any carrier ever be superior to

autograft—the gold standard—with regard to operative parameters and clinical outcome in humans? Pilot study results of the LT-CAGE™ Lumbar Tapered Fusion Device in humans [1] and the results from a prospective, randomized study [2] showed a trend toward faster fusion with the InFUSE™ Bone Graft and other data that were comparable with that in the patients who received autograft. We hypothesized that this trend would become a superior outcome in a larger study.

We used the ANCOVA method for an integrated analysis of four, large-scale multicenter sets of patient data. This analysis of prospectively gathered data has answered the question of the superiority of InFUSE™ Bone Graft over autograft for one particular human clinical use. This analysis of 679 patients represents the largest prospective combined study of a single-level anterior procedure using a single device for a single indication in the spinal literature. Because all patients received the same LT-CAGE implants, we had, for the first time, a data set large enough to determine whether InFUSE™ Bone Graft is equivalent to or superior to autograft bone. Because of the large sample size used in this analysis and its subsequent statistical power, the answer is an unequivocal "yes." The InFUSE patients had statistically superior outcomes in the following categories: shortened surgery time, reduced blood loss, shortened hospital stay, higher fusion rate, better Oswestry Low Back Pain Disability Questionnaire scores at all follow-up intervals, better Physical Component Scores and Pain Index scores on the SF-36 Health Survey at all follow-up intervals, fewer reoperations, and an earlier return to work.

The mean improvement in Oswestry pain scores for all postoperative time points for the InFUSE group was approximately 2 points. Because both groups started with

mean scores of approximately 50 on the 100-point Oswestry scale, a 2-point improvement at all time points represents improvement of approximately 4%. The PCS scores on the SF-36 scale also improved approximately 2 points in the InFUSE patients. Obviously any statistical decrease in pain at any time point would be considered significant and desirable by the patient. As seen in the return-to-work analysis, the statistically significant decrease in the InFUSE patients' pain, although not large, must be part of the explanation for their returning to work nearly two months earlier than the autograft patients.

The InFUSE patients obviously had none of the pain or problems associated with iliac crest graft harvesting. In the 402 autograft patients treated with open and laparoscopic surgery, 5 (1.25%) had infections at their harvest site, 2 (0.5%) had fractures at the graft site, and 5 (1.25%) had other adverse events related to their harvest site, that is, autograft transplant patients had a 3.0% chance of a significant graft site complication. In the autograft open group, nearly a third (32%) of the patients still had some pain at their harvest site two years after the surgery [2].

We believe this analysis demonstrates the superiority of using InFUSE™ Bone Graft. In fact, we found no disadvantage to using InFUSE™ Bone Graft for the surgical, hospital discharge, and major postoperative outcome measurements discussed. In addition, the InFUSE patients did not have the pain, morbidity, or complications associated with the second surgery of iliac crest graft harvest. The results of this integrated analysis coupled with the tremendous safety profile for the recombinant human bone morphogenetic protein (rhBMP-2) material used in the study [15] clearly indicates

that the use of InFUSE Bone Graft should now be the new gold standard for replacing autograft bone inside the LT-CAGE device for lumbar spinal fusions.

With its clear superiority, InFUSE™ Bone Graft may now be the new gold standard for replacing autograft bone inside the LT-CAGE™ device when used for lumbar spinal fusions. InFUSE Bone Graft is now used exclusively for this purpose in our institution.

ACKNOWLEDGMENTS

The author thanks the more than 60 clinical investigators who provided patients for this study and the Clinical Research group at Medtronic Sofamor Danek for their help in preparing the manuscript and the statistical analyses reported.

REFERENCES

[1] Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25:376-81.

[2] Burkus JK, Gornet MF, Dickman C, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. J Spinal Disord 2002;October (in press).

[3] Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2. A prospective study of clinical and radiographic outcomes. Spine 2001;26:2751-6.

[4] Boden SD. Overview of the biology of lumbar spine fusion and principles for selecting a bone graft substitute. Spine 2002;27:S26-31.

[5] McKay B, Sandhu HS. Use of recombinant human bone morphogenetic protein-2 in spinal fusion applications. Spine 2002;27(16 Suppl 1):S66-85.

[6] Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995;20:1326-37.

[7] Wozney JM. Overview of bone morphogenetic proteins. Spine 2002;27(16 Suppl 1):S2-8.

[8] Vaccaro AR, Kazuhiro C, Heller JG, Patel TC, Thalgott JS, Truumees E, Fischgrund JS, Craig MR, Berta SC, Wang JC. Bone grafting alternatives in spinal surgery. The Spine Journal 2002;2:206-15.

[9] Urist MR. Bone: formation by autoinduction. Science 1965;150:893-9.

[10] David SM, MD, Gruber HE, Meyer RA, Murakami T, Tabor OB, Howard BA, Wozney JM, Hanley EN. Lumbar spinal fusion using recombinant human bone morphogenetic protein in the canine. A comparison of three dosages and two carriers. Spine 1999;24:1973 –9.

[11] Boden SD, Schimandle JH, Hutton WC. The 1995 Volvo award in basic sciences. The use of an osteoconductive growth factor for lumbar spinal fusion. Part II: study of dose, carrier, and species. Spine 1995;20:2633-44.

[12] Sandhu HS, Kanim LE, Kabo JM, Toth JM, Zeegen EN, Liu D, Delamarter RB, Dawson EG. Effective doses of recombinant human bone morphogenetic protein-2 in experimental spinal fusion. Spine 1996;21:2115-22.

[13] Sandhu HS, Toth JM, Diwan AD, Seim HB, Kanim LE, Kabo JM, Turner AS. Histologic evaluation of the efficacy of rhBMP-2 compared with autograft bone in sheep spinal anterior interbody fusion. Spine 2002;27:567-75.

[14] Zdeblick TA, Ghanayem AJ, Rapoff AJ, Swain CS, Bassett T, Cooke ME, Markel M. Cervical interbody fusion cages. An animal model with and without bone morphogenetic protein. Spine 1998;23:758-65.

[15] Poynton AR, Lane JM. Safety profile for the clinical use of bone morphogenetic proteins in the spine. Spine 2002;27(16 Suppl 1):S40-8.

Table 1. Summary of study groups analyzed.

Study group	Graft type	Surgical approach	Randomized	Prospective	Number of patients
InFUSE™ Open	InFUSE™	Open	Yes	Yes	143
InFUSE™ Lap	InFUSE™	Laparoscopic	No	Yes	134
Autograft Open	Autograft	Open	Yes	Yes	136
Autograft Lap	Autograft	Laparoscopic	Yes	Yes	266

Table 2. Demographic information.

Variable [n(%)]	InFUSE™ Open (N=143)	InFUSE™ Lap (N=134)	InFUSE™ Total (N=277)	Autograft Open (N=136)	Autograft Lap (N=266)	Autograft Total (N=402)	p-value* INFUSE vs Autograft
Age (yrs.)							
n	143	134	277	136	266	402	.007
Mean	43.3	42.4	42.9	42.3	40.0	40.8	
SD	9.8	10.5	10.2	9.7	9.6	9.7	
Height (in.)							
n	143	134	277	135	262	397	.216
Mean	68.1	67.5	67.8	68.0	68.3	68.2	
SD	4.2	4.0	4.1	4.2	3.9	4.0	
Weight (lbs.)							
n	143	134	277	134	264	398	.146
Mean	179.1	169.8	174.6	181.1	177.6	178.8	
SD	33.1	38.3	36.0	37.0	37.9	37.6	
Sex [n(%)]							
Male	78 (54.5)	57 (42.5)	135 (48.7)	68 (50.0)	142 (53.4)	210 (52.2)	.391
Female	65 (45.5)	77 (57.5)	142 (51.3)	68 (50.0)	124 (46.6)	192 (47.8)	
Marital Status [n(%)]							
Single	24 (16.8)	24 (17.9)	48 (17.3)	18 (13.2)	52 (19.5)	70 (17.4)	.983
Married	95 (66.4)	91 (67.9)	186 (67.1)	91 (66.9)	177 (66.5)	268 (66.7)	
Divorced	18 (2.6)	14 (10.4)	32 (11.6)	20 (14.7)	30 (11.3)	50 (12.4)	
Separated	5 (3.5)	2 (1.5)	7 (2.5)	5 (3.7)	5 (1.9)	10 (2.5)	
Widowed	1 (0.7)	3 (2.2)	4 (1.4)	2 (1.5)	2 (0.8)	4 (1.0)	
Education Level [n(%)]							
< High School	13 (9.1)	7 (5.2)	20 (7.2)	17 (12.6)	25 (9.5)	42 (10.6)	.277
High School	45 (31.5)	39 (29.1)	84 (30.3)	39 (28.9)	86 (32.7)	125 (31.4)	
> High School	85 (59.4)	88 (65.7)	173 (62.5)	79 (58.5)	152 (57.8)	231 (58.0)	
Workers' Compensation [n(%)]							
Yes	47 (32.9)	42 (31.3)	89 (32.1)	47 (34.6)	89 (33.7)	136 (34.0)	.620
No	96 (67.1)	92 (68.7)	188 (67.9)	89 (65.4)	175 (66.3)	264 (66.0)	
Spinal Litigation [n(%)]							
Yes	18 (12.6)	11 (8.2)	29 (10.5)	22 (16.2)	29 (11.1)	51 (12.8)	.398
No	125 (87.4)	123 (91.8)	248 (89.5)	114 (83.8)	233 (88.9)	347 (87.2)	
Tobacco Used [n(%)]							
Yes	47 (32.9)	40 (29.9)	87 (31.4)	49 (36.0)	83 (31.2)	132 (32.8)	.738
No	96 (67.1)	94 (70.1)	190 (68.6)	87 (64.0)	183 (68.8)	270 (67.2)	
Alcohol Use [n(%)]							
Yes	39 (27.3)	66 (49.3)	105 (37.9)	43 (31.6)	94 (35.3)	137 (34.1)	.328
No	104 (72.7)	68 (50.7)	172 (62.1)	93 (68.4)	172 (64.7)	265 (65.9)	
Preop Work Status [n(%)]							
Working	68 (47.6)	70 (52.2)	138 (49.8)	50 (36.8)	118 (44.5)	168 (41.9)	.050
Not Working	75 (52.4)	64 (47.8)	139 (50.2)	86 (63.2)	147 (55.5)	233 (58.1)	

Table 3. Preoperative medical condition and medication usage [Number (%) of patients]

Variable	InFUSE™ Open (N=143)	InFUSE™ Lap (N=134)	InFUSE™ Total (N=277)	Autograft Open (N=136)	Autograft Lap (N=266)	Autograft Total (N=402)	*p*-value* INFUSE vs Autograft
Previous Back Surgery							
Yes	54 (37.8)	33 (24.6)	87 (31.4)	55 (40.4)	110 (41.4)	165 (41.0)	.012
No	89 (62.2)	101 (75.4)	190 (68.6)	81 (59.6)	156 (58.6)	237 (59.0)	
Previous Back Surgery							
1	39 (72.2)	16 (50.0)	55 (64.0)	34 (61.8)	78 (70.9)	112 (67.9)	.574
>1	15 (27.8)	16 (50.0)	31 (36.0)	21 (38.2)	32 (29.1)	53 (32.1)	
Non-narcotic Medications							
Yes	80 (55.9)	97 (72.4)	177 (63.9)	75 (55.1)	109 (41.0)	184 (45.8)	<.001
No	63 (44.1)	37 (27.6)	100 (36.1)	61 (44.9)	157 (59.0)	218 (54.2)	
Weak Narcotic Medications							
Yes	77 (53.8)	61 (45.5)	138 (49.8)	67 (49.3)	90 (33.8)	157 (39.1)	.006
No	66 (46.2)	73 (54.5)	139 (50.2)	69 (50.7)	176 (66.2)	245 (60.9)	
Strong Narcotic Medications							
Yes	31 (21.7)	17 (12.7)	48 (17.3)	33 (24.3)	42 (15.8)	75 (18.7)	.686
No	112 (78.3)	117 (87.3)	229 (82.7)	103 (75.7)	224 (84.2)	327 (81.3)	
Muscle Relaxant Medications							
Yes	45 (31.5)	49 (36.6)	94 (33.9)	37 (27.2)	39 (14.7)	76 (18.9)	<.001
No	98 (68.5)	85 (63.4)	183 (66.1)	99 (72.8)	227 (85.3)	326 (81.1)	

p-values are from Fisher's exact test or chi-square test.

Table 4. Preoperative evaluations of clinical endpoints

	InFUSE™			Autograft			*p*-value*
Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	INFUSE vs Autograft
Oswestry Pain Score							
n	143	134	277	136	264	400	.001
Mean	53.7	52.3	53.0	55.1	46.5	49.4	
SD	12.7	11.7	12.2	11.8	15.6	15.0	
SF-36 PCS							
n	142	134	276	136	263	399	.004
Mean	27.7	28.3	28.0	29.4	29.5	29.5	
SD	5.7	6.1	5.9	6.2	7.3	6.9	
SF-36 Pain Index							
n	143	134	277	136	263	399	.077
Mean	21.8	22.6	22.2	22.7	24.7	24.1	
SD	11.1	13.4	12.2	13.6	14.7	14.3	

*p-values are from analysis of variance.

Table 5. Surgery information.

		InFUSE™			Autograft			*p*-value*
Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	INFUSE vs Autograft
Operative Time (hrs)							<.001
n	143	134	277	136	265	401	
Mean	1.6	1.9	1.8	2.0	3.1	2.7	
SD	0.6	0.9	0.8	0.7	1.4	1.3	
Blood Loss (mL)							.024
n	142	134	276	136	263	399	
Mean	109.8	146.1	127.4	153.1	213.6	192.9	
SD	117.5	406.2	295.5	179.1	493.0	414.4	
Hospital Stay (days)							<.001
n	143	134	277	136	266	402	
Mean	3.1	1.2	2.2	3.3	3.0	3.1	
SD	1.6	1.1	1.7	1.3	3.8	3.2	
Treatment Levels [n (%)]							
L2-L3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	
L3-L4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	2 (0.5)	
L4-L5	37 (25.9)	21 (15.7)	58 (20.9)	32 (23.5)	21 (7.9)	53 (13.2)	
L5-L6	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	2 (0.8)	3 (0.7)	
L5-S1	106 (74.1)	113 (84.3)	219 (79.1)	103 (75.7)	240 (90.2)	343 (85.3)	
Operative Approach [n (%)]							
Retroperitoneal	116 (81.1)	28 (20.9)	144 (52.0)	109 (80.1)	9 (3.4)	118 (29.4)	
Transperitoneal	27 (18.9)	106 (79.1)	133 (48.0)	26 (19.1)	256 (96.2)	282 (70.1)	
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.4)	2 (0.5)	

p-values are from analysis of variance.

Table 6. Summary of success rates of radiographic fusion [Number (%) of Patients]

	InFUSE™			Autograft			*p*-value*
Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	INFUSE vs Autograft
6 Months							
Success	128 (97.0)	88 (92.6)	216 (95.2)	115 (95.8)	192 (95.5)	307 (95.6)	.633
Failure	4 (3.0)	7 (7.4)	11 (4.8)	5 (4.2)	9 (4.5)	14 (4.4)	
12 Months							
Success	127 (96.9)	95 (94.1)	222 (95.7)	112 (92.6)	202 (93.1)	314 (92.9)	.131
Failure	4 (3.1)	6 (5.9)	10 (4.3)	9 (7.4)	15 (6.9)	24 (7.1)	
24 Months							
Success	120 (94.5)	81 (94.2)	201 (94.4)	102 (88.7)	150 (89.8)	252 (89.4)	.022
Failure	7 (5.5)	5 (5.8)	12 (5.6)	13 (11.3)	17 (10.2)	30 (10.6)	

One-sided *p*-values are from logistic regression analysis with the model including bone graft type and surgical approach, adjusting the seven prognostic covariates. The interaction term between bone graft type and surgical approach is not significant and thus is not included.

Table 7. Summary of Oswestry Low Back Pain Disability scores

			InFUSE™			Autograft		*p*-value*	
Period	Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	INFUSE vs Autograft	
Preoperative	Pain Score								
	n	143	134	277	136	264	400		
	Mean	53.7	52.3	53.0	55.1	46.5	49.4		
	SD	12.7	11.7	12.2	11.8	15.6	15.0		
3 Months	Pain Score								
	n	141	127	268	134	252	386	.0041	
	Mean	33.5	30.2	32.0	34.2	33.7	33.9		
	SD	17.6	19.9	18.8	18.5	19.7	19.3		
6 Months	Pain Score								
	n	136	120	256	131	239	370	.0053	
	Mean	29.3	25.1	27.3	29.4	29.0	29.1		
	SD	18.8	20.4	19.6	18.2	20.1	19.4		
12 Months	Pain Score								
	n	130	114	244	125	224	349	.0013	
	Mean	25.5	20.4	23.1	25.6	25.7	25.7		
	SD	18.2	19.8	19.1	19.1	20.5	20.0		
24 Months	Pain Score								
	n	122	93	215	108	177	285	.0023	
	Mean	23.9	18.7	21.7	23.8	22.7	23.1		
	SD	18.8	19.3	19.2	20.7	20.9	20.8		

** One-sided *p*-values are from analysis of covariance with the model including bone graft type, surgical approach, and their interaction, adjusting the seven prognostic covariates. **QQ AU: Should this be a single asterisk? XQQ**

Table 8. Summary of SF-36 Health Survey scores

			InFUSE™			Autograft		*p*-value*
Period	Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	INFUSE vs Autograft
Preoperative	PCS							
	n	142	134	276	136	263	399	
	Mean	27.7	28.3	28.0	29.4	29.5	29.5	
	SD	5.7	6.1	5.9	6.2	7.3	6.9	
	Pain Index							
	n	143	134	277	136	263	399	
	Mean	21.8	22.6	22.2	22.7	24.7	24.1	
	SD	11.1	13.4	12.2	13.6	14.7	14.3	
3 Months	PCS							
	n	140	127	267	133	249	382	.0015
	Mean	36.6	37.3	36.9	35.9	35.1	35.4	
	SD	9.7	10.2	10.0	9.4	9.8	9.7	
	Pain Index							
	n	141	127	268	134	250	384	.0002
	Mean	47.4	50.4	48.8	44.1	43.4	43.6	
	SD	23.8	22.5	23.2	23.3	22.3	22.6	
6 Months	PCS							
	n	136	119	255	131	234	365	.0004
	Mean	39.4	41.0	40.1	38.6	37.8	38.1	
	SD	11.3	11.8	11.5	10.9	11.2	11.1	
	Pain Index							
	n	136	120	256	131	236	367	.0002
	Mean	53.0	54.8	53.8	50.5	46.3	47.8	
	SD	27.8	25.4	26.7	24.4	23.8	24.1	
12 Months	PCS							
	n	131	113	244	125	223	348	.0003
	Mean	41.3	43.4	42.3	40.8	40.0	40.3	
	SD	11.0	11.9	11.5	12.1	12.1	12.1	
	Pain Index							
	n	131	113	244	125	223	348	.0002
	Mean	55.0	60.8	57.7	53.5	52.1	52.6	
	SD	26.6	27.8	27.3	26.0	26.0	26.0	
24 Months	PCS							
	n	122	94	216	108	177	285	.0007
	Mean	42.4	45.0	43.6	42.1	42.5	42.4	
	SD	11.9	11.5	11.8	12.8	12.3	12.4	
	Pain Index							
	n	122	95	217	108	177	285	.0008
	Mean	58.5	63.9	60.9	56.4	57.1	56.8	
	SD	27.6	26.2	27.1	28.9	27.4	27.9	

** One-sided *p*-values are from analysis of covariance with the model including bone graft type, surgical approach, and their interaction, adjusting the seven prognostic covariates. **QQ AU: Should this be a single asterisk? XQQ**
PCS = Physical component score

Table 9. Summary of second surgeries.

Type of second surgery	InFUSE™			Autograft			*p*-value* InFUSE™ vs Autograft
	Open	Lap	Total (%)	Open	Lap	Total (%)	
Revisions	0/143	1/134	1/277 (0.36)	0/136	8/266	8/402 (1.99)	.0631
Removals	2/143	2/134	4/277 (1.44)	0/136	7/266	7/402 (1.74)	.5106
Supplemental Fixations	10/143	7/134	17/277 (6.14)	14/136	14/266	28/402 (6.97)	.3970
Reoperations	6/143	2/134	8/277 (2.89)	4/136	28/266	32/402 (7.96)	.0036

*One-sided *p*-values are from Fisher's exact test.

Table 10. Summary of time-to-event analysis for days to return to work (mean in days).

QQ AU: Why are there no entries under Preoperative Work Status? XQQ

	InFUSE™			Autograft		
Preoperative Work Status	Open	Lap	Total	Open	Lap	Total
	165.0	89.0	116.0	386.5	154.0	170.5

* One-sided *p*-value is from the proportional hazard regression (PHREG) procedure with the model including bone graft type and surgical approach, adjusting preoperative work status and the seven prognostic covariates. The interaction term between bone graft type and surgical approach is not significant and thus is not included.

ILLUSTRATIONS

Figure 1. A. Preoperative lateral radiograph shows isolated disc space collapse with radial osteophyte formation at the L5S1 level. B. Postoperative anteroposterior radiograph and C. lateral radiograph shows the tapered fusion cage in place. Normal disc space height segmental lordosis has been restored at the L5S1 vertebral interspace.

Table 2. Demographic information.

QQ AU: Asterisk must have a footnote. ANOVA? XQQ

Variable [n(%)]	INFUSE™ Open (N=143)	INFUSE™ Lap (N=134)	INFUSE™ Total (N=277)	Autograft Open (N=136)	Autograft Lap (N=266)	Autograft Total (N=402)	p-value* INFUSE vs Autograft
Age (yrs.)							.007
n	143	134	277	136	266	402	
Mean	43.3	42.4	42.9	42.3	40.0	40.8	
SD	9.8	10.5	10.2	9.7	9.6	9.7	
Height (in.)							.216
n	143	134	277	135	262	397	
Mean	68.1	67.5	67.8	68.0	68.3	68.2	
SD	4.2	4.0	4.1	4.2	3.9	4.0	
Weight (lbs.)							.146
n	143	134	277	134	264	398	
Mean	179.1	169.8	174.6	181.1	177.6	178.8	
SD	33.1	38.3	36.0	37.0	37.9	37.6	
Sex							
[n(%)]							.391
Male	78 (54.5)	57 (42.5)	135 (48.7)	68 (50.0)	142 (53.4)	210 (52.2)	
Female	65 (45.5)	77 (57.5)	142 (51.3)	68 (50.0)	124 (46.6)	192 (47.8)	
Marital Status							
[n(%)]							.983
Single	24 (16.8)	24 (17.9)	48 (17.3)	18 (13.2)	52 (19.5)	70 (17.4)	
Married	95 (66.4)	91 (67.9)	186 (67.1)	91 (66.9)	177 (66.5)	268 (66.7)	
Divorced	18 (2.6)	14 (10.4)	32 (11.6)	20 (14.7)	30 (11.3)	50 (12.4)	
Separated	5 (3.5)	2 (1.5)	7 (2.5)	5 (3.7)	5 (1.9)	10 (2.5)	
Widowed	1 (0.7)	3 (2.2)	4 (1.4)	2 (1.5)	2 (0.8)	4 (1.0)	
Education Level							
[n(%)]							.277
< High School	13 (9.1)	7 (5.2)	20 (7.2)	17 (12.6)	25 (9.5)	42 (10.6)	
High School	45 (31.5)	39 (29.1)	84 (30.3)	39 (28.9)	86 (32.7)	125 (31.4)	
> High School	85 (59.4)	88 (65.7)	173 (62.5)	79 (58.5)	152 (57.8)	231 (58.0)	
Workers' Compensation							
[n(%)]							.620
Yes	47 (32.9)	42 (31.3)	89 (32.1)	47 (34.6)	89 (33.7)	136 (34.0)	
No	96 (67.1)	92 (68.7)	188 (67.9)	89 (65.4)	175 (66.3)	264 (66.0)	
Spinal Litigation							
[n(%)]							.398
Yes	18 (12.6)	11 (8.2)	29 (10.5)	22 (16.2)	29 (11.1)	51 (12.8)	
No	125 (87.4)	123 (91.8)	248 (89.5)	114 (83.8)	233 (88.9)	347 (87.2)	
Tobacco Used							
[n(%)]							.738
Yes	47 (32.9)	40 (29.9)	87 (31.4)	49 (36.0)	83 (31.2)	132 (32.8)	
No	96 (67.1)	94 (70.1)	190 (68.6)	87 (64.0)	183 (68.8)	270 (67.2)	
Alcohol Use							
[n(%)]							.328
Yes	39 (27.3)	66 (49.3)	105 (37.9)	43 (31.6)	94 (35.3)	137 (34.1)	
No	104 (72.7)	68 (50.7)	172 (62.1)	93 (68.4)	172 (64.7)	265 (65.9)	
Preop Work Status							
[n(%)]							.050
Working	68 (47.6)	70 (52.2)	138 (49.8)	50 (36.8)	118 (44.5)	168 (41.9)	
Not Working	75 (52.4)	64 (47.8)	139 (50.2)	86 (63.2)	147 (55.5)	233 (58.1)	

InFUSE™ Autograft *p*-value*

Table 7. Summary of Oswestry Low Back Pain Disability scores

		InFUSE™			Autograft			*p*-value*
Period	Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	INFUSE vs Autograft
Preoperative	Pain Score							
	n	143	134	277	136	264	400	
	Mean	53.7	52.3	53.0	55.1	46.5	49.4	
	SD	12.7	11.7	12.2	11.8	15.6	15.0	
3 Months	Pain Score							
	n	141	127	268	134	252	386	.0041
	Mean	33.5	30.2	32.0	34.2	33.7	33.9	
	SD	17.6	19.9	18.8	18.5	19.7	19.3	
6 Months	Pain Score							
	n	136	120	256	131	239	320	.0053
	Mean	29.3	25.1	27.3	29.4	29.0	29.1	
	SD	18.8	20.4	19.6	18.2	20.1	19.4	
12 Months	Pain Score							
	n	130	114	244	125	224	349	.0013
	Mean	25.5	20.4	23.1	25.6	25.7	25.7	
	SD	18.2	19.8	19.1	19.1	20.5	20.0	
24 Months	Pain Score							
	n	122	93	215	108	177	285	.0023
	Mean	23.9	18.7	21.7	23.8	22.7	23.1	
	SD	18.8	19.3	19.2	20.7	20.9	20.8	

** One-sided *p*-values are from analysis of covariance with the model including bone graft type, surgical approach, and their interaction, adjusting the seven prognostic covariates. **QQ AU: Should this be a single asterisk? XQQ**

Table 8. Summary of SF-36 Health Survey scores

			InFUSE™			Autograft		*p*-value* INFUSE vs
Period	Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	Autograft
Preoperative	PCS							
	n	142	134	276	136	263	399	
	Mean	27.7	28.3	28.0	29.4	29.5	29.5	
	SD	5.7	6.1	5.9	6.2	7.3	6.9	
	Pain Index							
	n	143	134	277	136	263	399	
	Mean	21.8	22.6	22.2	22.7	24.7	24.1	
	SD	11.1	13.4	12.2	13.6	14.7	14.3	
3 Months	PCS							
	n	140	127	267	133	249	382	.0015
	Mean	36.6	37.3	36.9	35.9	35.1	35.4	
	SD	9.7	10.2	10.0	9.4	9.8	9.7	
	Pain Index							
	n	141	127	268	134	250	384	.0002
	Mean	47.4	50.4	48.8	44.1	43.4	43.6	
	SD	23.8	22.5	23.2	23.3	22.3	22.6	
6 Months	PCS							
	n	136	119	255	131	234	365	.0004
	Mean	39.4	41.0	40.1	38.6	37.8	38.1	
	SD	11.3	11.8	11.5	10.9	11.2	11.1	
	Pain Index							
	n	136	120	256	131	236	367	.0002
	Mean	53.0	54.8	53.8	50.8	46.3	47.8	
	SD	27.8	25.4	26.7	24.4	23.8	24.1	
12 Months	PCS							
	n	131	113	244	125	223	348	.0003
	Mean	41.3	43.4	42.3	40.8	40.0	40.3	
	SD	11.0	11.9	11.5	12.1	12.1	12.1	
	Pain Index							
	n	131	113	244	125	223	348	.0002
	Mean	55.0	60.8	57.7	53.5	52.1	52.6	
	SD	26.6	27.8	27.3	26.0	26.0	26.0	
24 Months	PCS							
	n	122	94	216	108	177	285	.0007
	Mean	42.4	45.0	43.6	42.1	42.5	42.4	
	SD	11.9	11.5	11.8	12.8	12.3	12.4	
	Pain Index							
	n	122	95	217	108	177	285	.0008
	Mean	58.5	63.9	60.9	56.4	57.1	56.8	
	SD	27.6	26.2	27.1	28.9	27.4	27.9	

** One-sided *p*-values are from analysis of covariance with the model including bone graft type, surgical approach, and their interaction, adjusting the seven prognostic covariates. **QQ AU: Should this be a single asterisk? XQQ**

PCS = Physical component score

Table 10. Summary of time-to-event analysis for days to return to work (mean in days).

QQ AU: Why are there no entries under Preoperative Work Status? XQQ

QQ AU: Why are there 2 asterisks in the body of the table and 1 in the footnote? Mistake or am I missing something? XQQ

	InFUSE™			Autograft			*p*-value** INFUSE vs Autograft
Preoperative Work Status	Open	Lap	Total	Open	Lap	Total	
	165.0	89.0	116.0	386.5	154.0	170.5	0.0156

* One-sided *p*-value is from the proportional hazard regression (PHREG) procedure with the model including bone graft type and surgical approach, adjusting preoperative work status and the seven prognostic covariates. The interaction term between bone graft type and surgical approach is not significant and thus is not included.

From: Treharne, Rick
Sent: Wednesday, October 9, 2002 02:40:09 PM
To: Lipscomb, Bailey; Ma, Guorong
Subject: FW: The Last Final No Question about it Revised ALL BMP POOLED Paper

Attachments: Final Revisions All BMP Outcomes.doc

I hope you don't find any bloopers in this manuscript...Rick

-----Original Message-----
From: Ken Burkus [SMTP:[redacted]
Sent: Wednesday, October 09, 2002 2:22 PM
To: Peter Wehrly; Rick Treharne; Bill Martin; Neil Beals; Julie Bearcroft
Cc: Joseph Pizzurro; Clark Charlton
Subject: The Last Final No Question about it Revised ALL BMP POOLED Paper

Sirs,

This final revision of the "Integrated BMP Data" manuscript is being readied to be sent into Journal of Spinal Disorders & Techniques for an expedited review.

Sincerely,
JK Burkus

Is INFUSE™ Bone Graft Superior to Autograft Bone? An Integrated Analysis of Clinical Trials Using the LT-CAGE™ Lumbar Tapered Fusion Device

J. Kenneth Burkus, M.D.*

Stephen E. Heim MD†

Matthew F. Gornet MD‡

Thomas A. Zdeblick MD§

* Staff Physician, Spine Service, The Hughston Clinic, P.C., [redacted]

† Staff Physician, Orthopaedic Associates of DuPage, Warrenville, Illinois

‡Staff Physician, Orthopaedic Center of St. Louis, St. Louis, Missouri

§Chairman, Department of Orthopaedics and Rehabilitation, University of Wisconsin, Madison, Wisconsin

FDA device/drug status: Approved for this indication.

Statement of Financial Relationship: The authors are consultants and clinical investigators for the company distributing the device studied.

Address correspondence and reprint requests to: J. K. Burkus, M.D., The Hughston Clinic, [redacted] Columbus, Georgia 31908-9517

ABSTRACT

Study Design. An integrated analysis of prospective studies of patients who received lumbar fusion cage implants by one of two surgical methods using one of two graft materials with a minimum follow-up of 2 years.

Objectives. We hypothesized that INFUSE™ Bone Graft is superior to autograft when used inside an LT-CAGE™ Lumbar Tapered Fusion device in patients undergoing anterior lumbar fusion. We increased our overall sample size by combining several clinical trials to increase the statistical power of the analysis.

Summary of Background Data. Recombinant bone morphogenetic protein, or rhBMP-2, marketed as INFUSE™ Bone Graft, is now commercially available in the United States. Multicenter human clinical studies of patients undergoing anterior lumbar fusion have been conducted using this material or autograft implanted in the LT-CAGE™ Lumbar Tapered Fusion device.

Methods: An integrated analysis of multiple clinical studies was performed using an analysis of covariance to adjust for preoperative variables in a total of 679 patients. Of these patients, 277 had their cages implanted with INFUSE™ Bone Graft, and 402 received autograft transferred from the iliac crest.

Results: The patients treated with INFUSE™ Bone Graft had statistically superior outcomes with regard to length of surgery, blood loss, hospital stay, reoperation rate, and median time to return to work. Oswestry Disability Index scores and the Physical Component Scores and Pain Index of the SF-36 scale at 3, 6, 12, and 24 months showed statistically superior outcomes in the INFUSE™ group. Similarly, fusion rates were statistically superior in the INFUSE™ group.

Conclusions: INFUSE™ Bone Graft should replace autograft bone inside the LT-CAGE™ device in patients undergoing anterior lumbar spinal fusions.

Keywords: Anterior lumbar interbody fusion, INFUSE™ Bone Graft, Bone morphogenetic protein, Fusion cage, Degenerative disc disease, Lumbar spine

INTRODUCTION

The surgical technique and indications for implanting the LT-CAGE™ Lumbar Tapered Fusion Device (Medtronic Sofamor Danek, Memphis, Tennessee) and reports of outcome measurements in patients in whom it has been implanted have been reported in the literature (1-3). The history, development, and method of use of the protein product, called rhBMP-2 (recombinant human bone morphogenetic protein), used in our study have also been reviewed (4-7), and the prospective, randomized trial that lead to the product's approval by showing equivalency in outcome between the INFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, Tennessee) and autograft was published in 2002 (2). The advantages to the patient and to the surgeon of not having to create a second surgical site and the complications and pain of iliac crest harvesting have also been reviewed (8).

The purpose of our analysis was to investigate the potential statistical superiority of INFUSE™ Bone Graft to autograft used inside the LT-CAGE™ Lumbar Tapered Fusion Device in surgical parameters, hospital stay, and clinical outcome in single-level spinal fusions. We integrated, or pooled, the results from similar large-scale clinical trials of the same device used for the same indication and measured in the same way to check for statistical superiority. These data came from both published (2,3) and unpublished studies.

INFUSE™ Bone Graft with the LT-CAGE™ device was approved by the U.S. Food and Drug Administration on July 2, 2002, for treating patients with degenerative disc disease and up to grade I spondylolisthesis using a single-level anterior spinal fusion

procedure. The approval was based primarily on the clinical data from a prospective, randomized, controlled clinical trial that is discussed in detail elsewhere (2). That study used the INFUSE™ Bone Graft with the LT-CAGE™ Tapered Lumbar Fusion Device in the investigational group patients and compared their results with those of the control group patients who received autograft inside the LT-CAGE™ device in open surgical procedures. Wyeth BioPharma, Cambridge, MA, genetically engineered the rhBMP-2 component. The absorbable collagen sponge component is manufactured by Integra LifeSciences, Plainsboro, NJ. Together, the components are distributed commercially under the trade name INFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, TN). This clinical trial was designed to establish statistical equivalence (noninferiority) between the INFUSE group and autograft group. The fusion success rate in the INFUSE group was 94.5% at 24 months after surgery compared with 88.7% in the autograft group. The probability of noninferiority of INFUSE Bone Graft to autograft was shown to be essentially 100%. The probability of superiority was 90.2%, which, albeit high, did not meet the minimum superiority criterion of 95% predefined in the prospective, randomized protocol. Fusion superiority was not shown probably because of insufficient sample size and, therefore, insufficient statistical power because that clinical trial was designed and sized only to show equivalence. Because the number of patients enrolled in that single study was not adequate to demonstrate statistical superiority, we combined the patient data from that randomized study with two additional sequential studies to assess the statistical superiority of the results in the INFUSE patients over those in the autograft controls.

METHODS

Our analysis combines data sets from a published randomized trial (2) that had two arms with those from two additional sequential clinical trials to increase the sample size and statistical power. Both of these two additional patient data sets were from patients who had the fusion cage implanted laparoscopically. One of these two patient data sets is from the clinical trial in which INFUSE™ Bone Graft was used with the LT-CAGE™ Tapered Lumbar Fusion Device and implanted laparoscopically. This study used the identical inclusion-exclusion criteria and procedures as the other studies. A portion of the results of this study from one site has been published (3). The second set of additional patient data comes from another clinical trial in which autograft and the LT-CAGE™ device were inserted using a laparoscopic surgical approach. The inclusion-exclusion criteria for these patients were identical to those for the patients in the randomized trial and the other laparoscopic arm of the study with the minor exception of not having a minimum Oswestry low back pain disability score for entry as was required for the other three sets of patients. These four prospective, multi-center clinical studies are summarized in Table 1. All patients were entered into these studies between 1996 and 1999.

The two treatment factors in these four patient data sets are bone graft type (INFUSE™ Bone Graft or autograft) and the surgical approach (open or laparoscopic). Our goal was to compare and analyze the results in the patients who received INFUSE™ Bone Graft with those in the patients who received autograft. The results from the two surgical approaches are pooled and the effects of surgical approach, if any, such as at early time points, are statistically adjusted so as not to affect the comparison between the

graft types. Thus, our analysis compared the results of 277 INFUSE™ Bone Graft patients with 402 autograft patients. All of the 679 patients had degenerative disc disease with up to grade 1 spondylolisthesis. All patients had two LT-CAGE devices implanted anteriorly at one lumbar level, and all were included in prospective, multi-centered studies using the same outcome measurement tools and methodology of analysis (Figure 1). More than 60 surgeons at 36 different sites enrolled the 679 patients. No single surgeon performed more than 10% of the cases. Hence, the outcomes represent typical results from a wide variety of surgeons with different degrees of experience.

Because not all of the four prospectively studied groups were randomized, the patients' demographic characteristics and prognostic factors could be different among the groups. Tables 2, 3, and 4 summarize demographic information, preoperative medical condition and medication usage, and preoperative measurements of several clinical endpoints, respectively. Among approximately 20 summarized variables, seven were found to be significantly different between the combined INFUSE group and the combined autograft group.

Statistical Analysis

The seven variables that were found to have statistically significant differences were age, previous back surgery, preoperative non-narcotic medication use, weak-narcotic medication use, muscle relaxant medication use, preoperative low back pain score on the Oswestry Disability Index, and preoperative SF-36 Physical Component Score. Because these seven prognostic factors could potentially affect the clinical outcomes and therefore confound the analysis of a study between the INFUSE and autograft groups, a statistical technique called analysis of covariance (ANCOVA) was

performed. With the use of this statistical methodology, the influences of these prognostic factors are adjusted for, and comparisons can be made between the INFUSE and autograft results. In essence, this statistical method makes it possible to have both groups start at the same level statistically for these seven factors before any differences in outcome are compared.

RESULTS

The statistical analysis of operative time, blood loss, and hospital stay for the INFUSE and autograft groups is shown in Table 5. This analysis reveals superior ($p < .05$) benefits of the combined INFUSE group compared with the autograft group for all three variables. The INFUSE group spent an average of 0.9 hours (54 minutes) less time under anesthesia, lost an average of 66 mL less blood (probably because of the shorter surgery time and not having a second surgery site), and, on average, left the hospital nearly a day (0.9) earlier than the autograft group.

The fusion success rate in the combined INFUSE group was 94.4% (201/213) at 24 months after surgery compared with 89.4% (252/282) in the autograft group (Table 6). This 5-percentage point difference was shown to be statistically significant by an analysis of covariance, with an adjusted *p*-value of .022. In short, fusion, the primary goal of performing the original surgery, was found to be statistically superior for the INFUSE patients.

In the combined INFUSE group, preoperative low back pain scores on the validated Oswestry Disability Index improved significantly over those in the autograft group for all time points—3, 6, 12, and 24 months—in the study (Table 7). The adjusted *p*-values were all statistically significant.

The Physical Component and Pain Index scores of the SF-36 Health Survey, which measures a patient's physical well being after surgery, are shown in Table 8. As with the Oswestry Disability Index low back pain scores, the results showed the statistical superiority of the combined INFUSE group to the autograft group for all time points after surgery.

Additional surgical events in the study patients are summarized in Table 9. Simple Fisher's exact tests show that the combined INFUSE groups had statistically fewer reoperations than patients who were implanted with autograft (p=.0036). At the two-year time point used in the study, the revision rate in INFUSE patients approached statistical superiority (p=.0631).

Although the difference was not statistically significant, 103 (74.6%) of the INFUSE patients who were working before surgery, returned to work after surgery compared with 109 (64.9%) patients in the autograft group. Again although not statistically significant, 49 (35.3%) of the INFUSE patients who were not working before surgery returned to work after surgery compared with 73 (31.3%) of the autograft patients. The difference that was found to be statistically significant was the time it took for the patients to return to work. A summary of time-to-event type analysis of return to work is contained in Table 10. The statistical comparison between the INFUSE and autograft groups was adjusted by the preoperative work status, the seven prognostic covariates, and the surgical approach. The median days to return to work was 54.5 days shorter for the LT-CAGE patients implanted with INFUSE Bone Graft. This finding was statistically significant in favor of the INFUSE patients (adjusted p-value = .0156).

DISCUSSION

Surgeons have long sought to find the best way to fuse two bones. Although allograft bone has been used with some degree of success, transplanting living bone from one part of the body to another has become the "gold standard" by which all other procedures are measured (8). Finding a substitute for human tissue has also been a noble goal of researchers for decades, and finding a bone graft substitute to replace autogenous bone seemed at times an impossible task. What material could researchers develop that would be better than a naturally occurring material?

Since the discovery of bone morphogenetic proteins (BMP) by Dr. Marshall Urist in 1965 (9), his dream, and those of many others, was to have BMP available in operating rooms as a safe and effective replacement for autograft. In July 2002, his dream became a reality in the United States with the FDA approval of rhBMP-2, a recombinant version of one of the family of BMPs. His goal, and the goal of other researchers like him, was for the substitute to be equal to autograft so harvesting of autograft bone from other parts of the body would no longer be necessary. Preclinical studies (5,6,10-14) have indicated the possibility that osteoinductive protein-containing materials may be superior to autograft in some applications and for some outcome measurements. Wozney (7) suggests that BMP can result in direct intramembranous ossification because in some animal models direct bone formation is observed after administration of the protein. Because chips of transferred autogenous graft may need to be resorbed or be remodeled before fusing and rhBMP-formed bone does not, this feature may explain why some animal studies had superior results with rhBMP-containing grafts when compared with autograft. However, the question remains: Can any recombinant BMP on any carrier ever be superior to

autograft—the gold standard—with regard to operative parameters and clinical outcome in humans? Pilot study results of the LT-CAGE™ Lumbar Tapered Fusion Device in humans (1) and the results from a prospective, randomized study (2) showed a trend toward faster fusion with the INFUSE™ Bone Graft and other data that were comparable with that in the patients who received autograft. We hypothesized that this trend would become a superior outcome in a larger study.

We used the ANCOVA method for an integrated analysis of four, large-scale multicenter sets of patient data. This analysis of prospectively gathered data has answered the question of the superiority of INFUSE™ Bone Graft over autograft for one particular human clinical use. This analysis of 679 patients represents the largest prospective combined study of a single-level anterior procedure using a single device for a single indication in the spinal literature. Because all patients received the same LT-CAGE implants, we had, for the first time, a data set large enough to determine whether INFUSE™ Bone Graft is equivalent to or superior to autograft bone. Because of the large sample size used in this analysis and its subsequent statistical power, the answer is an unequivocal "yes." The INFUSE patients had statistically superior outcomes in the following categories: shortened surgery time, reduced blood loss, shortened hospital stay, higher fusion rate, better Oswestry Low Back Pain Disability Questionnaire scores at all follow-up intervals, better Physical Component Scores and Pain Index scores on the SF-36 Health Survey at all follow-up intervals, fewer reoperations, and an earlier return to work.

As can be calculated from Table 7, for all postoperative time points, the change from preoperative scores for INFUSE patients was approximately 5 points better than for

the autograft control patients, about a 7% to 10% greater improvement from the preoperative score in favor of the INFUSE patients. As can be calculated from Table 8, the PCS scores on the SF-36 scale also had approximately a 12% to 15% greater improvement from the preoperative values in favor of the INFUSE patients than the control patients. Obviously, any statistical decrease in pain at any time point would be considered significant and desirable by the patient. The statistically significant decrease in the INFUSE patients' low back pain must be at least part of the explanation for their returning to work nearly two months earlier than the autograft patients.

The INFUSE patients obviously had none of the pain or problems associated with iliac crest graft harvesting. Iliac crest graft site pain was recorded on a separate 20-point numeric rating scale (2) by the patients who discriminated the low back pain from the iliac crest harvest site pain. In the autograft open group, nearly a third (32%) of the patients still had some pain at their harvest site two years after the surgery (2). In addition to pain, the 402 autograft patients treated with open and laparoscopic surgery, also had a 3.0% chance of a significant graft site complication: 5 (1.25%) had infections at their harvest site, 2 (0.5%) had fractures at the graft site, and 5 (1.25%) had other adverse events related to their harvest site.

We believe this analysis demonstrates the superiority of using INFUSE™ Bone Graft. In fact, we found no disadvantage to using INFUSE™ Bone Graft for the surgical, hospital discharge, and major postoperative outcome measurements discussed. In addition, the INFUSE patients did not have the pain, morbidity, or complications associated with the second surgery of iliac crest graft harvest. The results of this integrated analysis coupled with the comprehensive safety profile for the recombinant

human bone morphogenetic protein (rhBMP-2) material used in the study (15) clearly indicates that the use of INFUSE Bone Graft should now be the new gold standard for replacing autograft bone inside the LT-CAGE device for lumbar spinal fusions.

With its clear superiority, INFUSE™ Bone Graft may now be the new gold standard for replacing autograft bone inside the LT-CAGE™ device when used for lumbar spinal fusions. INFUSE Bone Graft is now used exclusively for this purpose in our institutions.

ACKNOWLEDGMENTS

The authors thank the more than 60 clinical investigators who provided patients for this study and the Clinical Research group at Medtronic Sofamor Danek for their help in data collection and the statistical analyses.

REFERENCES

1. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25:376-81.
2. Burkus JK, Gornet MF, Dickman C, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. J Spinal Disord 2002;October (in press).
3. Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2. A prospective study of clinical and radiographic outcomes. Spine 2001;26:2751-6.
4. Boden SD. Overview of the biology of lumbar spine fusion and principles for selecting a bone graft substitute. Spine 2002;27:S26-31.
5. McKay B, Sandhu HS. Use of recombinant human bone morphogenetic protein-2 in spinal fusion applications. Spine 2002;27(16 Suppl 1):S66-85.
6. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995;20:1326-37.
7. Wozney JM. Overview of bone morphogenetic proteins. Spine 2002;27(16 Suppl 1):S2-8.
8. Vaccaro AR, Kazuhiro C, Heller JG, Patel TC, Thalgott JS, Truumees E, Fischgrund JS, Craig MR, Berta SC, Wang JC. Bone grafting alternatives in spinal surgery. The Spine Journal 2002;2:206-15.
9. Urist MR. Bone: formation by autoinduction. Science 1965;150:893-9.

10. David SM, MD, Gruber HE, Meyer RA, Murakami T, Tabor OB, Howard BA, Wozney JM, Hanley EN. Lumbar spinal fusion using recombinant human bone morphogenetic protein in the canine. A comparison of three dosages and two carriers. Spine 1999;24:1973 –9.

11. Boden SD, Schimandle JH, Hutton WC. The 1995 Volvo award in basic sciences. The use of an osteoconductive growth factor for lumbar spinal fusion. Part II: study of dose, carrier, and species. Spine 1995;20:2633-44.

12. Sandhu HS, Kanim LE, Kabo JM, Toth JM, Zeegen EN, Liu D, Delamarter RB, Dawson EG. Effective doses of recombinant human bone morphogenetic protein-2 in experimental spinal fusion. Spine 1996;21:2115-22.

13. Sandhu HS, Toth JM, Diwan AD, Seim HB, Kanim LE, Kabo JM, Turner AS. Histologic evaluation of the efficacy of rhBMP-2 compared with autograft bone in sheep spinal anterior interbody fusion. Spine 2002;27:567-75.

14. Zdeblick TA, Ghanayem AJ, Rapoff AJ, Swain CS, Bassett T, Cooke ME, Markel M. Cervical interbody fusion cages. An animal model with and without bone morphogenetic protein. Spine 1998;23:758-65.

15. Poynton AR, Lane JM. Safety profile for the clinical use of bone morphogenetic proteins in the spine. Spine 2002;27(16 Suppl 1):S40-8.

Table 1. Summary of study groups analyzed.

Study group	Graft type	Surgical approach	Randomized	Prospective	Number of patients
INFUSE™ Open	INFUSE™	Open	Yes	Yes	143
INFUSE™ Lap	INFUSE™	Laparoscopic	No	Yes	134
Autograft Open	Autograft	Open	Yes	Yes	136
Autograft Lap	Autograft	Laparoscopic	No	Yes	266

Table 2. Demographic information.

Variable [n(%)]	INFUSE™ Open (N=143)	INFUSE™ Lap (N=134)	INFUSE™ Total (N=277)	Autograft Open (N=136)	Autograft Lap (N=266)	Autograft Total (N=402)	p-value* INFUSE vs Autograft
Age (yrs.)							
n	143	134	277	136	266	402	.007
Mean	43.3	42.4	42.9	42.3	40.0	40.8	
SD	9.8	10.5	10.2	9.7	9.6	9.7	
Height (in.)							
n	143	134	277	135	262	397	.216
Mean	68.1	67.5	67.8	68.0	68.3	68.2	
SD	4.2	4.0	4.1	4.2	3.9	4.0	
Weight (lbs.)							
n	143	134	277	134	264	398	.146
Mean	179.1	169.8	174.6	181.1	177.6	178.8	
SD	33.1	38.3	36.0	37.0	37.9	37.6	
Sex [n(%)]							
Male	78 (54.5)	57 (42.5)	135 (48.7)	68 (50.0)	142 (53.4)	210 (52.2)	.391
Female	65 (45.5)	77 (57.5)	142 (51.3)	68 (50.0)	124 (46.6)	192 (47.8)	
Marital Status [n(%)]							
Single	24 (16.8)	24 (17.9)	48 (17.3)	18 (13.2)	52 (19.5)	70 (17.4)	.983
Married	95 (66.4)	91 (67.9)	186 (67.1)	91 (66.9)	177 (66.5)	268 (66.7)	
Divorced	18 (2.6)	14 (10.4)	32 (11.6)	20 (14.7)	30 (11.3)	50 (12.4)	
Separated	5 (3.5)	2 (1.5)	7 (2.5)	5 (3.7)	5 (1.9)	10 (2.5)	
Widowed	1 (0.7)	3 (2.2)	4 (1.4)	2 (1.5)	2 (0.8)	4 (1.0)	
Education Level [n(%)]							
< High School	13 (9.1)	7 (5.2)	20 (7.2)	17 (12.6)	25 (9.5)	42 (10.6)	.277
High School	45 (31.5)	39 (29.1)	84 (30.3)	39 (28.9)	86 (32.7)	125 (31.4)	
> High School	85 (59.4)	88 (65.7)	173 (62.5)	79 (58.5)	152 (57.8)	231 (58.0)	
Workers' Compensation [n(%)]							
Yes	47 (32.9)	42 (31.3)	89 (32.1)	47 (34.6)	89 (33.7)	136 (34.0)	.620
No	96 (67.1)	92 (68.7)	188 (67.9)	89 (65.4)	175 (66.3)	264 (66.0)	
Spinal Litigation [n(%)]							
Yes	18 (12.6)	11 (8.2)	29 (10.5)	22 (16.2)	29 (11.1)	51 (12.8)	.398
No	125 (87.4)	123 (91.8)	248 (89.5)	114 (83.8)	233 (88.9)	347 (87.2)	
Tobacco Used [n(%)]							
Yes	47 (32.9)	40 (29.9)	87 (31.4)	49 (36.0)	83 (31.2)	132 (32.8)	.738
No	96 (67.1)	94 (70.1)	190 (68.6)	87 (64.0)	183 (68.8)	270 (67.2)	
Alcohol Use [n(%)]							
Yes	39 (27.3)	66 (49.3)	105 (37.9)	43 (31.6)	94 (35.3)	137 (34.1)	.328
No	104 (72.7)	68 (50.7)	172 (62.1)	93 (68.4)	172 (64.7)	265 (65.9)	
Preop Work Status [n(%)]							
Working	68 (47.6)	70 (52.2)	138 (49.8)	50 (36.8)	118 (44.5)	168 (41.9)	.050
Not Working	75 (52.4)	64 (47.8)	139 (50.2)	86 (63.2)	147 (55.5)	233 (58.1)	

* For continous variables, *p*-values are from ANOVA, and for categorical variables, they are from Fisher's exact tests or the chi-square test.

Table 3. Preoperative medical condition and medication usage [Number (%) of patients]

Variable	INFUSE™ Open (N=143)	INFUSE™ Lap (N=134)	INFUSE™ Total (N=277)	Autograft Open (N=136)	Autograft Lap (N=266)	Autograft Total (N=402)	*p*-value* INFUSE vs Autograft
Previous Back Surgery							
Yes	54 (37.8)	33 (24.6)	87 (31.4)	55 (40.4)	110 (41.4)	165 (41.0)	.012
No	89 (62.2)	101 (75.4)	190 (68.6)	81 (59.6)	156 (58.6)	237 (59.0)	
Previous Back Surgery							
1	39 (72.2)	16 (50.0)	55 (64.0)	34 (61.8)	78 (70.9)	112 (67.9)	.574
>1	15 (27.8)	16 (50.0)	31 (36.0)	21 (38.2)	32 (29.1)	53 (32.1)	
Non-narcotic Medications							
Yes	80 (55.9)	97 (72.4)	177 (63.9)	75 (55.1)	109 (41.0)	184 (45.8)	<.001
No	63 (44.1)	37 (27.6)	100 (36.1)	61 (44.9)	157 (59.0)	218 (54.2)	
Weak Narcotic Medications							
Yes	77 (53.8)	61 (45.5)	138 (49.8)	67 (49.3)	90 (33.8)	157 (39.1)	.006
No	66 (46.2)	73 (54.5)	139 (50.2)	69 (50.7)	176 (66.2)	245 (60.9)	
Strong Narcotic Medications							
Yes	31 (21.7)	17 (12.7)	48 (17.3)	33 (24.3)	42 (15.8)	75 (18.7)	.686
No	112 (78.3)	117 (87.3)	229 (82.7)	103 (75.7)	224 (84.2)	327 (81.3)	
Muscle Relaxant Medications							
Yes	45 (31.5)	49 (36.6)	94 (33.9)	37 (27.2)	39 (14.7)	76 (18.9)	<.001
No	98 (68.5)	85 (63.4)	183 (66.1)	99 (72.8)	227 (85.3)	326 (81.1)	

*p-values are from Fisher's exact test or chi-square test.

Table 4. Preoperative evaluations of clinical endpoints

	INFUSE™			Autograft			*p*-value*
Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	INFUSE vs Autograft
Oswestry Pain Score							
n	143	134	277	136	264	400	.001
Mean	53.7	52.3	53.0	55.1	46.5	49.4	
SD	12.7	11.7	12.2	11.8	15.6	15.0	
SF-36 PCS							
n	142	134	276	136	263	399	.004
Mean	27.7	28.3	28.0	29.4	29.5	29.5	
SD	5.7	6.1	5.9	6.2	7.3	6.9	
SF-36 Pain Index							
n	143	134	277	136	263	399	.077
Mean	21.8	22.6	22.2	22.7	24.7	24.1	
SD	11.1	13.4	12.2	13.6	14.7	14.3	

*p-values are from analysis of variance.

Table 5. Surgery information.

Variable	INFUSE™ Open (N=143)	INFUSE™ Lap (N=134)	INFUSE™ Total (N=277)	Autograft Open (N=136)	Autograft Lap (N=266)	Autograft Total (N=402)	*p*-value* INFUSE vs Autograft
Operative Time (hrs)							
n	143	134	277	136	265	401	
Mean	1.6	1.9	1.8	2.0	3.1	2.7	<.001
SD	0.6	0.9	0.8	0.7	1.4	1.3	
Blood Loss (mL)							
n	142	134	276	136	263	399	
Mean	109.8	146.1	127.4	153.1	213.6	192.9	.024
SD	117.3	406.2	295.3	179.1	493.0	414.4	
Hospital Stay (days)							
n	143	134	277	136	266	402	
Mean	3.1	1.2	2.2	3.3	3.0	3.1	<.001
SD	1.6	1.1	1.7	1.3	3.8	3.2	
Treatment Levels [n (%)]							
L2-L3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	
L3-L4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	2 (0.5)	
L4-L5	37 (25.9)	21 (15.7)	58 (20.9)	32 (23.5)	21 (7.9)	53 (13.2)	
L5-L6	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	2 (0.8)	3 (0.7)	
L5-S1	106 (74.1)	113 (84.3)	219 (79.1)	103 (75.7)	240 (90.2)	343 (85.3)	
Operative Approach [n (%)]							
Retroperitoneal	116 (81.1)	28 (20.9)	144 (52.0)	109 (80.1)	9 (3.4)	118 (29.4)	
Transperitoneal	27 (18.9)	106 (79.1)	133 (48.0)	26 (19.1)	256 (96.2)	282 (70.1)	
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.4)	2 (0.5)	

*p-values are from analysis of variance.

Table 6. Summary of success rates of radiographic fusion [Number (%) of Patients]

	INFUSE™			Autograft			*p*-value*
Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	INFUSE vs. Autograft
6 Months							
Success	128 (97.0)	88 (92.6)	216 (95.2)	115 (95.8)	192 (95.5)	307 (95.6)	.633
Failure	4 (3.0)	7 (7.4)	11 (4.8)	5 (4.2)	9 (4.5)	14 (4.4)	
12 Months							
Success	127 (96.9)	95 (94.1)	222 (95.7)	112 (92.6)	202 (93.1)	314 (92.9)	.131
Failure	4 (3.1)	6 (5.9)	10 (4.3)	9 (7.4)	15 (6.9)	24 (7.1)	
24 Months							
Success	120 (94.5)	81 (94.2)	201 (94.4)	102 (88.7)	150 (89.8)	252 (89.4)	.022
Failure	7 (5.5)	5 (5.8)	12 (5.6)	13 (11.3)	17 (10.2)	30 (10.6)	

*One-sided *p*-values are from logistic regression analysis with the model including bone graft type and surgical approach, adjusting the seven prognostic covariates. The interaction term between bone graft type and surgical approach is not significant and thus is not included.

Table 7. Summary of Oswestry Low Back Pain Disability scores

		INFUSE™			Autograft			p-value*
Period	Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	INFUSE vs Autograft
Preoperative	Pain Score							
	n	143	134	277	136	264	400	
	Mean	53.7	52.3	53.0	55.1	46.5	49.4	
	SD	12.7	11.7	12.2	11.8	15.6	15.0	
3 Months	Pain Score							
	n	141	127	268	134	252	386	.0041
	Mean	33.5	30.2	32.0	34.2	33.7	33.9	
	SD	17.6	19.9	18.8	18.5	19.7	19.3	
6 Months	Pain Score							
	n	136	120	256	131	239	370	.0053
	Mean	29.3	25.1	27.3	29.4	29.0	29.1	
	SD	18.8	20.4	19.6	18.2	20.1	19.4	
12 Months	Pain Score							
	n	130	114	244	125	224	349	.0013
	Mean	25.5	20.4	23.1	25.6	25.7	25.7	
	SD	18.2	19.8	19.1	19.1	20.7	20.0	
24 Months	Pain Score							
	n	122	93	215	108	177	285	.0023
	Mean	23.9	18.7	21.7	23.8	22.7	23.1	
	SD	18.8	19.3	19.2	20.7	20.9	20.8	

* One-sided p-values are from analysis of covariance with the model including bone graft type, surgical approach, and their interaction, adjusting the seven prognostic covariates.

Table 8. Summary of SF-36 Health Survey scores.

		INFUSE™			Autograft			*p*-value*
Period	Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	INFUSE vs Autograft
Preoperative	PCS							
	n	142	134	276	136	263	399	
	Mean	27.7	28.3	28.0	29.4	29.5	29.5	
	SD	5.7	6.1	5.9	6.2	7.3	6.9	
	Pain Index							
	n	143	134	277	136	263	399	
	Mean	21.8	22.6	22.2	22.7	24.7	24.1	
	SD	11.1	13.4	12.2	13.6	14.7	14.3	
3 Months	PCS							
	n	140	127	267	133	249	382	.0015
	Mean	36.6	37.3	36.9	35.9	35.1	35.4	
	SD	9.7	10.2	10.0	9.4	9.8	9.7	
	Pain Index							
	n	141	127	268	134	250	384	.0002
	Mean	47.4	50.4	48.8	44.1	43.4	43.6	
	SD	23.8	22.5	23.2	23.3	22.3	22.6	
6 Months	PCS							
	n	136	119	255	131	234	365	.0004
	Mean	39.4	41.0	40.1	38.6	37.8	38.1	
	SD	11.3	11.8	11.5	10.9	11.2	11.1	
	Pain Index							
	n	136	120	256	131	236	367	.0002
	Mean	53.0	54.8	53.8	50.5	46.3	47.8	
	SD	27.8	25.4	26.7	24.4	23.8	24.1	
12 Months	PCS							
	n	131	113	244	125	223	348	.0003
	Mean	41.3	43.4	42.3	40.8	40.0	40.3	
	SD	11.0	11.9	11.5	12.1	12.1	12.1	
	Pain Index							
	n	131	113	244	125	223	348	.0002
	Mean	55.0	60.8	57.7	53.5	52.1	52.6	
	SD	26.6	27.8	27.3	26.0	26.0	26.0	
24 Months	PCS							
	n	122	94	216	108	177	285	.0007
	Mean	42.4	45.0	43.6	42.1	42.5	42.4	
	SD	11.9	11.5	11.8	12.8	12.3	12.4	
	Pain Index							
	n	122	95	217	108	177	285	.0008
	Mean	58.5	63.9	60.9	56.4	57.1	56.8	
	SD	27.6	26.2	27.1	28.9	27.4	27.9	

* One-sided *p*-values are from analysis of covariance with the model including bone graft type, surgical approach, and their interaction, adjusting the seven prognostic covariates.
PCS = Physical component score

Table 9. Summary of second surgeries.

Type of second surgery	INFUSE™			Autograft			*p*-value* INFUSE™ vs Autograft
	Open	Lap	Total (%)	Open	Lap	Total (%)	
Revisions	0/143	1/134	1/277 (0.36)	0/136	8/266	8/402 (1.99)	.0631
Removals	2/143	2/134	4/277 (1.44)	0/136	7/266	7/402 (1.74)	.5106
Supplemental Fixations	10/143	7/134	17/277 (6.14)	14/136	14/266	28/402 (6.97)	.3970
Reoperations	6/143	2/134	8/277 (2.89)	4/136	28/266	32/402 (7.96)	.0036

*One-sided *p*-values are from Fisher's exact test.

Table 10. Summary of time-to-event analysis for days to return to work (median in days).

INFUSE™			Autograft			*p*-value* INFUSE vs Autograft
Median in Days						
Open	Lap	Total	Open	Lap	Total	
165.0	89.0	116.0	386.5	154.0	170.5	0.0156

* One-sided *p*-value is from the proportional hazard regression (PHREG) procedure with the model including bone graft type and surgical approach, adjusting preoperative work status and the seven prognostic covariates. The interaction term between bone graft type and surgical approach is not significant and thus is not included.

LEGEND OF FIGURES

Figure 1. A. Preoperative lateral radiograph shows isolated disc space collapse with radial osteophyte formation at the L5-S1 level. B. Postoperative anteroposterior radiograph and C, lateral radiograph shows the tapered fusion cage in place. Normal disc space height segmental lordosis has been restored at the L5-S1 vertebral interspace.

From: Woodward, Lyndsay
Sent: Monday, June 7, 2004 04:16:12 PM
To: Treharne, Rick
CC: Lipscomb, Bailey; Ma, Guorong; Hood, Tara; English, Judy; Newbill, Cathy; Bearcroft, Julie, PhD
Subject: RE: Combined pivotal and pilot Bone Dowel BMP paper

Attachments: Final Revised ADVERSE EVENT TABLE 02-23-04.doc; Final Revised Second Surgery Table 02-23-04.doc; Adverse Event Table 02-12-04.doc; Second Surgery Table 02-2004.doc; Bone Dowel Combined Antibody Results Table.doc

Rick,

Please see the attached information that was requested for the paper on the Bone Dowel IDE Study:

(1) Please note that on page 7, the total number of control patients should be 52 not 54. There were 22 control patients in the pilot study and 30 control patients in the pivotal study.
(2) As requested by Guorong and Julie Bearcroft, I am attaching the AE and Patient Accountability Tables for both the pivotal and pilot studies.
(3) I have created a table for the combined antibody results for both the pivotal and pilot studies.

Please let me know if any further information is needed.

Thanks,

Lyndsay

-----Original Message-----
From: Lipscomb, Bailey
Sent: Monday, June 07, 2004 11:22 AM
To: Ma, Guorong; Woodward, Lyndsay
Subject: FW: Combined pivitol and pilot Bone Dowel BMP paper

Please provide the information for Dr. Burkus' paper. Thanks. Bailey
-----Original Message-----
From: Treharne, Rick
Sent: Monday, June 07, 2004 10:00 AM
To: Lipscomb, Bailey
Cc: Hood, Tara
Subject: FW: Combined pivitol and pilot Bone Dowel BMP paper

I read this and think it reads really well. Would you ask Guorong or someone to fill in the blanks that have a //// mark please? Thanks...Rick

-----Original Message-----
From: J. Kenneth Burkus [mailto:[redacted]
Sent: Sunday, June 06, 2004 10:20 PM
To: Bearcroft, Julie; Beals, Neil; Treharne, Rick; Lipscomb, Bailey; Lipscomb, Bailey; Marotta, James, Dr.; Martin, Bill
Cc: Lynn Sanders; Vicki K Earnest
Subject: Combined pivitol and pilot Bone Dowel BMP paper

Ma'am and sirs,

I have attached a first draft of the combined pivotal and pilot bone dowel BMP manuscript.

I am working on the Tables and Illustrations.

However, I need some help with the data.

I have no combined data on the work status, antibody formation, and revision surgeries.

I hope that we can make some progress on the data and the manuscript this week so that I can show it to the Big Guy this weekend at the LSSG meeting.

Best,
Ken Burkus

SECTION II - TABLE 3
IDE #G970124

ADVERSE EVENTS[1] - rhBMP-2/ACS/ALLOGRAFT BONE DOWEL PIVOTAL (As of 1/28/04)

	Surgery		Postoperative (1 day - <1 Month)		6 Weeks (≥1 - <2 Months)		3 Months (≥2 - <5 Months)		6 Months (≥5 - <9 Months)		12 Months (≥9 - <19 Months)		24 Months (≥19 - <3 Months)		Total Discrete Adverse Events		# of Patients Reporting	
Complication	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV N=55	Control N=30	Infuse™ BD #(% of 55)	Control #(% of 30)
Anatomical/Technical Difficulty	1	2													1	2	1(1.8)	2(6.7)
Back and/or Leg Pain			2	2	1	2		3	2	3	4	4	2	1	11	15	9(16.4)	12 (40.0)
Cancer											1				1	0	1(1.8)	0(0.0)
Cardio/Vascular	1	1	2											1	3	2	3(5.5)	2(6.7)
Gastrointestinal			8	6						1				1	8	8	8(14.5)	8(26.7)
Graft Site Related				1											0	1	0(0.0)	1(3.3)
Implant Displacement/ Loosening/Breakage							1								1	0	1(1.8)	0(0.0)
Infection	1		3	2						1			1	1	5	4	5(9.1)	3(10.0)
Neurological			3	1	1		2		6	3	3		1		16	4	15(27.3)	4(13.3)
Non-Union (OUTCOME PENDING)									1	2		1			1	3	1(1.8)	3(10.0)
Other		1	2	7			1				2	1	2	5	7	14	7(12.7)	11(36.7)
Other Pain				1	2		3	1	4		4	2	3	1	16	5	12(21.8)	4(13.3)
Respiratory			2	3						1					2	4	2(3.6)	4(13.3)
Spinal Event								1	1		2				3	1	3(5.5)	1(3.3)
Subsidence					1										1	0	1(1.8)	0(0.0)
Trauma			2		2		2	5	4	2		5	2	2	12	14	10(18.2)	9(30.0)
Urogenital			4	2			1				2				7	2	7(12.7)	2(6.7)
Vascular Intra-Op	1														1	0	1(1.8)	0(0.0)

[1] Since fusion is a primary effectiveness endpoint, non-unions reported as adverse events by the investigator are not included in the table if the nonunion resulted in a second surgery. These non-unions are captured in the secondary surgery table and the fusion table.

CONFIDENTIAL

rhBMP-2/CRM/CD HORIZON® Spinal System-Pivotal Study (3 Sites only)

Summary of SF-36 Health Survey Scores

Period	Variable	Investigational			Control			Smoking vs Non-Smoking		
		Smoking (N=30)	Non-Smoking (N=66)	P-value *	Smoking (N=26)	Non-Smoking (N=70)	P-value *	Smoking (N=56)	Non-Smoking (N=136)	P-values *
Preoperative	PCS									
	n	30	65	0.138	26	70	0.638	56	135	0.186
	Mean	26.4	28.1		26.8	27.5		26.6	27.9	
	Std	5.2	6.2		6.4	7.0		5.7	6.6	
	Min	5.2	6.2		6.4	7.0		16.6	9.1	
	Max	5.2	6.2		6.4	7.0		40.7	46.9	
	MCS									
	n	30	65	0.210	26	70	0.961	56	135	0.338
	Mean	38.0	41.1		41.0	41.1		39.4	41.2	
	Std	10.7	12.4		10.9	12.6		10.8	12.5	
	Min	10.7	12.4		10.9	12.6		20.3	12.9	
	Max	10.7	12.4		10.9	12.6		61.5	69.3	
6 Months	PCS									
	n	25	65	0.057	25	62	0.030	50	127	0.006
	Mean	30.6	40.2		33.6	38.4		34.5	39.4	
	Std	10.4	10.7		9.2	9.3		9.8	10.9	
	Min	10.4	10.7		9.2	9.3		13.6	16.6	
	Max	10.4	10.7		9.2	9.3		56.9	63.1	
	PCS Change from Preop									
	n	25	64	0.273	25	62	0.096	50	126	0.052
	Mean	9.2	12.1		7.0	10.9		8.1	11.5	
	Std	10.3	11.3		8.6	10.4		9.5	10.8	
	Min	10.3	11.3		8.6	10.4		-8.2	-18.8	
	Max	10.3	11.3		8.6	10.4		30.2	34.1	
	P-Value *	10.3	11.3		8.6	10.4		<0.001	<0.001	
	MCS									
	n	25	65	0.918	25	62	0.431	50	127	0.228
	Mean	39.0	46.5		48.7	46.4		43.8	46.4	
	Std	12.4	13.7		11.4	12.6		12.8	13.1	
	Min	12.4	13.7		11.4	12.6		13.2	14.9	
	Max	12.4	13.7		11.4	12.6		66.9	66.8	
	MCS Change from Preop									
	n	25	64	0.255	25	62	0.345	50	126	0.778
	Mean	1.9	5.7		7.5	4.8		4.7	5.3	
	Std	10.1	11.5		10.9	12.4		10.8	11.9	
	Min	10.1	11.5		10.9	12.4		-16.7	-40.8	
	Max	10.1	11.5		10.9	12.4		23.3	35.6	
	P-Value *	10.1	11.5		10.9	12.6		0.003	<0.001	

Program: (t_sf36) Date: (01MAR06) Page 1 of 2

* P-values are from ANOVA.

rhBMP-2/CRM/CD HORIZON® Spinal System-Pivotal Study (3 Sites only)

Summary of SF-36 Health Survey Scores

Period	Variable	Investigational			Control			Smoking vs Non-Smoking		
		Smoking (N=30)	Non-Smoking (N=66)	P-value *	Smoking (N=26)	Non-Smoking (N=70)	P-value *	Smoking (N=56)	Non-Smoking (N=136)	P-values *
12 Months	PCS									
	n	25	66	0.058	23	64	0.631	48	130	0.080
	Mean	35.0	40.1		37.2	38.4		36.0	39.3	
	Std	11.8	11.3		11.4	10.1		13.5	10.7	
	Min	11.8	11.3		11.4	10.1		14.9	16.7	
	Max	11.8	11.3		11.4	10.1		58.5	58.6	
	PCS Change from Preop									
	n	25	65	0.253	23	64	0.922	48	129	0.396
	Mean	9.7	12.0		11.2	10.9		9.9	11.5	
	Std	12.8	12.3		7.9	10.6		10.7	11.4	
	Min	12.8	12.3		7.9	10.6		-10.4	-17.0	
	Max	12.8	12.3		7.9	10.6		33.5	36.4	
	P-Value *	12.8	12.3		7.9	10.6		<0.001	<0.001	
	MCS									
	n	25	66	0.166	23	64	0.181	48	130	0.832
	Mean	42.4	46.7		48.0	45.3		45.6	46.0	
	Std	10.6	13.9		13.7	13.2		11.5	12.6	
	Min	10.6	13.9		11.7	11.2		16.1	17.0	
	Max	10.6	13.8		11.7	11.2		66.7	65.6	
	MCS Change from Preop									
	n	25	65	0.799	23	64	0.230	48	129	0.458
	Mean	4.9	5.6		7.5	3.5		6.2	4.6	
	Std	10.6	12.0		14.4	13.2		12.5	12.6	
	Min	10.6	12.0		14.4	13.2		-22.3	-31.6	
	Max	10.6	12.0		14.4	13.2		25.5	33.0	
	P-Value *	10.6	12.0		14.4	13.2		0.001	<0.001	
24 Months	PCS									
	n	23	50	0.044	21	46	0.642	44	96	0.080
	Mean	33.2	38.7		37.5	38.9		35.3	38.8	
	Std	10.1	10.7		12.7	10.9		11.5	10.7	
	Min	10.1	10.7		12.7	10.9		16.0	16.4	
	Max	10.1	10.7		12.7	10.9		59.4	60.5	
	PCS Change from Preop									
	n	23	49	0.330	21	46	0.563	44	95	0.490
	Mean	7.4	10.3		10.5	10.7		9.0	10.5	
	Std	10.9	12.0		9.5	12.1		10.3	12.0	
	Min	10.9	12.0		9.5	12.1		-8.8	-17.0	
	Max	10.9	12.0		9.5	12.1		35.7	34.5	
	P-Value *	10.9	12.0		9.5	12.1		<0.001	<0.001	
	MCS									
	n	23	50	0.081	21	46	0.389	44	96	0.533
	Mean	42.3	47.8		48.9	45.9		45.4	46.9	
	Std	10.0	13.3		14.4	12.4		12.6	12.9	
	Min	10.0	13.3		14.4	12.4		16.9	20.2	
	Max	10.0	13.3		14.4	12.4		70.8	65.1	
	MCS Change from Preop									
	n	23	49	0.713	21	46	0.879	44	95	0.888
	Mean	5.5	6.6		7.0	6.4		6.2	6.5	
	Std	11.7	12.1		17.3	11.2		14.5	11.6	
	Min	11.7	12.1		17.3	11.2		-22.1	-23.3	
	Max	11.7	12.1		17.3	11.2		41.9	35.9	
	P-Value *	11.7	12.1		17.3	11.2		0.007	<0.001	

Program: (t_sf36) Date: (01MAR06) Page 2 of 2

* P-values are from ANOVA.

From: Zhu, Youjun
Sent: Monday, June 12, 2006 08:15:55 AM
To: Ma, Guorong
Subject: FW: smoking paper

Attachments: THE_IMPACT_OF_SMOKING[1]...6-12-06.doc; Figures and tables for smoking paper.ppt

-----Original Message-----
From: Bearcroft, Julie, PhD
Sent: Sunday, June 11, 2006 6:45 PM
To: Beals, Neil; Meyer, Matt; McKay, Bill; Norman, Dawn; Keller, Jim; Zhu, Youjun
Subject: Fw: smoking paper

Please review this and provide comments to me. I will collate them and respond to Dr Glassman.
Thanks,

Julie ----------
Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: sdg[redacted]
To: Bearcroft, Julie, PhD
Cc: JKE[redacted] JDIMAR[redacted]>; lcarreon[redacted]
Sent: Sun Jun 11 15:58:03 2006
Subject: smoking paper

Hi Julie, John, Ken and Leah
Attached is a draft of the smoking paper. I also attached the slides which will comprise the figures (more or less).
Julie - I'm not sure that the statistical analysis from your data corresponds exactly to the comparisons that I make in the paper, so we made need to work on that a bit. Also, I am missing a few minor data points, but I think we can fill in the blanks.
Let me know what you think. Remember, it is only a draft.
Regards
Steve

THE IMPACT OF SMOKING ON LUMBAR FUSION USING A rhBMP-2 MATRIX

Introduction:

Cigarette smoking has been identified as an important risk factor for both nonunion and poor clinical outcome in lumbar spine fusion surgery (Glassman, Anderson, Kwon and Brown). In particular, smoking has been shown to markedly diminish fusion rate for the challenging healing environment associated with posterolateral spine fusion procedures. A variety of strategies have been advocated to offset this negative impact of cigarette smoking. They include smoking abatement (Glassman, Whitesides), spinal instrumentation and circumferential fusion. (Mirovski, Kwon) The advent of biologic osteoinductive graft alternatives has introduced a new set of potential options in the management of this difficult clinical problem.

Recent experience with bone morphogenic proteins (BMP) has documented their potency as an iliac crest bone graft (ICBG) substitute (Burkus 1,Burkus 2, Glassman, Canadian study etc) and generated high expectations for achieving fusion in complex and difficult cases. The question, therefore, is whether BMPs can overcome the adverse effect of smoking on lumbar fusion. Preclinical studies suggest that BMPs are able to reverse the negative influence of nicotine in animal models. (Patel, Silcox) It remains unclear if a similar benefit will be seen in humans, and if so, what amount of BMP will be required to achieve that improvement. The purpose of this study is to examine the influence of smoking on fusion rate and outcome in a large series of patients treated with an rhBMP-2 matrix (AMPLIFY) or iliac crest bone graft as part of a randomized IDE trial for single level lumbar fusion.

Methods

We reviewed the clinical and radiographic records of 148 patients who underwent single level lumbar fusion at one of three spine centers. Patients were studied as part of an IRB approved, FDA regulated, randomized nonblinded trial of rhBMP-2 matrix for lumbar spinal fusion. It is important to note that the patients were randomized based upon bone graft technique (rhBMP-2 versus ICGB), not smoking status, and that this is a retrospective review of that data.

Inclusion criteria for this study were single level lumbar DDD in patients over 18 years of age with no greater than Grade I spondylolisthesis. Exclusion criteria included autoimmune diseases, chronic steroid dependence, ODI less than 50, and high risk for noncompliance with study protocol. All patients underwent single level fusion with adjunctive screw/rod instrumentation. All patients were evaluated at a minimum two year follow-up.

Posterior lumbar decompression and instrumentation was performed according to a standardized technique based on the IDE study protocol. In the ICGB group a bone graft harvest was performed through a separate fascial incision over the iliac crest and the quantity of bone obtained was recorded. In the rhBMP-2 group, an HA/TCP and collagen compression resistant matrix was combined with 20 mg. rhBMP-2 per side at a concentration of 2 mg/ml. Local bone was excluded as per IDE protocol in the rhBMP-2 group.

Clinical outcome measures included ODI, SF-36, back and leg pain scores. Outcome measures were performed at 6 weeks, 3 months, 6 months, and 1 and 2 years post-op. Radiographic measures were plain x-ray with flexion/extension views and fine cut CT scan with sagittal and

coronal reconstruction. CT scans were performed at 6 months, 1 year and 2 years post-op. Fusion was defined as contiguous bony bridging on CT scan with less than 3 degrees of motion on flexion/extension views by independent radiologist's review.

Results

The 148 patients studied included 71 males and 77 females. Mean age was 50.5 (range 18-78) years (Julie – I don't have the exact numbers). Overall there were 42 smokers and 106 nonsmokers. There were 21 smokers and 55 nonsmokers in the rhBMP-2 group and 21 smokers and 51 nonsmokers in the ICBG group. There were no statistically significant differences in demographic parameters between the four smoking/graft montage subgroups (Table 1).

At 2 years postop, solid fusion was demonstrated in all 55 nonsmokers in the rhBMP-2 group (100%). Successful fusion was seen in 20 of 21 smokers in the rhBMP-2 group (95.2%). Fusion was achieved in 48 of 51 nonsmokers in the ICBG group (94.1%), but only 16 of 21 smokers (76.2%) in the ICBG group (Figure 1.). There was a statistically significant difference between fusion rate in the smoker/ICBG group versus the other three groups (p=0.042). (Julie – Have I presented the stat accurately?) There was also a significant difference in fusion rate between all smokers (85.7%) and all nonsmokers (97.2%) (p=0.016).

At every postop interval, statistically significant improvement from baseline was observed for ODI and SF-36 PCS measures in both smokers and nonsmokers. (Fig. 2) Statistically significant improvement was also seen for VAS back and leg pain scores in both smokers and nonsmokers

(Fig. 3). Although improvement was statistically significant in both groups, the mean SF-36, ODI scores were consistently better for nonsmokers (Fig. 4).

At two years post-op, ODI improved a mean 26.4 points in rhBMP-2 nonsmokers, 24.6 points in ICBG nonsmokers, 22.1 points in rhBMP-2 smokers and 21.0 points in ICBG smokers. SF-36 PCS improved a mean 10.3 points in rhBMP-2 nonsmokers, 11.0 points in ICBG nonsmokers, 7.1 points in rhBMP-2 smokers and 11.8 points in ICBG smokers. Improvement in back pain scores was a mean 7.5 points in rh-BMP-2 nonsmokers, 7.2 points in ICBG nonsmokers, 7.8 points in rhBMP-2 smokers, and 6.3 points in ICBG smokers.

Assessment of SF-36 MCS scores revealed a statistically significant improvement at 2 years postop in nonsmokers but only a trend toward improvement in smokers. Magnitude of SF-36 MCS improvement at 2 years postop was 6.8 points in rhBMP-2 nonsmokers, 6.3 points in ICBG nonsmokers, 4.9 points in rhBMP-2 smokers and 5.0 points in ICBG smokers. (Julie – I don't have MCS data in this version. Should I exclude it?) While there were no statistically significant differences in return to work rate, nonsmokers were more likely to be working both preoperatively (44.3% vs. 21.4%) and postoperatively (46.7% vs. 27.5%) (p=0.027).

DISCUSSION

Cigarette smoking is detrimental in patients undergoing lumbar fusion surgery. Smoking has been associated with decreased fusion rate, diminished clinical outcomes, limitation in functional rehabilitation and poorer overall patient satisfaction (Glassman, Anderson, McGeary, Kwon,

Mooney). Most of the attention has been focused on fusion status, particularly for posterolateral fusion where healing is a challenge even in an ideal host.

The relationship between smoking and spinal fusion has been investigated in a variety of animal models (Lee, Daftari, Silcox, Wing). The mechanism by which nicotine inhibits fusion healing has been demonstrated to include decreased revascularization of the bone graft (Daftari). More recently, nicotine receptors with an anti-inflammatory function have been identified (Wang, Miao). Given the known inhibition of spine fusion associated with nonsteroidal anti-inflammatory medications (Glassman 2, Reuben, Park), this pathway may represent a second mechanism where by nicotine interferes with fusion healing. Importantly, cigarette smoking has been shown to adversely affect clinical outcomes independent of the diminution in fusion rate (Glassman, Anderson, Hilibrand). Contributing factors may include an accelerated rate of disc degeneration (Battie) or a compromised general health status. Preoperative smoking abatement is the ideal solution because it has been demonstrated to increase fusion rate and to improve outcomes. (Wing, Glassman) Unfortunately, not all patients are able or willing to quit smoking, therefore, alternative surgical strategies which may offset the negative influence of smoking have been sought.

Initially, pedicle screw fixation was seen as a mechanism to avoid nonunion in complex cases and compromised hosts. Unfortunately, rigid stabilization alone has been insufficient to assure fusion in cigarette smokers (Anderson, Kwon, Hadley). Lumbar interbody fusion has also been advocated to enhance fusion rate in smokers (Mirovsky). Higher fusion rates are routinely reported with interbody grafting techniques, but the accuracy of radiographic assessment has

been questioned (Cook). From a clinical standpoint, the occurrence of surgical nonunion in smokers remains a substantial unresolved issue.

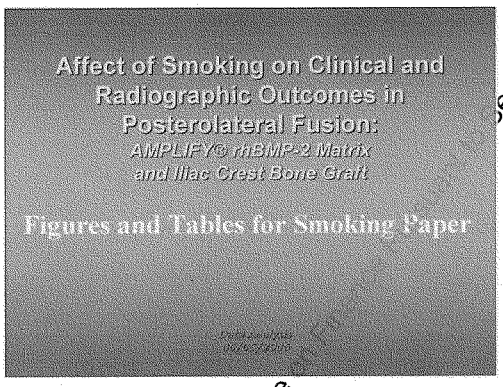
The advent of osteoinductive biologic bone graft alternatives, particularly BMPs, offers another potential tool to achieve fusion in difficult hosts such as cigarette smokers. Preclinical studies have heightened expectations by demonstrating a reversal of the nicotinic effect in rabbits with both rhBMP-2 (Silcox) and rhBMP-7 (Patel). A small human pilot study also suggested that rhBMP-7 might generate a similar effect in clinical application (Govender). The authors caution that the study, which included only four smokers, must be considered very preliminary. A study of early fusion rates with high dose rhBMP-2 (2 mg/ml, 20 mg per side) versus ICBG, was also encouraging (Glassman 3). This study, which included 16 smokers, demonstrated a more robust fusion among smokers in the rhBMP-2 group, but the differences were not statistically significant.

In the present study, fusion rate based on plain radiographs and CT scan assessment was analyzed in 148 patients at 2 year follow-up after single level posterolateral lumbar fusion. The data was collected as part of a prospective randomized trial of rhBMP-2 versus iliac crest bone graft. The study cohort, from three spine centers, included 42 smokers and 106 nonsmokers. It is important to recognize that patients were not randomized based upon smoking status, and that this is a retrospective review of a limited subset from the overall IDE trial. Also, the dose and concentration of rhBMP-2 (2 mg/ml, 20 mg per side) is substantially greater than that available in INFUSE Bone Graft.

Given these constraints, the use of rhBMP-2 appears to enhance fusion rate in smokers. The fusion rate was 100% in the nonsmoker/rhBMP-2 group, 94.1% in the nonsmoker/ICBG group, 95.2% in the smoker/rhBMP-2 group and only 76.2% in the smoker/ICBG group. The difference in fusion rate between rhBMP-2 and ICBG in the smokers was statistically significant (p=0.042). (Julie – I'm not sure that this is exactly the comparison that you did.) There was also a significant difference in fusion rate comparing all smokers (85.7%) and all nonsmokers (97.2%) (p=0.016).

Despite the improvement in fusion rate with rhBMP-2, clinical outcomes measures were still adversely affected in smokers. Although the differences were generally not statistically significant, nonsmokers had better ODI and SF-36 PCS scores at all intervals. Nonsmokers were also significantly more likely to be working both pre and postoperatively.

The results of this study suggest that rhBMP-2 matrix (2 mg/ml, 20 mg. per side) substantially enhances fusion rate in cigarette smokers undergoing single level posterolateral lumbar fusion. The findings are also consistent with prior studies which indicate that smoking is detrimental to clinical outcome independent of fusion status. (Glassman, Anderson) Therefore, the authors conclude that while rhBMP-2 matrix is a valuable tool for lumbar fusion in smokers, smoking abatement is still the optimal management technique for patients undergoing lumbar fusion surgery.

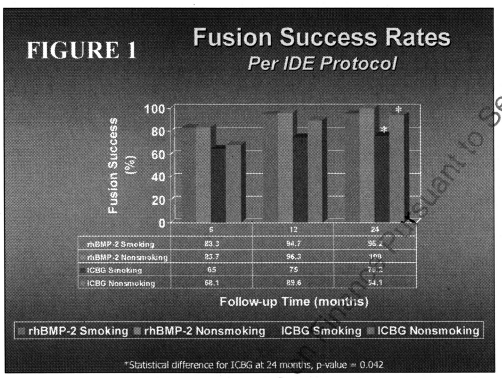


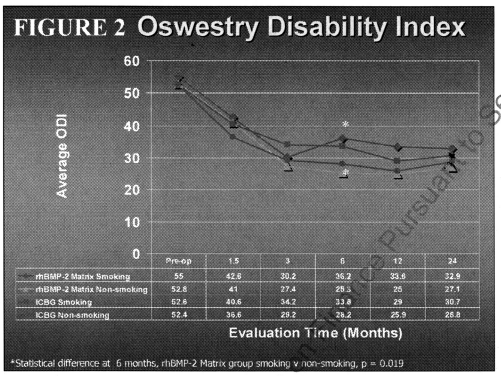
Data presented in this slide presentation is taken from data analyzed on 8/10/01 and presented in pivotal IDE submission

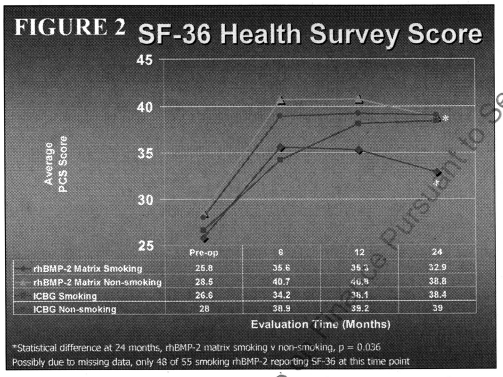
TABLE 1 Patient Demographics

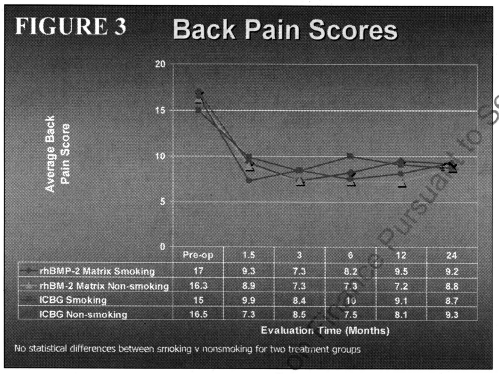
	rhBMP-2 Matrix		ICBG	
	smoking	non-smoking	smoking	non-smoking
N	21	55	21	51
Average Age (yr)	50.8	51.8	48.1	51.7
Average Weight (lb)	180.2	189.2	187.7	197.8
Male/female	11/10	28/30	13/8	22/29
Worker's compensation (%)	4.8	14.8	23.8	13.7
Spinal litigation (%)	4.8	3.6	4.8	13.7

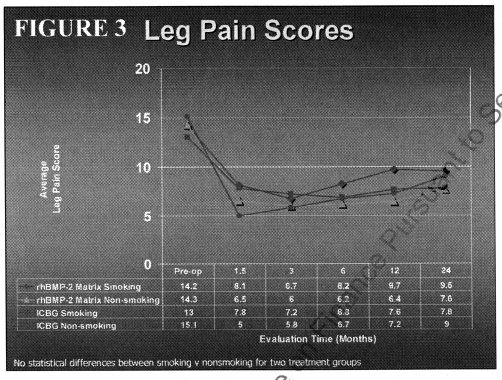
No statistical differences comparing smoking v nonsmoking for investigational or control groups

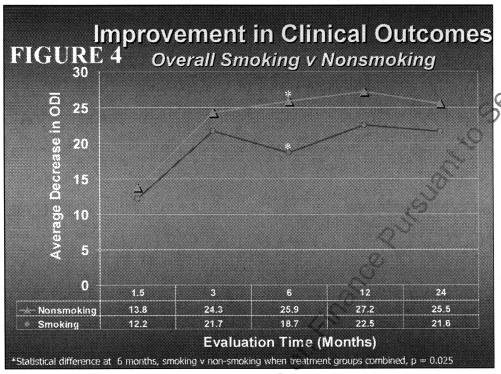


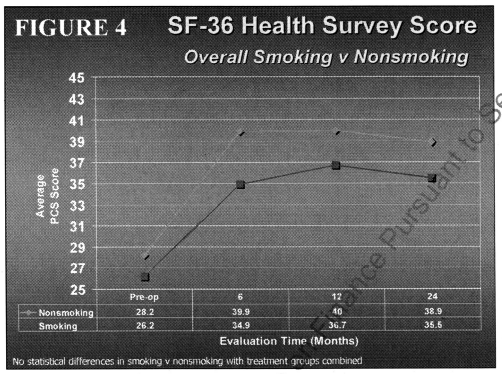












From: Ma, Guorong
Sent: Wednesday, June 21, 2006 11:37:00 AM
To: Bearcroft, Julie, PhD; Keller, Jim
CC: Zhu, Youjun
Subject: RE:

Attachments: 2YrBMP-CRMSRS2006_06-07-06v2_Guorong.doc

Julie,

Please see my comments in blue inserted in the manuscript.

The adverse event categories are not exactly the same as the PMA. Thus, I did not comment on them.

As we discussed before, IDE fusion was calculated using both X-rays and CTs, not just X-rays alone.

From 12 months to 24 months, there was a trend that as compared with the control, the BMP group got slightly worse in ODI, back and leg pain, % patients working, and so on. This does not necessarily reflect the truth. Rather, it may be due to the fact that the 24-month results were from only a fraction of patients. Also, the difference in fusion rates at 24 months was almost significant and it may well be when we have all the patients. Considering that we are now close to finalize the database for 24-month data and we may tell a better story with all the data, it may be worthwhile to think whether or not we want to publish this right now, not to mention the regulatory implication with the PMA under review.

Jim,

Because the new SOP on publication policy is not in effective, it is all up to you to make the call as far as the clinical/regulatory concern.

Thanks,

Guorong

From: Bearcroft, Julie, PhD

Sent: Wednesday, June 21, 2006 7:56 AM
To: Ma, Guorong
Subject: FW:

Guorong -
Youjun suggested that I forward this manuscript from the AMPLIFY study to you for review.
I will collate MSD input and feedback to the authors.
Thanks for your help,
julie

From: Zhu, Youjun
Sent: Wednesday, June 21, 2006 7:51 AM
To: Bearcroft, Julie, PhD
Subject: RE:

Julie,

General speaking, all of the manuscripts we assisted should go to Guorong's review first, could you please have him to review your paper?

Thanks,

Youjun

From: Bearcroft, Julie, PhD
Sent: Wednesday, June 21, 2006 7:27 AM
To: LCarreon[redacted]
Cc: Keller, Jim; Norman, Dawn; Zhu, Youjun; Beals, Neil; Meyer, Matt; Lanctot, Rodney; McKay, Bill; Hatcher, Brian
Subject: FW:

Leah -
Thanks for the updated version. I will coordinate the review of this manuscript internally. I would recommend that you provide a copy to Carol Binns concurrently for review by all of the authors. I will collate the response from the internal review and provide feedback to Carol.

I also know that the deadline is quickly approaching. Last time I talked with Dr Dimar, he was targeting submission by the end of the month. Please verify that this target is correct.

Thank you again for all of your hard work on this manuscript.

julie

From: Leah Carreon [redacted]
Sent: Tuesday, June 20, 2006 10:38 AM
To: Bearcroft, Julie, PhD
Cc: JDIMAR[redacted]
Subject:

Julie—

Here is the latest version of the SRS Manuscript. Data from the CT Scan reviews were incorporated. Please feel free to review and disseminate for changes/suggestions as you see fit.

Leah Y Carreon MD, MSc
Clinical Research Director
Spine Institute
Phone: [redacted]
Fax: [redacted]

A large-scale, level 1, clinical and radiographic analysis of an optimized rhBMP-2 formulation as an autograft replacement in posterolateral lumbar spine fusion

John R. Dimar II, MD*, Steven D. Glassman, MD*, J. Kenneth Burkus, MD†, Philip W. Pryor‡, MD, James W. Hardacker. MD‡, Scott D. Boden, MD§

*Spine Institute for Special Surgery, Louisville, KY; †The Hughston Clinic, Columbus, GA; ‡The Spine Institute, Carmel, IN; § Emory Spine Center, Emory University School of Medicine, Atlanta, GA

Purpose: To determine the feasibility of using recombinant human bone morphogenetic protein-2 with a compression resistant matrix (rhBMP-2/CRM) as an iliac crest bone graft (ICBG) substitute in patients undergoing posterolateral fusion.

Methods: In this ongoing prospective study, 463 patients with symptomatic single-level degenerative disc disease with ≤ Grade 1 spondylolisthesis were treated with decompression and instrumented single-level posterolateral fusion through an open midline approach. Patients were randomly assigned to either the rhBMP-2/CRM (AMPLIFY™, Medtronic Sofamor Danek) group (239 patients) or the ICBG group (224 patients). ODI, SF-36, and back and leg pain scores were determined preoperatively and at 1.5, 3, 6, 12 and 24 months postoperatively. Two independent radiologists reviewed radiographs and CT scans taken at 6, 12, and 24 months postoperatively. Fusion was defined as the presence of bilateral, continuous trabeculated bone connecting the transverse processes, translation of ≤3 mm and angulation of <5° on flexion-extension radiographs, and absence of cracking as evidenced by radiolucent lines completely through the fusion mass.

Results: No significant differences existed in demographics existed between the groups. Mean operative time in the rhBMP-2 group (2.5 hours) was less than in the ICBG group (2.9 hours) ($p<0.001$). Average blood loss in the rhBMP-2 group was 343.1 ml compared with 448.6 ml in the ICBG group ($p<0.001$). Average hospital stay was similar in both groups. No differences existed between groups in adverse events except cumulative nonunion rate reported by investigator was lower in the rhBMP-2 group (2.5%; 6 patients) than in the ICBG group (7.1%;16 patients) ($p=.042$). Based on fine-cut CT Scans with coronal and sagittal reconstructions, at 12 months, 86.9% of patients in the rhBMP-2 group and 71.3% in the ICBG group had evidence of bilateral bridging bone ($p<0.001$). At 24 months, 93.6% in the rhBMP-2 group had bilateral bridging bone compared with 82.6% in the ICBG group ($p=0.024$). Both groups showed similar improvements in clinical outcomes and reduced pain.

Conclusions: The use of rhBMP-2 can eliminate the need for harvesting iliac crest bone in successful posterolateral lumbar fusions.

Deleted: and

Deleted: fusion

Deleted: were fused

Deleted:

INTRODUCTION

Posterolateral fusion combined with pedicle instrumentation is frequently employed for the treatment of degenerative disease of the lumbosacral spine. Various indications include degenerative disc disease, spondylolisthesis, and instability. The results of instrumented posterolateral fusions in large clinical studies have shown varying rates of fusion and clinical outcomes [1-6]. Traditional sources of grafting material include autograft obtained locally from the iliac crest or from distal sources and different types of allograft [3-6].

Previous studies have demonstrated the ability of recombinant human bone morphogenetic protein (rhBMP-2) to achieve a solid fusion [7-9]. Recently prospective randomized human clinical studies demonstrated equivalent fusion rates and clinical outcomes with rhBMP-2 and a collagen sponge (Infuse) versus autograft when using either cortical bone dowels or threaded interbody cages in anterior lumbar interbody techniques [10-11]. A small pilot study on humans demonstrated similar results with rhBMP-2 combined with biphasic calcium phosphate versus iliac crest autograft for posterolateral fusions [12]. Currently, a prospective randomized FDA IDE study comparing iliac crest bone graft (ICBG) to rhBMP-2 combined with a carrier consisting of bovine collagen and tricalcium/hydroxyapatite (Compression resistant matrix, CRM) for single-level posterolateral fusions is ongoing. The purpose of our report is to present the two year radiographic results and clinical outcomes using rhBMP-2/CRM or ICBG in single-level instrumented fusions for lumbosacral degenerative disease.

MATERIAL AND METHODS

There were 463 patients enrolled in a multi-center prospective, randomized, nonblinded, FDA IDE study. There were 29 participating investigational sites with 83 spine surgeons. All of the patients were treated with a single-level instrumented fusion using Horizon M8 (is this accurate?) (Medtronic Sofamor Danek, Memphis, TN USA) pedicle screw and rod instrumentation. Exclusion criteria included a previous attempt at fusion at the intended surgical level, significant osteoporosis (less than 2 SD below normal on DEXA), autoimmune disease, malignancy, pregnancy, or the inability to harvest graft due to previous surgical procurement. Patients were randomly assigned to one of two groups: the control group received autogenous iliac crest bone graft (ICBG) and the investigational group received rhBMP-2/CRM (Medtronic Sofamor Danek, Memphis, TN, USA). The dose of rhBMP-2 used in this study is higher (2.0mg/cc for a total dose of 40mg, 20mg per side) than that of commercially available INFUSE (1.5mg/cc for a total dose of 16mg, 8 mg per side).

The indications for surgery were symptomatic, single-level lumbosacral degenerative disease from L2/3 to L5/S1 of at least six months duration that had not responded to conservative care. The clinical symptoms included low back pain with or without radicular leg pain. Additional enrollment criteria were a Grade I or less spondylolisthesis and no previous fusion.

A standard open posterior approach was used for both the ICBG and rhBMP-2/CRM groups. Local bone graft obtained during the decompression was discarded. Bone graft from the iliac crest in the ICBG group was obtained in a standard open fashion. The bone graft was morselized and placed in the lateral gutters on the decorticated bony surface of the transverse processes and along the pars interarticularis.

The rhBMP-2 was reconstituted using sterile water into two 5 ml syringes containing 20mg of rhBMP-2. The CRM was cut lengthwise with a scalpel into two

Deleted: 476

Deleted: Infuse

Deleted: ,

Deleted: , or both

Deleted: , although degenerative disease adjacent to a previous fusion was acceptable

equal pieces using a cutting template. The reconstituted rhBMP-2 from each syringe was then uniformly distributed to each piece of the CRM and allowed to stand for a minimum of five minutes. The rhBMP-2/CRM sponges were all implanted within 60 minutes following preparation. In no instance was the sponge of insufficient length to span the transverse processes in a single-level fusion. As required by the protocol, any local bone graft obtained from the decompression was discarded in the rhBMP-2/CRM group.

Clinical data were collected preoperatively and post operatively at six weeks, 3 months, 6 months, 12months, and 24 months post operatively. The validated outcome instruments employed included the Oswestry Low Back Pain Disability Index (ODI), the Short Form 36 (SF-36), back pain and leg pain scores, and graft site pain. Data on work status, patient satisfaction, and adverse events were also recorded. Neurological examination including motor function, sensory function, reflexes, and straight leg raise were recorded.

Plain radiographs, lateral flexion and extension radiographs, and CT Scans with sagittal and coronal reconstruction were used to evaluate the fusion in both groups post operatively at 6, 12, and 24 months. The CT imaging protocol consisted of one millimeter continuous non-overlapping axial slices that were taken without bone filter. The window and level settings were set to optimize trabecular bone detail (2000/350 on GE Scanners). The field of view was made as small as possible but still encompassed the complete vertebra in between and including the transverse processes. The radiographs and CT Scans were evaluated by two independent radiologists who were blinded to which patient group they were evaluating (is this true?).

The rhBMP-2/CRM and ICBG group values were compared using ANOVA for continuous variables and Fisher's exact test for categorical variables for independent samples across each time interval.

RESULTS

All the patients were past the 12-month evaluation point, but the 24-month follow-ups are ongoing. There were 282 subjects who had any follow-up data at two years postoperatively, 137 in the ICBG group and 145 in the rhBMP-2/CRM group. Randomization resulted in a similar distribution of baseline characteristics in the two study groups as shown in Table 1.

The average surgical time for the control patients was 2.9 hours which was significantly longer ($p<0.001$) than the 2.5 hours observed in the rhBMP-2/CRM group (Table 2). The average blood loss was 448.6 ml for the control patients which was also significantly greater ($p<0.001$) than the 333.1 ml blood loss observed with the rhBMP-2/CRM group. There was no statistically significant difference in length of hospital stay between the two groups. No surgeries were abandoned due to technical problems. There were no unanticipated intra-operative complications related to the fusion procedure.

The SF-36 physical component summary (PCS) scores were similar in both groups at all time intervals (Figure 1) and showed statistically significant improvement compared to pre-operative scores in both the ICBG and rhBMP-2/CRM groups Table 3 [Comments: p-values showing significant improvement for within groups are not shown, but p-values comparing between the groups are shown, which are not significant. I would not show those between groups.]. The ODI scores were similar in both groups over all time intervals (Figure 2) and showed statistically significant improvement compared to pre-operative scores in both the ICBG and rhBMP-2/CRM groups Table 4 [Comments: p-values showing significant improvement for within groups are not shown, but p-values

Deleted:
Deleted:
Deleted: the Oswestry Low Back Pain Disability Index (ODI),
Deleted: , back pain and leg pain scores
Deleted: an
Deleted: as
Deleted: available for initial review
Deleted: that might be independently related to the study outcomes
Deleted: s
Deleted: cc
Deleted: s
Deleted: cc
Deleted: (PCS)
Deleted: .

comparing between the groups are shown, which are not significant. I would not show those between groups.]. [I would change the order ODI and PCS]

The back pain scores (on a 0-20 scale, the sum of pain intensity on a scale of 0-10 and pain frequency on a scale of 0-10) for the ICBG and rhBMP-2/CRM groups improved from pre operative scores of 15.8 and 15.6 to 8.1 and 7.8 at 24 months, respectively. Both groups showed similar improvements over all time intervals (Figure 3) with no statistically significant difference in their 24 month back pain scores. The leg pain scores following surgery and demonstrated that both the ICBG and rhBMP-2/CRM groups improved in a similar manner over all time intervals (Figure 4). Leg pain scores improved from 14.0 in both groups, to 7.4 in the ICBG group and 7.1 in the rhBMP-2/CRM group at 24 months. There was no statistically significant difference in their 24 month leg pain scores.

Pain resulting from iliac crest harvest was measured using donor site pain scores. These were collected only from the ICBG group. The mean donor site score after discharge was 11.3, which improved to 7.9 six weeks after surgery. There was minimal improvement on subsequent follow-up periods up to 24 months. Patients in the ICBG group still had persistent donor site pain with a mean pain score of 5.0 at 24 months after surgery (Figure 5).

41.1% of subjects in the ICBG group were working prior to surgery and 48.5% were able to return to work at 24 months (Figure 6). 34.7% of the subjects in the rhBMP-2/CRM group were working prior to surgery, and 40.7%16 returned to work at 24 months postoperatively.

The IDE protocol-defined fusion analysis [which utilized both plain radiographs and CTs] at 12 months showed that 87.4% of patients in the rhBMP-2 group and 82.4% in the ICBG group had evidence of fusion (p=.199). At 24 months, 94.9% in the rhBMP-2/CRM group were fused compared with 86.8% in the ICBG group (p=.074). Fine-cut CT Scans with sagittal and coronal reconstructions showed that 74.4% of the subjects in the rhBMP-2/CRM group and 56.4% in the ICBG group had evidence of bilateral bridging bone at 6 months (p<0.001). At 12 months, 86.9% of subjects in the rhBMP-2/CRM group and 71.3% in the ICBG group had evidence of bilateral bridging bone (p<0.001) At 24 months, the rate was 93.6% in the rhBMP-2 group compared to 82.6% in the ICBG group (p=0.024)(Figure 7). There were twice as many nonunions in the ICBG group compared to the rhBMP-2/CRM group.

The most common complication which may have been related to the surgery were infections of various types at different sites. There was a higher incidence of superficial wound infections in the ICBG group. There was no difference in the incidence of deep wound infections, wound drainage or development of wound hematoma. Sixteen patients in the ICBG group complained of continued pain from the bone graft donor site that required active treatment. One patient developed a donor site infection. No adverse events were observed that could be directly attributable to the use of rhBMP-2/CRM.

DISCUSSION

The guiding principle for the surgical treatment of painful or unstable lumbosacral degenerative spinal disease remains the ability to achieve a solid fusion. Although autologous ICBG is the gold standard, the morbidity associated with graft harvest has led surgeons to seek viable alternatives, such as allografts, ceramics, and various types of growth factors [16-20]. These graft substitutes have demonstrated great variability in achieving fusion. Additionally, they present their own unique problems including

5

Deleted: hip
Deleted: hip pain
Deleted: hip
Deleted: P
Formatted: Font: Not Bold
Deleted: 2
Deleted: 37
Deleted: fusion
Deleted: fusion
Deleted: of
Deleted: were fused
Deleted: of

decreased success of fusion [21], limited availability, and the potential for rejection or immunologic reaction [17, 18].

The development of tissue biologics has resulted in the clinical availability of recombinant human bone morphogenetic protein (rhBMP-2 and rhBMP-7) for fusion [22]. These naturally occurring bone proteins appear to stimulate bone healing via a cascade mechanism that results in the dedifferentiation of primitive mesenchymal cell into osteoblasts that promote bone healing [23]. The effectiveness of rhBMP-2 in achieving a solid fusion has been demonstrated in numerous experimental animal studies [24]. Subsequently, clinical trials have demonstrated similar fusion rates and clinical outcomes when ICBG was compared to rhBMP-2 combined with a collagen sponge carrier (Infuse) and a lordotic threaded interbody cage (LT-cage) [10, 11]. As a result of these findings the FDA approved the use of rhBMP-2 as a bone graft substitute for anterior lumbar interbody fusions in 2002.

A recent randomized human pilot study evaluated rhBMP-2 combined with biphasic calcium phosphate granules versus autograft in achieving a successful posterior lateral fusion [10]. The study demonstrated a 40% fusion rate in the autograft group versus a 100% fusion rate with the investigational group when evaluated by radiographs. Oswestry and SF-36 outcome measures demonstrated significant but similar improvement of all groups at the end of the study. Although the authors sited several deficiencies, most notably the lack of a 24 month follow-up on all the subjects, the study presented strong evidence of the efficacy of rhBMP-2 in achieving a successful radiographically confirmed fusion in humans.

As part of an ongoing FDA regulated IDE study rhBMP-2 is now being evaluated for use in single-level posterolateral fusions combined with pedicle screw/rod instrumentation. This report reviews our two year clinical outcomes and fusion rates based on CT scans. This study utilizes a specifically designed carrier, that combines tricalcium phosphate and hydroxyapatite granules with a collagen matrix. This combination provides significant resistance to compression when placed in the lateral gutters. It is also important to emphasize that this study uses a higher concentration of rhBMP-2 (2.0mg/ml vs 1.5mg/ml) when compared to the concentration utilized in previous clinical studies.

Deleted: for 282 subjects

Comment [LYC1]: Pre-clinical studies have shown that the concentration per carrier is more critical than the actual amount of BMP)

Although local bone graft is rarely discarded in clinical practice, the quality and quantity of local bone grafts are highly variable. In this study, local bone graft was discarded in both groups to allow for a direct comparison of the fusion rates of rhBMP-2/CRM to ICBG without local bone graft as a confounding variable.

The results of this study demonstrate significant improvement of the ODI, SF-36, Jeg and back pain scores in both groups over all time intervals. There were differences in operative time and blood loss, which were significantly less in the rhBMP2/CRM group as compared to the ICBG group. The length of hospital stay was the same for both groups.

Deleted: ODI,

An equally important measure of the success of a fusion procedure, beyond the radiographic evidence of fusion, is how the patient feels and functions after surgery. The use of validated patient-based clinical outcome measures such as the Oswestry Disability Index and the SF-36 provide a self-assessment of the patient's functional improvement rather than the clinician's perception [13]. Most of the improvement in ODI scores and SF-36 PCS occurred within the first three months after surgery, in both groups. This improvement was maintained all through the subsequent follow-up periods up to 24 months. The improvement in PCS at 24 months in both groups was well above the 5.41

point threshold in the literature for clinically significant improvement [25]. The decrease in ODI scores at 24 months in both groups was greater than 15 points [comments: I think the 15-point value refers to patient-based meaningful improvement. The group-based value would be 4-5 points], which is also above that necessary to demonstrate treatment efficacy [26, 27].

Most of the improvement in back pain and leg pain scores was noted within the first six weeks after surgery, and was maintained throughout the entire follow-up period. The 6.9 point decrease in back pain in the rhBMP-2/CRM group and 7.7 in the ICBG group indicates a clinically significant diminution in back pain following surgery. The 7.9 point decrease in leg pain in the rhBMP-2/CRM group and 8.4 in the ICBG group indicates a clinically significant diminution in leg pain following surgery.

The rates of fusion in previously published articles varies widely form 60% to 98%1. This may be due to the use of plain radiographs with flexion extension views and CT Scans which are known to be inaccurate with error rates estimated from 20 to 40%. When fusion was assessed using the IDE protocol-defined criteria that use plain radiographs and CTs, the rhBMP-2/CRM group had smaller differences in fusion rates as compared with the ICBG group and these rates were higher than that observed when fine-cut CT Scans were used. [Comments: if just plain radiographs are used, the fusion rates would be lower than those just from CTs. The IDE fusion rates use both for determining bridging bone.] Subjects in the ICBG group demonstrated lower fusion rates over all time intervals compared to the rhBMP-2/CRM group when fine-cut CT Scans with reconstructions were used to assess fusions. The use of fine-cut CT scans with sagittal and coronal reconstructions may increase the accuracy by which fusions are assessed by its ability to demonstrate the robustness of the fusion and the presence of bilateral confluent bridging bone. At the 24 month follow-up period, there were twice as many patients in the ICBG group with established nonunions.

Deleted: both groups

Deleted: similar

The incidence of deep wound infections, wound drainage or development of wound hematoma was similar in both groups. There was a higher incidence of superficial wound infections in the ICBG group which may be due to the need for significant retraction to access the iliac crest through the same incision for bone graft harvest.

CONCLUSION

This study demonstrates that, for patients with a single-level degenerative disease, an instrumented posterolateral fusion with ICBG and rhBMP-2/CRM exhibit similar clinical outcomes two years after surgery. The rhBMP-2/CRM group demonstrated significantly decreased intra operative blood loss and decreased operative time when compared to the ICBG group. The rhBMP-2/CRM demonstrated an improved fusion rate when compared to the ICBG group at 24 months. There were no significant differences in complications between the two groups. In conclusion, rhBMP-2/CRM demonstrated similar clinical outcomes and increased fusion rates when compared to ICBG for a single-level instrumented posterolateral fusion.

Table 1. Patient Demographic Data

	rhBMP-2/CRM	ICBG
Age (years)	53.2	52.3
Gender (%Male)	45.2	42.4
Workmen's Comp (%)	11.3	12.5
Smoker (%)	26.4	26.3

Table 2. Surgical data

	rhBMP-2/CRM	ICBG	p=value
OR Time	2.5	2.9	<0.001
EBL	343.1	448.6	<0.001
Hospital Stay	4.1	4.0	0.609

Table 3. Mean change in SF-36 PCS compared to pre-operatively on each follow-up period

Mean Change in SF-36 PCS	rhBMP-2/CRM	ICBG	p=value
6 weeks	3.8	4.5	0.378
3 months	9.5	8.8	0.465
6 months	12.9	10.9	0.073
12 months	13.7	11.6	0.070
24 months	12.7	12.8	0.990

Table 4. Mean Improvement in ODI compared to pre-operatively on each follow-up period

Mean Improvement in ODI	rhBMP-2/CRM	ICBG	p=value
6 weeks	12.9	13.9	0.580
3 months	22.1	21.2	0.610
6 months	26.0	24.4	0.382
12 months	26.9	25.4	0.452
24 months	27.2	25.6	0.582

Deleted: 9

Deleted: 4

Deleted: 9

Deleted: 7

Deleted: 1

Deleted: 3

Deleted: change

Deleted: Change

Deleted: 5

Deleted: 5.8

Deleted: 2

Table 5. Complications

	rhBMP-2/CRM	ICBG
Wound Drainage	4	3
Superficial Infection	5	15
Deep Infection	5	5
Wound Hematoma	1	0
Epidural Hematoma	2	0
Malignancy*	7	4
Anemia	26	29
UTI	8	9
Infection (Other sites)	27	19
Infection (Total)	46	48
Nonunion	11	22
AIF	6	10
PSF	0	6
Symptomatic	2	5
Asymptomatic	3	1
Dural Tear	14	18
Adjacent Level Degeneration	3	7
Surgical	2	5
Nonsurgical	1	2
Renal Stones	7	4
Pulmonary	17	9
Ileus	10	4
Technical Problems	9	6
Death	3	4
Donor Site Complaints	0	16
Donor Site Infection	0	1

*Cancer types in the rhBMP-2/CRM group include Follicular, Squamous Cell, Laryngeal, Pancreatic, Prostate, Lung and Basal Cell; in the ICBG group types include NonHodgkin's Lymphoma, Breast, Colon and an unknown Primary

FIGURES

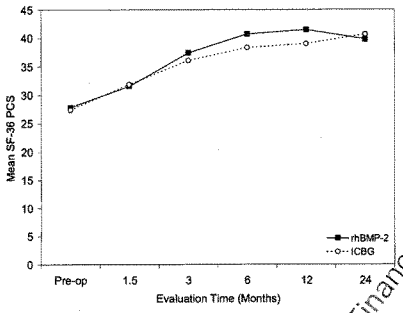


Figure 1. Comparison of SF-36 PCS in the ICBG and rhBMP-2/CRM groups.

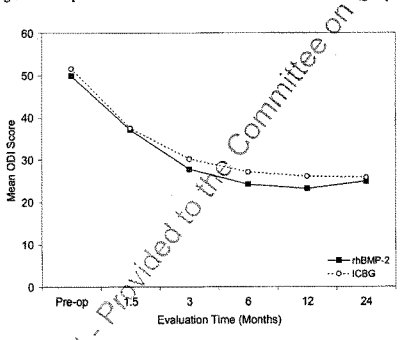


Figure 2. Comparison of ODI in the ICBG and rhBMP-2/CRM groups.

10

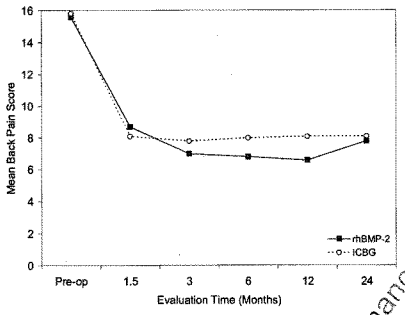


Figure 3. Comparison of mean back pain scores in the ICBG and rhBMP-2/CRM groups.

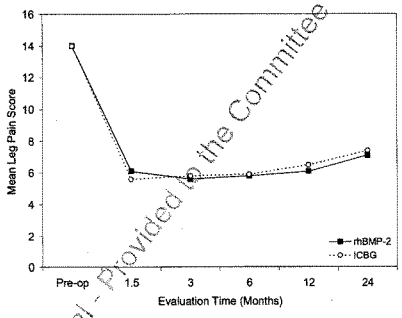


Figure 4. Comparison of mean leg pain scores in the ICBG and rhBMP-2/CRM groups.

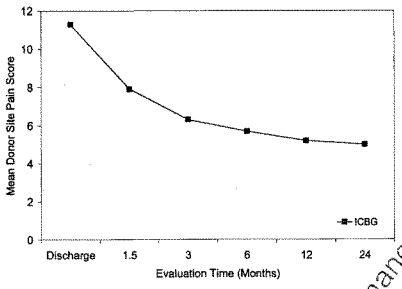


Figure 5. Mean donor site pain scores in the ICBG group.

Deleted: hip

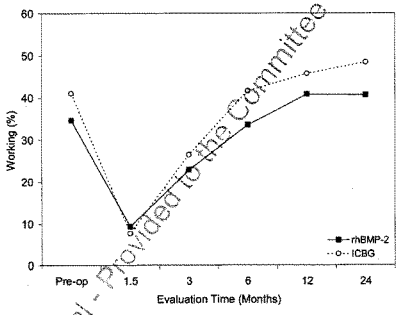


Figure 6. Percentage of subjects working in the ICBG and rhBMP-2/CRM groups.

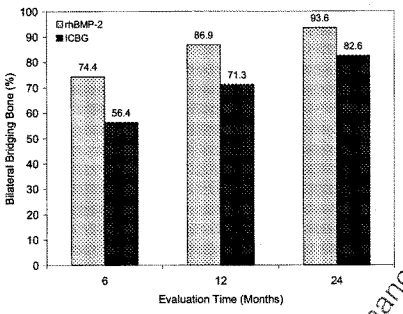


Figure 7. Percentage of subjects with bilateral confluent bridging bone on fine-cut CT Scans with reconstructions the ICBG and rhBMP-2/CRM groups.

REFERENCES

1. Bono CM, Lee CK: Critical Analysis of Trends in Fusion for Degenerative Disc Disease Over the Past 20 Years. Spine. Feb 15;29(4):455-63.
2. An HS, Lynch K, Toth J: Prospective Compatison of Autograft vs. Allograft for Adult Posterolateral Lumbar Spine Fusion: Differences Among Freeze-Dried, Frozen, and Mixed Grafts. J Spinal Disord. Apr;8(2):131-5, 1995
3. An HS, Lynch K, Toth J: Prospective Compatison of Autograft vs. Allograft for Adult Posterolateral Lumbar Spine Fusion: Differences Among Freeze-Dried, Frozen, and Mixed Grafts. J Spinal Disord. Apr;8(2):131-5, 1995
4. Dawson EG, Lotysch M 3rd, Urist MR: Intertransverse Process Lumbar Arthrodesis with Autogenous Bone Graft. Clin Orthop Jan-Feb;(154):90-6,1981
5. Dimar, Glassman, Burkus, Carreon: A Comparison of Prospective Clincial Outcome Measures for Anterior vs. Posterior Single-level Spine Fusion. IMAST Program July 2004
6. Jorgenson SS, Lowe TG, France J, Sabin J: A prospective analysis of autograft versus allograft in posterolateral lumbar fusion in the same patient. A minimum of 1 – year follow-up in 144 patients. Spine Sep 15;19(18):2048-53, 1994
7. Martin GJ Jr, Boden SD, Marone MA, Moskovitz PA: Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: important lessons learned regarding dose, carrier, and safety. J Spinal Disord. Jun;12(3):179-86, 1999
8. Yoon ST, Park JS, Kim KS, Li J, Attallah-Wasif ES, Hutton WC, Boden SD: ISSLS Prize Winner: LMP-1 Upregulates Intervertebral Disc Cell Production of Proteoglycans and BMPs in Vitro and in Vivo. Spine 29(23):2603-11, 2004
9. Boden SD, Schimandle JH, Hutton WC, Chen MI: 1995 Volvo Award in Basic Science. The Use of an Osteoinductive Growth Factor for Lumbar Spine Fusion. Part I: Biology of Spinal Fusion. Spine 15; 20(24):2626-32, 1995
10. Burkus JK, Gornet MF, Dickman CA, Zdeblick TA: Anterior Lumbar Interbody Fusion Using rhBMP-2 with Tapered Interbody Cages. J Spinal Disord Tech 15(5):337-49, 2002
11. Burkus JK, Dorchak JD, Sanders DL,: Radiographic Assessment of Interbody Fusion Using Recombinant Human Bone Morphogenetic Protein Type 2. Spine 15; 8(4):372-7, 2003
12. Boden SD, Kang J, Harvinder S, Heller JG: Use of Recombinant Human Bone Morphogenetic Protein-2 to Achieve Posterolateral Lumbar Spine. Spine. Dec 1;27(23):2662-73, 2002
13. Ware JE Jr, Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. Jun;30(6):473-83, 1992
14. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD: The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. Jan;32(1):40-66, 1994
15. Fairbank JC, Couper J, Davies JB, O'Brien JP: The Oswestry low back pain disability questionnaire. Physiotherapy. Aug;66(8):271-3, 1980
16. Glassman SD, Dimar JR, Carreon LY, Campbell MJ, Johnson JR and Puno RM. Initial fusion rates with rh-BMP-2 and HA-TCP/Collagen carrier in posterolateral fusion. In Publication.
17. Boden SD. Overview of the biology of lumbar spine fusion and principles for selecting a bone graft substitute. Spine, 2002; 27(16S):S26-S31.

18. Ludwig SC, Kowalski JM and Boden SD. Osteoinductive bone graft substitutes. Eur Spine J, 2000; 9(Suppl 1):S119-S125.
19. Lind M and Bunger C. Factors stimulating bone formation. Eur Spine J, 2000; 9(Suppl 1):S102-S109.
21. Vaccaro AR, Sharon AD, Tuan RS, Kang JD, An HS, et al. The use of biologic materials in spinal fusion. Orthopedics, 2001; 24(2):191-197.
22. Carreon LY, Glassman SD, Anekstein Y, Puno RM. Platelet gel (AGF) fails to increase fusion rates in instrumented posterolateral fusions. Spine. 2005 May 1;30(9):E243-6.
23. Urist MR: Bone: formation by autoinduction. Science. 1965 Nov 12;150(698):893-9
24. Martin GJ Jr, Boden SD, Marone MA, Marone MA, Moskovitz PA: Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: important lessons learned regarding dose, carrier, and safety. J Spinal Disord. Jun;12(3):179-86, 1999
25. Suh DY, Boden SD, Louis-Ugbo J, Mayr M, Murakami H, Kim HS, Minamide A, Hutton WC. Delivery of recombinant human bone morphogenetic protein-2 using a compression-resistant matrix in posterolateral spine fusion in the rabbit and in the non-human primate. Spine. 2002 Feb 15;27(4):353-60.
26. Ware JE, Kosinski M, Keller SK. SF-36® Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: The Health Institute, 1994.
27. Fairbank JCT, Pynsent PB: The Oswestry Disability Index. SPINE 2000;25(22):2940-2953.
28. Walsh TL, Hanscom B, Lurie JD, Weinstein JN: Is a condition-specific instrument for patients with low back pain/leg symptoms really necessary? The responsiveness of the Oswestry Disability index, MODEMS and the SF-36. Spine 2003 Mar 15;28(6):607-15.

From: Bearcroft, Julie, PhD
Sent: Thursday, August 10, 2006 06:18:47 PM
To: Ma, Guorong; Keller, Jim; Zhu, Youjun
CC: Beals, Neil; Lanctot, Rodney
Subject: FW: smoking paper

Attachments: THE_EFFICACY_OF_rhBMP-2..8-10-6.doc

Please review the revised draft manuscript produced by Dr Glassman. If you wish to suggest changes, please email me no later than Monday (14th) morning.
julie

From: sdg[redacted]
Sent: Thursday, August 10, 2006 9:56 AM
To: Bearcroft, Julie, PhD
Cc: Meyer, Matt
Subject: smoking paper

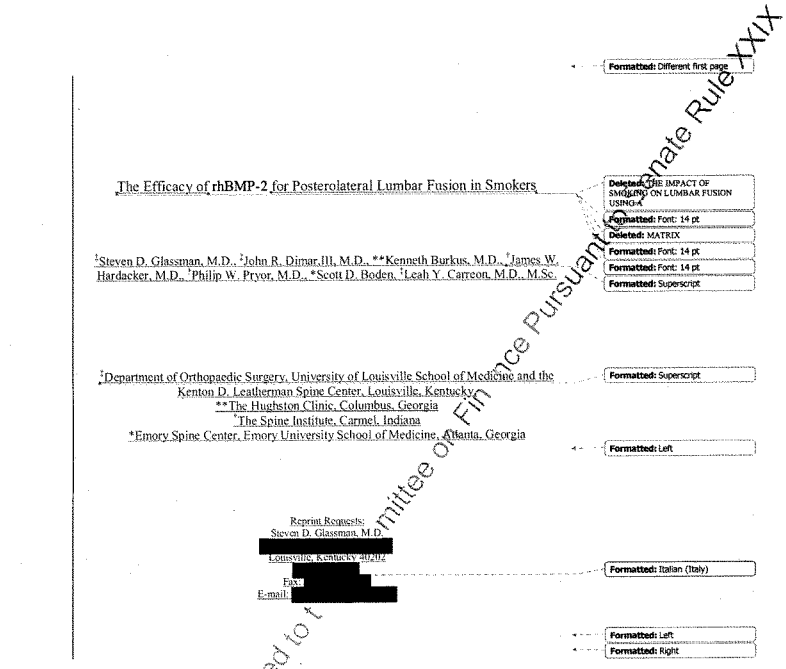
Hi Julie
Attached is a revised version to include the CT data. Since there was no substantial change in the results (and given your comment on the IDE format) I left the FDA fusion success criteria as the primary evaluation method. I also reported the CT evaluation technique, in a secondary fashion.
The changes are in the last paragraph of the methods section, the third paragraph of the results section, and the third to last paragraph of the discussion section.
Leah will add another Figure which mirrors Figure 1. for the CT data.
The only unresolved issue is the % fused calculation for the ICBG smokers using the CT technique. My guess is that we are missing one patient as compared to the other analysis.
Let me know what you think. I would rather that you and I are in agreement before it goes out to the other authors.
Thanks
Steve

-----Original Message-----
From: TAllgeyer[redacted]
To: sdg[redacted]
Sent: Thu, 10 Aug 2006 9:45 AM

I made the changes you sent over. Cutting and pasting didn't work too well. I had to manually remove the markups even after turning off the markups.

Tana Allgeyer
Administrative Assistant
[redacted]
Spine Institute
[redacted]
Louisville, KY 40202
Fax: [redacted]

size=2 width="100%" align=center>



The Efficacy of rhBMP-2 for Posterolateral Lumbar Fusion in Smokers

[1]Steven D. Glassman, M.D., [2]John R. Dimar,III, M.D., **Kenneth Burkus, M.D., [3]James W. Hardacker, M.D., [3]Philip W. Pryor, M.D., *Scott D. Boden, [1]Leah Y. Carreon, M.D., M.Sc.

[1]Department of Orthopaedic Surgery, University of Louisville School of Medicine and the Kenton D. Leatherman Spine Center, Louisville, Kentucky
**The Hughston Clinic, Columbus, Georgia
[3]The Spine Institute, Carmel, Indiana
*Emory Spine Center, Emory University School of Medicine, Atlanta, Georgia

Reprint Requests:
Steven D. Glassman, M.D.
[redacted]
Louisville, Kentucky 40202
Fax:
E-mail: [redacted]

Formatted: Different first page
Deleted: THE IMPACT OF SMOKING ON LUMBAR FUSION USING A
Formatted: Font: 14 pt
Deleted: MATRIX
Formatted: Font: 14 pt
Formatted: Font: 14 pt
Formatted: Superscript
Formatted: Superscript
Formatted: Left
Formatted: Italian (Italy)
Formatted: Left
Formatted: Right

Formatted: Right

Abstract

Study Design: Retrospective review of prospectively collected data, as part of an IRB approved, FDA regulated, randomized nonblinded IDE trial of rhBMP-2 matrix for lumbar spinal fusion.

Objectives: The purpose of this study is to examine the influence of smoking on fusion rate and outcome in a large series of patients treated with an rhBMP-2 matrix (AMPLIFY) or iliac crest bone graft as part of a randomized IDE trial for single level lumbar fusion.

Summary of Background Data: Preclinical studies suggest that BMPs are able to reverse the negative influence of nicotine on fusion healing in animal models. It remains unclear if a similar benefit will be seen in humans, and if so, what amount of BMP will be required to achieve that improvement.

Methods: We reviewed the clinical and radiographic records of 144 patients who underwent single level lumbar fusion at one of three spine centers. Clinical outcome measures included ODI, SF-36, back and leg pain scores. Radiographic measures were plain x-ray with flexion/extension views and fine cut CT scan with sagittal and coronal reconstruction.

Results: At 2 years post-op, solid fusion was demonstrated in all 55 nonsmokers in the rhBMP-2 group (100%). Successful fusion was seen in 20 of 21 smokers in the rhBMP-2 group (95.2%). Fusion was achieved in 48 of 51 nonsmokers in the ICBG group (94.1%), but only 16 of 21 smokers (76.2%) in the ICBG group.

Deleted: ¶

Formatted: Line spacing: Double

Formatted: Right

Conclusions: The results of this study suggest that rhBMP-2 enhances fusion rate in cigarette smokers undergoing single level instrumented posterolateral lumbar fusion. Despite the improvement in fusion rate with rhBMP-2, clinical outcomes measures were still adversely affected in smokers.

Key words: Lumbar fusion, rhBMP-2, smoking, bone graft

Key points

Formatted: Bullets and Numbering

- rhBMP-2 enhances fusion rate in smokers
- Clinical outcome measures are worse in smokers
- Smoking abatement prior to lumbar fusion surgery is recommended

Formatted: Right

Mini-abstract:

This study examines the influence of smoking on fusion rate and outcome in patients treated with rhBMP-2 or ICBG as part of a randomized IDE trial for single level lumbar fusion. The results suggest that rhBMP-2 enhances fusion rate in smokers. Clinical outcomes measures were still adversely affected in smokers.

Formatted: Right

INTRODUCTION

Deleted: Introduction:

Cigarette smoking has been identified as an important risk factor for both nonunion and poor clinical outcome in lumbar spine fusion surgery (Glassman, Anderson, Kwon and Brown). In particular, smoking has been shown to markedly diminish fusion rate for the challenging healing environment associated with posterolateral spine fusion procedures. A variety of strategies have been advocated to offset this negative impact of cigarette smoking. They include smoking abatement (Glassman, Whitesides), spinal instrumentation and circumferential fusion. (Mirovski, Kwon) The advent of biologic osteoinductive graft alternatives has introduced a new set of potential options in the management of this difficult clinical problem.

Deleted:

Deleted: Canadian study etc

Recent experience with bone morphogenic proteins (BMP) has documented their potency as an iliac crest bone graft (ICBG) substitute (Burkus 1,Burkus 2, Glassman, Abraham EP, Alexander DI) and generated high expectations for achieving fusion in complex and difficult cases. The question, therefore, is whether BMPs can overcome the adverse effect of smoking on lumbar fusion. Preclinical studies suggest that BMPs are able to reverse the negative influence of nicotine on fusion healing in animal models(Patel, Silcox). It remains unclear if a similar benefit will be seen in humans and, if so, what amount of BMP will be required to achieve that improvement. The purpose of this study is to examine the influence of smoking on fusion rate and outcome in a large series of patients treated with an rhBMP-2 matrix (AMPLIFY) or iliac crest bone graft as part of a randomized IDE trial for single level lumbar fusion.

Deleted: .

Deleted: .

Formatted: Right

Deleted: Methods

METHODS

We reviewed the clinical and radiographic records of 148 patients who underwent single level lumbar fusion at one of three spine centers. Patients were studied as part of an IRB approved, FDA regulated, randomized nonblinded IDE trial of rhBMP-2 matrix for lumbar spinal fusion. It is important to note that the patients were randomized based upon bone graft technique (rhBMP-2 vs. ICBG), not smoking status, and that this is a retrospective review of that data.

Deleted: cmus ICGB

Inclusion criteria for this study were single level lumbar degenerative disc disease in patients over 18 years of age with no greater than Grade I spondylolisthesis. Exclusion criteria included autoimmune diseases, chronic steroid dependence, ODI less than 30, and high risk for noncompliance with study protocol. All patients underwent single level fusion with adjunctive screw/rod instrumentation. All patients were evaluated at a minimum two year follow-up.

Deleted: DDD

Deleted: 50

Posterior lumbar decompression and instrumentation was performed according to a standardized technique based on the IDE study protocol. In the ICGB group, a bone graft harvest was performed through a separate fascial incision over the iliac crest and the quantity of bone obtained was recorded. In the rhBMP-2 group, a 10 cc HA/TCP and collagen compression resistant matrix was combined with 20 mg. rhBMP-2 per side at a final graft concentration of 2 mg/ml. Local bone was excluded as per IDE protocol in both groups.

Deleted: a

Deleted: the

Deleted: rhBMP-2

Clinical outcome measures included ODI, SF-36, back and leg pain scores. Outcome measures were performed at 6 weeks, 3 months, 6 months, and 1 and 2 years post-op. Radiographic

Formatted: Line spacing: Double

Formatted: Right

measures were plain x-ray with flexion/extension views and fine cut CT scan with sagittal and coronal reconstruction. CT scans were performed at 6 months, 1 year and 2 years post-op. Fusion success, evaluated as per the IDE protocol, was defined as bilateral bridging trabecular bone on CT with less than 3 degrees of translation and less than 5 degrees of angulation on flexion/extension views. Fusion was also evaluated, as per the standard of more recent literature, based upon the presence of contiguous bridging bone on fine cut CT scan with coronal and sagittal reconstructions. Both fusion criteria were assessed by independent radiologist's review.

Deleted: Clinical outcome measures included ODI, SF-36, back and leg pain scores. Outcome measures were performed at 6 weeks, 3 months, 6 months, and 1 and 2 years post-op. Radiographic measures were plain x-ray with flexion/extension views and fine cut CT scan with sagittal and coronal reconstruction. CT scans were performed at 6 months, 1 year and 2 years post-op. Fusion was defined by the IDE protocol as contiguous bony bridging

Deleted: on CT scan

Deleted: with less than 3 degrees of motion on flexion/extension views by independent radiologist's review.

Formatted: Right

Deleted: Results

RESULTS

Deleted: 50.5 (

Deleted: 2 for all of the 148 patients)

Deleted: (but CT don't have the exact numbers)

The 148 patients studied included 71 males and 77 females. Mean age was 51.1 (range 18-78) years. Overall, there were 42 smokers and 106 nonsmokers. There were 21 smokers and 55 nonsmokers in the rhBMP-2 group and 21 smokers and 51 nonsmokers in the ICBG group. There were no statistically significant differences in demographic parameters between the four smoking/graft montage subgroups (Table 1).

At 2 years post-op, successful fusion, by IDE protocol criteria, was demonstrated in all 55 nonsmokers in the rhBMP-2 group (100%). Successful fusion was seen in 20 of 21 smokers in the rhBMP-2 group (95.2%). Fusion was achieved in 48 of 51 nonsmokers in the ICBG group (94.1%), but only 16 of 21 smokers (76.2%) in the ICBG group (Figure 1). There was a statistically significant difference between fusion rate in the smoker/ICBG group versus the nonsmoker/ICBG group (p=0.042), but no statistically significant difference between the smoker/rhBMP-2 and nonsmoker/rhBMP-2 groups (p=0.276). There was also a significant difference in fusion rate between all smokers (85.7%) and all nonsmokers (97.2%) (p=0.016). The higher fusion rate in the smoker/rhBMP-2 group versus the smoker/ICBG group was not significant (p=0.184).

Assessment of fusion status based on CT scan criteria demonstrated similar findings. Solid fusion was identified in 54 of 55 nonsmokers (98.1%) and 20 of 21 smokers (95.2%) in the rhBMP-2 group. Solid fusion was documented in 46 of 51 (90.2%) nonsmokers and 16 of 21

Formatted: Right

CHECK DATA (76.2%) in the ICBG group. (Add Figure then renumber) None of the differences were statistically significant.

At every post-op interval, statistically significant improvement from baseline was observed for ODI and SF-36 PCS measures in both smokers and nonsmokers. (Fig. 2) Statistically significant improvement was also seen for VAS back and leg pain scores in both smokers and nonsmokers (Fig. 3). Although improvement was statistically significant in both groups, the mean SF-36, ODI scores were consistently better for nonsmokers (Fig. 4).

At two years post-op, ODI improved a mean 26.4 points in rhBMP-2 nonsmokers, 24.6 points in ICBG nonsmokers, 22.1 points in rhBMP-2 smokers and 21.0 points in ICBG smokers. SF-36 PCS improved a mean 10.2 points in rhBMP-2 nonsmokers, 11.2 points in ICBG nonsmokers, 7.1 points in rhBMP-2 smokers and 11.6 points in ICBG smokers. Improvement in back pain scores was a mean 7.4 points in rh-BMP-2 nonsmokers, 7.5 points in ICBG nonsmokers, 7.9 points in rhBMP-2 smokers, and 6.1 points in ICBG smokers.

Assessment of SF-36 MCS scores revealed a statistically significant improvement at 2 years post-op in nonsmokers but only a trend toward improvement in smokers. Magnitude of SF-36 MCS improvement at 2 years post-op was 7.9 points in rhBMP-2 nonsmokers, 6.1 points in ICBG nonsmokers, 5.5 points in rhBMP-2 smokers and 6.5 points in ICBG smokers. While there were no statistically significant differences in return to work rate comparing rhBMP-2 and ICBG subgroups, nonsmokers were more likely to be working both preoperatively (44.3% vs. 21.4%) (p=0.014) and post-operatively (46.7% vs. 27.5%) (p=0.074).

Deleted: At 2 years postop, solid fusion was demonstrated in all 25 nonsm[... [1]
Deleted: other three groups(the [... [2]
Deleted: nonsmoker/ICBG grou[... [3]
Deleted: (Julie – Have I presente[... [4]
Deleted: There was also a signi[... [5]
Deleted: There was not a statisti[... [6]
Deleted: ¶ [... [7]
Deleted: postop
Deleted: 10.3(
Deleted:)
Deleted: 11.0(
Deleted:)
Deleted: 11.8 (
Deleted:)
Deleted: 7.5 (
Deleted:)
Deleted: 7.2 (
Deleted:)
Deleted: 7.8 (
Deleted:)
Deleted: 6.3 (
Deleted:)
Deleted: postop
Deleted: 6.8 (
Deleted:)
Deleted: 6.3 (
Deleted:)
Deleted: 4.9 (
Deleted:)
Deleted: 5.9(
Deleted:)
Deleted: (Julie – I don't have M[... [8]
Deleted: (
Deleted: in each group between[... [9]
Deleted: nonsmoking
Deleted: nonsmoking
Deleted:)
Deleted: ,
Deleted: postop
Deleted: (p=0.027)
Deleted: ¶

Formatted: Right

DISCUSSION

Cigarette smoking is detrimental in patients undergoing lumbar fusion surgery. Smoking has been associated with decreased fusion rate, diminished clinical outcomes, limitation in functional rehabilitation and poorer overall patient satisfaction (Glassman, Anderson, McGeary, Kwon, Mooney). Most of the attention has been focused on fusion status, particularly for posterolateral fusion procedures where healing is a challenge even in an ideal host.

The relationship between smoking and spinal fusion has been investigated in a variety of animal models (Lee, Daftari, Silcox, Wing, Theiss). The mechanism by which nicotine inhibits fusion healing appears to be multifactorial. The effect of nicotine has been demonstrated to include decreased revascularization of the bone graft (Daftari) and an alteration in gene expression (Theiss). More recently, nicotine receptors with an anti-inflammatory function have been identified (Wang, Miao). Given the known inhibition of spine fusion associated with nonsteroidal anti-inflammatory medications (Glassman 2, Reuben, Park), this pathway may represent an additional mechanism whereby nicotine interferes with fusion healing.

Deleted: second
Deleted:
Deleted:

Importantly, cigarette smoking has been shown to adversely affect clinical outcomes independent of the diminution in fusion rate (Glassman, Anderson, Kwon). Contributing factors may include an accelerated rate of disc degeneration (Battie) or a compromised general health status. Preoperative smoking abatement is the ideal solution because it has been demonstrated to increase fusion rate and to improve outcomes. (Wing, Glassman) Unfortunately, not all patients

Deleted: . Illiteand
Formatted: Highlight

Formatted: Right

Deleted:

are able or willing to quit smoking; therefore, alternative surgical strategies which may offset the negative influence of smoking have been sought.

Initially, pedicle screw fixation was seen as a mechanism to avoid nonunion in complex cases and compromised hosts. Unfortunately, rigid stabilization alone has been insufficient to assure fusion in cigarette smokers (Anderson, Kwon, Hadley). Lumbar interbody fusion has also been advocated to enhance fusion rate in smokers (Mirovsky). Higher fusion rates are routinely reported with interbody grafting techniques, but the accuracy of radiographic assessment has been questioned, (Cook). From a clinical standpoint, the occurrence of surgical nonunion in smokers remains a substantial unresolved issue.

Deleted:

The advent of osteoinductive biologic bone graft alternatives, particularly BMPs, offers another potential tool to achieve fusion in difficult hosts such as cigarette smokers. Preclinical studies have heightened expectations by demonstrating a reversal of the nicotinic effect in rabbits with both rhBMP-2 (Silcox) and rhBMP-7 (Patel). A small human pilot study suggested that rhBMP-7 might generate a similar effect in clinical application (Govender). The authors caution that the study, which included only four smokers, must be considered very preliminary. A study of early fusion rates with high dose rhBMP-2 (2 mg/ml, 20 mg per side) versus ICBG, was also encouraging (Glassman 3). This study, which included 16 smokers, demonstrated a more robust fusion among smokers in the rhBMP-2 group, but the differences were not statistically significant.

Deleted: also

Formatted: Right

In the present study, fusion rate based on plain radiographs and CT scan assessment was analyzed in 148 patients at 2 year follow-up after single level posterolateral lumbar fusion. The data was collected as part of a prospective randomized trial of rhBMP-2 versus iliac crest bone graft. The study cohort, from three spine centers, included 42 smokers and 106 nonsmokers. It is important to recognize that patients were not randomized based upon smoking status, and that this is a retrospective review of a limited subset from the overall IDE trial. Also, the dose and concentration of rhBMP-2 (2 mg/ml, 20 mg per side) is substantially greater than that in commercially available, INFUSE Bone Graft.

Deleted: in

Given these constraints, the use of rhBMP-2 appears to enhance fusion rate in smokers. The fusion rate was 100% in the nonsmoker/rhBMP-2 group, 94.1% in the nonsmoker/ICBG group, 95.2% in the smoker/rhBMP-2 group and only 76.2% in the smoker/ICBG group based on IDE protocol criteria. The difference in fusion rate at 24 months between rhBMP-2 (20/21) and ICBG (16/21) in the smokers did not reach statistical significance (p=0.184). There was, however, a significant difference in fusion rate comparing all smokers (85.7%) and all nonsmokers (97.2%) (p=0.016). A similar disparity in fusion status was demonstrated using a criteria of bridging bone on fine cut CT scan with coronal and sagittal reconstructions, which is the present "state of the art" for fusion assessment (Molinari, Glassman – Initial fusion rates, Burkus – with Dorchak, Cizek).

Deleted: Given these constraints, the use of rhBMP-2 appears to enhance fusion rate in smokers. The fusion rate was 100% in the nonsmoker/rhBMP-2 group, 94.1% in the nonsmoker/ICBG group, 95.2% in the smoker/rhBMP-2 group and only 76.2% in the smoker/ICBG group. The difference in fusion rate at 24 months between rhBMP-2 (20/21) and ICBG (16/21) in the smokers

Deleted: was

Deleted: did

Deleted: (

Deleted: not

Deleted:)

Deleted: reach statistical

Deleted: ly

Deleted: significance

Deleted: t

Deleted:

Deleted: (p=0.042

Deleted: (p=0.184

Deleted:)

Deleted:).

Deleted: (Julie – I'm not sure that this is exactly the comparison that you did.)

Deleted: There was, however,

Deleted: also

Deleted: a significant difference in fusion rate comparing all smokers (85.7%) and all nonsmokers (97.2%) (p=0.016). ¶

Deleted: improvement in

Despite the excellent fusion rate with rhBMP-2, clinical outcomes measures were still adversely affected in smokers. Although the differences were generally not statistically significant,

Formatted: Right

nonsmokers had better ODI and SF-36 PCS scores at all intervals. Nonsmokers were also significantly more likely to be working both pre and post-operatively.

Deleted: postop

The results of this study suggest that AMPLIFY™ rhBMP-2 Matrix (2 mg/ml, 20 mg. per side) may enhance fusion rate in cigarette smokers undergoing single level instrumented posterolateral lumbar fusion. The findings are also consistent with prior studies which indicate that smoking is detrimental to clinical outcome independent of fusion status. (Glassman, Anderson) Therefore, the authors conclude that while rhBMP-2 matrix is a valuable tool for lumbar fusion in smokers, smoking abatement is still the optimal management technique for patients undergoing lumbar fusion surgery.

Deleted: matrix

Deleted: substantially

Deleted: s

Deleted: ,

Deleted: ; however,

Formatted: Right

FIGURE LEGEND

Formatted: Indent: Left: 0 pt, Hanging: 72 pt

Figure 1 Graph showing the percentage of patients fused at 12 months and 24 months among the four subgroups.

Figure 2 Graph showing the mean ODI scores (a) and the mean SF-36 PCS (b) of the four subgroups pre-operatively and at the different follow-up intervals.

Figure 3 Graph showing the mean back pain VAS (a) and the mean leg pain VASS (b) of the four subgroups pre-operatively and at the different follow-up intervals.

Figure 4 Graph showing the mean ODI scores (a) and the mean SF-36 PCS (b) of the all the smokers and nonsmokers in each bone graft group combined.

Fusion with rhBMP-2 in Smokers

Formatted: Right

Table 1. Demographic data of the four subgroups.

Formatted: Line spacing: single

Formatted: Centered

	rhBMP-2 Matrix		ICBG	
	Smokers	Nonsmokers	Smokers	Nonsmokers
N	21	55	21	51
Mean Age (years)	50.8	51.8	48.1	51.7
Mean Weight (lbs)	180.2	189.2	187.7	187.8
Male/Female Ratio	11/10	25/30	13/8	22/29
Workmens' Compensation (%)	4.8	14.5	23.8	13.7
Spinal Litigation (%)	4.8	3.6	4.8	13.7

Formatted: Right

Formatted: Font: Bold

BIBLIOGRAPHY

Glassman SD, Anagnost SC, Parker A, et al: The effect of cigarette smoking and smoking cessation on spinal fusion. Spine 2000;20:2608-2615.

Andersen T, Christensen FB, Laursen M et al: Smoking as a predictor of negative outcome in lumbar spinal fusion. Spine 2001;23:2623-2628.

Kwon BK, Hilibrand AS, Malloy K et al: A critical analysis of the literature regarding surgical approach and outcome for adult low-grade isthmic spondylolisthesis. J Spinal Disord Tech 2005;18:S30-40.

Brown CW, Orme TJ, Richardson HD: The rate of pseudoarthrosis (surgical nonunion) in patients who are smokers and patients who are nonsmokers: a comparison study. Spine 1986;11(9):942-943.

Whitesides TE, Hanley EN, Fellrath RF: Controversies Smoking Abstinence. Is it necessary before spinal fusion? Spine 1994;17:2012-2014.

Mirovsky Y, Halperin N, Anekstein Y et al: Good results of circumferential spine fusion in smokers, using autograft and allograft. Cell and Tissue Banking 2002;3:169-173.

Formatted: Right

Burkus 1 JK, Gornet MF, Dickman CA et al: Anterior lumbar interbody fusion using rhBMP-2 with tapered inter body cages. J Spinal Disord Tech 2002;15(5):337-347.

Burkus 2 JK, Sandhu HS, Gornet MF et al: Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery. J Bone Joint Surg AM 2005;87(6):1205-1212.

Abraham EP, Alexander DL, Bailey SI et al: Evaluation of a new rhBMP-2 formulation in two-level posterolateral lumbar spine fusion. Abstract presented to the American Academy of Orthopaedic Surgeons. 2005;No. 002.

Alexander DL, Abraham EP, Bailey SI et al: A new rhBMP-2 formulation in posterolateral lumbar spine fusion: a prospective, randomized study. Abstract presented to the American Academy of Orthopaedic Surgeons. 2005;No. 003.

Patel TC, Erulkar JS, Grauer JN et al: Osteogenic protein-1 overcomes the inhibitory effect of nicotine on posterolateral lumbar fusion. Spine 2001;15:1656-1661.

Silcox DH, Boden SD, Schimandle JH, et als. Reversing the inhibitory effect of nicotine on spinal fusion using an osteoinductive protein extract. Spine 1998;23(3):291-296.

Formatted: Right

McGeary DD, Mayer TG, Gatchel RJ et al: Smoking status and psychosocioeconomic outcomes of functional restoration in patients with chronic spinal disability. Spine J 2004;4(2):170-175.

Mooney V, McDermott KL, Song J: Effects of smoking and maturation on long-term maintenance of lumbar spinal fusion success. J Spinal Disord 1999;5:380-385.

Lee TC, Ueng SWN, Chen HH, et al: The effect of acute smoking on spinal fusion: An experimental study among rabbits. J Trauma 2005;59(2):401-407.

Daftari TK, Whitesides TE,Heller JG et al: Nicotine on the revascularization of bone graft. Spine 1994;8:904-911.

Wing KJ, Fisher CG, O'Connell JX et al: Stopping nicotine exposure before surgery. Spine 2000;1:30-34.

Theiss SM, Boden SD, Hair G et al: The effect of nicotine on gene expression during spine fusion. Spine 2000;20:2588-2594.

Wang H, Yu MJ, Ochani M et al: Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. Nature 2003;421:384-388.

Miao FJ, Green PG, Benowitz N et al: Central terminals of nociceptors are targets for nicotine suppression of inflammation. Neuroscience 2004;123(3):777-784.

Glassman SD, Rose SM, Dimar JR et al: The Effect of Postoperative Nonsteroidal Anti-inflammatory Drug Administration on Spinal Fusion. Spine 1998;23(7):834-838.

Reuben SS, Ablett D, Kaye R: High dose nonsteroidal anti-inflammatory drugs compromise spinal fusion. Can J Anesth 2005;52:5:506-512.

Park SY, Moon SH, Park MS et al: The effects of Ketorolac injected via patient controlled analgesic postoperatively on spinal fusion. Yonsei Med J 2005;2:245-251.

Battie MC, Videman T, Gill K et al: Smoking and lumbar intervertebral disc degeneration: an MRI study of identical twins. Spine 1991;16:1015-1021.

Hadley M, Reddy S: Smoking and the human vertebral column: A review of the impact of cigarette use on vertebral bone metabolism and spinal fusion. Neurosurgery 1997;41:116-124.

Cook SD, Patron LP, Christakis PM et al: Comparison of methods for determining the presence and extent of anterior lumbar interbody fusion. SPINE 2004;29(10):1118-1123.

Formatted: Right

Formatted: Indent: Left: 0 pt, Hanging: 36 pt

Formatted: Font: 12 pt, Not Bold, No underline

Formatted: Font: 12 pt

Formatted: Font: 12 pt

Formatted: Indent: Left: 0 pt, Hanging: 36 pt

Govender PV, Rampersaud YR, Rickards L et al: Use of Osteogenic protein-1 in spinal fusion: literature review and preliminary results in a prospective series of high-risk cases. Neurosurg Focus 2002;13(6):e4:1-6.

Glassman S, Dimar J, Carreon L, et al: Initial Fusion Rates with rh-BMP-2 and an HA-TCP/Collagen Carrier in Posterolateral Fusion. Spine 2005;30(15):1694-1698.

Formatted: Right

Formatted: Indent: Left: 0 pt, Hanging: 36 pt

Formatted: Font: 12 pt, Not Bold, No underline

Formatted: Justified, Indent: Left: 0 pt, Hanging: 36 pt

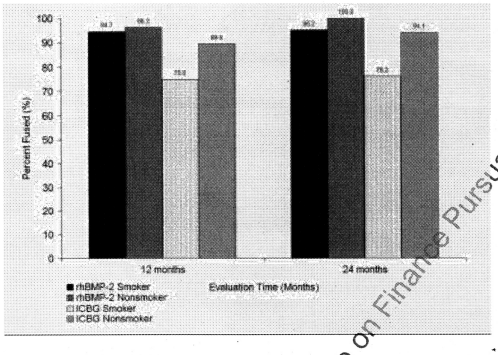
Formatted: Font: 12 pt

Formatted: Font: 12 pt

Fusion with rhBMP-2 in Smokers

Formatted: Right

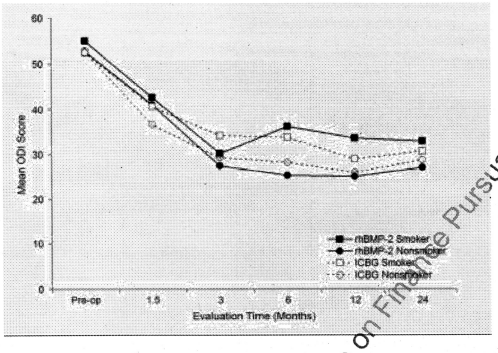
Figure 1



Formatted: Justified, Indent: Left: 0 pt, Hanging: 36 pt

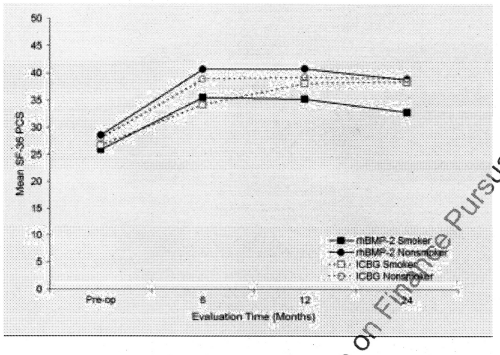
Formatted: Right

Figure 2a



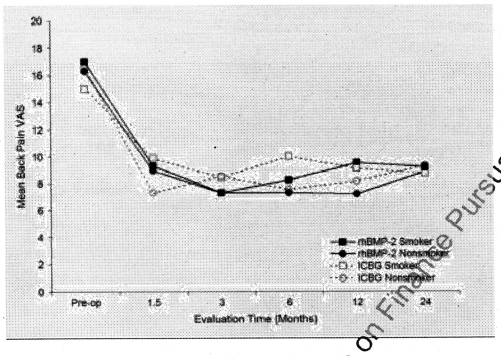
Formatted: Right

Figure 2b



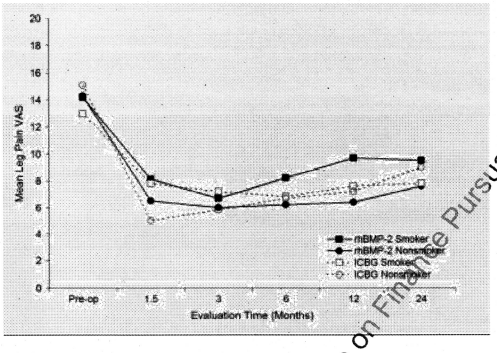
Formatted: Right

Figure 3a



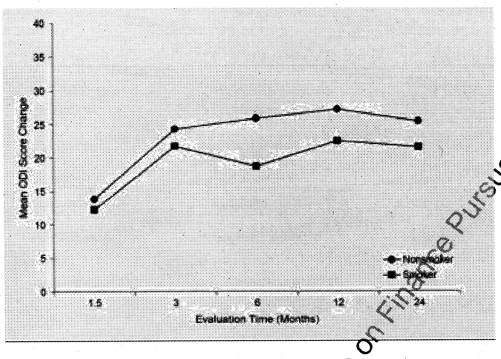
Formatted: Right

Figure 3b



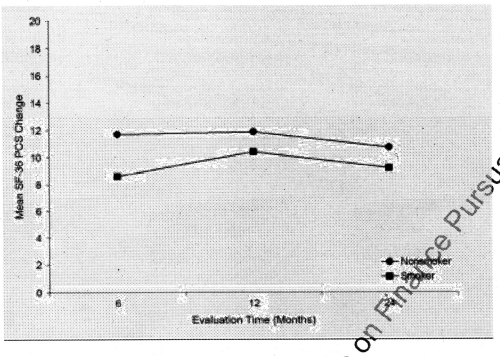
Formatted: Right

Figure 4a



Formatted: Right

Figure 4b



Page 9: [1] Deleted 8/10/2006 9:20:00 AM

At 2 years postop, solid fusion was demonstrated in all 55 nonsmokers in the rhBMP-2 group (100%). Successful fusion was seen in 20 of 21 smokers in the rhBMP-2 group (95.2%). Fusion was achieved in 48 of 51 nonsmokers in the ICBG group (94.1%), but only 16 of 21 smokers (76.2%) in the ICBG group (Figure 1.). There was a statistically significant difference between fusion rate in the smoker/ICBG group versus the

Page 9: [2] Deleted 8/10/2006 9:20:00 AM

other three groups(the p-value only for smoking vs nosmoking in the control group)

Page 9: [3] Deleted 8/10/2006 9:20:00 AM

nonsmoker/ICBG group (p=0.042), but no statistically significant difference between the smoker/rhBMP-2 and nonsmoker/rhBMP-2 groups (p=0.276).

Page 9: [4] Deleted 8/10/2006 9:20:00 AM

(Julie – Have I presented the stat accurately?)

Page 9: [5] Deleted 8/10/2006 9:20:00 AM

There was also a significant difference in fusion rate between all smokers (85.7%) and all nonsmokers (97.2%) (p=0.016). The higher fusion rate in the smoker/rhBMP-2 group versus the smoker/ICBG group was not significant (p=0.184).

Page 9: [6] Deleted 8/10/2006 9:20:00 AM

There was not a statistically significant difference in fusion success when comparing the nonsmoker/rhBMP-2 and nonsmoker/rhBMP-2 groups (p=0.276)

Page 9: [7] Deleted 8/10/2006 9:20:00 AM

Page 9: [8] Deleted 6/27/2006 12:04:00 PM

(Julie – I don't have MCS data in this version. Should I exclude it? You can include it but it does not show a trend in its behavior making it difficult to interpret relative to the smoking/nonsmoking issue?)

Page 9: [9] Deleted **6/27/2006 12:07:00 PM**

in each group between smoking and

From: Bearcroft, Julie, PhD
Sent: Thursday, May 15, 2008 01:08:07 PM
To: JDIMAR[redacted]
CC: 'Leah Carreon'[redacted]; Williams, Celeste
Subject: FW: RE: AMPLIFY Documents

Attachments: Title Page.doc; Table 5.1.doc; Table 4.1.doc; Table 3.1.doc; Table 2.1.doc; Table 1.1.doc; Table 6.1.doc; AMP_Figures.doc; jbjs_Reviewer_03.doc; JBJS_Amplify_Manuscript REVISION_5.doc

John -

Please find the edited documents below in response to the reviewer comments on the AMPLIFY manuscript. Celeste Williams PhD, Technology Manager, has been taking the lead in working with Guorong Ma, Biostatistics, and Steven Kepes, Clinical Affairs, to help augment the manuscript and address the reviewers comments. Celeste is new to Technology Management and hopefully, you will have an opportunity in the near future to meet her personally.

Track changes is used in the attachments so that you can clearly see what changes we are proposing. Within the reviewer letter, there are also a couple sections your input as the physician is definitely required; however, we have often provided some factual information from the database, that you may helpful in responding to their questions. These have been highlighted in yellow for easy identification. If you think of other information that you may need, please let Celeste and I know and we will be happy to work with other groups to help fill in any knowledge gaps.

As we have discussed and I addressed in an earlier email, additional information was added to help address the reviewer's question on diagnoses. To address you concern, I have set up a meeting with some of the key personnel to discuss alternative plans in the event that this does not address the question adequately.

If you think of anything else, please don't hesitate to contact me.

julie

From: Williams, Celeste
Sent: Thursday, May 15, 2008 11:44 AM
To: Bearcroft, Julie, PhD
Subject: RE: AMPLIFY Documents

A Large-scale, Clinical and Radiographic Analysis of an Optimized rhBMP-2 Formulation as an Autograft Replacement in Posterolateral Lumbar Spine Fusion

John R. Dimar II, MD*, Steven D. Glassman, MD*, J. Kenneth Burkus, MD†, Philip W. Pryor‡, MD, James W. Hardacker. MD‡, Leah Y. Carreon MD, MSc*

*Leatherman Spine Center [redacted] Louisville, Kentucky 40202

†The Hughston Clinic, P.C. [redacted] Columbus, GA 31909

‡The Spine Institute [redacted] Carmel, IN 46032

Corresponding Author:

John R. Dimar II MD, Leatherman Spine Center [redacted] Louisville, Kentucky 40202

Phone: [redacted]

Fax: [redacted]

email: [redacted]

Medtronic Confidential –
Provided to the Committee on Finance Pursuant to Senate Rule XXIX

Table 5. Summary of Numbers (%) of Patients Who Reported Any or Possible† Device-Related Adverse Events

Deleted: 6

Adverse Event Category	Any Adverse Event					Possible† Device-Related Adverse Event				
	rhBMP-2 matrix group (n = 239)		ICBG group (n = 224)		p Value *	rhBMP-2 matrix group (n = 239)		ICBG group (n = 224)		p Value *
	Operative	Up to 24 Months	Operative	Up to 24 Months		Operative	Up to 24 Months	Operative	Up to 24 Months	
Patients who had any adverse events	20 (8.4)	209 (87.4)	20 (8.9)	198(88.4)	0.777	0 (0.0)	21 (8.8)	3 (1.3)	35 (15.6)	0.032
Anatomic/ technical difficulty	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	1.000					
Arthritis/Bursitis	0 (0.0)	22 (9.2)	0 (0.0)	17 (7.6)	0.616	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	0.234
Back and/or leg pain	0 (0.0)	104 (43.5)	0 (0.0)	90 (40.2)	0.510	0 (0.0)	4 (1.7)	0 (0.0)	5 (2.2)	0.745
Cancer ◊	0 (0.0)	8 (3.3)	0 (0.0)	2 (0.9)	0.107					
Cardiovascular	2 (0.8)	52 (21.8)	0 (0.0)	54 (24.1)	0.581					
Carpal Tunnel Syndrome	0 (0.0)	9 (3.8)	0 (0.0)	6 (2.7)	0.604					
Death	0 (0.0)	3 (1.3)	0 (0.0)	4 (1.8)	0.717					
Dural Injury	13 (5.4)	14 (5.9)	18 (8.0)	18 (8.0)	0.367	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0.484
Gastrointestinal	0 (0.0)	37 (15.5)	0 (0.0)	33 (14.7)	0.897					
Graft Site Related	0 (0.0)	0 (0.0)	0 (0.0)	17 (7.6)	< 0.001					
Implant Displacement /Loosening	0 (0.0)	1 (0.4)	1 (0.4)	3 (1.3)	0.358	0 (0.0)	1 (0.4)	1 (0.4)	3 (1.3)	0.358
Infection	0 (0.0)	39 (16.3)	0 (0.0)	45 (20.1)	0.335					
Malpositioned Implant	1 (0.4)	5 (2.1)	0 (0.0)	2 (0.9)	0.451	0 (0.0)	4 (1.7)	0 (0.0)	2 (0.9)	0.686
Neurological	0 (0.0)	70 (29.3)	0 (0.0)	60 (26.8)	0.605	0 (0.0)	2 (0.8)	0 (0.0)	1 (0.4)	1.000
Non-Union Failure	0 (0.0)	6 (2.5)	0 (0.0)	19 (8.0)	0.011	0 (0.0)	6 (2.5)	0 (0.0)	18 (8.0)	0.011
Non-Union Outcome Pending	0 (0.0)	5 (2.1)	0 (0.0)	5 (2.2)	1.000	0 (0.0)	5 (2.1)	0 (0.0)	4 (1.8)	1.000
Other	1 (0.4)	70 (29.3)	0 (0.0)	62 (27.7)	0.758					
Other pain	0 (0.0)	29 (12.1)	0 (0.0)	28 (12.5)	1.000					
Respiratory	0 (0.0)	15 (6.3)	0 (0.0)	12 (5.4)	0.697					
Spinal Event	2 (0.1)	17 (7.1)	0 (0.0)	18 (8.0)	0.728					
Trauma	0 (0.0)	67 (28.0)	0 (0.0)	59 (26.3)	0.754					
Urogenital	0 (0.0)	26 (10.9)	0 (0.0)	21 (9.4)	0.646					
Vertebral fracture	3 (1.3)	3 (1.3)	3 (1.3)	5 (2.2)	0.492	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0.484

* p Values were obtained by Fisher's exact test for comparing the rates up to 24 months between the treatment groups.
† Possibly device-related adverse events refer to implant or implant/surgical procedure-related adverse events.
◊ Cancer types in the rhBMP-2 matrix group were basal cell carcinoma, lung, lymphoma, ovarian, pancreatic, prostate, squamous cell carcinoma, and vocal cord; in the ICBG group, cancer types were anal cancer, colon, and lymphoma.

Deleted: 3

Deleted: 7

Table 4. Mean Improvement from Preoperative Score in SF-36 Physical Component Summary Score at Each Follow-Up Interval.

Follow-Up Interval	n (# evaluated)	rhBMP-2 matrix group	ICBG group	n (# evaluated)	P-value * (between treatment Groups)
6 wks ± 2 wks	225	3.8 ± 8.0	4.5 ± 8.7	212	0.733
3 mo ± 2 wks	226	9.5 ± 10.2	8.8 ± 10.0	210	0.122
6 mo ± 1 mo	221	12.9 ± 11.0	11.0 ± 11.1	206	0.020
12 mo ± 2 mo	220	13.7 ± 11.9	11.7 ± 11.4	201	0.020
24 mo ± 2 mo	204	13.2 ± 11.9	12.3 ± 12.3	183	0.175

* P-values comparing outcomes at time interval. Note statistically significant improvement from the pre-operative status was noted in both groups at all time intervals (P<0.001).

Table 3. Mean Improvement from Preoperative Score in Oswestry Disability Index Score at Each Follow-up Interval.

Follow-Up Interval	**n** (# evaluated)	rhBMP-2 matrix Group	**n** (# evaluated)	ICBG Group	P-value * (between treatment groups)
6 wks ± 2 wks	231	12.9 ± 20.1	214	13.9 ± 17.2	0.530
3 mo ± 2 wks	229	22.1± 19.4	213	21.2 ± 17.3	0.127
6 mo ± 1 mo	226	26.0 ± 18.9	206	24.5 ± 17.0	0.100
12 mo ± 2 mo	223	26.9 ± 19.9	203	25.6 ± 19.0	0.119
24 mo ± 2 mo	208	26.7 ± 19.9	183	25.5 ± 20.7	0.111

* P-values comparing outcomes at time interval. Note statistically significant improvement from the pre-operative status was noted in both groups at all time intervals (P<0.001).

Table 2. Surgical Data

Variable	rhBMP-2 matrix Group (n=239)	ICBG Group (n=224)	P-value (between treatment groups)	Absolute Difference (95% CI)
Operative time	2.5 ± 0.09	2.9 ± 1.0	<0.001	(0.23,0.57)
Blood loss	343.1 ± 264.5	448.6 ± 301.7	<0.001	(53.76, 157.24)
Hospital stay	4.1 ± 2.3	4.0 ± 1.9	0.701	(-0.29, 049)

Table 1. Patient Demographics

Characteristic	rhBMP-2 Matrix Group (n = 239)	Iliac Crest Bone Graft Group (n = 224)	P Value*
Age (years), mean (range)	53.2 (20-81)	52.3 (18-86)	0.408
Height (cm), mean (range)	170.4 (149.9-200.7)	169.7 (147.3-198.1)	0.380
Weight (kg), mean (range)	84.9 (47.2-164.2)	85.5 (44.9-141.5)	0.720
Male (%)	108 (45.2)	95 (42.4)	0.575
White (%)	218 (91.2)	203 (90.6)	0.848
Married (%)	176 (73.9)	155 (69.2)	0.457
College education or higher (%)	151 (63.2)	120 (54.1)	0.136
Workers' compensation (%)	27 (11.3)	28 (12.5)	0.774
Involved in litigation (%)	6 (2.5)	15 (6.7)	0.042
Tobacco use (%)	63 (26.4	59 (26.3)	1.000
Alcohol use (%)	90 (37.7)	78 (34.8)	0.562
Working before surgery (%)	83 (34.7)	92 (41.1)	0.180
Previous back surgery (%)	73 (30.5)	62 (27.7)	0.540
Total Waddell signs, no. positive (%)	219 (91.6)	209 (93.3)	0.508
Medication use (%)			
Nonnarcotic	154 (64.7)	140 (62.5)	0.630
Weak narcotic	116 (48.5)	116 (51.8)	0.516
Strong narcotic	38 (16.0)	41 (18.4)	0.537
Muscle relaxant	55 (23.1)	55 (24.7)	0.743

*For continuous variables, p values were derived from analysis of variance for categorical variables, they were derived by Fisher's exact test.

Table 6. Second Surgery Events through 24 Month Follow-Up

Surgical Procedure	Total Events Through 24 Months	
	rhBMP-2 matrix Group (n=239)	ICBG Group (n=224)
Revisions	4 (1.7%)	4 (1.8%)
Removals, Non-Elective	10 (4.2%)	23 (10.3%)
Supplemental Fixations	6 (2.5%)	9 (4.0%)

Definitions:

Revision: A procedure that adjusts or in any way modifies the original implant configuration.

Removals, Non-elective: A procedure that removes one or more components of the original implant configuration without replacement with the same type of device.

Supplemental fixation: A procedure in which additional spinal devices not approved as part of the original protocol are placed.

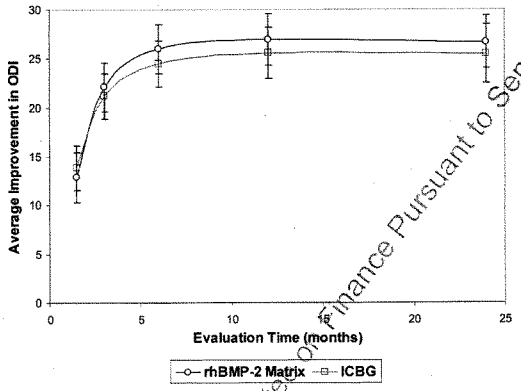


Figure 1. Comparison of mean Oswestry Disability Index scores in the ICBG and rhBMP-2 matrix groups at each follow-up interval. Lower scores represent decreasing disability.

		RHBMP-2	ICBG
SD			
	1.5	20.1	17.2
	3	19.4	17.3
	6	18.9	17
	12	19.9	19
	24	19.9	20.7
SE			
	1.5	2.592	2.305
	3	2.513	2.323
	6	2.464	2.322
	12	2.612	2.614
	24	2.704	2.999

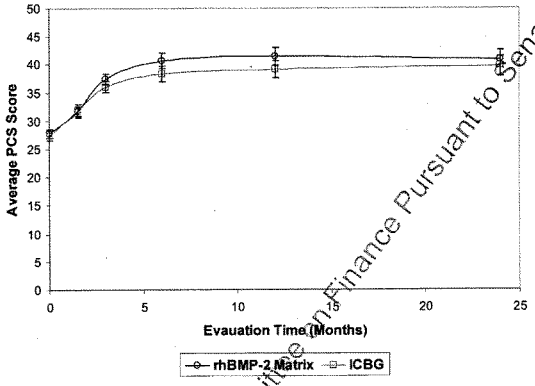


Figure 2. Comparison of mean SF-36 Physical Component Summary scores in the ICBG and rhBMP-2 matrix groups.

SD	RHBMP-2	ICBG
0	6.30	6.70
1.5	7.50	7.70
3	7.50	7.70
6	11.00	10.40
12	12.10	11.10
24	11.70	12.00
SE		
0	0.799	0.877
1.5	0.974	1.037
3	0.974	1.041
6	1.441	1.420
12	1.588	1.535
24	1.594	1.739

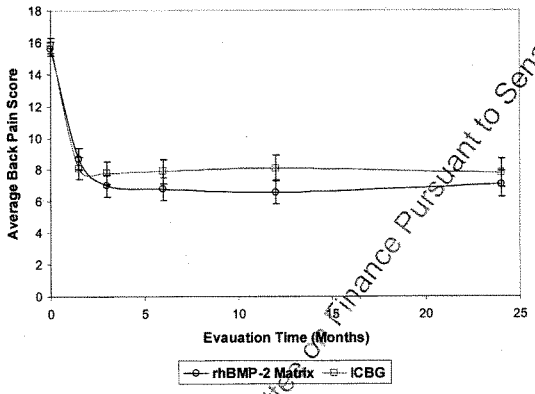


Figure 3. Comparison of mean back pain scores in the ICBG and rhBMP-2 matrix groups.

SD	RHBMP-2	ICBG
0	3.50	3.60
1.5	5.20	5.10
3	5.20	5.40
6	5.60	5.60
12	5.70	5.90
24	5.90	6.30
SE		
0	0.444	0.471
1.5	0.671	0.685
3	0.675	0.725
6	0.730	0.765
12	0.748	0.812
24	0.802	0.913

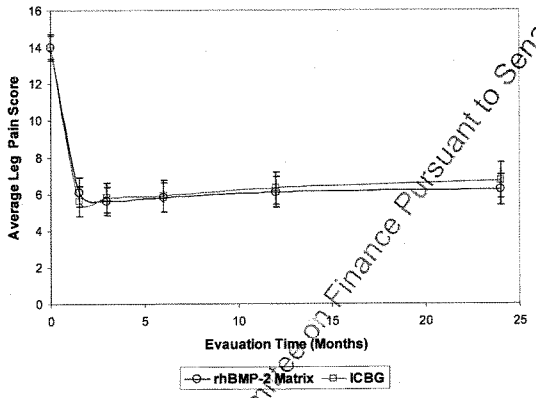


Figure 4. Comparison of mean leg pain scores in the ICBG and rhBMP-2 matrix groups.

		RHBMP-2	ICBG
SD			
	0	4.80	5.30
	1.5	5.90	5.90
	3	5.80	5.90
	6	6.00	6.20
	12	6.30	6.30
	24	6.20	6.70
SE			
	0	0.610	0.696
	1.5	0.761	0.792
	3	0.751	0.792
	6	0.782	0.847
	12	0.827	0.867
	24	0.843	0.971

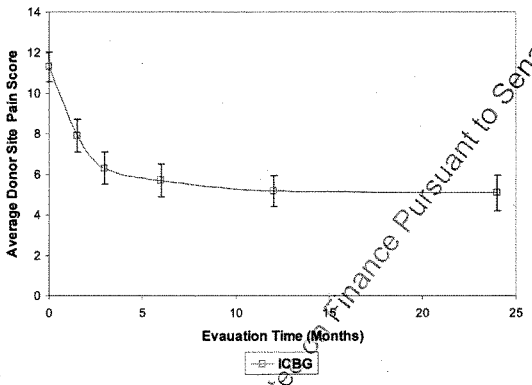


Figure 5. Mean donor site pain scores in the ICBG group.

SD	ICBG
0	5.70
1.5	6.00
3	5.90
6	5.80
12	5.50
24	6.00
SE	
0	0.760
1.5	0.806
3	0.789
6	0.792
12	0.758
24	0.877

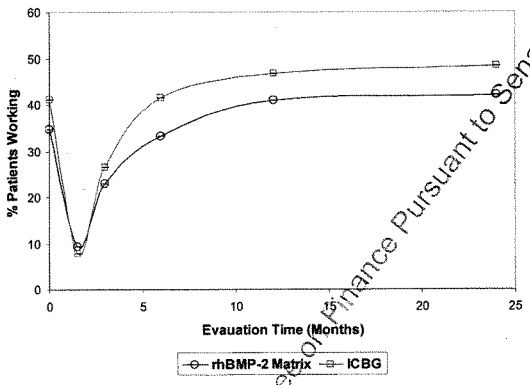


Figure 6. Percentage of subjects working in the ICBG and rhBMP-2 matrix groups.

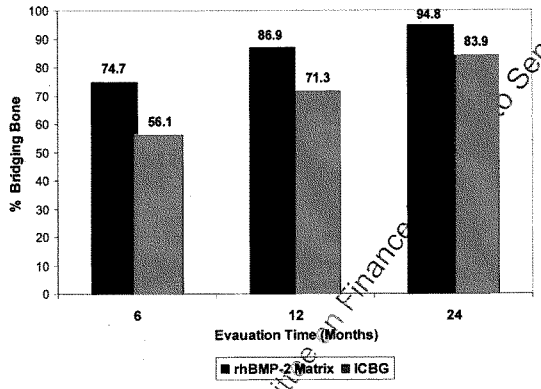


Figure 7. Percentage of subjects with bilateral confluent bridging bone reported by independent radiologists as observed on fine-cut CT scans with reconstructions for the ICBG and rhBMP-2 matrix groups. Differences between groups was statistically significant at all time points ($P<0.001$).

Confidential

The Journal of Bone and Joint Surgery

From: The Journal of Bone and Joint Surgery <[redacted]>
To: jdima[redacted] lcarreon[redacted]
Sent: Wed, 9 Apr 2008 9:21 am
Subject: Revise Manuscript

April 9, 2008 9:17:41

Dear Dr. Dimar:

Your manuscript entitled, "A Large-scale, Level 1, Clinical and Radiographic Analysis of an Optimized rhBMP-2 Formulation as an Autograft Replacement in Posterolateral Lumbar Spine Fusion," number JBJS-D-08-00200, has been reviewed by Consultant Reviewers to The Journal. There was considerable interest in your manuscript. However, our Consultant Reviewers did have questions and concerns that need to be addressed before further consideration can be given to your manuscript. These are listed below.

I hope that you are able to address these concerns in a revised manuscript accompanied by a cover letter outlining your point-by-point response to each concern. Please resubmit to The Journal within 60 days so that a final decision can be made with regard to publication. The due date for revision will be Jun [redacted] 2008 12:00:00:000AM.

When you are ready to resubmit your manuscript, go to the JBJS Web site, http[redacted] your Username and Password[redacted]

Sincerely,
Charles R. Clark, MD
Deputy Editor

Reviewer #1:

The manuscript describes a clinical and radiographic analysis of instrumented single level fusions and associated patient pain assessments over a two year time interval. The authors compared a formulation of tricalcium phosphate/hydroxyapatite/animal collagen (as a carrier) containing recombinant BMP-2 with morselized autogenous iliac crest bone. The general findings of the study were that there were no differences between the two treatment options with respect to fusion and diminution of patient pain at two years. Pain reductions were generally mostly achieved in about 6 weeks with little change (improvement) thereafter. The authors reported that, in general, patients undergoing the harvesting of iliac crest bone continued to experience pain at the two year assessment time interval, lending further evidence of donor site morbidity as a reason for the need for fusion procedures that do not involve such second site bone harvest.

It is accepted that autograft materials represent the "gold standard" for this procedure when wishing to assess the efficacy of some new product (and this study is, after all, a report associated with an FDA monitored clinical study), however, the quality and variability of allograft (specifically ground demineralized bone materials) is perhaps not as variable as the authors imply and it might be worthwhile to have compared the BMP product in this particular study with a formulation containing ground allograft demineralized bone that did not present second site morbidity issues and which would have presented a more balanced combination of bone morphogenetic proteins at the surgical site. The authors might then have been comparing apples to apples.

- This study was a randomized, controlled trial designed to establish equivalent overall success outcomes under a current investigational device exemption (IDE) for the purposes of regulatory approval of a new rhBMP-2 formulation. Under FDA guidance, the control group was chosen to reflect the most proven graft technology, which is iliac crest bone graft (ICBG). Therefore, we report the two-year radiographic results and clinical outcomes using rhBMP-2 matrix as a replacement for autograft in single-level instrumented posterolateral fusions for lumbosacral degenerative disease. Allograft and DBM products are not recommended nor approved for use as an autograft replacement. They are approved for use in conjunction with autograft.

Confidential

Reviewer #2:

Criticisms:
1. The authors are claiming in their conclusion that degenerative lumbar disease is being successfully treated with posterolateral fusion. The word selection here is very dangerous. I suspect that the majority of patients who are being labeled with the very broad-nonspecific diagnosis of "degenerative conditions" actually had specific diagnosis of stenosis and degenerative sponylolisthesis. While the investigators setup the inclusion criteria under the very broad category of "degenerative disease" what was the more specific underlying diagnosis? Most likely stenosis and degenerative spondylolisthesis are the real diagnosis that were being treated successfully. Furthermore, the treatment was included decompression as a major part of the surgical technique, which most likely is the driver in the improvement in leg pain. The danger is that we put out in a landmark paper that "degenerative disease" can be treated with fusion could be incorrectly used as justification for many unnecessary surgeries.

The authors need to provide clear data on these issues. Please include a table that indicates the percent of patients who had stenosis, spondylolisthesis, laminectomy.

- In accordance with the FDA-approved protocol, comprehensive inclusion/exclusion criteria with diagnostic characterizations, that were confirmed radiographically, were used to define the patient populations. The manuscript is updated with more specific inclusion/exclusion criteria information along with a description of the required diagnostic characteristics.

2. Discuss why non-union was considered to be established at 6-12 months when fusion rates were increasing from 6-12 months and even to 24 months?

- Success and failure rates of fusion were both assessed at the defined intervals from 6 – 24 months by independent radiologists per the criteria defined in the manuscript. Nonunion was not 'considered established' at the earlier time points unless it was identified surgically during a second surgical procedure. The manuscript has been updated to reflect this more clearly.

3. Table 5. Adverse events. Define "Spinal Event". Does this include continued radiculopathy or recurrent or new stenosis?

- Spinal event is defined as a stenosis or spondylosis at any level, not only the index surgical level.

The authors don't explicitly talk about the any recurrent stenosis or inadequate

decompression that needed to be addressed? What if any such events were there? If there is none of these issues to be reported then, it needs to be discussed and pointed out to the reader.

- There were no surgical interventions related to recurrent stenosis or inadequate decompressions in any of the patients.
- Adverse effects associated with the two implant treatments as well as the surgical interventions related to the effects are reported in tables 5 and 6.

4. Did the CT-scans show any heterotopic ossification in the surrounding soft-tissue?

- There were no reports of heterotopic ossification in the surrounding soft tissue.

5. What constitutes "non-elective removal"?

- A non-elective removal is defined as a second surgery involving removal of the components of the original implant treatment in which (a) fusion has not developed, (b) is the result of adverse effect, or (c) is not at the discretion of the patient or an investigator. The definitions for all classifications is included in the postscript notes.

6. Why aren't there error bars (95% confidence interval) on the figures?

- The manuscript is updated to include error bars (95% CI) on the figures.

7. Average age of 52-53 seems younger than expected for most patients undergoing posterolateral fusion for stenosis and degenerative spondylolisthesis. Plz help reader understand why this age group is so young.

- Dr Dimar – this requires your input. Some information that may be helpful… Disc herniation was reported in 86.2% of the rhBMP-2 treatment group and 89.7% of the ICBG group, and such symptomatic patients tend to be younger than patients with spinal stenosis or spondylolisthesis.

8. Was prior exposure to rhBMP-2 considered an exclusion criteria?

- YES. The manuscript is updated to provide more details on the inclusion/exclusion criteria.

9. The paper is very poorly proofread. Please proofread carefully before resubmitting the manuscript.

- The manuscript has been proofread to eliminate spelling and grammatical errors.

Specific:
1. Page 3 line 7.
Change "autograft, obtained locally from the iliac crest or from distal sources," to "autograft, obtained locally from decompression, iliac crest, or other sources," This will be more consistent with authors own wording in the methods section and standard verbiage in the literature.

- The manuscript changed to read: "… autograft, obtained locally from decompression, iliac crest, or from distal sources, and different types of allograft [2-5]."

2. Page 3 line 10
Change "solid fusion" to "solid fusion in animal models"

- Manuscript changed to read: " Previous animal studies modeling interbody fusions have demonstrated the ability of recombinant human bone morphogenetic protein (rhBMP-2) to achieve a solid fusion [6-8]."

3. Page 4 line 3-5.
Change "We report...degenerative disease." to "We report the 2 year radiographic and clinical results from this FDA trial."

- Manuscript changed to read: "We report the two-year radiographic results and clinical outcomes using rhBMP-2 matrix or iliac crest bone graft (ICBG) from this FDA-regulated trial in single-level instrumented posterolateral fusions for lumbosacral degenerative disease."

4. Page 4 line 14
"Additional enrollment criteria were a grade 1 or less sponylolisthesis" Does this mean that the patient had to have a grade 1 spondylolisthesis? In other words if patients did not have spondylolisthesis were they excluded from the study? Plz make these issues more clear.

- No, under the inclusion criteria, patients with no greater than grade 1 spondylolisthesis could be included.

5. Page 5 line 1. AMPLIFY rhBMP-2 Matrix is not described. Please indicate that the carrier is a ceramic carrier made primarily of TCP/HA. Indicate the percentage and manufacturer of the ceramic carrier.

- Manuscript updated to read: "The matrix was a bovine Type I collagen carrier containing ceramic particles composed of 15% hydroxyapatite/85% β-tricalcium phosphate formed into a 20 cc block"

6. Page 5 line 12
Was it really "sterile water" or was it "sterile buffer"?

- The rhBMP-2 kit was prepared according to manufacturer's instructions with sterile water, and the manuscript updated to read: " The rhBMP-2 was reconstituted using sterile water into two 5-mL syringes containing 20 mg of rhBMP-2 and an appropriate buffering agent in each. "

7. Page 5 line 18
How was the minimum and maximum times chosen and is it different from infuse?

- The times were chosen according to manufacturer's instructions and were based on evidence in animal studies. Times were comparable to the INFUSE kit

8. Page 6 line 12
Did all investigation sites use GE scanners as suggested by this wording?

- No, only the imaging protocol was standardized. Manuscript updated to read: "(e.g., 2000/350 on GE Scanners)."

9. Page 10 line 13
"ICGB" should be "ICBG"

- Manuscript updated and corrected to "ICBG"

10. Page 11 line 22
"These naturally occurring bone proteins." is a non-sequetor as the previous sentence refers to recombinant BMPs which are not naturally occurring molecules. The recombinant proteins are homodimers created in a lab and may well have different glycosylation. Furthermore the pharmacologic doses of recombinant protein may be very different in its mechanisms to "natural" bone healing.

- Manuscript changed to read: "Bone morphogenetic proteins are naturally occurring bone proteins that stimulate bone healing"

11. Table 4 is confusing. It is not clear that the p values in the 3rd column is referring to the difference between the rhBMP-2 vs ICBG group at each time point. This is made even more confusing as the text below the table refers to differences between preop and followup instead of discussing the across group difference p values in column 3 first.

- The p-values in the column refer to differences between the groups. The table has been updated to clearly state this association.

12. Figure 7. Place p values to indicate difference between groups at each time point.

- Figure title updated to include the P-values.

Reviewer #3:

I appreciate the opportunity to review the manuscript entitled, "A Large-scale, Level 1, Clinical and Radiographic Analysis of an Optimized rhBMP-2 Formulation as an Autograft Replacement in Posterolateral Lumbar Spine Fusion." This is a FDA IDE study comparing the use of rhBMP-2 and iliac crest bone graft in single level instrumented posterolateral fusion. The authors present their 2 year follow-up data that includes several outcome measures. The authors conclude that rhBMP-2 produces earlier and higher fusion rates than iliac crest while eliminating the associated morbidity of harvesting iliac crest bone graft. Overall, I thought that this was an interesting study; however, I have a few comments that I would like to share with the authors. This manuscript would be beneficial to the literature if the authors can address the concerns below.

Introduction:
I would ask the authors to include their hypothesis for the study. I assume that the authors have one for radiographic standards as well as functional outcome. Simply reporting the results is not sufficient enough as it needs to be known that a focused and clear research question was asked.

- Manuscript updated to include a hypothesis.

Materials and methods:
Why was a higher dose chosen than what is commercially available? Three times the available amount might be cost prohibitive?

- A new formulation using an optimized rhBMP-2 concentration … for posterolateral fusions demonstrated excellent results in nonhuman primates [14, 15]. The manuscript updated to read: " dose and concentration of rhBMP-2 used in this study was based upon prior formula validation work in preclinical animal and pilot clinical trials and was higher (2.0 mg/cc for a total dose of 40 mg) than that of commercially available rhBMP-2.."

It is unclear why a decompression was performed in all patients as some patients did not have radicular leg pain and only mechanical back pain. Please clarify.

Dr Dimar – Your input is needed here as well. Again some information you may find helpful…

The surgical plan did not expressly state that decompression was necessary

- The approved IDE protocol required such surgeries with the discarding of bone to allow for a direct comparison of the fusion rates of rhBMP-2 matrix to ICBG.
- Only 2.9% (7/239) of the rhBMP-2 population had no pre-operative leg pain, and 5.4 % (12/224) of the ICBG group.
- Disc Herniation was observed in 86.2% of the rhBMP-2 treatment group and 89.7% of the ICBG group, with decreased disc height reported in 59.8% of the rhBMP-2 group and 60% of the ICBG group.

Page 4, line 22: How was the randomization done? Please explain

Dr Dimar – Your call on whether you want to include additional language in the manuscript. The answer to their question is.

- Under the IDE protocol for regulatory approval, the randomization for the schedule was centrally generated by the study sponsor on a 1:1 basis, stratified by site and using a fixed block size of 4. The randomization mechanism was blind to both investigators and patients to eliminate bias by the investigator. Sealed envelopes were provided by the study sponsor with sequential numbers. Blinding for investigators and patients was maintained through confirmation of eligibility and informed consent. Blinding was not possible after surgery since control patients were required to have a second surgery site for harvesting autograft. Independent radiographic reviewers, however, were blinded to the treatments throughout the study.

Postoperatively did the patients where any type of brace?

- Yes. The Postoperative regimen included wearing external orthosis for ambulation approximately six weeks following surgery. The Material and Methods section updated to clarify this information.

Page 6, Lines 7-9: Did all patients obtain a CT scan at these intervals? In the results section, I suggest reporting the avg time in which the scans were obtained as I am sure there is some variation. It would also help to support the authors conclusion of an earlier fusion.

- The CT scans were performed within ± 2 weeks for the 6 weeks and 3 months time points, and within ± 1 month for all other time points. The manuscript has been updated to include this information.

Page 6, 14-17: Were all of the fusion parameters needed to be considered a

successful fusion? Later in the manuscript, only bridging bone was mentioned as a parameter for fusion success. Please clarify.

- Yes. As outlined in the IDE protocol, fusion is defined as the presence of bilateral, continuous trabeculated bone connecting the transverse processes, translation of less than or equal to 3 mm and angulation of less than 5° on flexion-extension radiographs, and absence of cracking

Results:
In the abstract, the authors state that 463 patients were enrolled in the study at 2 years. However, in the manuscript only 90% or 410 patients were available for assessment. I would ask the authors to further clarify this in that the demographic and surgical data likely included all of the 463 patients while the outcome data only included the 410 patients who reached the 2 year benchmark.

- There were a total of 463 patients at preoperative and surgery/discharge evaluations and varying numbers of patients at subsequent evaluation periods because small numbers of patients were lost to follow-ups. All available, observed data at each time period were reported. We have added information in the summary tables where the numbers of patients evaluated at each period should be clear.

Page 9, lines 2-5: Leg pain scores improved significantly in both groups ($p<0.001$) yet no difference in the 24 month scores ($p=0.214$). Do the authors mean between the two groups at 24 months?

- Yes, in which the preoperative score was used as a covariate.

Page 9, lines 16-22: I assume that this fusion rate was determined on plain radiographs. Correct? The more accurate fusion rate is found in page 10, lines 3-8 with the use of CT scans. I suggest reflecting these values in the abstract instead of those for plain radiographs. Again, were all factors present to be considered a successful fusion. The authors might want to consider reporting those who did not achieve a complete fusion, how many of the parameters did they have (bridging bone, absence of cracking, translation of less than 3mm, etc).

- According to IDE protocol, fusion success was determined primarily with plain film radiography. CTs, although read in every case, were used only to confirm failures identified in plain films or as confirmation in instances where the plain films were indeterminate for bridging bone.

  For the purposes of regulatory approval, the prospectively defined IDE protocol defined the utilization of plain film radiographs to analyze success according to the parameters defined previously (bridging bone, translation $\leq$ 3mm, etc) for fusion; therefore, we report the IDE fusion success rate in the abstract. The CT

values for bridging bone are reported for discussion and reader interpretation purposes.

Page 10, line 19: What is considered non-elective removal of device?

- A non-elective removal involves any surgical removal of the components of the original implant treatment in which (a) fusion has not developed, (b) is not a result of adverse effect, (c) is not at the discretion of the patient or an investigator. The definition is included in the figure containing the chart.

Page 10, lines 17-23 and page 11, lines 1-8: These two paragraphs state similar information. I would suggest revising these paragraphs.

- The manuscript updated and the paragraphs revised to remove the repeated information.

Discussion

I agree that a major limitation is the dosage of the rhBMP-2 used. Perhaps outside the scope of this manuscript, it would be interesting to see a cost analysis of using this higher dosage regimen.

- Dosage and concentration of rhBMP-2 used in this study was based upon prior formula validation work in preclinical animal and pilot clinical trials and was higher (2.0 mg/cc for a total dose of 40 mg) than that of commercially available rhBMP-2.
- A cost analysis study of this higher dosage regimen lies outside the scope of this the FDA-regulated trials.

Page 14, lines 20-22: Again, was bridging bone the only parameter used or were all parameters used to be considered a successful fusion

- All parameters as outlined by the IDE protocol required for a successful fusion.

Other comments:

Title: "Level I" is unnecessary since the Journal has a specific area for this below the abstract.

- Manuscript updated and the term removed from the title.

Abstract: Page 1, line 2: Why is it pivotal? This is not needed.
Before using abbreviations, define them. i.e. FDA IDE, rhBMP-2

- Manuscript updated and full names/descriptions provided before abbreviations.

Introduction: page 3, line 8: Consistent formatting for references

- Manuscript updated to have consistent formatting of the form, [ref #], for all references.

Materials and Methods: page 4 lines 12-13 double negative, consider ... "six months' duration that failed nonoperative care."
***

- Manuscript updated to read: "..six months' duration that failed nonoperative care."

Methodology Editor:
The authors should state their hypotheses.

- Manuscript updated to read "The study was designed to establish equivalent overall success outcomes, which is a combination of radiographic, clinical and safety outcomes for the purposes of regulatory approval of this new rhBMP-2 formulation. We report the two-year radiographic results and clinical outcomes using rhBMP-2 matrix or iliac crest bone graft (ICBG) ..."

The use of a one-sided p-value is unjustified. I appreciate that the authors hypothesized superiority a priori, but it is plausible that either arm could be superior.

- One-sided p-values are reported for comparing treatment group differences in most clinical outcomes in accordance with the prospectively defined IDE protocol for regulatory approval. Surgery data, adverse events, and additional surgical procedures are reported with two-sided p values.

- The reason for defining and using one-sided p-values was that the primary study hypothesis for regulatory approval was a non-inferiority hypothesis. If the non-inferiority was established, then the superiority hypothesis was examined. This methodology is valid since it is a so-called "closed" test.

- For this study, it is reported that most of the outcomes were not significantly different between the treatment groups with the exception of fusion. Two-sided p-values only make the differences less significant. They do not change the significance status. Therefore, the conclusion would not change. Thus, considering none of the study conclusions would change, we reported the one-sided p-values in accordance with the prospectively defined protocol.

Surely a power analysis was performed for the FDA. The power and sample size considerations should be presented in the paper. In particular, what effect size was the study powered to document?

- The sample size determination was based on the primary study hypothesis of the IDE protocol for the primary study endpoint, overall success. A delta value of 10% in success rate was used as the margin, a minimal clinically meaningful difference. The sample size of 208 patients per treatment arm was required with a significance level of 0.05 and a power of 80%. The enrollment target was increased by 10-15% additional patients to account for the potential patients lost in follow-up.

State whether there were crossovers (assigned one regimen, received the other) and how these were handled analytically.

- There were two crossovers in the study. They were analyzed based on the treatment received (i.e., "as-treated" analysis).

Clarify the meaning of the p-values in Figures 3 and 4. Do these refer to differences between groups (ICBG vs BMP)?

Dr Dimar – Since we did not receive the figures, please address this question. If we can help in any way, please let me know. I suspect they reflect differences between the groups at their respective time point.

The discussion is too long.

- In the manuscript, the discussion has been edited.

ABSTRACT

Background: This study reports on the two-year follow-up results from a pivotal, multicenter, prospective, randomized Food and Drug Administration (FDA) Investigational Device Exemption (IDE) study comparing iliac crest bone graft (ICBG) to recombinant human bone morphogenetic protein (rhBMP-2) combined with a carrier consisting of bovine collagen and β-tricalcium phosphate/hydroxyapatite to create a compression resistant matrix for single-level posterolateral fusions.

Methods: 463 patients with symptomatic single-level degenerative disc disease with up to Grade 1 spondylolisthesis were treated with decompression and single-level instrumented posterolateral fusion through an open midline approach. Patients were randomly assigned to either the rhBMP-2 matrix group (239 patients) or the autogenous iliac crest bone graft (ICBG) group (224 patients). Oswestry Disability Index, SF-36, and back and leg pain scores were determined preoperatively and at 1.5, 3, 6, 12 and 24 months postoperatively. Two independent radiologists reviewed radiographs and CT scans taken at 6, 12, and 24 months postoperatively. Fusion was defined as the presence of bilateral, continuous trabeculated bone, translation ≤ 3 mm and angulation ≤ 5° on flexion-extension radiographs, and absence radiolucent lines through the fusion mass.

Results: The mean operative time and blood loss in the rhBMP-2 matrix group was less than in the ICBG group ($P < 0.001$). Average hospital stay was similar in both groups. Both groups showed similar improvements in clinical outcomes and reduced pain. At 24 months, 60% of the ICBG group reported donor site pain. At 24 months, 95.9% in the rhBMP-2 matrix group were fused compared with 89.3% in the ICBG group ($P = 0.014$) and there was a significant difference in nonunion failures reported as adverse events (17 ICBG vs. 6 rhBMP-2 matrix, p=0.017). Also,

Deleted: FDA IDE

Deleted: rhBMP-2

Deleted: .

Deleted: ICBG

Deleted: ≤

Deleted:

Deleted: ¶

Deleted: <

Deleted: 23

Deleted: . There

Deleted: no

Deleted: in the percentage of patients who had

Deleted: number

Deleted:

Deleted: of surgeries for

Deleted: nonunion failures.

Deleted: between the groups (13 ICBG vs 6 rhBMP-2 matrix, p=0.0999).

Deleted:

Deleted: However

the number of patients requiring second surgeries was higher in the ICBG group compared to the rhBMP-2 matrix group (36 vs. 20).

Conclusions: Using rhBMP-2 decreases operative time and blood loss and produces earlier and higher fusion rates than ICBG in posterolateral lumbar fusion. Clinical outcomes are similar to those with ICBG. Thus, the need for harvesting iliac crest bone is eliminated along with the morbidities associated with the harvest procedure.

Level of Evidence: Level I

INTRODUCTION

Posterolateral fusion combined with pedicle instrumentation is frequently employed for the treatment of degenerative disease of the lumbosacral spine. Various indications include degenerative disc disease, spondylolisthesis, and instability. The results of instrumented posterolateral fusions in large clinical studies have shown varying rates of fusion and clinical outcomes [1-5]. Traditional sources of grafting material include autograft, obtained locally from decompression, iliac crest, or from distal sources, and different types of allograft [2-5].

Previous animal studies modeling interbody fusions have demonstrated the ability of recombinant human bone morphogenetic protein (rhBMP-2) to achieve a solid fusion [6-8]. Recently, prospective, randomized human clinical studies demonstrated superior fusion rates and clinical outcomes with rhBMP-2 and a collagen sponge (INFUSE® Bone Graft, Medtronic Sofamor Danek, Memphis, TN) versus autograft when using either cortical bone dowels or threaded interbody cages in anterior lumbar interbody techniques [9,10]. Nonhuman primate studies have demonstrated that rhBMP-2 delivered on an absorbable collagen sponge required the use of adjunctive osteoconductive bulking agents to produce successful posterolateral spine

Deleted: revision
Deleted: was
Deleted: , p=0.0148
Deleted: the
Formatted: Not Superscript/ Subscript
Deleted: additional

fusion [11-13]. A new formulation using an optimized rhBMP-2 concentration and a compression resistant carrier developed specifically for posterolateral fusions demonstrated excellent results in nonhuman primates [14, 15]. A randomized human pilot study documented the ability of a new rhBMP-2 formulation consisting of a 2 mg/cc rhBMP-2 concentration combined with biphasic calcium phosphate granules versus autograft in achieving a successful posterolateral fusion [16]. The study demonstrated a 40% fusion rate in the autograft group versus a 100% fusion rate with the rhBMP-2 group when evaluated by radiographs and CT scans. Although the authors cited several deficiencies, most notably the lack of a 24-month follow-up on all subjects, the study presented evidence of the feasibility of rhBMP-2 in achieving a successful radiographically confirmed fusion in humans. Currently, a prospective randomized Food and Drug Administration (FDA) Investigational Device Exemption (IDE) study is ongoing comparing iliac crest bone graft (ICBG) to rhBMP-2 combined with a compression resistant carrier consisting of bovine collagen and β-tricalcium phosphate/hydroxyapatite (rhBMP-2 matrix) for single-level posterolateral fusions. The IDE clinical trial was designed as a one-sided non-inferiority trial with a secondary hypothesis of superiority. The study was designed to establish equivalent overall success outcomes, which are a combination of radiographic, clinical and safety outcomes, for the purposes of regulatory approval of the new rhBMP-2 formulation. We report the two-year radiographic results and clinical outcomes using rhBMP-2 matrix or iliac crest bone graft (ICBG) from this FDA-regulated trial in single-level instrumented posterolateral fusions for lumbosacral degenerative disease.

Deleted: 14

Deleted: A small, prospective, randomized, clinical investigation also demonstrated excellent posterolateral fusion results for rhBMP-2 combined with biphasic calcium phosphate as compared to iliac crest autograft [16].

Deleted: study

MATERIALS AND METHODS

For a delta value of 10% in success rate, a significance level of 0.05 and a power of 80%, the sample size was determined to be 208 patients per treatment arm. Four hundred sixty-three patients were treated in this multi-center, prospective, randomized, controlled FDA-approved IDE study. Sixty-three spine surgeons performed surgery in the study at 29 investigational sites. Randomization was performed centrally on a one-to-one basis and stratified by site. Surgeons and patients were blinded to the randomization schedule.

The indications for surgery were symptomatic, single-level lumbosacral degenerative disease from L2/3 to L5/S1 of at least six months' duration that failed nonoperative care. Clinical symptoms included low back pain with or without radicular leg pain. Degenerative disc disease was confirmed by patient history, objective physical findings and neuroradiographic studies. Radiographic studies confirmed one or more of the following: instability (angulation ≥ 5° and/or translation ≥ 4 mm), osteophyte formation, decreased disc height, thickening of ligamentous tissue, disc degeneration or herniation, and facet joint degeneration. Additional enrollment criteria were at least 18 years old, a grade 1 or less spondylolisthesis, no previous fusion, and a minimum pre-operative Oswestry Disability Index score of 30. Exclusion criteria included a previous attempt at fusion at the intended surgical level, condition which requires medications that may interfere with fusion, significant osteoporosis (less than 2 standard deviations below normal on DEXA bone densitometry scan), autoimmune disease, previous exposure to injectable collagen or any rhBMP, endocrine or metabolic disorder known to affect osteogenesis, malignancy, infection, pregnancy, or the inability to harvest graft because of a previous surgical procurement.

All patients were treated with a single-level instrumented fusion using CD Horizon® (Medtronic Sofamor Danek, Memphis, TN USA) pedicle screw and rod instrumentation. Patients

Deleted: had not responded to

Deleted: were

Deleted: were performed to

were randomly assigned to one of two groups: the control group who received autogenous iliac crest bone graft (ICBG) or the investigational group who received rhBMP-2 matrix (AMPLIFY rhBMP-2 Matrix™, Medtronic Sofamor Danek, Memphis, TN, USA). The dose and concentration of rhBMP-2 used in this study was based upon prior formula validation work in preclinical animal and pilot clinical trials and was higher (2.0 mg/cc for a total dose of 40 mg) than that of commercially available rhBMP-2, or INFUSE® Bone Graft (Medtronic Sofamor Danek, Memphis, TN, USA), which is 1.5 mg/cc for a total dose of 12 mg per large kit. The matrix was a bovine Type I collagen carrier containing ceramic particles composed of 15% hydroxyapatite/85% β-tricalcium phosphate formed into a 20 cc block. This composition was specifically chosen based on histological evidence in animal demonstrating that this composition of ceramic could resorb at a rate comparable to new bone formation [14].

A standard open posterior approach was used for both the ICBG and rhBMP-2 matrix groups. Bone graft from the iliac crest in the ICBG group was obtained in a standard open fashion through a separate fascial incision. The bone graft was morselized and placed in the lateral gutters on the decorticated bony surface of the transverse processes and along the pars interarticularis. As required by the protocol, any local bone graft obtained from the decompression was discarded in both groups. Patients were instructed to wear an external orthosis for ambulation approximately six weeks post-operatively.

The rhBMP-2 was reconstituted according to manufacturer's instructions using sterile water into two 5-mL syringes containing 20 mg of rhBMP-2 and an appropriate buffering agent in each. The matrix measuring 4.7cm in length x 3.8cm in width x 1.1cm in thickness was cut lengthwise with a scalpel into two equal pieces (1.9 cm in width) of 10 cc each using a cutting template. The reconstituted rhBMP-2 from each syringe was then uniformly distributed to each

piece of the matrix producing a 2 mg/cc concentration of rhBMP-2 in the matrix. The rhBMP-2 matrices were allowed to stand for a minimum of 5 minutes and were implanted within 60 minutes after preparation. In no instance was the matrix of insufficient length to span the transverse processes in a single-level fusion.

Clinical data were collected preoperatively and postoperatively at 6 weeks, 3 months, 6 months, 12 months, and 24 months. The validated outcome instruments used were the Oswestry Low Back Pain Disability Index (ODI) [17], the Medical Outcomes Study Short Form 36 (SF-36) [18,19], back pain and leg pain scores and, in the ICBG group, graft site pain scores. Patients were asked to rate the frequency and intensity of their pain on a scale of 0 to 10 and the scores were summed to derive a 20-point numerical rating scale. Data on work status, patient satisfaction, and adverse events were also recorded. Results of neurological examinations, which included motor function, sensory function, reflexes, and straight leg raise, were recorded.

Plain radiographs, lateral flexion and extension radiographs, and computed tomography (CT) scans with sagittal and coronal reconstructions were used to evaluate the fusion in both groups at 6, 12, and 24 months after surgery. Films were required to be obtained within a specific time window around each collection time point, for example, within ± 1 month of the scheduled follow-up. The CT imaging protocol consisted of 1 millimeter continuous nonoverlapping axial slices that were taken without bone filter. The window and level settings were set to optimize trabecular bone detail (e.g., 2000/350 on GE Scanners). The field of view was made as small as possible but still encompassed the complete vertebra in between and including the transverse processes.

Fusion success was defined by the IDE protocol as the presence of bilateral, continuous trabeculated bone connecting the transverse processes, translation of less than or equal to 3 mm

and angulation of less than 5° on flexion-extension radiographs, and absence of cracking, as evidenced by radiolucent lines through the fusion mass. All parameters must be met in order to be considered a fusion success. The radiographs and computed tomography scans were evaluated by two independent radiologists who were blinded to which patient group they were evaluating and a third adjudicate reviewer was used as needed.

The analysis dataset consisted of all patients who were surgically treated. Statistical comparisons were primarily based on the observed and recorded follow-up data. A small number of patients required an additional surgical procedure (removal, revision, or supplemental fixation); their outcomes were recorded as a treatment failure. For other outcome variables, the last observations taken before the additional surgical procedures or interventions were carried forward using the Last Observation Carried Forward technique for all future evaluation periods.

For comparing patients' demographic and preoperative measures, p values for continuous variables were from the analysis of variance, and those for categorical variables were from Fisher's exact test.

For comparing success or event rates, Fisher's exact test was used for assessing a superiority hypothesis. For comparing continuous outcome measurements such as the Oswestry score, analysis of covariance was used, with the preoperative score as the covariate. For assessing the statistical significance of postoperative improvement in outcome scores from preoperative status within each treatment group, a paired t test was used.

One-sided p values were reported for comparing treatment group differences in most clinical outcomes because the study hypotheses defined in the investigational device exemption protocol for those outcomes were one sided, except for surgery data, adverse events, and

Deleted: 2 independent

Deleted: validating

Deleted: A

Deleted: the

additional surgical procedures, as well as for days to return to work, for which two-sided p values were reported.

RESULTS

Of the 463 patients enrolled at surgery and discharge evaluation, 410 (90%) of expected subjects were available for assessment at two years after surgery: 194 in the ICBG group and 216 in the rhBMP-2 matrix group. At all time points, at least 90% of expected patients were evaluated, in which data was collected within the following windows: 6 wks ± 2 wks, 3 mo ± 2 wks, 6 mo ± 1mo, 12 mo ± 2 mo and 24 mo ± 2 mo. Seven patients had died due to causes unrelated to surgery during the two-year follow-up. Randomization resulted in a similar distribution of baseline characteristics in the two study groups as shown in Table 1.

The average surgical time for the ICBG patients was significantly longer, than that observed in the rhBMP-2 matrix group with a difference of 0.4 hours ($P < 0.001$, 95% CI 0.23 to 0.57 hours) (Table 2). The average blood loss was 448.6 mL for the ICBG patients, which was significantly greater ($P < 0.001$, 95% CI 53.76 to 157.24 mL) than the 343.1 mL blood loss observed with the rhBMP-2 matrix group. The average volume of bone graft obtained from the iliac crest in the ICBG patients was 36mL. There was no statistically significant difference in length of hospital stay between the two groups ($P = 0.701$, 95% CI -0.29 to 0.49 days). No surgeries were abandoned because of technical problems, and there were no unanticipated intraoperative complications related to the fusion procedure.

The ODI scores were similar in both groups over all time intervals (Fig. 1) and showed statistically significant improvement when compared with preoperative scores ($P < 0.001$) in both the ICBG and rhBMP-2 matrix groups at all time intervals (Table 3). The SF-36 Physical

Deleted: A p value of less than 0.05 was considered to be statistically significant.¶

Deleted: four hundred ten

Deleted: 2

Deleted: ICBG

Deleted: GB

Deleted: 1

Deleted: 2.9 hours, which was significantly

Deleted: ($P < 0.001$)

Deleted: the 2.5 hours

Deleted: 2

Deleted: . There

Deleted: 3

Component Summary (PCS) scores were similar in both groups at all time intervals (Fig. 2) and showed statistically significant improvement when compared with preoperative scores ($P < 0.001$) in both the ICBG and rhBMP-2 matrix groups (Table 4).

Average back pain scores for the ICBG and rhBMP-2 matrix groups improved significantly from preoperative scores of 15.8 and 15.6 to 7.8 and 7.1 at 24 months, respectively ($P < 0.001$, 95% CI of 7.61 to 9.39 for rhBMP-2 and 7.02 to 8.98 for ICBG). Both groups showed similar improvements over all time intervals (Fig. 3) with no statistically significant difference between groups in the 24-month average back pain scores ($P = 0.145$, 95% CI -0.51 to 1.91). Leg pain scores after surgery in both the ICBG and rhBMP-2 matrix groups improved in a similar manner over all time intervals (Fig. 4). The average leg pain score improved from 14.0 in both groups, to 6.7 in the ICBG group and 6.2 in the rhBMP-2 matrix group at 24 months ($P < 0.001$, 95% CI of 6.78 to 8.82 for rhBMP-2 and 6.13 to 8.47 for ICBG). There was no statistically significant difference between groups in the 24-month leg pain scores ($P = 0.214$, 95% CI -0.79 to 1.79).

Pain resulting from bone harvest in the ICBG group was measured using donor site pain scores. The mean pain score at discharge of 11.3 improved to 7.9 at 6 weeks after surgery and to 6.3 at 3 months postoperatively. There was minimal improvement at subsequent follow-up periods up to 24 months. A large number of patients in the ICBG group (60%) still had persistent donor site pain, with a mean pain score of 5.4 at 24 months after surgery (Fig. 5).

Of the 224 subjects in the ICBG group, 41.1% were working before surgery. At 24 months, 48.4% were able to return to work (Fig. 6). Of the 239 rhBMP-2 matrix group patients, 34.7% were working before surgery. After surgery, 42% of the subjects were working at 24 months.

Deleted: 4

Deleted: ir

Deleted: among

Independent radiologists determined fusion utilizing the plain film radiographs primarily according to the IDE protocol-defined analysis. In patients in whom the plain films did not exhibit bridging bone, CT scans were then used to determine the presence of bridging bone. Assessment in this manner showed that statistical differences in fusion success occurred at two time intervals between the two groups. At 6 months, 79.1% of patients in the rhBMP-2 matrix group and 65.3% in the ICBG group achieved fusion success ($P = 0.002$). At 12 months, 87.5% in the rhBMP-2 matrix group had achieved fusion success compared with 82.5% in the ICBG group ($P = 0.107$). At 24 months, 95.9% in the rhBMP-2 matrix group had achieved fusion success compared with 89.3% in the ICBG group ($P = 0.014$).

Fine-cut CT scans with sagittal and coronal reconstructions showed that 74.7% of the subjects in the rhBMP-2 matrix group and 56.1% in the ICBG group had evidence of bilateral bridging bone at 6 months ($P < 0.001$). At 12 months, 86.9% of subjects in the rhBMP-2 matrix group and 71.5% in the ICBG group had evidence of bilateral bridging bone ($P < 0.001$). At 24 months, the rate was 94.8% in the rhBMP-2 group compared with 83.9% in the ICBG group ($P \leq 0.001$) (Fig. 7).

Adverse events showed no significant differences between both study groups for all event categories (Table 5) with the significant exception of 17 graft site related events in the ICBG group ($P < 0.001$). There were no noted adverse events identified that were specifically attributed to the use of rhBMP-2 matrix in the study group. There were no reports of heterotopic ossification in the surrounding soft tissue. The incidence of operative adverse events was not significantly different between the groups: 8.4 % (20/239) in the rhBMP-2 matrix group and 8.9% (20/224) in the ICBG group. Serious adverse events such as death, neurologic injury and cardiovascular injury demonstrated no significant differences between the two groups.

Deleted: Using plain radiographs and CT scans,

Deleted: ,

Deleted: , whereby assessment by plain films was considered first.

Deleted: 4

Deleted: 3

Deleted: 8

Deleted: –

Deleted: 5

Deleted: There was at least one adverse operative event observed in the 8.4 % (20/239) rhBMP-2 matrix group which was not significantly different when compared to the 8.9% (20/224) incidence in the ICGB group.

Deleted: There were no noted adverse events identified that were specifically attributed to the use of rhBMP-2 matrix in the study group.¶

The need for a second surgery overall following the index surgery showed no significant differences (Table 6). The number of patients requiring a second surgery following the index surgery was statistically higher in the ICBG group compared to the rhBMP-2 matrix group (36 control vs. 20 investigational, P=0.0148). The most common second surgery classification in both groups was non-elective removal of the device at an incidence of 4.2% (10/239) in the rhBMP-2 matrix group and 10.3% (23/224) in the ICBG group. There were no surgical interventions related to recurrent stenosis or inadequate decompressions in any of the patients. In the ICBG group, 7.6% (17/224) of the patients had a surgically identified nonunion at the second surgery compared to only 2.5% (6/239) in the rhBMP-2 matrix group (P=0.017).

DISCUSSION

The guiding principle for the surgical treatment of painful or unstable lumbosacral degenerative spinal disease remains the ability to achieve a solid fusion. Although autologous ICBG is the gold standard, the morbidity associated with graft harvest has led surgeons to seek viable alternatives, such as allografts, ceramics, and various types of autologous growth factors [20-24]. These graft substitutes have demonstrated great variability in achieving fusion with the greatest success achieved when used in addition to the iliac crest bone graft and not as an alternative to iliac crest bone graft. Additionally, they present their own unique problems including decreased success of fusion [25], limited availability, and the potential for rejection or immunologic reaction [21, 22]. Consider editing/moving to introduction for reduction in length

The development of osteoinductive bone grafting options has resulted in the clinical availability of recombinant human bone morphogenetic protein (rhBMP-2 and rhBMP-7) for

Deleted: 6

Deleted: vs

Deleted:

Deleted:

Deleted: Of the

Deleted:

Deleted: revision surgery

Deleted: there were

Deleted: 5.8

Deleted: 3

Deleted: who upon instrumentation removal had a surgically identified nonunion compared to only

Deleted: for

Deleted: p

Deleted: 0999)

Deleted: The number of patients requiring a second surgery following the index surgery was statistically higher in the ICBG group compared to the rhBMP-2 matrix group (36 control vs 20 investigational, p=0.0148). The most common second surgery classification in both groups was non-elective removal of the device with an incidence of 4.2% (10/239) in the rhBMP-2 matrix group and 10.3% (23/224) in the ICBG group. In the ICBG group, 5.8% (13/224) of the patients had a surgically identified nonunion at the second surgery, compared to only 2.5% (6/239) in the rhBMP-2 matrix group. This difference was not statistically significant (p=0.0999).

Formatted: Highlight

Formatted: Highlight

spinal fusion [26]. Bone morphogenetic proteins are naturally occurring proteins that stimulate bone healing via a cascade mechanism that results in the differentiation of primitive mesenchymal cells and preosteoblasts into osteoblasts that promote bone formation and, ultimately, healing [27]. The effectiveness of rhBMP-2 in achieving a solid interbody fusion has been demonstrated in numerous experimental animal studies [6-8]. Subsequently, clinical trials have demonstrated similar fusion rates and clinical outcomes when ICBG was compared with rhBMP-2 combined with a collagen sponge carrier (INFUSE® Bone Graft) and a lordotic threaded interbody cage (LT-CAGE®) [9]. As a result of these findings, the FDA approved the use of rhBMP-2 as an iliac crest bone graft replacement for lumbar interbody fusion in 2002.

Consider editing/moving to introduction for reduction in length

Moved to introduction for space. As part of an ongoing FDA-regulated IDE study, in which a new rhBMP-2 formulation was evaluated for use in single-level posterolateral fusions combined with pedicle screw and rod instrumentation, We used a specifically designed carrier that combines β-tricalcium phosphate and hydroxyapatite granules with a collagen matrix. This combination provided significant resistance to compression by the musculature when placed in the lateral gutters while providing a high binding affinity for rhBMP-2 and a suitable resorption profile to optimize bone formation. It is also important to emphasize that in this study we used a higher concentration of rhBMP-2 (2.0 mg/cc versus 1.5 mg/cc) than was used in previous clinical studies with an absorbable collagen sponge carrier.

Although local bone graft is rarely discarded in clinical practice, the quality and quantity of local bone grafts are highly variable. In this study, local bone graft was discarded in both treatment groups to allow for a direct comparison of the fusion rates of the rhBMP-2 matrix to ICBG without local bone graft as a confounding variable.

Deleted: These

Deleted:

Deleted: r

Deleted: bone

Deleted: A recent randomized human pilot study evaluated a new rhBMP-2 formulation consisting of a 2 mg/cc concentration combined with biphasic calcium phosphate granules versus autograft in achieving a successful posterolateral fusion [16]. The study demonstrated a 40% fusion rate in the autograft group versus a 100% fusion rate with the rhBMP-2 matrix group when evaluated by radiographs and CT scans. ODI and SF-36 outcome measures demonstrated significant but similar improvement in both groups at the end of the study. Although the authors cited several deficiencies—most notably the lack of a 24-month follow-up on all subjects—the study presented evidence of the feasibility of rhBMP-2 in achieving a successful radiographically confirmed fusion in humans.

Formatted: Highlight

Deleted: ¶

Deleted: rhBMP-2 is now being

Deleted: . We

Deleted: reviewed our two-year clinical outcomes and fusion rates based on CT scans in subjects.

Deleted: s

Perioperative measures indicated improvements in operative time and blood loss, which were significantly less in the rhBMP-2 matrix group than in the ICBG group. The length of hospital stay was the same for both groups. Because of the nature of adverse event reporting in FDA-regulated trials, most patients experienced an adverse event over the two-year course of the study. There were no statistical differences in adverse events with the exception of iliac crest graft-related complications which occurred in 17 (7.4%) of control patients.

An equally important measure of the success of a fusion procedure, beyond the radiographic evidence of fusion, is how the patient feels and functions after surgery. The use of validated patient-based clinical outcome measures such as the Oswestry Disability Index and the SF-36 provide a self-assessment of the patient's functional improvement rather than the clinician's perception [17]. Most of the improvement in ODI scores and SF-36 PCS occurred within the first three months after surgery, in both groups. This improvement was maintained through the subsequent follow-up periods up to 24 months. The improvement in PCS at 24 months in both groups was well above the 5.41 point threshold in the literature for clinically significant improvement [28]. The decrease in ODI scores at 24 months in both groups was greater than 25 points, which is also above that necessary to demonstrate treatment efficacy [29, 30].

Most of the improvement in back pain and leg pain scores was noted within the first 6 weeks after surgery, and was maintained throughout the entire follow-up period of 24 months. The 8.4-point average decrease in back pain in the rhBMP-2 matrix group and 8.1-point average decrease in the ICBG group indicates a clinically significant diminution in back pain after surgery. The 7.3-point average decrease in leg pain in the rhBMP-2 matrix group and 6.6-point average decrease in the ICBG group indicates a clinically significant diminution in leg pain after

surgery. More importantly is that two years after surgery, more than half of the patients in the ICBG group still complained of pain from the donor graft site.

The rates of fusion in previously published articles vary widely from 60% to 98%. This may be due to the use of plain radiographs with flexion-extension views which are known to be inaccurate with error rates estimated from 20 to 40% [31-33]. When fusion success was determined using the IDE-protocol-defined criteria as specified in the methodology, the rhBMP-2 matrix group had significantly higher fusion success rates compared to the ICBG group at 6 and 24 months postoperatively. Using thin-cut CT scans only, bilateral bridging bone was reported by the independent radiologists significantly more often in the rhBMP-2 matrix group than in the ICBG group at all 3 time points.

Deleted: blinded

In a separate study derived from a subset of this patient population, rhBMP-2 matrix produced a more robust fusion mass than ICBG as judged from CT scans alone [20]. The use of fine-cut CT scans with sagittal and coronal reconstructions may increase the ability to demonstrate the robustness of the fusion and the presence of bilateral confluent bridging bone.

A previous report [34] in a prospective study of patients undergoing single level posterolateral fusion had shown no correlation between fusion success and clinical outcomes with an average follow-up of two years. However, long-term follow-up averaging over 7 years of the same patient group did result in a correlation between the two [35]. Patients diagnosed with spinal stenosis and degenerative spondylolisthesis did benefit from a solid arthrodesis with statistical improvements in back and leg pain compared to patients with pseudoarthrosis. Perhaps a longer-term follow-up of this series will be able to detect clinical differences between these groups as a consequence of the radiographic differences detected short term.

At the 24-month follow-up period, there were twice as many patients in the ICBG group with established nonunions. Similarly, there were twice as many non-elective surgical procedures to remove hardware in the ICBG group. Possible reasons for a higher number of patients undergoing removal of the instrumentation in the ICBG group included: (1) the potential for surgeon bias (*i.e.* they expected a higher fusion rate in the rhBMP-2 matrix group and, therefore, were quicker to surgically explore fusion in those patients who received ICBG), (2) a quantitatively higher incidence of non-unions in the ICBG group resulting in persistent pain, and (3) uncertainty as to whether or not pain was originating from the fusion or from residual pain at the ICBG donor site. Interestingly, the timing of second surgeries for pseudarthrosis was similar in both groups. The majority of these surgical events took place between 6 and 12 months. This was the case for all six rhBMP-2 matrix surgeries and eight ICBG surgeries. One control patient underwent surgery before 6 months and another four did so between 12 and 24 months after the index surgery.

Deleted:
Deleted: 4
Deleted:
Deleted:
Formatted: Font: Italic
Deleted: more
Deleted: uncertainty as to whether or not the pain is originating from the fusion or from residual pain at the ICBG donor site, and
Deleted:
Deleted: 6
Deleted: 8

CONCLUSION

This study demonstrates that, for patients with a single-level degenerative disease, an instrumented posterolateral fusion with ICBG and rhBMP-2 matrix provides excellent clinical improvement and exhibits similar clinical outcomes two years after surgery. The rhBMP-2 matrix group demonstrated significantly decreased intraoperative blood loss and decreased operative time relative to the ICBG group. The rhBMP-2 matrix demonstrated an improved fusion success rate when compared with the ICBG group at 24 months. Two years after surgery, 60% of patients in the ICBG group still complained of donor site pain. There were no significant differences in complications between the two groups with the exception of graft harvesting related complications which were avoided with the use of rhBMP-2 matrix. In

Deleted: 2

conclusion, rhBMP-2 matrix decreases operative time and blood loss with earlier higher fusion rates and similar clinical outcomes as ICBG and can eliminate the need for harvesting iliac crest bone in successful posterolateral lumbar fusion surgery.

REFERENCES

1. Bono CM, Lee CK. Critical analysis of trends in fusion for degenerative disc disease over the past 20 years: influence of technique on fusion rate and clinical outcome. Spine 2004;29:455-63.

2. An HS, Lynch K, Toth J. Prospective comparison of autograft vs. allograft for adult posterolateral lumbar spine fusion: differences among freeze-dried, frozen, and mixed grafts. J Spinal Disord 1995;8:131-5.

3. Dawson EG, Lotysch M 3rd, Urist MR. Intertransverse process lumbar arthrodesis with autogenous bone graft. Clin Orthop 1981;154:90-6.

4. Dimar J, Glassman S, Burkus JK, Carreon L. A comparison of prospective clincial outcome measures for anterior vs. posterior single-level spine fusion. IMAST Program July 2004

5. Jorgenson SS, Lowe TG, France J, Sabin J. A prospective analysis of autograft versus allograft in posterolateral lumbar fusion in the same patient. A minimum of 1-year follow-up in 144 patients. Spine 1994;19:2048-53.

6. Sandhu HS, Toth JM, Diwan AD, et al. Histological evaluation of the efficacy of rhBMP-2 compared with autograft bone in sheep spinal anterior interbody fusion. Spine 2002;27:567-75.

7. Boden SD, Martin GJ Jr, Horton WC, et al. Laparoscopic anterior spinal arthrodesis with rhBMP-2 in a titanium interbody threaded cage. J Spinal Disord 1998;11:95-101.

8. Hecht BP, Fischgrund JS, Herkowitz HN, et al. The use of recombinant human bone morphogenetic protein-2)rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999;24:629-36.

9. Burkus JK, Heim SE, Gornet MF, Zdeblick TA: Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-CAGE lumbar tapered fusion device. J Spinal Disord Tech 2003;16:113-22

10. Burkus JK, Sandhu HS, Gornet MF, Longley MC. Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery. J Bone Joint Surg Am. 2005;87:1205-12.

11. Martin JG Jr, Boden SD, Marone MA, Marone MA, Moskovitz PA. Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: important lessons learned regarding dose, carrier, and safety. J Spinal Disord 1999;12:179-86.

12. Barnes B, Boden SD, Louis-Ugbo J, et al. Lower dose of rhBMP-2 achieves spine fusion when combined with an osteoconductive bulking agent in non-human primates. Spine 2005;30:1127-33.

13. Akamaru T, Suh D, Boden SD, et al. Simple carrier matrix modifications can enhance delivery of recombinant human bone morphogenetic protein-2 for posterolateral spine fusion. Spine 2003;28:429-34.

14. Suh DY, Boden SD, Louis-Ugbo J, et al. Delivery of recombinant human bone morphogenetic protein-2 using a compression-resistant matrix in posterolateral spine fusion in the rabbit and in the non-human primate. Spine. 2002;27:353-60.

Deleted: nonjuman

Formatted: German (Germany)

Formatted: German (Germany)

15. Boden SD, Martin GJ Jr, Morone MA, et al. Posterolateral lumbar intertransverse process spine arthrodesis with recombinant human bone morphogenetic protein 2/hydroxyapatite-tricalcium phosphate after laminectomy in the nonhuman primate. Spine. 1999;24:1179-85.

16. Boden SD, Kang J, Harvinder S, Heller JG. Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial: 2002 Volvo Award in clinical studies. Spine. 2002;27:2662-73.

17. Fairbank JC, Couper J, Davies JB, O'Brien JP. The Oswestry low back pain disability questionnaire. Physiotherapy 1980; 66:271-3.

18. Ware JE Jr, Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;306:473-83.

19. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994;32:40-66.

20. Glassman SD, Dimar JR, Carreon LY, et al. Initial fusion rates with recombinant human bone morphogenetic protein-2/compression resistant matrix and hydroxyapatite and tricalcium phosphate/collagen carrier in posterolateral spinal fusion. Spine 2005;30;1694-98.

21. Boden SD. Overview of the biology of lumbar spine fusion and principles for selecting a bone graft substitute. Spine 2002;27(16S):S26-S31.

22. Ludwig SC, Kowalski JM and Boden SD. Osteoinductive bone graft substitutes. Eur Spine J 2000; 9(Suppl 1):S119-S125.

23. Lind M, Bunger C. Factors stimulating bone formation. Eur Spine J 2000;9(Suppl 1):S102-S109.

24. Vaccaro AR, Sharon AD, Tuan RS, et al. The use of biologic materials in spinal fusion. Orthopedics 2001;24:191-197.

25. Carreon LY, Glassman SD, Anekstein Y, Puno RM. Platelet gel (AGF) fails to increase fusion rates in instrumented posterolateral fusions. Spine. 2005;30:E243-6.

26. Urist MR: Bone: formation by autoinduction. Science. 1965;150:893-9

27. Wozney JM. The bone morphogenetic protein family and osteogenesis [review]. Mol Reprod Dev 1992; 32:160-167

28. Ware JE, Kosinski M, Keller SK. SF-36® Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: The Health Institute, 1994.

29. Fairbank JCT, Pynsent PB: The Oswestry Disability Index. Spine 2000;25:2940-52.

30. Walsh TL, Hanscom B, Lurie JD, Weinstein JN. Is a condition-specific instrument for patients with low back pain/leg symptoms really necessary? The responsiveness of the Oswestry Disability index, MODEMS and the SF-36. Spine 2003;28:607-15.

31. Blumenthal SL, Gill K. Can lumbar spine radiographs accurately determine fusion in postoperative patients? Correlation of routine radiographs with a second surgical look at lumbar fusions. Spine. 1993;18:1186-9.

32. Brodsky AE, Kovalsky ES, Kahlil MA. Correlation of radiologic assessment of lumbar spine fusions with surgical exploration. Spine. 1991;16(6 Suppl):S261-5.

33. Kant AP, Daum WJ, Dean SM, Uchida T. Evaluation of lumbar spine fusion. Plain radiographs versus direct surgical exploration and observation. Spine 1995;20:2313-7.

34. Fischgrund JS, Mackay M, Herkowitz HN, Brower R, Montgomery DM, Kurz LT. 1997 Volvo Award Winner in Clinical Studies: Degenerative Lumbar Spondylolisthesis With Spinal Stenosis: A Prospective, Randomized Study Comparing Decompressive Laminectomy and

Arthrodesis With and Without Spinal Instrumentation. Spine. 22(24):2807-2812, December 15, 1997.

35.Kornblum MB, Fischgrund JS, Herkowitz HN, Abraham DA, Berkower DL, Ditkoff JS. Degenerative Lumbar Spondylolisthesis with Spinal Stenosis: A Prospective Long-Term Study Comparing Fusion and Pseudarthrosis. Spine. 29(7):726-733, April 1, 2004.

FIGURE LEGENDS

Figure 1. Comparison of mean Oswestry Disability Index scores in the ICBG and rhBMP-2 matrix groups at each follow-up interval. Lower scores represent decreasing disability.

Figure 2. Comparison of mean SF-36 Physical Component Summary scores in the ICBG and rhBMP-2 matrix groups.

Figure 3. Comparison of mean back pain scores in the ICBG and rhBMP-2 matrix groups.

Figure 4. Comparison of mean leg pain scores in the ICBG and rhBMP-2 matrix groups.

Figure 5. Mean donor site pain scores in the ICBG group.

Figure 6. Percentage of subjects working in the ICBG and rhBMP-2 matrix groups.

Figure 7. Percentage of subjects with bilateral confluent bridging bone reported by independent radiologists as observed on fine-cut CT scans with reconstructions for the ICBG and rhBMP-2 matrix groups. Differences between groups was statistically significant at all time points ($P \leq 0.001$).

From: Carol Binns [redacted]
Sent: Monday, October 7, 2002 09:38:53 AM
To: Treharne, Rick
Subject: Re: Burkus Manuscript

Attachments: All BMP Outcomes paper.4.doc

bvgRick,
Attached is the final copy of the manuscript. I am awaiting Dr. Burkus' go-ahead to send it. I spoke with him this morning after our phone conversation.
Carol
----- Original Message -----
From: "Treharne, Rick" <[redacted]>
To: [redacted]
Sent: Monday, October 07, 2002 9:30 AM
Subject: Burkus Manuscript

>
> > Carol,
> >
> > I heard that the Burkus et al paper was submitted to The Spine Journal.
> > Did you have a chance to look at my suggested wordsmithing before it went
> > in? Whatever the case, can I please be sent a copy of the manuscript as
> > submitted as well as the cover letter? Thanks...Rick
> >
> > -----Original Message-----
> > From: Treharne, Rick
> > Sent: Thursday, October 03, 2002 4:09 PM
> > To: [redacted]
> > Subject: Burkus Manuscript
> >
> > Carol,
> >
> > Here is the manuscript with a few suggested changes. Look them over and
> > see what you think.
> >
> > I checked with the statistician and it is Fisher's exact test--so I have
> > changed the footnote to the table accordingly. Also, the reference to
> > ANOVA in the footnote to Table 2 is correct, even though ANCOVA is used
> in

> > the text. (In case you were wondering.) If it is too late to add these
> > changes now, then maybe these changes can be added later. If you do
> > revise it again, please send me a new version for our files.
> > Thanks...Rick
> >
> > << File: All BMP Outcomes paper.3.doc >>

Is INFUSE™ Bone Graft Superior to Autograft Bone? An Integrated Analysis of Clinical Trials Using the LT-CAGE™ Lumbar Tapered Fusion Device

J. Kenneth Burkus, M.D.*

Stephen E. Heim MD†

Matthew F. Gornet MD‡

Thomas A. Zdeblick MD§

* Staff Physician, Spine Service, The Hughston Clinic, P.C., [redacted]

† Staff Physician, Orthopaedic Associates of DuPage, Warrenville, Illinois

‡Staff Physician, Orthopaedic Center of St. Louis, St. Louis, Missouri

§Chairman, Department of Orthopaedics and Rehabilitation, University of Wisconsin, Madison, Wisconsin

FDA device/drug status: Approved for this indication.

Statement of Financial Relationship: The authors are consultants and clinical investigators for the company distributing the device studied.

Address correspondence and reprint requests to: J. K. Burkus, M.D., The Hughston Clinic [redacted] Columbus, Georgia 31908-9517

ABSTRACT

Background context: A product containing recombinant bone morphogenetic protein, rhBMP-2, marketed as INFUSE™ Bone Graft, is now commercially available in the United States. ~~Three~~ Multicenter human clinical studies of patients undergoing anterior lumbar fusion have been conducted using this material or autograft and the LT-CAGE™ Lumbar Tapered Fusion device, in which the material was implanted.

Purpose: We hypothesized that INFUSE™ Bone Graft is superior to autograft when used inside an LT-CAGE™ Lumbar Tapered Fusion device in patients undergoing anterior lumbar fusion. We increased our overall sample size by combining several ~~smaller~~ clinical trials to increase the statistical power of the analysis.

Study design/setting: An integrated analysis of prospective studies of patients who received lumbar fusion cage implants by one of two surgical methods using one of two graft materials with a minimum follow-up of 2 years.

Patient Sample: A total of 679 patients from 36 sites were implanted with the LT-CAGE™ Lumbar Tapered Fusion Device for single-level degenerative disc disease with up to grade 1 spondylolisthesis. Of these patients, 277 had their cages implanted with INFUSE™ Bone Graft, and 402 received autograft transferred from the iliac crest.

Outcome Measures: After surgery, fusion was assessed at 6, 12, and 24 months and pain was measured on the Oswestry Disability Index and the SF-36 Health Survey at 3, 6, 12, and 24 months. The surgery-to-return-to-work interval and second surgeries were recorded.

Methods: An integrated analysis of multiple clinical studies was performed using an analysis of covariance to adjust for preoperative variables.

Results: The patients treated with INFUSE™ Bone Graft had statistically superior outcomes with regard to length of surgery, blood loss, hospital stay, reoperation rate, and median time to return to work. Oswestry Disability Index scores and the Physical Component Scores and Pain Index of the SF-36 scale at 3, 6, 12, and 24 months showed statically superior outcomes in the INFUSE™ group. Similarly, fusion rates were statistically superior at 6, 12, and 24 months in the INFUSE™ group.

Conclusions: INFUSE™ Bone Graft should become the new gold standard and should replace autograft bone inside the LT-CAGE™ device in patients undergoing anterior lumbar spinal fusions.

Keywords: Anterior lumbar interbody fusion, INFUSE™ Bone Graft, Bone morphogenetic protein, Fusion cage, Degenerative disc disease, Lumbar spine

INTRODUCTION

The surgical technique and indications for implanting the LT-CAGE™ Lumbar Tapered Fusion Device (Medtronic Sofamor Danek, Memphis, Tennessee) and reports of outcome measurements in patients in whom it has been implanted have been reported in the literature [1-3]. The history, development, and method of use of the protein product, called rhBMP-2 (recombinant human bone morphogenetic protein), used in our study have also been reviewed [4-7], and the prospective, randomized trial that lead to the product's approval by showing equivalency in outcome between the INFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, Tennessee) and autograft was published in 2002 [2]. The advantages to the patient and to the surgeon of not having to create a second surgical site and the complications and pain of iliac crest harvesting have also been reviewed [8].

The purpose of our analysis was to investigate the potential statistical superiority of INFUSE™ Bone Graft to autograft used inside the LT-CAGE™ Lumbar Tapered Fusion Device in surgical parameters, hospital stay, and clinical outcome in single-level spinal fusions. We integrated, or pooled, the results from similar large-scale clinical trials of the same device used for the same indication and measured in the same way to check for statistical superiority. These data came from both published [2,3] and unpublished studies.

INFUSE™ Bone Graft with the LT-CAGE™ device was approved by the U.S. Food and Drug Administration on July 2, 2002, for treating patients with degenerative disc disease and up to grade I spondylolisthesis using a single-level anterior spinal fusion

procedure. The approval was based primarily on the clinical data from a prospective, randomized, controlled clinical trial that is discussed in detail elsewhere [2]. That study used the INFUSE™ Bone Graft with the LT-CAGE™ Tapered Lumbar Fusion Device in the investigational group patients and compared their results with those of the control group patients who received autograft inside the LT-CAGE™ device in open surgical procedures. Wyeth BioPharma, Cambridge, MA, genetically engineered the rhBMP-2 component. The absorbable collagen sponge component is manufactured by Integra LifeSciences, Plainsboro, NJ. Together, the components are distributed commercially under the trade name INFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, TN). This clinical trial was designed to establish statistical equivalence (noninferiority) between the INFUSE group and autograft group. The fusion success rate in the INFUSE group was 94.5% at 24 months after surgery compared with 88.7% in the autograft group. The probability of noninferiority of INFUSE Bone Graft to autograft was shown to be essentially 100%. The probability of superiority was 90.2%, which, albeit high, did not meet the minimum superiority criterion of 95% predefined in the prospective, randomized protocol. Fusion superiority was not shown probably because of insufficient sample size and, therefore, insufficient statistical power~~The~~ nor should it have since that clinical trial was designed ~~with patients' participation~~ and sized o nly to show equivalence. Since the number of patients enrolled in that single study was not adequate to demonstrate statistical superiority, we combined the patient data from that randomized study with two additional sequential studies to assess the statical superiority of the results in the INFUSE patients over those in the autograft controls.

METHODS

Our analysis combines ~~the two patient~~ data sets from a published randomized trial [2] which had two arms with those from two additional sequential clinical trials to increase the sample size and statistical power. ~~Two patient data sets involved an open surgical technique through which the LT-CAGE™ Tapered Lumbar Fusion Device was implanted [2].~~ Both of these two other patient data sets ~~involved the~~ were from patients that had the fusion cage implanted laparoscopically. One of these two patient data sets is from the clinical trial in which INFUSE™ Bone Graft was used with the LT-CAGE™ Tapered Lumbar Fusion Device and implanted laparoscopically. This study used the identical inclusion-exclusion criteria and procedures as the other studies. ~~; however, patients in this study were not randomly assigned to treatment groups because a control group was not part of the protocol.~~ A portion of the results of this study from one site has been published [3]. The second set of additional patient data comes from another clinical trial in which autograft and the LT-CAGE™ device were inserted using a laparoscopic surgical approach. The inclusion-exclusion criteria for these patients were identical to those for the patients in the randomized trial and the other laparoscopic arm of the study with the minor exception of not having a minimum Oswestry low back pain disability score for entry as was required for all the other three sets of patients. These four prospective, multi-center clinical studies are summarized in Table 1. All patients were entered into these studies between 1996 and 1999.

The two treatment factors in these four patient data sets are bone graft type (INFUSE™ Bone Graft or autograft) and the surgical approach (open or laparoscopic). Our goal was to compare and analyze the results in the patients who received INFUSE™

Bone Graft with those in the patients who received autograft. The results from the two surgical approaches are pooled and the effects of surgical approach, if any, such as at early time points, are statistically adjusted so as not to affect the comparison between the graft types. Thus, our analysis compared the results of 277 INFUSE™ Bone Graft patients with 402 autograft patients. All of the 679 patients had degenerative disc disease with up to grade 1 spondylolisthesis. All patients had two LT-CAGE devices implanted anteriorly at one lumbar level, and all were included in prospective, multi-centered studies using the same outcome measurement tools and methodology of analysis (Figure 1). More than 60 surgeons at 36 different sites enrolled the 679 patients. No single surgeon performed more than 10% of the cases. Hence, the outcomes represent typical results from a wide variety of surgeons with different degrees of experience.

Because not all of the four prospectively studied groups were randomized, the patients' demographic characteristics and prognostic factors could be different among the groups. Tables 2, 3, and 4 summarize demographic information, preoperative medical condition and medication usage, and preoperative measurements of ~~some~~ several clinical endpoints, respectively. Among approximately 20 summarized variables, seven were found to be significantly different between the combined INFUSE group and the combined autograft group.

Statistical Analysis

The seven variables that were found to have statistically significant differences were age, previous back surgery, preoperative non-narcotic medication use, weak-narcotic medication use, muscle relaxant medication use, preoperative low back pain score on the Oswestry Disability Index, and preoperative SF-36 Physical Component

Score. Because these seven prognostic factors could potentially affect the clinical outcomes and therefore confound the analysis of a study between the INFUSE and autograft groups, a statistical technique called analysis of covariance (ANCOVA) was performed. With the use of this statistical methodology, the influences of these prognostic factors are adjusted for, and comparisons can be made between the INFUSE and autograft results. In essence, this statistical method makes it possible to have both groups start at the same level statistically for these seven factors before any differences in outcome are compared.

RESULTS

The statistical analysis of operative time, blood loss, and hospital stay for the INFUSE and autograft groups is shown in Table 5. This analysis reveals superior ($p < .05$) benefits of the combined INFUSE group compared with the autograft group for all three variables. The INFUSE group spent an average of 0.9 hours (54 minutes) less time under anesthesia, lost an average of 66 mL less blood (probably because of the shorter surgery time and not having a second surgery site), and, on average, left the hospital nearly a day (0.9) earlier than the autograft group.

The fusion success rate in the combined INFUSE group was 94.4% (201/213) at 24 months after surgery compared with 89.4% (252/282) in the autograft group (Table 6). This 5-percentage point difference was shown to be statistically significant by an analysis of covariance, with an adjusted *p*-value of .022. In short, fusion, the primary goal of performing the original surgery, was found to be statistically superior for the INFUSE patients.

In the combined INFUSE group, preoperative low back pain scores on the validated Oswestry Disability Index improved significantly over those in the autograft group for all time points—3, 6, 12, and 24 months—in the study (Table 7). The adjusted *p*-values were all ~~highly~~ statistically significant.

The Physical Component and Pain Index scores of the SF-36 Health Survey, which measures a patient's physical well being after surgery, are shown in Table 8. As with the Oswestry Disability Index low back pain scores, the results showed the statistical superiority of the combined INFUSE group to the autograft group for all time points after surgery.

Additional surgical events in the study patients are summarized in Table 9. Simple Fisher's exact tests show that the combined INFUSE groups had statistically fewer reoperations than patients who were implanted with autograft (p=.0036). At the two-year time point used in the study, the revision rate in INFUSE patients approached statistical superiority (p=.0631).

Although the difference was not statistically significant, 103 (74.6%) of the INFUSE patients who were working before surgery, returned to work after surgery compared with 109 (64.9%) patients in the autograft group. Again although not statistically significant, 49 (35.3%) of the INFUSE patients who were not working before surgery returned to work after surgery compared with 73 (31.3%) of the autograft patients. The difference that was found to be statistically significant was the time it took for the patients to return to work. A summary of time-to-event type analysis of return to work is contained in Table 10. The statistical comparison between the INFUSE and autograft groups was adjusted by the preoperative work status, the seven prognostic

covariates, and the surgical approach. The median days to return to work was 54.5 days shorter for the LT-CAGE patients implanted with INFUSE Bone Graft. This finding was statistically significant in favor of the INFUSE patients (adjusted *p*-value = .0156).

DISCUSSION

Surgeons have long sought to find the best way to fuse two bones. Although allograft bone has been used with some degree of success, transplanting living bone from one part of the body to another has become the "gold standard" by which all other procedures are measured [8]. Finding a substitute for human tissue has also been a noble goal of researchers for decades, and finding a bone graft substitute to replace autogenous bone seemed at times an impossible task. What material could researchers develop that would be better than a naturally occurring material?

Since the discovery of bone morphogenetic proteins (BMP) by Dr. Marshall Urist in 1965 [9], his dream, and those of many others, was to have BMP available in operating rooms as a safe and effective replacement for autograft. In July 2002, his dream became a reality in the United States with the FDA approval of rhBMP-2, a recombinant version of one of the family of BMPs. His goal, and the goal of other researchers like him, was for the substitute to be equal to autograft so harvesting of autograft bone from other parts of the body would no longer be necessary. Preclinical studies [5,6,10-14] have indicated the possibility that osteoinductive protein-containing materials may be superior to autograft in some applications and for some outcome measurements. Wozney [7] suggests that BMP can result in direct intramembranous ossification because in some animal models direct bone formation is observed after administration of the protein. Because chips of transferred autogenous graft may need to be resorbed or be remodeled before fusing and

rhBMP-formed bone does not, this feature may explain why some animal studies had superior results with rhBMP-containing grafts when compared with autograft. However, the question remains: Can any recombinant BMP on any carrier ever be superior to autograft—the gold standard—with regard to operative parameters and clinical outcome in humans? Pilot study results of the LT-CAGE™ Lumbar Tapered Fusion Device in humans [1] and the results from a prospective, randomized study [2] showed a trend toward faster fusion with the INFUSE™ Bone Graft and other data that were comparable with that in the patients who received autograft. We hypothesized that this trend would become a superior outcome in a larger study.

We used the ANCOVA method for an integrated analysis of four, large-scale multicenter sets of patient data. This analysis of prospectively gathered data has answered the question of the superiority of INFUSE™ Bone Graft over autograft for one particular human clinical use. This analysis of 679 patients represents the largest prospective combined study of a single-level anterior procedure using a single device for a single indication in the spinal literature. Because all patients received the same LT-CAGE implants, we had, for the first time, a data set large enough to determine whether INFUSE™ Bone Graft is equivalent to or superior to autograft bone. Because of the large sample size used in this analysis and its subsequent statistical power, the answer is an unequivocal "yes." The INFUSE patients had statistically superior outcomes in the following categories: shortened surgery time, reduced blood loss, shortened hospital stay, higher fusion rate, better Oswestry Low Back Pain Disability Questionnaire scores at all follow-up intervals, better Physical Component Scores and Pain Index scores on the SF-

36 Health Survey at all follow-up intervals, fewer reoperations, and an earlier return to work.

As seen in Table 7, the improvement in mean Oswestry pain scores for all postoperative time points for the INFUSE group was approximately 2 points, the change from pre-operative scores was about 5 points for all time points, about a 7-10% scale improvement. As seen in Table 8, the mean PCS scores on the SF-36 scale also improved approximately 2 points for the INFUSE patients at all time points, representing approximately a 12-15% scale improvement from the pre-operative values. Obviously any statistical decrease in pain at any time point would be considered significant and desirable by the patient. The statistically significant decrease in the INFUSE patients' low back pain must be at least part of the explanation for their returning to work nearly two months earlier than the autograft patients.

The INFUSE patients obviously had none of the pain or problems associated with iliac crest graft harvesting, the pain from which was recorded on a separate 20-point iliac crest pain scale [2] so as to discriminate the low back pain from the iliac crest harvest site pain. In the autograft open group, nearly a third (32%) of the patients still had some pain at their harvest site two years after the surgery [2]. In addition to pain, the 402 autograft patients treated with open and laparoscopic surgery, ~~there was~~ also had a 3.0% chance of a significant graft site complication: 5 (1.25%) had infections at their harvest site, 2 (0.5%) had fractures at the graft site, and 5 (1.25%) had other adverse events related to their harvest site.

We believe this analysis demonstrates the superiority of using INFUSE™ Bone Graft. In fact, we found no disadvantage to using INFUSE™ Bone Graft for the surgical,

hospital discharge, and major postoperative outcome measurements discussed. In addition, the INFUSE patients did not have the pain, morbidity, or complications associated with the second surgery of iliac crest graft harvest. The results of this integrated analysis coupled with the ~~tremendous~~ excellent and comprehensive safety profile for the recombinant human bone morphogenetic protein (rhBMP-2) material used in the study [15] clearly indicates that the use of INFUSE Bone Graft should now be the new gold standard for replacing autograft bone inside the LT-CAGE device for lumbar spinal fusions.

With its clear superiority, INFUSE™ Bone Graft may now be the new gold standard for replacing autograft bone inside the LT-CAGE™ device when used for lumbar spinal fusions. INFUSE Bone Graft is now used exclusively for this purpose in our institutions.

ACKNOWLEDGMENTS

The authors thank the more than 60 clinical investigators who provided patients for this study and the Clinical Research group at Medtronic Sofamor Danek for their help in data collection and the statistical analyses.

REFERENCES

[1] Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25:376-81.

[2] Burkus JK, Gornet MF, Dickman C, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. J Spinal Disord 2002;October (in press).

[3] Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2. A prospective study of clinical and radiographic outcomes. Spine 2001;26:2751-6.

[4] Boden SD. Overview of the biology of lumbar spine fusion and principles for selecting a bone graft substitute. Spine 2002;27:S26-31.

[5] McKay B, Sandhu HS. Use of recombinant human bone morphogenetic protein-2 in spinal fusion applications. Spine 2002;27(16 Suppl 1):S66-85.

[6] Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995;20:1326-37.

[7] Wozney JM. Overview of bone morphogenetic proteins. Spine 2002;27(16 Suppl 1):S2-8.

[8] Vaccaro AR, Kazuhiro C, Heller JG, Patel TC, Thalgott JS, Truumees E, Fischgrund JS, Craig MR, Berta SC, Wang JC. Bone grafting alternatives in spinal surgery. The Spine Journal 2002;2:206-15.

[9] Urist MR. Bone: formation by autoinduction. Science 1965;150:893-9.

[10] David SM, MD, Gruber HE, Meyer RA, Murakami T, Tabor OB, Howard BA, Wozney JM, Hanley EN. Lumbar spinal fusion using recombinant human bone morphogenetic protein in the canine. A comparison of three dosages and two carriers. Spine 1999;24:1973 –9.

[11] Boden SD, Schimandle JH, Hutton WC. The 1995 Volvo award in basic sciences. The use of an osteoconductive growth factor for lumbar spinal fusion. Part II: study of dose, carrier, and species. Spine 1995;20:2633-44.

[12] Sandhu HS, Kanim LE, Kabo JM, Toth JM, Zeegen EN, Liu D, Delamarter RB, Dawson EG. Effective doses of recombinant human bone morphogenetic protein-2 in experimental spinal fusion. Spine 1996;21:2115-22.

[13] Sandhu HS, Toth JM, Diwan AD, Seim HB, Kanim LE, Kabo JM, Turner AS. Histologic evaluation of the efficacy of rhBMP-2 compared with autograft bone in sheep spinal anterior interbody fusion. Spine 2002;27:567-75.

[14] Zdeblick TA, Ghanayem AJ, Rapoff AJ, Swain CS, Bassett T, Cooke ME, Markel M. Cervical interbody fusion cages. An animal model with and without bone morphogenetic protein. Spine 1998;23:758-65.

[15] Poynton AR, Lane JM. Safety profile for the clinical use of bone morphogenetic proteins in the spine. Spine 2002;27(16 Suppl 1):S40-8.

Table 1. Summary of study groups analyzed.

Study group	Graft type	Surgical approach	Randomized	Prospective	Number of patients
INFUSE™ Open	INFUSE™	Open	Yes	Yes	143
INFUSE™ Lap	INFUSE™	Laparoscopic	No	Yes	134
Autograft Open	Autograft	Open	Yes	Yes	136
Autograft Lap	Autograft	Laparoscopic	No	Yes	266

Table 2. Demographic information.

Variable [n(%)]	INFUSE™ Open (N=143)	INFUSE™ Lap (N=134)	INFUSE™ Total (N=277)	Autograft Open (N=136)	Autograft Lap (N=266)	Autograft Total (N=402)	p-value* INFUSE vs Autograft
Age (yrs.)							
n	143	134	277	136	266	402	.007
Mean	43.3	42.4	42.9	42.3	40.0	40.8	
SD	9.8	10.5	10.2	9.7	9.6	9.7	
Height (in.)							
n	143	134	277	135	262	397	.216
Mean	68.1	67.5	67.8	68.0	68.3	68.2	
SD	4.2	4.0	4.1	4.2	3.9	4.0	
Weight (lbs.)							
n	143	134	277	134	264	398	.146
Mean	179.1	169.8	174.6	181.1	177.6	178.8	
SD	33.1	38.3	36.0	37.0	37.9	37.6	
Sex [n(%)]							
Male	78 (54.5)	57 (42.5)	135 (48.7)	68 (50.0)	142 (53.4)	210 (52.2)	.391
Female	65 (45.5)	77 (57.5)	142 (51.3)	68 (50.0)	124 (46.6)	192 (47.8)	
Marital Status [n(%)]							
Single	24 (16.8)	24 (17.9)	48 (17.3)	18 (13.2)	52 (19.5)	70 (17.4)	.983
Married	95 (66.4)	91 (67.9)	186 (67.1)	91 (66.9)	177 (66.5)	268 (66.7)	
Divorced	18 (2.6)	14 (10.4)	32 (11.6)	20 (14.7)	30 (11.3)	50 (12.4)	
Separated	5 (3.5)	2 (1.5)	7 (2.5)	5 (3.7)	5 (1.9)	10 (2.5)	
Widowed	1 (0.7)	3 (2.2)	4 (1.4)	2 (1.5)	2 (0.8)	4 (1.0)	
Education Level [n(%)]							
< High School	13 (9.1)	7 (5.2)	20 (7.2)	17 (12.6)	25 (9.5)	42 (10.6)	.277
High School	45 (31.5)	39 (29.1)	84 (30.3)	39 (28.9)	86 (32.7)	125 (31.4)	
> High School	85 (59.4)	88 (65.7)	173 (62.5)	79 (58.5)	152 (57.8)	231 (58.0)	
Workers' Compensation [n(%)]							
Yes	47 (32.9)	42 (31.3)	89 (32.1)	47 (34.6)	89 (33.7)	136 (34.0)	.620
No	96 (67.1)	92 (68.7)	188 (67.9)	89 (65.4)	175 (66.3)	264 (66.0)	
Spinal Litigation [n(%)]							
Yes	18 (12.6)	11 (8.2)	29 (10.5)	22 (16.2)	29 (11.1)	51 (12.8)	.398
No	125 (87.4)	123 (91.8)	248 (89.5)	114 (83.8)	233 (88.9)	347 (87.2)	
Tobacco Used [n(%)]							
Yes	47 (32.9)	40 (29.9)	87 (31.4)	49 (36.0)	83 (31.2)	132 (32.8)	.738
No	96 (67.1)	94 (70.1)	190 (68.6)	87 (64.0)	183 (68.8)	270 (67.2)	
Alcohol Use [n(%)]							
Yes	39 (27.3)	66 (49.3)	105 (37.9)	43 (31.6)	94 (35.3)	137 (34.1)	.328
No	104 (72.7)	68 (50.7)	172 (62.1)	93 (68.4)	172 (64.7)	265 (65.9)	
Preop Work Status [n(%)]							
Working	68 (47.6)	70 (52.2)	138 (49.8)	50 (36.8)	118 (44.5)	168 (41.9)	.050
Not Working	75 (52.4)	64 (47.8)	139 (50.2)	86 (63.2)	147 (55.5)	233 (58.1)	

* For continuous variables, *p*-values are from ANOVA, and for categorical variables, they are from Fisher's exact tests or the chi-square test.

Table 3. Preoperative medical condition and medication usage [Number (%) of patients]

Variable	INFUSE™ Open (N=143)	INFUSE™ Lap (N=134)	INFUSE™ Total (N=277)	Autograft Open (N=136)	Autograft Lap (N=266)	Autograft Total (N=402)	p-value* INFUSE vs Autograft
Previous Back Surgery							
Yes	54 (37.8)	33 (24.6)	87 (31.4)	55 (40.4)	110 (41.4)	165 (41.0)	.042
No	89 (62.2)	101 (75.4)	190 (68.6)	81 (59.6)	156 (58.6)	237 (59.0)	
Previous Back Surgery							
1	39 (72.2)	16 (50.0)	55 (64.0)	34 (61.8)	78 (70.9)	112 (67.9)	.574
>1	15 (27.8)	16 (50.0)	31 (36.0)	21 (38.2)	32 (29.1)	53 (32.1)	
Non-narcotic Medications							
Yes	80 (55.9)	97 (72.4)	177 (63.9)	75 (55.1)	109 (41.0)	184 (45.8)	<.001
No	63 (44.1)	37 (27.6)	100 (36.1)	61 (44.9)	157 (59.0)	218 (54.2)	
Weak Narcotic Medications							
Yes	77 (53.8)	61 (45.5)	138 (49.8)	67 (49.3)	90 (33.8)	157 (39.1)	.006
No	66 (46.2)	73 (54.5)	139 (50.2)	69 (50.7)	176 (66.2)	245 (60.9)	
Strong Narcotic Medications							
Yes	31 (21.7)	17 (12.7)	48 (17.3)	33 (24.3)	42 (15.8)	75 (18.7)	.686
No	112 (78.3)	117 (87.3)	229 (82.7)	103 (75.7)	224 (84.2)	327 (81.3)	
Muscle Relaxant Medications							
Yes	45 (31.5)	49 (36.6)	94 (33.9)	37 (27.2)	39 (14.7)	76 (18.9)	<.001
No	98 (68.5)	85 (63.4)	183 (66.1)	99 (72.8)	227 (85.3)	326 (81.1)	

*p-values are from Fisher's exact test or chi-square test.

Table 4. Preoperative evaluations of clinical endpoints

	INFUSE™			Autograft			*p*-value*
Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	INFUSE vs Autograft
Oswestry Pain Score							
n	143	134	277	136	264	400	.001
Mean	53.7	52.3	53.0	55.1	46.5	49.4	
SD	12.7	11.7	12.2	11.8	15.6	15.0	
SF-36 PCS							
n	142	134	276	136	263	399	.004
Mean	27.7	28.3	28.0	29.4	29.5	29.5	
SD	5.7	6.1	5.9	6.2	7.3	6.9	
SF-36 Pain Index							
n	143	134	277	136	263	399	.077
Mean	21.8	22.6	22.2	22.7	24.7	24.1	
SD	11.1	13.4	12.2	13.6	14.7	14.3	

*p-values are from analysis of variance.

Table 5. Surgery information.

Variable	INFUSE™ Open (N=143)	INFUSE™ Lap (N=134)	INFUSE™ Total (N=277)	Autograft Open (N=136)	Autograft Lap (N=266)	Autograft Total (N=402)	p-value* INFUSE vs Autograft
Operative Time (hrs)							
n	143	134	277	136	265	401	<.001
Mean	1.6	1.9	1.8	2.0	3.1	2.7	
SD	0.6	0.9	0.8	0.7	1.4	1.3	
Blood Loss (mL)							
n	142	134	276	136	263	399	.024
Mean	109.8	146.1	127.4	153.1	213.6	198.9	
SD	117.3	406.2	295.3	179.1	493.0	414.4	
Hospital Stay (days)							
n	143	134	277	136	266	402	<.001
Mean	3.1	1.2	2.2	3.3	3.0	3.1	
SD	1.6	1.1	1.7	1.3	3.8	3.2	
Treatment Levels [n (%)]							
L2-L3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	
L3-L4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	2 (0.5)	
L4-L5	37 (25.9)	21 (15.7)	58 (20.9)	32 (23.5)	21 (7.9)	53 (13.2)	
L5-L6	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	2 (0.8)	3 (0.7)	
L5-S1	106 (74.1)	113 (84.3)	219 (79.1)	103 (75.7)	240 (90.2)	343 (85.3)	
Operative Approach [n (%)]							
Retroperitoneal	116 (81.1)	28 (20.9)	144 (52.0)	109 (80.1)	9 (3.4)	118 (29.4)	
Transperitoneal	27 (18.9)	106 (79.1)	133 (48.0)	26 (19.1)	256 (96.2)	282 (70.1)	
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.4)	2 (0.5)	

*p-values are from analysis of variance.

Table 6. Summary of success rates of radiographic fusion [Number (%) of Patients]

	INFUSE™			Autograft			*p*-value*
Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	INFUSE vs Autograft
6 Months							
Success	128 (97.0)	88 (92.6)	216 (95.2)	115 (95.8)	192 (95.5)	307 (95.6)	.833
Failure	4 (3.0)	7 (7.4)	11 (4.8)	5 (4.2)	9 (4.5)	14 (4.4)	
12 Months							
Success	127 (96.9)	95 (94.1)	222 (95.7)	112 (92.6)	202 (93.1)	314 (92.9)	.131
Failure	4 (3.1)	6 (5.9)	10 (4.3)	9 (7.4)	15 (6.9)	24 (7.1)	
24 Months							
Success	120 (94.5)	81 (94.2)	201 (94.4)	102 (88.7)	150 (89.8)	252 (89.4)	.022
Failure	7 (5.5)	5 (5.8)	12 (5.6)	13 (11.3)	17 (10.2)	30 (10.6)	

*One-sided *p*-values are from logistic regression analysis with the model including bone graft type and surgical approach, adjusting the seven prognostic covariates. The interaction term between bone graft type and surgical approach is not significant and thus is not included.

Table 7. Summary of Oswestry Low Back Pain Disability scores

		INFUSE™			Autograft			p-value*
Period	Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	INFUSE vs Autograft
Preoperative	Pain Score							
	n	143	134	277	136	264	400	
	Mean	53.7	52.3	53.0	55.1	46.5	49.4	
	SD	12.7	11.7	12.2	11.8	15.6	15.0	
3 Months	Pain Score							
	n	141	127	268	134	252	386	.0641
	Mean	33.5	30.2	32.0	34.2	33.7	33.9	
	SD	17.6	19.9	18.8	18.5	19.7	19.3	
6 Months	Pain Score							
	n	136	120	256	131	239	370	.0053
	Mean	29.3	25.1	27.3	29.4	29.0	29.1	
	SD	18.8	20.4	19.6	18.2	20.1	19.5	
12 Months	Pain Score							
	n	130	114	244	125	224	349	.0013
	Mean	25.5	20.4	23.1	25.6	25.7	25.7	
	SD	18.2	19.8	19.1	19.1	20.2	20.0	
24 Months	Pain Score							
	n	122	93	215	108	177	285	.0023
	Mean	23.9	18.7	21.7	23.8	22.7	23.1	
	SD	18.8	19.3	19.2	20.7	20.9	20.8	

* One-sided *p*-values are from analysis of covariance with the model including bone graft type, surgical approach, and their interaction, adjusting the seven prognostic covariates.

Table 8. Summary of SF-36 Health Survey scores.

		INFUSE™			Autograft			p-value*
Period	Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	INFUSE vs Autograft
Preoperative	PCS							
	n	142	134	276	136	263	399	
	Mean	27.7	28.3	28.0	29.4	29.5	29.5	
	SD	5.7	6.1	5.9	6.2	7.3	6.9	
	Pain Index							
	n	143	134	277	136	263	399	
	Mean	21.8	22.6	22.2	22.7	24.7	24.1	
	SD	11.1	13.4	12.2	13.6	14.7	14.3	
3 Months	PCS							
	n	140	127	267	133	249	382	.0015
	Mean	36.6	37.3	36.9	35.9	35.1	35.3	
	SD	9.7	10.2	10.0	9.4	9.8		
	Pain Index							
	n	141	127	268	134	250	384	.0002
	Mean	47.4	50.4	48.8	44.1	43.4	43.6	
	SD	23.8	22.5	23.2	23.3	22.3	22.6	
6 Months	PCS							
	n	136	119	255	131	234	365	.0004
	Mean	39.4	41.0	40.1	38.6	37.8	38.1	
	SD	11.3	11.8	11.5	10.9	11.2	11.1	
	Pain Index							
	n	136	120	256	131	236	367	.0002
	Mean	53.0	54.8	53.8	50	46.3	47.8	
	SD	27.8	25.4	26.7	24	23.8	24.1	
12 Months	PCS							
	n	131	113	244	125	223	348	.0003
	Mean	41.3	43.4	42.3	40.8	40.9	40.3	
	SD	11.0	11.9	11.5	12.1	12.1	12.1	
	Pain Index							
	n	131	113	244	125	223	348	.0002
	Mean	55.0	60.8	57.7	53.5	52.1	52.6	
	SD	26.6	27.8	27.3	26.0	26.0	26.0	
24 Months	PCS							
	n	122	94	216	108	177	285	.0007
	Mean	42.4	45.0	43.6	42.1	42.5	42.4	
	SD	11.9	11.5	11.8	12.8	12.3	12.4	
	Pain Index							
	n	122	95	217	108	177	285	.0008
	Mean	58.5	63.9	60.9	56.4	57.1	56.8	
	SD	27.6	26.2	27.1	28.9	27.4	27.9	

* One-sided *p*-values are from analysis of covariance with the model including bone graft type, surgical approach, and their interaction, adjusting the seven prognostic covariates.
PCS = Physical component score

Table 9. Summary of second surgeries.

Type of second surgery	INFUSE™			Autograft			*p*-value* INFUSE™ vs Autograft
	Open	Lap	Total (%)	Open	Lap	Total (%)	
Revisions	0/143	1/134	1/277 (0.36)	0/136	8/266	8/402 (1.99)	.0631
Removals	2/143	2/134	4/277 (1.44)	0/136	7/266	7/402 (1.74)	.5106
Supplemental Fixations	10/143	7/134	17/277 (6.14)	14/136	14/266	28/402 (6.97)	.3970
Reoperations	6/143	2/134	8/277 (2.89)	4/136	28/266	32/402 (7.96)	.0036

*One-sided *p*-values are from Fisher's exact test.

Table 10. Summary of time-to-event analysis for days to return to work (median in days).

INFUSE™			Autograft			*p*-value* INFUSE vs Autograft
Median in Days						
Open	Lap	Total	Open	Lap	Total	
165.0	89.0	116.0	386.5	154.0	170.5	0.0156

* One-sided *p*-value is from the proportional hazard regression (PHREG) procedure with the model including bone graft type and surgical approach, adjusting preoperative work status and the seven prognostic covariates. The interaction term between bone graft type and surgical approach is not significant and thus is not included.

LEGEND OF FIGURES

Figure 1. A. Preoperative lateral radiograph shows isolated disc space collapse with radial osteophyte formation at the L5-S1 level. B. Postoperative anteroposterior radiograph and C, lateral radiograph shows the tapered fusion cage in place. Normal disc space height segmental lordosis has been restored at the L5-S1 vertebral interspace.

From: Treharne, Rick
Sent: Friday, January 10, 2003 04:42:15 PM
To: Burkus, J. Kenneth
BCC: Lipscomb, Bailey; Ma, Guorong
Subject: PLIF Study Paper

Attachments: PLIF BMP paper.1.doc; Burkus PLIF Paper 01-09-03.doc

In the attachment to the left I have a red-lined edited version of the document you sent us. Many of the changes I made are highlighted. On the right is a cleaned up version with a few extra changes in the text. I highlighted in red where I had questions or where references are needed. What we think you wanted in the tables and figures are attached to the cleaned up version on the right. I suggest you just look at the text on the right.

In looking over the data, I was impressed with how well the BMP patients actually did. So much so that I added a few paragraphs at the end that you may not agree with, but which basically say that future studies are needed. I think the data support such a conclusion. I also took the liberty to add a paragraph about the neuro results and a discussion of the iliac crest pain vs. the anterior study. I also added an Acknowledgement section. Take a look and see what you think. You can delete or edit as you wish, or send it out for review by your co-authors.

I will be out of the country Jan. 13-24, but if you have statistical questions you can email Guorong Ma here or Bailey Lipscomb. We would like to help you any way we can to put this paper out. We can help find the references too if you like. It is the first posterior spine use of BMP and is certainly worthy of publication in SPINE.

I hope you had a nice trip to New York...>Rick

A Prospective, Randomized Posterior Lumbar Interbody Fusion Study using rhBMP-2 with Cylindrical Interbody Cages

Regis Haid, MD[‡]

Joseph Alexander MD [†]

Charlie Branch MD[*]

J. Kenneth Burkus MD[§]

[‡] Professor, Department of Neurosurgery, Emory University, Atlanta, Georgia

[†] Assistant professor, Department of Neurosurgery

[*] Chairman, Department of Neurosurgery,

[§] Spine Surgeon at The Hughston Clinic, Columbus, Georgia

Address correspondence and reprint requests to J.K. Burkus, MD, The Hughston Clinic, [redacted]

ABSTRACT

Study Design. In a multi-center, prospective, randomized, nonblinded, 2-year study, 67 patients who underwent a single-level posterior lumbar interbody fusion with two paired cylindrical threaded titanium fusion devices were randomized into two groups: one received autogenous iliac crest bone graft, the other, recombinant human bone morphogenetic protein-2 (rhBMP-2) on a collagen sponge carrier.

Objectives. The objective of the study was to determine the clinical and radiographic outcomes in patients treated for single-level degenerative lumbar disc disease with posterior interbody fusion using stand-alone cylindrical threaded titanium fusion cages with autogenous bone graft or rhBMP-2 and an absorbable collagen sponge carrier.

Summary of Background Data. In a large series of human patients undergoing anterior lumbar interbody fusion with a tapered titanium fusion cage, rhBMP-2 has been shown to promote osteoinduction and fusion and to decrease operative time and blood loss.

Methods. In this prospective nonblinded study, 67 patients were randomized into 2 groups that underwent interbody fusion using two cylindrical threaded fusion cages: the investigational group (34 patients) that received rhBMP-2 on an absorbable collagen sponge and a control group (33 patients) that received autogenous iliac crest bone graft. Assessment of a patient's clinical outcome was based on low back and leg pain, numerical rating scales, Short Form-SF36 questionnaire, Oswestry Low Back Pain Disability questionnaire, and work status. Plain radiographs and computed tomographic scans were used to evaluate fusion at 6,12 and 24 months postoperatively.

Deleted: randomly divided

Deleted: questionnaires

Deleted: s

Deleted: scores

Deleted: and

Results. Mean operative time (2.6 hours) and blood loss (322.8 mL) were less in the investigational rhBMP-2 group than in the autograft control group (3.0 hours and 372.7 mL). At 24 months, the investigational group's fusion rate of 92.3% was higher than the control's at 77.8%. At all postoperative intervals, the mean Oswestry, back pain and leg pain scores and both the mental and physical components of the SF36 improved in both treatment groups compared with the preoperative scores. **In the control group, two adverse events related to harvesting of the iliac crest graft occurred in two patients (6.1%), and, at 24 months after surgery, 3.0% patients still reported graft site discomfort. Conclusions.** Although not statistically different, on average the investigational group had shorter operative times and less blood loss. At 24 months, this group had a fusion rate that was more than 14 percentage points greater than the control group. All clinical outcome measurements that were studied showed, on average, greater improvement in the investigational (rhBMP-2) patients with a statistically significant improvement in back pain. Overall results show that the use of rhBMP-2 can eliminate the need for harvesting iliac crest graft and a positive trend for being an equivalent or better replacement for autograft for use in successful posterior lumbar interbody fusions.

Deleted: was
Deleted: less
Deleted: ??
Deleted: adverse
Deleted: ??
Deleted: ??
Deleted: ??
Deleted: discomfort
Deleted: and ??% were bothered by the appearance of graft site.¶
Deleted: The

Key words: posterior lumbar interbody fusion, bone morphogenetic protein, osteoinduction, radiography, interbody fusion cages

Key points:

- At 24 months, the average rate of fusion for patients treated with rhBMP-2 was more than 14 percentage points higher (92.3% vs. 77.8%) than for patients treated with autograft. This difference, while large and promising, was not statistically different (p=0.250).
- The average operative time was 2.6 hours for patients treated with rhBMP-2 compared with 3.0 hours in the autograft group. Although not statistically different, the change was nearly so (p=0.065).
- Blood loss was tended to be less for patients treated with rhBMP-2 than for patients who underwent iliac crest bone graft harvesting.
- At all postoperative assessment intervals, patients in each treatment groups showed improvement in Oswestry disability scores, in back and leg pain outcomes and in both the PCS and MCS scores of the SF36.
- The use of rhBMP-2 in posterior lumbar interbody fusion procedures eliminates the complications of iliac crest bone harvesting including postoperative pain,.

Deleted: ??This difference was statistically significant??

Deleted: ??This difference was statistically significant??

Deleted: and scarring. ¶

Précis

In a 2-year prospective randomized study of 67 patients, the investigational group that received rhBMP-2 with paired cylindrical cage devices had a higher rate of fusion, reduced operative times, and decreased blood loss when compared with the control group that received the same cylindrical cage device filled with autogenous bone graft. Clinical outcomes showed greater improvement in the rhBMP-2 group at 3, 6, 12 and 24 months. The rhBMP-2 group avoided the complications that can arise from an iliac crest bone harvesting procedure.

INTRODUCTION

Posterior lumbar interbody fusion (PLIF) is an effective treatment for patients with symptomatic degenerative disc disease, spondylolithesis and other painful discogenic syndromes. Fusion of the degenerative and unstable lumbar spinal motion segment can give significant relief from this disabling and often progressive condition. PLIF limits the extent of posterolateral soft tissue exposure, muscle stripping, and injury. With this technique, the surgeon uses the traditional posterior approach to the lumbar spine; however, dissection is limited laterally to the facet joints. Through this approach, direct neural decompression can be completed, disc space height and sagittal balance can be restored, and intervertebral grafts can be placed in a biomechanically advantageous position.

Lumbar spine stabilization procedures that limit the extent of posterior spinal muscles exposure have some significant advantages. With PLIF surgical techniques, the fusion bed is within the disc space and it eliminates the exposure of the transverse processes. The PLIF approach to the lumbosacral spine enables the surgeon to re-establish the normal anatomic alignment and relationships of the spinal motion segment while avoiding excessive injury to the posterior paravertebral muscles.

Cloward (add reference) presented his technique for this innovative procedure in 1953. In his surgical technique, he described using a wide laminectomy and facetectomies that would allow for the placement of large structural bone grafts in the denuded and meticulously prepared disc space. Later, Lin (add reference) modified this intervertebral grafting technique of structural grafts. This modified PLIF technique involves filling the disc space with cancellous bone strips. It allows for preservation of a

Deleted: demanding procedure

Deleted: modified

portion the posterior elements and avoids the complication of insertion of large structural grafts. Additional modifications of the bone graft technique and bone graft materials have been made. Kushlich (add reference)and Ray (add reference) introduced the idea of using threaded interbody fusion cages inserted through a PLIF approach as means of stabilizing the lumbar motion segment, increasing rates of fusion and improving clinical outcomes.

Deleted: Kutlich
Deleted:

Recombinant human bone morphogenetic protein 2 (rhBMP-2) applied to an absorbable collagen sponge carrier has been shown to promote osteoinduction and fusion in the lumbar spine. In a large series of patients who underwent stand-alone anterior lumbar interbody fusion with fusion cages, rhBMP-2 was shown to enhance rates of fusion, reduce surgical time and improve clinical outcomes (add reference). To further evaluate this method of bone graft replacement, we evaluated the clinical and radiographic outcomes at 24 months of 67 patients who underwent a single level PLIF. We compared the outcomes in the investigational patients (rhBMP-2) with those in the control patients (autogenous bone).

MATERIALS AND METHODS

Study Design. **Between March 1999 and December 1999**67 patients with degenerative disc disease completed surgery in this prospective, randomized, nonblinded, FDA approved study at 14 investigational sites. All patients underwent a single-level posterior lumbar fusion with two paired INTER FIX™ devices (Medtronic Sofamor Danek, Memphis, TN). The interbody fusion cages were used as stand-alone construct in the disc space from L2 to S1, with the majority being L4-L5. Patients were randomly assigned in a 1:1 manner to one of two groups: the investigational group received rhBMP-2 on an absorbable collagen sponge carrier and the control group received autogenous iliac crest bone graft. INFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, TN) is the trademarked name for recombinant human bone morphogenetic protein-2 applied to an absorbable collagen sponge.

Patient Data. Preoperatively, all patients had symptomatic, single-level degenerative lumbar disc disease and symptoms of disabling low back or leg pain, or both, of at least 6 months duration that had not responded to nonoperative treatments. The two treatment groups were similar demographically (Table 1). **No statistically significant differences ($p < 0.05$) were found for any of the pre-operative variables.** The rhBMP-2 group consisted of 34 patients and the control group consisted of 33 patients. The average age at surgery was 46.3 years for the rhBMP-2 group and 46.1 years for the control group. In the rhBMP-2 group, 18 patients (52.9%) had used tobacco within 6 months before surgery compared with 15 patients (45.5%) in the control group. The percentage of patients with pending litigation was 8.8% and 3.0% in the rhBMP-2 and

Deleted: 1977 and 1977
Deleted: s
Deleted: 14
Deleted: inFUSE
Deleted: ™
Deleted: months'
Deleted: There were 22
Deleted: 17?
Deleted:

control groups, respectively. The percentage of patients seeking worker's compensation was 23.5% in the rhBMP-2 group and 27.3.6% in the control group.

Clinical and Radiographic Outcome Measurements. Patient assessments were completed preoperatively, during hospitalization, and postoperatively at 6 weeks and at 3, 6, 12, and 24 months. Clinical outcomes were assessed using back, leg, and graft site pain questionnaires, short form SF36, Oswestry Low Back Pain Disabilityquestionnaire, and work status. Back and leg symptoms were assessed separately on a visual analog scale. , Both intensity of pain and duration of pain in back and leg symptoms were measured on a ten-point numerical rating scale. Adding the numeric rating scores for pain intensity and pain duration allowed examiners to derive a composite back and leg pain score—i.e., ranging from 0 (no pain) to 20 (maximum pain).

Radiographs and computed tomography (CT) scans were used to evaluate fusion at 6, 12, and 24 months after surgery. Plain radiographs including standing lateral and flexion-extension lateral were obtained at each interval. Thin-cut 1-mm CT scans were taken at 6, 12 and 24 months. Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent, blinded radiologist was used to adjudicate conflicting fusion findings. Fusion was defined as an absence of radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation less than 5° on flexion-extension radiographs, and continuous bone growth connecting the vertebral bodies. Patients who had secondary surgeries because of persistent low back symptoms and clinically suspected nonunions were considered as

Deleted: scores

Deleted: Back and leg pain intensity and the duration of these symptoms were assessed using a 20-point numeric rating scale

Deleted: pain

Deleted: given

Deleted:

Deleted: a

Deleted: visual analog

Deleted: There was 77 agreement between the radiologists reviewing the studies. At 6, 12, and 24 months after surgery, agreement between the independent reviewers was 72%. ¶

Deleted: trabecular

having failed fusions and were classified as failures in all fusion calculations, regardless of their independent radiological assessment.

Clinical and Radiographic Follow-up. **The rate of patient return for follow-up was at least 89.6% at all postoperative periods. At 12 months, the rate of patient return for both treatment groups was at least 90 %. At 24 months, the follow-up rate for the investigational group was 89.6% and the control group rate was 100%.**

Surgical Technique.

An open posterior interbody fusion procedures was carried out in each patient. Preoperatively, the patients disc space was templated to determine the appropriate intraoperative disc space distraction and cage size. Plain radiographs we reassessed to determine normal disc space height of the adjacent spinal motion segments. Axial CT scan or MR images were used to establish the anterior-posterior dimension of the disc space to ensure proper cage sizing.

The patient was placed in the prone position on padded bolsters that support the chest and pelvis and suspend the abdomen. Care was taken to ensure that the pelvis is extended to ensure that lumbar lordosis was preserved. The operating room table accommodated plain radiographs or fluoroscopy.

A complete laminectomy with facetectomies or extensive bilateral laminotomies and facetectomies with preservation of the midline elements was performed in each case. The lateral borders of the disc were exposed along with the traversing and exiting nerve roots. Bilateral annulotomies were made and a complete discectomy was carried through these annular windows. The annulotomies were placed lateral to the dural tube. The midportion of the lateral annular window was centered adjacent to the medial wall of pedicle. The anterior

Deleted: ??
Deleted:
Deleted: ??
Deleted: ??
Deleted: was
Deleted: ??
Deleted: are assessed
Deleted: are used
Deleted: is taken
Deleted: are placed

and lateral walls of the annulus were preserved; the entire nucleus is removed. Cartilaginous end plates were resected using curettes.

Reduction of sagittal and frontal plane deformities was achieved through disc space height restoration and annular tensioning. Inserting progressively larger dilators into the collapsed disc restored disc space height and the normal sagittal contours of the spine.

The vertebral end plates were prepared with reamers that uniformly cut a channel through the adjacent bony end plates. Great care was taken to visualize and gently retract both the traversing and exiting nerve roots. These soft tissue elements were protected by a tubular reamer guide, which was impacted into the disc space prior to reaming. Care was taken to ensure that the endplate cuts were made parallel and equally into each end plates.

The INTER FIX™ cages were packed with either the rhBMP-2 soaked sponges or morcellized autograft prior to insertion. The cages were sequentially inserted in the disc space and away from any soft tissue or neural elements. The cages were not routinely recessed within the disc space. The majority of the cages were left flush to the posterior cortical wall of the vertebral bodies. Their position was assessed intraoperatively with plain radiographs or fluoroscopy.

Iliac crest bone graft harvesting

The control group received autogenous iliac crest graft placed within the cages. The bone graft was harvested from the outer table of the iliac wing. The graft was morcellized using a rongeur and was tightly packed into the cages before their insertion.

rhBMP-2 preparation

The rhBMP-2 used was reconstituted using sterile water and was used as a single dose of 1.5 mg/mL in all study patients. The 1.5 mg rhBMP-2/mL solution was

Deleted: is taken

Deleted: are

Deleted: INTERFIX

Deleted:

Deleted: morcellized

applied to a bovine collagen sponge and allowed to bind to the sponge for 15 minutes. **The dosage of rhBMP-2 varied by patient depending on cage size, with the total dose ranging from 4.0 mg to 8.0 mg.** The rhBMP-2 soaked sponge was then placed in the hollow central portion of the INTER FIX™ device before its insertion into the prepared disc space. No additional sponges were placed outside of the devices. No autogenous grafts were used in the investigational group.

Postoperatively, patients were placed in a soft lumbar corset. Activities were advanced by the treating physician. Isometric strengthening and exercise program were started at six weeks postoperatively.

Statistical Methods

The data from this clinical trial were analyzed using the statistical software package SAS® version 6.12. For comparisons between the groups for continuous variables, *p*-values are from ANOVA, and for categorical variables, they are from Fisher's exact test or chi-square test. For changes (improvements) from the preoperative within each group, the p-values are from the paired t-test.

RESULTS

Surgery

The mean operative time in the investigational rhBMP-2 group (2.6 hours) was less than in the control group (3.0 hours) (Table 2). The average blood loss in the rhBMP-2 group was 322.8 ml as compared to 372.7 ml in the control group. The average hospital stay was less in the investigational group (3.4 days for the investigational group vs. 5.2 days for the control group). None of these differences between treatment groups

Deleted: ??
Deleted: ??
Deleted: INTERFIX
Deleted: ??
Deleted: P
Deleted:
Deleted: test, ??
Deleted: wth
Deleted:
Deleted:

was statistically significant. There were no unanticipated device-related adverse events in either treatment group.

Complications

Vascular events.

One control patient developed deep venous thrombosis and was treated with anticoagulation medications.

Iliac crest graft site. In the control group, adverse events related to harvesting of the iliac crest graft were identified in two patients (6.1%). These events included one case of pain and one hematoma. Neither of these patients required additional surgery. There were no graft site adverse events in the investigational group since the use of rhBMP-2 precluded the need to harvest bone graft.

The level of postoperative pain and morbidity associated with the iliac crest graft harvesting was measured using numeric rating scales for pain intensity and duration (Figure 1). After surgery, all of the control patients experienced hip donor site pain. The highest levels of pain were noted immediately after surgery with a mean score of 11.6 points out of 20 points. The percentage of patients experiencing pain decreased over time; however, at 24 months after surgery, 60% of the control patients still experienced pain (i.e., had scores grater than 0). At two years, the graft site pain scores averaged 5.5 points out of 20 and 13.3% of the patients still felt that the appearance of the graft site bothered them some.

Deleted: ??
Deleted: a
Deleted: were
Deleted: , adverse
Deleted: ??
Deleted: (??%).
Deleted: ?? infections and ??
Deleted: s
Deleted: ??
Deleted: an
Deleted: Table
Deleted:
Deleted: ??
Deleted: nearly ??one-third??
Deleted: (??%)
Deleted: ,
Deleted: ??
Deleted: points
Deleted: ,

Antibody Testing

Antibody results. Antibodies to rhBMP-2, bovine Type I collagen, and human Type I collagen were evaluated preoperatively and 3 months postoperatively using enzyme-linked immunosorbent assays (ELISAs). None of the patients in either group tested positive for antibodies to rhBMP-2 or human Type I collagen. The incidence of bovine Type I collagen antibody formation in the investigational group was 13.3% whereas the incidence in the control group was 35.7%. No negative clinical consequence to the positive collagen antibody test results was evident.

Deleted: ??
Deleted: ??
Deleted: The results were similar between the investigational and control groups (??% and ??%, respectively).
Deleted: ??There appeared to be
Deleted: no negative clinical consequence to positive antibody test results
Deleted: ??

Clinical Outcomes

Oswestry Disability Questionnaire scores. The Oswestry Low Back Pain Disability Questionnaire measured pain associated with activities. The Oswestry Questionnaire was administered preoperatively as well as at each postoperative visit. At all postoperative visits, both treatment groups demonstrated highly significant improvements as compared with the preoperative scores (Figure 2,). At all postoperative time intervals after the first 6-week follow-up period, the investigational group showed greater improvements over the control group in the mean overall Oswestry scores. At last follow-up at 24 months, the mean improvements in the Oswestry scores were 29.6 points in the investigational group and 24.9 points in the controls (Figure 3)In the rhBMP-2 group, 69% of patients showed an improvement of at least 15points in their disability scores at 12 months after surgery as compared with 55.6% of patients in the control group. At 24 months,

Deleted: statistical
Deleted: that were maintained through two years
Deleted: Table
Deleted: ??
Deleted: ??
Deleted: Figure ??).
Deleted: ??%
Deleted: %
Deleted: ??%

the 76.0% of the investigational group was improved and compared favorably with 64.3% improved in the control group.(See Table 3)

Back Pain. The mean back pain scores at all postoperative periods were improved from the preoperative mean values for both treatment groups. The mean improvements in back pain scores at all five postoperative intervals studied were greater for the investigational group than for the control autograft group (Figure 4). **At 24 month the average improvement in back pain in the investigation group was almost twice that of the control group 9 point improvement vs. 4.5 point improvement). This difference was highly significant with a p-value of 0.0002.**

Leg Pain. Leg pain was assessed in a similar manner using a 20-point numeric rating scale that reflects both the intensity and duration of painful symptoms. Mean leg pain scores improved significantly after surgery in each group (Figure 5). At each study interval average leg pain scores were less (better) in the investigational group when compared to the control group. Similarly, the investigational group also showed higher average improvement scores at each interval studied. **At 24 months, the average improvement in leg pain was 7.7 points in the investigational group compared to 6.5 points in the control group. This difference was not statistically significant.**

Short Form SF36. At all postoperative intervals studied the investigational group showed greater improvement in the physical component of the short form SF36 when compared to the controls (Figure 6).

Work Status. Many factors affect a patient's work status, such as the nature of the work performed and ability of the work place to accommodate work restrictions.

Deleted: ??%
Deleted: ??%
Deleted: (?? point
Deleted: ??
Deleted: Statistics??
Deleted: for
Deleted: Table
Deleted: However, at each
Deleted: ??
Deleted: ??
Deleted: Statistics??
Deleted: both
Deleted: and mental
Deleted: s
Deleted: s

Prior to surgery, in the investigational group only 26.5% were gainfully employed while over 45.5% of the control patients were employed (Table 3). **For patients who were working before surgery, the median return to work time was 43 days in the investigational group and 137 days in the control group**. Although striking, this difference was not statistically significant. At last follow-up, more people in the investigational treatment group were working than were working before their surgery. At 2 years following surgery in the investigational group, 12 patients were employed while only 9 were employed before surgery. At the 24-month follow-upin the control group, 18 were working before surgery and 14 were working at two years after surgery. In other words, percent of the investigational patients working went from 26.5% before surgery to 35.3% at two years, while in the control group the rate went from 45.5% to 42.4%. Although none of these changes are statistically significant, the trend is promising and may be reflective of the statistically significant difference of lower back pain in the investigational patients.

Deleted: 22%??
Deleted: 40
Deleted: ??
Deleted: ??
Deleted: 14
Deleted: 8
Deleted: The percentage of people working in the control group remained unchanged a
Deleted: .1
Deleted: 14

Patient Satisfaction. **At 12 and 24 months after surgery, the results were similar in each treatment group. At 24 months, 72.6% of the investigational patients and 80.0% of the controls were satisfied** (answering definitely true or mostly true) **with their surgical outcomes. In the investigational group, 69.0% said they would undergo surgery again** (answering definitely true or mostly true) **compared with 83.3% of the control patients who would undergo surgery again. In the investigational group, 72.4% believed that they were helped as much as they had expected to be from the surgery; 70.0% of the control group felt they had been. None of these subjective differences was statistically significant.**

Deleted: ??
Deleted: ??%
Deleted: ??%
Deleted: ??%
Deleted: ??%
Deleted: ??%
Deleted: ??

Radiographic Outcomes

Cage placement

Cage placement was assessed on both plain radiographs and thin-cut CT scan. The CT scans were found to reflect more accurately the position of the cage in relation to the spinal canal posteriorly and neuroforamina laterally. There were no differences between the two patient groups regarding cage placement(Did you want an X-ray or CT or a figure?). Only 6% of patients in each group (2/34 investigational group; 2/33 control group) showed cages that were countersunk 3mm or more from the posterior margin of the vertebral body. Approximately one-third of patients in each group had cages that extended into the spinal canal on postoperative CT studies (11/34 investigational group; 10/33 control group). The remainder of the cages were placed either flush to the posterior cortex of the vertebral bodies or were recessed by only 2mm or less.

Deleted: more accurately

Deleted: (Figure)

Sagittal plane balance

Nearly one third of patients (19/67; 28%) postoperatively had some sagittal plane imbalance following surgery. At the last follow-up, 6 patients had some residual spondylolithesis from failure to fully reduce the deformity at the time of surgery (up to Grade I spondylolisthesis was allowed) and two patients developed spondylolithesis postoperatively. Eleven patients had residual retrolithesis following surgery.

Deleted: Preoperatively, 22 patients had a grade 1 spondylolithesis.

Intradiscal bone formation

Fusion status of the study patients was evaluated on plain radiographs and CT scans. At six months after surgery, 93.1% of patients in both the investigational and control groups had evidence of fusion At 12 months, in the investigational group the

Deleted: (Table)

fusion rate dropped to 85.2% while the control group maintained a fusion rate of 92%. This decrease in fusion ratemay have, in part, been related to poor follow-up in the investigational group at the 12-month time frame. **(Seven investigational and eight control patients were recorded as non-union because they failed to obtain radiographs during this time period.)** At 24 months, the investigational group had a 92.3% fusion rate, which was more than 14 percentage points higher than that of the control group (77.8%). While this difference was not statistically significant, it does show a positive trend in favor of the investigational group.

Bone formation outside of the disc space

The thin cut 1.0 mm CT scans were able to identify new bone formation adjacent to the interbody fusion cages. New bone formation extending outside of the disc space and into the spinal canal or neuroforamina was found in 28 patients (23 investigational and 5 controls. *Sagittal plane balance.* In the control group, one of the 5 patients (20%) with bone in the spinal canal had a residual unreduced spondylolithesis following surgery. New bone formation was identified in the canal posterior to the unreduced superior vertebra. In the control group, new bone formation was identified in four patients extending into the spinal canal in patients with normal segmental sagittal plane balance.

In the investigational group, 10 of the 23 patients (43%) with bone in the spinal canal had some residual postoperative sagittal plane imbalance. Five patients (5/23; 22%) had spondylolithesis and 5 (5/23;22%) had retrolithesis. In each of these cases, new bone formation occurred posterior to the unreduced vertebral body. Thirteen

Deleted: is
Deleted: was
Deleted: 22
Deleted: patients
Deleted: Column two
Deleted: Interval. In the control group, 30 patients (92%) showed evidence of fusion at one year. However, at
Deleted:
Deleted: . Five patients (15%) in the control group had new formation in the spinal canal while 23 patients (68%) in the investigational group had bone formation outside of the disc space. ¶

patients had a normal segmental sagittal plane balance and new bone formation in the spinal canal.

Cage placement.

In the investigational group cage placement was strongly associated with the development of bone in the spinal canal. In the investigational group 39% of patients with cages placed at the margin or within 2mm of the margin of the posterior vertebral cortex developed some bone in the spinal canal. Twelve percent of patients in the control group with cages placed within 2mm of the vertebral margins developed bone in the spinal canal.

Secondary Surgical Procedures

In the investigational group, 3 of 34 (8.8%) had second surgery failures; 4 of 34 (11.8%) had second spinal surgeries, but not failures; and 7 of 34 (20.6%) had some type of secondary spinal surgery. Two investigational patients received supplemental fixation for presumed psuedarthrosis.

In the control group, 3 of 33 (9.1%) had second surgery failures; 3 of 33 (9.1%) had second spinal surgeries, but not failures; and 9 of 33 (27.3%) had some type of secondary spinal surgery. Three control patients received supplemental fixation for presumed pseudarthrosis..

Deleted: 77 patients (77%) had a second surgery and 77 patients (77%) in the control group had second surgeries. 77 investigational patients underwent supplemental fixation for presumed pseudarthrosis. 77 underwent supplemental fixation after posterior decompression for persistent radicular symptoms after the initial surgery. 9 in the control group, 77 patients underwent supplemental posterior fixation for a presumed pseudarthrosis and 77 underwent supplemental posterior fixation for persistent discogenic pain.

DISCUSSION

Threaded cylindrical cages represent a new, distinct class of segmental spinal fixation devices. These devices were not designed as spacers that require segmental stabilization; rather, they were designed as stand-alone intervertebral devices that function as an "instrumented PLIF." Threaded interbody devices are biomechanically different from interbody spacers. Biomechanical studies have shown that cage size has some significance in stand-alone cage fusions; however, stand-alone cages do not significantly increase spinal stiffness in studies using human cadavers.(add reference) Larger cages improve stiffness in rotation and lateral bending. Reduction of motion in flexion is not significantly improved with larger cages. Larger cages require more extensive facet joint resection or complete facetectomy, which further destabilizes the spinal motion segment. A cylindrical device increases in its medial-lateral dimension equal to its increase in height, which necessitates greater mobilization and retraction of the neural elements.

Deleted: i
Deleted: is
Deleted: of

Initial clinical studies reported high rates of fusion and clinical success in certain centers. These results have not been widely reproduced. Authors of clinical and radiographic studies on stand-alone interbody implants without supplemental fixation have reported fusion rates between 83% and 100%. Hacker (20) compared two groups of patients treated for disabling back pain. One group was treated with a stand-alone PLIF using BAK implants, and the other group was treated with combined anteroposterior fusion. He found equal patient satisfaction between the two groups. Ray (48) presented a prospective series of 236 patients treated with stand-alone interbody fusion and reported a 96% fusion rate at two years after surgery. These fusion criteria

did correlate with improved clinical outcomes. In this study group, only 65% had good to excellent clinical outcomes on the Prolo scale and 14% had a poor result.

This study shows that extra bone formation in the spinal canal may occur following PLIF procedures with cylindrical interbody fusion cages. Bone formation in the spinal canal occurred in both the control group and investigational group. Bone formation in the spinal canal appears to be a multi-factorial event. Bone formation in the spinal canal is largely dependent upon cage placement and sagittal balance of the instrumented vertebral motion segment. Patients with residual sagittal plane imbalance form bone behind the unreduced vertebral segment. This may be the result of lifting of a periosteal flap along the posterior cortex of the listhesed vertebral body. Cages placed that were not recessed within the confines of the disc space margins were also associated with bone formation in the spinal canal.

rhBMP-2 on an absorbable collagen sponge has been shown to induce bone formation in the intervertebral disc space. Prior studies have shown that this montage will routinely produce a fusion zone extending 3mm around the cage. It is not surprising that bone may extend into the spinal canal when cages containing rhBMP-2 are not recessed 3mm or more within the confines of the disc space.

The PLIF procedure using threaded cylindrical fusion cages disrupts a wide channel, which includes the posterior margin of the disc, the posterior longitudinal ligament and annular structures. This injury can result in adjacent bone formation, which can extend into the spinal canal. This new bone formation is best visualized on

Deleted: This study is a prospective clinical evaluation of a stand-alone PLIF procedure. The randomized patient groups did not statistically significant differences in the variables assessed. Clinical and radiographic follow-up exceeded 72% at all intervals. The use of recombinant human bone morphogenetic protein has been shown to accelerate fusion in both animal models and in human clinical trials. Improved clinical outcomes with the use of rhBMP-2 with stand-alone interbody cages have also been established in clinical trials.

Deleted: S

Deleted: S

Deleted: R

CT scan. Both the control group and investigational group exhibited bone formation outside of the disc space following this procedure.

Bone formation in the spinal canal had no discernable influence on patient outcomes. Bone formation in the spinal canal following the PLIF procedure with stand-alone cylindrical interbody fusion cages appears to be a radiographic finding alone with no associated clinical sequalae.

This study, because of its small size, amounted to a pilot study of the ability of a bone morphogenetic protein to replace autograft in a stand-alone PLIF cage procedure. Even though the number of patients was small, a statistically significant improvement in back pain in the rhBMP-2 investigational patients was found. Although the other findings were not statistically different, if just the clinical outcome data at two years are examined (Table 3), all of the outcomes measured, except for the subject question given to the patients about satisfaction, favored the investigational group. These findings imply that a larger study would have shown statistical improvements in all clinically important outcomes. Predicting such a result can be based not only upon the data in the pilot study data presented here, but also upon the large-scale human clinical spinal trials of rhBMP-2 already conducted. The same protein studied here, used in the same concentration inside metal cages for the same lumbar indication but from a different approach (anterior), has been shown to be superior to autograft., (add reference to superiority paper in press in Journal of Spinal Disorders). The direction of implantation of a cage should not affect the ability of INFUSE Bone Graft contained inside to form bone.

In conclusion, this detailed, independent review of the results, which represent the first use of osteoinductive proteins in a PLIF procedure, are encouraging. These findings along with other studies for other indications imply that future larger PLIF studies with rhBMP-2 are needed. In future studies using modified surgical techniques, such as using more recessed cages to allow for extra posterior bone formation, adding steps to minimize bleeding, and/or adding secondary instrumentation may be beneficial. Further, possibly modifying patient selection, such as entering patients with less vertebral slip, may also help minimize the confounding variables. All of these changes may produce even better, more convincing evidence that INFUSE Bone Graft can also be used as substitute for autograft in PLIF procedures.

ACKNOWLEDGEMENTSSpecial thanks to the following doctors who were principal or co-principal clinical investigators at the 14 sites for this study. These surgeons in alphabetical order are Drs.C. William Bacon, Steven Barnes, Charles Branch, Randall Dryer, Paul Geibel, Fred Geisler, Scott Graham, Peter Holiday, Timothy Holt, Zenko Hrynkiw, Dennis Maiman, David Masel, Bruce Mathern, Christopher Meyer, Phillip Tibbs, and Frank Tomecek. The work of the Clinical Research Department at Medtronic Sofamor Danek in collecting the clinical data and performing the statistical analyses is acknowledged.

Deleted: ¶

REFERENCES

. Boden SD, Schimandle JH, Hutton WC. 1995 Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 1995;20:2633-44.

. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25:376-81.

. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. Neurosurg Focus 2001;10:1-9.

. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999;24:629-36.

. Sandhu HS, Kanim LEA, Toth JM, et al. Experimental spinal fusion with recombinant human bone morphogenetic protein-2 without decortication of osseous elements. Spine 1997;22:1171-80.

. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995; 20:1326-37.

. Urist MR. Bone: Formation by autoinduction. Science 1965;150:893-9.

TABLE 1.

Patient Demographics

	INFUSE Bone Graft	Iliac Crest Autograft
Age (yr.)	46.3	46.1
Weight (lbs.)	180.5	176.8
Sex (% males)	50.0	45.5
Worker's Compensation (%)	23.5	27.3
Spinal Litigation (%)	8.8	3.0
Tobacco Use (%)	52.9	45.5
Previous Surgery (%)	32.3	39.4

A Prospective, Randomized Posterior Lumbar Interbody Fusion Study Using rhBMP-2 with Cylindrical Interbody Cages

Regis Haid, MD[‡]

Joseph Alexander MD [†]

Charlie Branch MD*

J. Kenneth Burkus MD[§]

[‡] Professor, Department of Neurosurgery, Emory University, Atlanta, Georgia

[†] Assistant professor, Department of Neurosurgery

* Chairman, Department of Neurosurgery,

[§] Spine Surgeon at The Hughston Clinic, Columbus, Georgia

Address correspondence and reprint requests to J.K. Burkus, MD, The Hughston Clinic, [redacted]

ABSTRACT

Study Design. In a multi-center, prospective, randomized, non-blinded, 2-year study, 67 patients who underwent a single-level posterior lumbar interbody fusion with two paired cylindrical threaded titanium fusion devices were randomized into two groups: one received recombinant human bone morphogenetic protein-2 (rhBMP-2) on a collagen sponge carrier, the other autogenous iliac crest bone graft.

Objectives. The objective of the study was to determine the clinical and radiographic outcomes in patients treated for single-level degenerative lumbar disc disease with a posterior interbody fusion using stand-alone cylindrical threaded titanium fusion cages with autogenous bone graft or rhBMP-2 and an absorbable collagen sponge carrier.

Summary of Background Data. In a large series of human patients undergoing open anterior lumbar interbody fusion with a tapered titanium fusion cage, rhBMP-2 on a bovine collagen sponge has been shown to decrease operative time and blood loss, to promote osteoinduction and fusion, and to be a safe and effective substitute for iliac crest harvesting.

Methods. In this prospective non-blinded study, 67 patients were randomized into 2 groups that underwent interbody fusion using two cylindrical threaded fusion cages: the investigational group (34 patients) that received rhBMP-2 on an absorbable collagen sponge and a control group (33 patients) that received autogenous iliac crest bone graft. Assessment of a patient's clinical outcome was based on low back and leg pain numerical rating scales, Short Form SF36 questionnaire, Oswestry Low Back Pain Disability questionnaire, and work status. Plain radiographs and computed tomographic scans were used to evaluate fusion at 6,12 and 24 months postoperatively.

Results. The mean operative time and blood loss for the investigational rhBMP-2 group was 2.6 hours and 322.8 mL, respectively. For the autograft control group these values were 3.0 hours and 372.7 mL. Although not statistically different, at 24 months, the investigational group's fusion rate of 92.3% was higher than the control's at 77.8%. At all postoperative intervals, the mean Oswestry, back pain and leg pain scores and physical components of the SF36 improved in both treatment groups compared with the preoperative scores. A statistically significant difference in the change in back pain was found at 24 months for the investigational group. In the control group, two adverse events related to harvesting of the iliac crest graft occurred in two patients (6.1%), and, at 24 months after surgery, 3.0% of the patients still reported graft site discomfort.

Conclusions. Although not statistically different, on average the investigational group had shorter operative times and less blood loss. At 24 months, this group had a fusion rate that was more than 14 percentage points greater than the control group. All clinical outcome measurements that were studied showed, on average, greater improvement in the investigational (rhBMP-2) patients with a statistically significant improvement in back pain. Overall results show that the use of rhBMP-2 can eliminate the need for harvesting iliac crest graft and a positive trend for being an equivalent or better replacement for autograft for use in successful posterior lumbar interbody fusions. Further studies of the use of rhBMP-2 in PLIF cage procedures are needed.

Key words: posterior lumbar interbody fusion, bone morphogenetic protein, osteoinduction, radiography, interbody fusion cages

Key points:

- At 24 months, the average rate of fusion for patients treated with rhBMP-2 was more than 14 percentage points higher (92.3% vs. 77.8%) than for patients treated with autograft. This difference, while large and promising, was not statistically different (p=0.250).
- The average operative time was 2.6 hours for patients treated with rhBMP-2 compared with 3.0 hours in the autograft group. Although not statistically different, the change was nearly so (p=0.065).
- Blood loss tended to be less for patients treated with rhBMP-2 than for patients who underwent iliac crest bone graft harvesting.
- At all postoperative assessment intervals, patients in both treatment groups showed improvement in Oswestry disability scores, in back and leg pain outcomes and in the PCS scores of the SF36.
- The use of rhBMP-2 in posterior lumbar interbody fusion procedures eliminates the complications of iliac crest bone harvesting including postoperative pain.
- Future studies of the use of INFUSE Bone Graft in PLIF cages are needed.

Précis

In a 2-year prospective randomized study of 67 patients, the investigational group that received rhBMP-2 paired with cylindrical cage devices tended to have a higher rate of fusion, reduced operative times, and decreased blood loss when compared with the control group that received the same cylindrical cage device filled with autogenous bone graft. Clinical outcomes trended towards greater improvement in the rhBMP-2 group at 3, 6, 12 and 24 months. At 2-years, the rhBMP-2 group had statistically less back pain. The rhBMP-2 group avoided the complications that can arise from an iliac crest bone harvesting procedure.

INTRODUCTION

Posterior lumbar interbody fusion (PLIF) is an effective treatment for patients with symptomatic degenerative disc disease, spondylolithesis and other painful discogenic syndromes. Fusion of the degenerative and unstable lumbar spinal motion segment can give significant relief from this disabling and often progressive condition. PLIF limits the extent of posterolateral soft tissue exposure, muscle stripping, and injury. With this technique, the surgeon uses the traditional posterior approach to the lumbar spine; however, dissection is limited laterally to the facet joints. Through this approach, direct neural decompression can be completed, disc space height and sagittal balance can be restored, and intervertebral grafts can be placed in a biomechanically advantageous position.

Lumbar spine stabilization procedures that limit the extent of posterior spinal muscles exposure have some significant advantages. With PLIF surgical techniques, the fusion bed is within the disc space and it eliminates the exposure of the transverse processes. The PLIF approach to the lumbosacral spine enables the surgeon to re-establish the normal anatomic alignment and relationships of the spinal motion segment while avoiding excessive injury to the posterior paravertebral muscles.

Cloward (**add reference**) presented his technique for this innovative procedure in 1953. In his surgical technique, he described using a wide laminectomy and facetectomies that would allow for the placement of large structural bone grafts in the denuded and meticulously prepared disc space. Later, Lin (**add reference**) modified this intervertebral grafting technique of structural grafts. This modified PLIF technique involves filling the disc space with cancellous bone strips, allowing for preservation of a

portion the posterior elements and avoiding the complication of insertion of large structural grafts. Additional modifications of the bone graft technique and bone graft materials have been made. Kushlich **(add reference)**and Ray **(add reference)** introduced the idea of using threaded interbody fusion cages inserted through a PLIF approach as a means of stabilizing the lumbar motion segment, increasing rates of fusion and improving clinical outcomes.

Recombinant human bone morphogenetic protein 2 (rhBMP-2) applied to an absorbable collagen sponge carrier has been shown**(add references)** to promote osteoinduction and fusion in the lumbar spine. In a large series of patients who underwent stand-alone anterior lumbar interbody fusion with fusion cages, rhBMP-2 was shown to enhance rates of fusion, reduce surgical time and improve clinical outcomes **(add reference)**. To further evaluate this method of bone graft replacement, we evaluated the clinical and radiographic outcomes at 24 months of 67 patients who underwent a single level PLIF. We compared the outcomes in the investigational patients (rhBMP-2) with those in the control patients (autogenous bone).

MATERIALS AND METHODS

Study Design. Between March 1999 and December 1999, 67 patients with degenerative disc disease completed surgery in this prospective, randomized, non-blinded, FDA approved study at 14 investigational sites. All patients underwent a single-level posterior lumbar fusion with two paired INTER FIX™ devices (Medtronic Sofamor Danek, Memphis, TN). The interbody fusion cages were used as stand-alone construct in the disc space from L2 to S1, with the majority being L4-L5. Patients were randomly assigned in a 1:1 manner to one of two groups: the investigational group received rhBMP-2 on an absorbable collagen sponge carrier and the control group received autogenous iliac crest bone graft taken from a posterior approach. INFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, TN) is the trademarked name for recombinant human bone morphogenetic protein-2 applied to an absorbable collagen sponge.

Patient Data. Preoperatively, all patients had symptomatic, single-level degenerative lumbar disc disease and symptoms of disabling low back or leg pain, or both, of at least 6 months duration that had not responded to non-operative treatments. The two treatment groups were similar demographically (Table 1). No statistically significant differences ($p < 0.05$) were found for any of the pre-operative variables. The rhBMP-2 group consisted of 34 patients and the control group consisted of 33 patients. The average age at surgery was 46.3 years for the rhBMP-2 group and 46.1 years for the control group. In the rhBMP-2 group, 18 patients (52.9%) had used tobacco within 6 months before surgery compared with 15 patients (45.5%) in the control group. The percentage of patients with pending litigation was 8.8% and 3.0% in the rhBMP-2 and

control groups, respectively. The percentage of patients seeking worker's compensation was 23.5% in the rhBMP-2 group and 27.3.6% in the control group.

Clinical and Radiographic Outcome Measurements. Patient assessments were completed preoperatively, during hospitalization, and postoperatively at 6 weeks and at 3, 6, 12, and 24 months. Clinical outcomes were assessed using back, leg, and graft site pain questionnaires, short form SF36, Oswestry Low Back Pain Disability questionnaire, and work status. Back and leg symptoms were assessed separately on a visual analog scale. Both intensity of pain and duration of pain in back and leg symptoms were measured on a ten-point numerical rating scale. Adding the numeric rating scores for pain intensity and pain duration allowed examiners to derive a composite back and leg pain score—i.e., ranging from 0 (no pain) to 20 (maximum pain).

Radiographs and computed tomography (CT) scans were used to evaluate fusion at 6, 12, and 24 months after surgery. Plain radiographs including standing lateral and flexion-extension lateral were obtained at each interval. Thin-cut 1-mm CT scans were taken at 6, 12 and 24 months. Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent, blinded radiologist was used to adjudicate conflicting fusion findings. Fusion was defined as an absence of radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation less than 5° on flexion-extension radiographs, and continuous bone growth connecting the vertebral bodies. Patients who had secondary surgeries because of persistent low back symptoms and clinically suspected non-unions were considered as

having failed fusions and were classified as failures in all fusion calculations, regardless of their independent radiological assessment.

Clinical and Radiographic Follow-up. The rate of patient return for follow-up was at least 89.6% at all postoperative periods. At 12 months, the rate of patient return for both treatment groups was at least 90 %. At 24 months, the follow-up rate for the investigational group was 89.6% and the control group rate was 100%.

Surgical Technique.

An open posterior interbody fusion procedure was carried out in each patient. Preoperatively, the patients disc space was templated to determine the appropriate intraoperative disc space distraction and cage size. Plain radiographs were reassessed to determine normal disc space height of the adjacent spinal motion segments. Axial CT scan or MR images were used to establish the anterior-posterior dimension of the disc space to ensure proper cage sizing.

The patient was placed in the prone position on padded bolsters that support the chest and pelvis and suspend the abdomen. Care was taken to extend the pelvis to ensure that lumbar lordosis was preserved. The operating room table accommodated plain radiographs or fluoroscopy.

A complete laminectomy with facetectomies or extensive bilateral laminotomies and facetectomies with preservation of the mid-line elements was performed in each case. The lateral borders of the disc were exposed along with the traversing and exiting nerve roots. Bilateral annulotomies were made and a complete discectomy was carried through these annular windows. The annulotomies were placed lateral to the dural tube. The midportion of the lateral annular window was centered adjacent to the medial wall

of pedicle. The anterior and lateral walls of the annulus were preserved; the entire nucleus was removed. Cartilaginous end plates were resected using curettes.

Reduction of sagittal and frontal plane deformities was achieved through disc space height restoration and annular tensioning. Inserting progressively larger dilators into the collapsed disc restored disc space height and the normal sagittal contours of the spine.

The vertebral end plates were prepared with reamers that uniformly cut a channel through the adjacent bony end plates. Great care was taken to visualize and gently retract both the traversing and exiting nerve roots. These soft tissue elements were protected by a tubular reamer guide, which was impacted into the disc space prior to reaming. Care was taken to ensure that the endplate cuts were made parallel and equally into each end plate.

The INTER FIX™ cages were packed with either the rhBMP-2 soaked sponges or morsecellized autograft prior to insertion. The cages were sequentially inserted in the disc space and away from any soft tissue or neural elements. The cages were not routinely recessed within the disc space. The majority of the cages were left flush to the posterior cortical wall of the vertebral bodies. Their position was assessed intraoperatively with plain radiographs or fluoroscopy.

Iliac crest bone graft harvesting

The control group received autogenous iliac crest graft placed within the cages. The bone graft was harvested from the outer table of the iliac wing. The graft was morscellized using a rongeur and was tightly packed into the cages before their insertion.

rhBMP-2 preparation

The rhBMP-2 was reconstituted using sterile water and was used as a single dose of 1.5 mg/mL in all study patients. The 1.5 mg rhBMP-2/mL solution was applied to a bovine collagen sponge and allowed to bind to the sponge for 15 minutes. The dosage of rhBMP-2 varied by patient depending on cage size, with the total dose ranging from 4.0 mg to 8.0 mg. The rhBMP-2 soaked sponge was then placed in the hollow central portion of the INTER FIX™ device before its insertion into the prepared disc space. No additional sponges were placed outside of the devices. No autogenous grafts were used in the investigational group.

Postoperatively, patients were placed in a soft lumbar corset. The treating physician decided when the patient would advance in activities. Isometric strengthening and exercise program were started at six weeks postoperatively.

Statistical Methods

The data from this clinical trial were analyzed using the statistical software package SAS® version 6.12. For comparisons between the groups for continuous variables, *p*-values are from ANOVA, and for categorical variables, they are from Fisher's exact test or chi-square test. For changes (improvements) from the preoperative within each group, the p-values are from the paired t-test.

RESULTS

Surgery

The mean operative time in the investigational rhBMP-2 group (2.6 hours) was less than in the control group (3.0 hours) (Table 2). The average blood loss in the rhBMP-2 group was 322.8 ml as compared to 372.7 ml in the control group. The

average hospital stay was less in the investigational group (3.4 days for the investigational group vs. 5.2 days for the control group). None of these differences between treatment groups was statistically significant, although the time of surgery approached significance (p=0.065). No unanticipated device-related adverse events occurred in either treatment group.

Complications

Vascular events.

One control patient developed deep venous thrombosis and was treated with anticoagulation medications.

Iliac crest graft site. In the control group, adverse events related to harvesting of the iliac crest graft were identified in two patients (6.1%). These events included one case of pain and one hematoma. Neither of these patients required additional surgery. Obviously, no graft site adverse events occurred in the investigational group since the use of rhBMP-2 precluded the need to harvest bone graft.

The level of postoperative pain and morbidity associated with the iliac crest graft harvesting was measured using numeric rating scales for pain intensity and duration (Figure 1). After surgery, all of the control patients experienced hip donor site pain. The highest levels of pain were noted immediately after surgery with a mean score of 11.6 points out of 20 points. The percentage of patients experiencing pain decreased over time; however, at 24 months after surgery, 60% of the control patients still experienced pain (i.e., had scores greater than 0). At two years, the graft site pain scores averaged 5.5 points out of 20 and 13.3% of the patients still felt that the appearance of the graft site bothered them some and 3.0% of the patients still reported graft site discomfort.

Antibody Testing

Antibody results. Antibodies to rhBMP-2, bovine Type I collagen, and human Type I collagen were evaluated preoperatively and 3 months postoperatively using enzyme-linked immunosorbent assays (ELISAs). None of the patients in either group tested positive for antibodies to rhBMP-2 or human Type I collagen. The incidence of bovine Type I collagen antibody formation in the investigational group was 13.3% whereas the incidence in the control group was 35.7%. No negative clinical consequence to the positive collagen antibody test results was evident.

Clinical Outcomes

Oswestry Disability Questionnaire scores. The Oswestry Low Back Pain Disability Questionnaire measured pain associated with activities. The Oswestry Questionnaire was administered preoperatively as well as at each postoperative visit. At all postoperative visits, both treatment groups demonstrated highly significant improvements as compared with the preoperative scores (Figure 2). At all postoperative time intervals after the first 6-week follow-up period, the investigational group showed greater improvements over the control group in the mean overall Oswestry scores. At last follow-up at 24 months, the mean improvements in the Oswestry scores were 29.6 points in the investigational group and 24.9 points in the controls (Figure 2). In the rhBMP-2 group, 69% of patients showed an improvement of at least 15 points in their disability scores at 12 months after surgery as compared with 65.6% of patients in the control group. At 24 months, the 76.0% of the investigational

group was improved and compared favorably with 64.3% improved in the control group. (Table 3)

Back Pain. The mean back pain scores at all postoperative periods were improved from the preoperative mean values for both treatment groups. The mean improvements in back pain scores at all five postoperative intervals studied were greater for the investigational group than for the control autograft group (Figure 4). At 24 months, the average improvement in back pain in the investigational group was almost twice that of the control group (9 point improvement vs. 4.5 point improvement). This difference was highly significant with a p-value of 0.009.

Leg Pain. Leg pain was assessed in a similar manner using a 20-point numeric rating scale that reflects both the intensity and duration of painful symptoms. Mean leg pain scores improved significantly after surgery in each group (Figure 5). At each study interval average leg pain scores were less (better) in the investigational group when compared to the control group. Similarly, the investigational group also showed higher average improvement scores at each interval studied. At 24 months, the average improvement in leg pain was 7.7 points in the investigational group compared to 6.5 points in the control group. This difference was not statistically significant.

Short Form SF-36. At all postoperative intervals studied the investigational group showed greater improvement in the physical component of the short form SF36 when compared to the controls (Figure 6).

Neurological Status. Preoperatively and at all five post-operative time points, the motor, sensory, reflexes, and straight leg raise measurements were essentially the same for both treatment groups and showed no statistical differences. At 24 months,

using the protocol criteria for determining overall neurological success, which represents a combination of the four neurological measurements, both groups had 100% success. Table 3 contains the change from pre-operative results at 24 months for the motor, sensory, reflex, and straight leg raise measurements.

Work Status. Many factors affect a patient's work status, such as the nature of the work performed and ability of the work place to accommodate work restrictions. Prior to surgery, in the investigational group only 26.5% were gainfully employed while over 45.5% of the control patients were employed (Table 3). For patients who were working before surgery, the median return to work time was 43 days in the investigational group and 137 days in the control group. Although striking, this difference was not statistically significant. At last follow-up, more people in the investigational treatment group were working than were working before their surgery. At 2 years following surgery in the investigational group, 12 patients were employed while only 9 were employed before surgery. In the control group, 15 were working before surgery and 14 were working at two years after surgery. In other words, the percent of the investigational patients working went from 26.5% before surgery to 35.3% at two years, while in the control group the rate went from 45.5% to 42.4%. Although none of these changes are statistically significant, the trend is promising and may be reflective of the statistically significant difference of lower back pain in the investigational patients.

Patient Satisfaction. At 12 and 24 months after surgery, the results were similar in each treatment group. At 24 months, 72.4% of the investigational patients and 80.0% of the control patients were satisfied (answering definitely true or mostly true) with their surgical outcomes. In the investigational group, 69.0% said they would undergo surgery

again (answering definitely true or mostly true) compared with 83.3% of the control patients who would undergo surgery again. In the investigational group, 72.4% believed that they were helped as much as they had expected to be from the surgery; 70.0% of the control group felt they had been. None of these subjective differences was statistically significant.

Radiographic Outcomes

Cage placement

Cage placement was assessed on both plain radiographs and thin-cut CT scan. The CT scans were found to reflect more accurately the position of the cage in relation to the spinal canal posteriorly and neuroforamina laterally. No differences between the two patient groups regarding cage placement were detected. **(In the draft you sent us you asked for a table here, but we wondered if you meant for an X-ray or CT here? Because so many other tables and figures are included in the manuscript, you might consider not having anything since the sentence alone may be sufficient.)** Only 6% of patients in each group (2/34 investigational group; 2/33 control group) showed cages that were countersunk 3mm or more from the posterior margin of the vertebral body. Approximately one-third of patients in each group had cages that extended into the spinal canal on postoperative CT studies (11/34 investigational group; 10/33 control group). The remainder of the cages were placed either flush to the posterior cortex of the vertebral bodies or were recessed by only 2mm or less.

Sagittal Plane Balance

Nearly one third of patients (19/67; 28%) postoperatively had some sagittal plane imbalance following surgery. At the last follow-up, 6 patients had some residual

spondylolithesis from failure to fully reduce the deformity at the time of surgery (up to Grade I spondylolisthesis was allowed) and two patients developed spondylolithesis postoperatively. Eleven patients had residual retrolithesis following surgery.

Intradiscal bone formation

Fusion status of the study patients was evaluated on plain radiographs and CT scans. At six months after surgery, 93.1% of patients in both the investigational and control groups had evidence of fusion. At 12 months, in the investigational group the fusion rate dropped to 85.2% while the control group maintained a fusion rate of 92%. This decrease in fusion rate may have, in part, been related to poor follow-up in the investigational group at the 12-month time frame. (Seven investigational and eight control patients were recorded as non-union because they failed to obtain radiographs during this time period.) At 24 months, the investigational group had a 92.3% fusion rate, which was more than 14 percentage points higher than that of the control group (77.8%). While this difference was not statistically significant, it does show a positive trend in favor of the investigational group.

Bone formation outside of the disc space

The thin cut 1.0 mm CT scans were able to identify new bone formation adjacent to the interbody fusion cages. New bone formation extending outside of the disc space and into the spinal canal or neuroforamina was found in 28 patients (23 investigational and 5 controls.

Sagittal plane balance.

In the control group, one of the 5 patients (20%) with bone in the spinal canal had a residual unreduced spondylolithesis following surgery. New bone formation was

identified in the canal posterior to the unreduced superior vertebra. In the control group, new bone formation was identified in four patients extending into the spinal canal in patients with normal segmental sagittal plane balance.

In the investigational group, 10 of the 23 patients (43%) with bone in the spinal canal had some residual postoperative sagittal plane imbalance. Five patients (5/23; 22%) had spondylolithesis and 5 (5/23;22%) had retrolithesis. In each of these cases, new bone formation occurred posterior to the unreduced vertebral body. Thirteen patients had a normal segmental sagittal plane balance and new bone formation in the spinal canal.

Cage placement.

In the investigational group cage placement was strongly associated with the development of bone in the spinal canal. In the investigational group 39% of patients with cages placed at the margin or within 2mm of the margin of the posterior vertebral cortex developed some bone in the spinal canal. Twelve percent of patients in the control group with cages placed within 2mm of the vertebral margins developed bone in the spinal canal.

Secondary Surgical Procedures

In the investigational group, 3 of 34 (8.8%) had second surgery failures; 4 of 34 (11.8%) had second spinal surgeries, but not failures; and 7 of 34 (20.6%) had some type of secondary spinal surgery. Two investigational patients received supplemental fixation for presumed pseudarthrosis.

In the control group, 3 of 33 (9.1%) had second surgery failures; 3 of 33 (9.1%) had second spinal surgeries, but not failures; and 9 of 33 (27.3%) had some type of secondary spinal surgery. Three control patients received supplemental fixation for presumed pseudarthrosis.

DISCUSSION

Threaded cylindrical cages represent a new, distinct class of segmental spinal fixation devices. These devices were not designed as spacers that require segmental stabilization; rather, they were designed as stand-alone intervertebral devices that function as an "instrumented PLIF." Threaded interbody devices are biomechanically different from interbody spacers. Biomechanical studies have shown that cage size has some significance in stand-alone cage fusions; however, stand-alone cages do not significantly increase spinal stiffness in studies using human cadavers. **(add reference)** Larger cages improve stiffness in rotation and lateral bending. Reduction of motion in flexion is not significantly improved with larger cages. Larger cages require more extensive facet joint resection or complete facetectomy, which further destabilizes the spinal motion segment. A cylindrical device increases in its medial-lateral dimension equal to its increase in height, which necessitates greater mobilization and retraction of the neural elements.

Initial clinical studies reported high rates of fusion and clinical success in certain centers. These results have not been widely reproduced.**(add references)** Authors of clinical and radiographic studies on stand-alone interbody implants without supplemental fixation have reported fusion rates between 83% and 100% **(add references)**. Hacker **(add reference)** compared two groups of patients treated for disabling back pain; one group was treated with a stand-alone PLIF using BAK implants, and the other group was treated with combined anteroposterior fusion. He found equal patient satisfaction between the two groups. Ray **(add reference)** presented a prospective series of 236 patients treated with stand-alone interbody fusion

and reported a 96% fusion rate at two years after surgery. These fusion criteria did correlate with improved clinical outcomes. In this study group, only 65% had good to excellent clinical outcomes on the Prolo scale and 14% had a poor result.

However, performing PLIF procedures or any other type of spinal fusion with autograft from the iliac crest comes with a price in pain for the patient. Figure 1 shows that the iliac crest graft site pain in this study was found to be similar to that measured in the same way for a larger study of the LT-CAGE Device **(add reference to Burkus et al J. Spinal Disorders 15 (5):337, 2002)** with two exceptions. First, in this study the pain at 24 months was 5.5 on a scale of 20, while in the anterior LT-CAGE study, the value was 1.8. Second, in this posterior INTER FIX study, 60% of the patients had some pain at 24 months, while in the LT-CAGE study 32% did. Although these were two different studies using different surgeons, different numbers of cases (30 vs.118), and different sizes of cages (the INTER FIX cage is cylindrical and the LT-CAGE version is a smaller volume tapered design), these results are consistent with a review of other studies that showed that a posterior approach to the iliac crest is more painful for the patients. **(Reference DW Polly and TR Kuklo "Bone Graft Donor Site Pain" SRS abstract 2002)** For whatever reason, the measured iliac crest graft site pain scores in this study imply that, from the patients' point of view, the need for an autograft replacement in PLIF cylindrical cage procedures is greater than in ALIF tapered cage procedures.

This study shows that extra bone formation in the spinal canal may occur following PLIF procedures with cylindrical interbody fusion cages regardless of the source of the bone graft since bone formation in the spinal canal occurred in both the

control and investigational groups. Bone formation in the spinal canal appears to be a multi-factorial event. Bone formation in the spinal canal is largely dependent upon cage placement and sagittal balance of the instrumented vertebral motion segment. Patients with residual sagittal plane imbalance form bone behind the unreduced vertebral segment. This may be the result of lifting of a periosteal flap along the posterior cortex of the listhesed vertebral body. Cages placed that were not recessed within the confines of the disc space margins were also associated with bone formation in the spinal canal.

rhBMP-2 on an absorbable collagen sponge has been shown to induce bone formation in the intervertebral disc space.**(Reference)** Prior studies have shown that this montage will routinely produce a fusion zone extending 3mm around the cage. It is not surprising that bone may extend into the spinal canal when cages containing rhBMP-2 are not recessed 3mm or more within the confines of the disc space.

The PLIF procedure using threaded cylindrical fusion cages disrupts a wide channel, which includes the posterior margin of the disc, the posterior longitudinal ligament and annular structures. This injury can result in adjacent bone formation, which can extend into the spinal canal. This new bone formation is best visualized on CT scan. Both the control group and investigational group exhibited bone formation outside of the disc space following this procedure.

Bone formation in the spinal canal had no discernable influence on patient outcomes. Bone formation in the spinal canal following the PLIF procedure with stand-alone cylindrical interbody fusion cages appears to be a radiographic finding alone with no associated clinical sequalae.

This study, because of its small size, amounted to a pilot study of the ability of a bone morphogenetic protein to replace autograft in a stand-alone PLIF cage procedure. Even though the number of patients was small, a statistically significant improvement in back pain in the rhBMP-2 investigational patients was found. Although the other findings were not statistically different, if just the surgical and clinical outcome data at two years are examined (Tables 2 & 3), all of the outcomes measured (except for two out of three of the subject patient satisfaction questions) favored the investigational group. These finding imply that a larger study would have shown statistical equivalence or improvement in all clinically important outcomes. Predicting such a result can be based not only upon the data in the pilot study presented here, but also upon the large-scale human clinical spinal trials of rhBMP-2 already conducted. The same protein studied here, used in the same concentration inside metal cages for the same lumbar indication but from a different approach (anterior), has been shown in a 679 patient analysis to be superior to autograft. **(suggest adding a reference to superiority paper in press in Journal of Spinal Disorders).** The direction of implantation of a cage should not affect the ability of INFUSE Bone Graft contained inside to form bone.

In conclusion, this detailed, independent review of the results, which represent the first use of osteoinductive proteins in a PLIF procedure, are encouraging. These findings along with other studies for other indications imply that future larger PLIF studies with rhBMP-2 are needed. In future studies using modified surgical techniques, such as using more recessed cages to allow for extra posterior bone formation, adding steps to minimize bleeding and surgical variables, using narrower, non-cylindrical cages that would be easier to put in and cause less tissue destruction, and/or adding

secondary instrumentation may be beneficial. Further, possibly modifying patient selection, such as entering patients with less vertebral slip, may also help minimize the confounding variables. All of these changes may produce more convincing evidence that INFUSE Bone Graft can also be used as a substitute for autograft in PLIF cage procedures.

ACKNOWLEDGEMENTS

Special thanks to the following doctors who were principal or co-prinicipal clinical investigators at the 14 sites for this study. These surgeons in alphabetical order are Drs.C. William Bacon, Steven Barnes, Charles Branch, Randall Dryer, Paul Geibel, Fred Geisler, Scott Graham, Peter Holiday, Timothy Holt, Zenko Hrynkiw, Dennis Maiman, David Masel, Bruce Mathern, Christopher Meyer, Phillip Tibbs, and Frank Tomecek. The work of the Clinical Research Department at Medtronic Sofamor Danek in collecting the clinical data and performing the statistical analyses is acknowledged.

REFERENCES

. Boden SD, Schimandle JH, Hutton WC. 1995 Volvo Award Winner in Basic Sciences: The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 1995;20:2633-44.

. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25:376-81.

. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. Neurosurg Focus 2001;10:1-9.

. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999;24:629-36.

. Sandhu HS, Kanim LEA, Toth JM, et al. Experimental spinal fusion with recombinant human bone morphogenetic protein-2 without decortication of osseous elements. Spine 1997;22:1171-80.

. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995; 20:1326-37.

. Urist MR. Bone: Formation by autoinduction. Science 1965;150:893-9.

Table 1

Patient Demographic Information

Variable	Investigational (n=34)	Control (n=33)	p-value *
Age (years) [mean (range)]	46.3 (25.8 – 66.1)	46.1 (28.5 – 70.9)	0.928
Weight (lb) [mean ± s.d.]	180.5 ± 38.4	172.8 ± 35.7	0.400
Gender [n (%)]			
Male	17 (50)	15 (45.5)	0.808
Female	17 (50)	18 (54.5)	
Worker's compensation [n (%)]	8 (23.5)	9 (27.3)	0.784
Spinal litigation [n (%)]	3 (8.8)	1 (3.0)	0.614
Tobacco used [n (%)]	18 (52.9)	15(45.5)	0.628
Alcohol use [n (%)]	15 (44.1)	9 (27.3)	0.204
Preoperative work status [n (%) working]	9 (26.5)	15 (45.5)	0.131
Previous back surgery [n (%)]	12 (35.3)	13 (39.4)	0.803

- For continuous variables, p-values are from ANOVA and for categorical variables, they are from Fisher's exact.

Table 2

Surgical Parameters

	Investigational	Control
Mean operative time	2.6 hours	3.0 hours
Average blood loss	322.8 ml	372.7 ml
Average hospital stay	3.4 days	5.2 days

Table 3

24 Month Clinical Outcome Parameters

	Investigational	Control
Improvement Points in Oswestry Score	29.6	24.9
% Patients with ≥15 point Oswestry Improvement	69%	55.6%
% Patients with Oswestry Improvement	76.0%	64.3%
Back Pain Improvement from Pre-Op (Points)	9*	4.5
Leg Pain Average Improvement from Pre-Op (Points)	7.7	6.5
Motor change from Pre-Op	4.5	2.8
Sensory Change from Pre-Op	8.0	2.8
Reflex change from Pre-Op	7.0	5.4
Straight Leg Raise change from Pre-Op	48.0	39.3
Net Change in % patients working	+8.8%	-3.1%
Median return to work time	43 days	137 days
Fusion rate	97.3%	77.8%

*statistically different

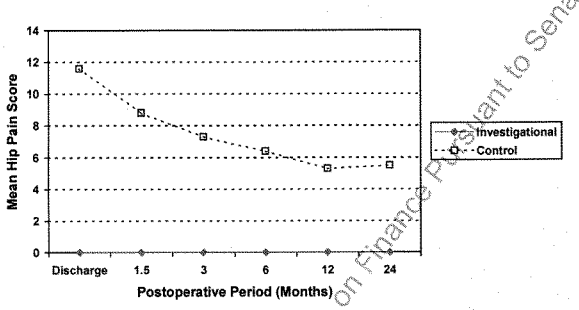


Figure 1. **Mean hip pain scores over the time**

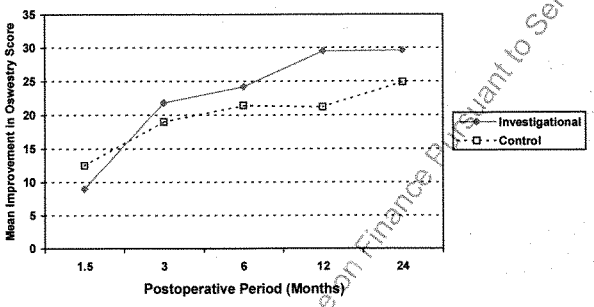


Figure 2. **Mean improvement in Oswestry scores over the time**

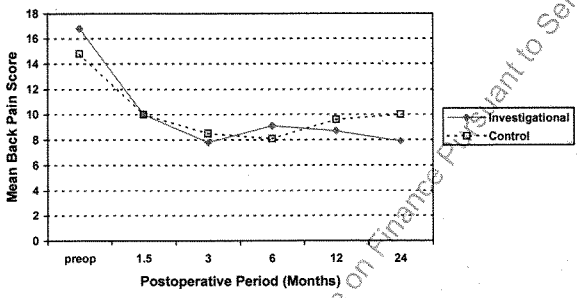


Figure 3. **Mean back pain scores over the time**

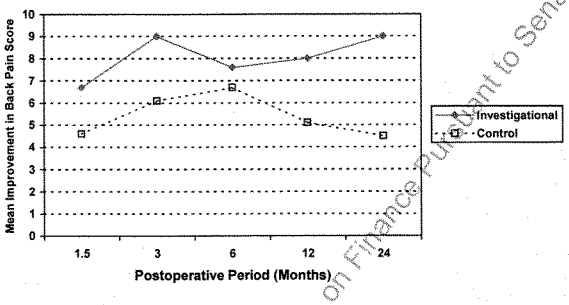


Figure 4. **Mean improvement in back pain scores over the time**

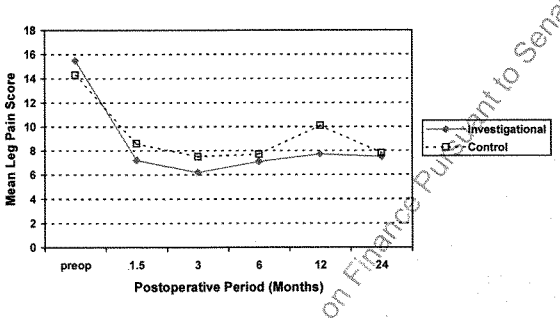


Figure 5. **Mean leg pain scores over the time**

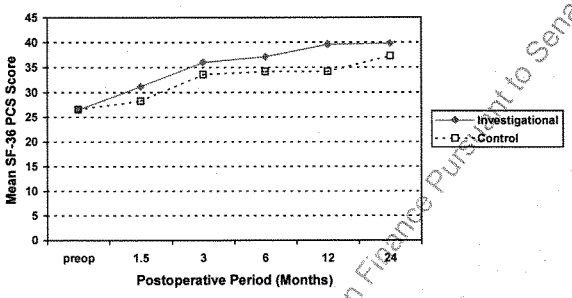


Figure 6. **Mean SF-36 PCS scores over the time**

From: Burkus, J. Kenneth
Sent: Monday, May 19, 2003 12:04:52 PM
To: Treharne, Rick
Subject: CONFIDENTIAL

Attachments: PLIF BMP paper.submited.doc

Posterior Lumbar Interbody Fusion Using rhBMP-2 with Cylindrical Interbody Cages

Regis W. Haid, Jr., MD*

Charles L. Branch, Jr., MD†

Joseph T. Alexander, MD‡

J. Kenneth Burkus, MD§

*Professor, Department of Neurosurgery, Emory University School of Medicine, Atlanta, Georgia

†Professor and Chair, Department of Neurosurgery, Wake Forest School of Medicine, Winston-Salem, North Carolina

‡Assistant Professor, Department of Neurosurgery, Wake Forest School of Medicine, Winston-Salem, North Carolina

§Spine Surgeon, The Hughston Clinic, Columbus, Georgia

Address correspondence and reprint requests to J. K. Burkus, MD, The Hughston Clinic, [redacted]

ABSTRACT

Background context: In a large series of human patients undergoing open anterior lumbar interbody fusion with a tapered titanium fusion cage, rhBMP-2 on a bovine collagen sponge has been shown to decrease operative time and blood loss, to promote osteoinduction and fusion, and to be a safe and effective substitute for iliac crest harvesting.

Purpose: The purpose of the study was to determine the clinical and radiographic outcomes in patients treated for single-level degenerative lumbar disc disease with a posterior interbody fusion using stand-alone cylindrical threaded titanium fusion cages with either autogenous bone graft or rhBMP-2 and an absorbable collagen sponge carrier.

Study design/setting: In a, prospective, randomized, nonblinded, 2-year study at 14 investigational sites, 67 patients underwent posterior lumbar interbody fusion using two paired cylindrical threaded titanium fusion devices. Patients were randomly assigned to one of two groups: one received recombinant human bone morphogenetic protein-2 (rhBMP-2) on a collagen sponge carrier, the other autogenous iliac crest bone graft.

Patient sample: Between March 1999 and December 1999, 67 patients with symptomatic, single-level degenerative lumbar disc disease of at least 6 months duration underwent a single-level posterior lumbar interbody fusion.

Outcome measures: Clinical outcomes were measured using low back and leg pain numerical rating scales, the Short Form 36, Oswestry Low Back Pain Disability Questionnaire, and work status. Plain radiographs and computed tomographic scans were used to evaluate fusion at 6,12 and 24 months after surgery. For comparisons between the groups for continuous variables, *P*-values are from ANOVA, and for categorical variables, they are from Fisher's exact tests or chi-

Deleted: 02/20/2003

square tests. For changes (improvements) from the preoperative within each group, the *P* values are from paired *t* tests.

Methods: In this prospective nonblinded study, 67 patients were randomized into 2 groups that underwent interbody fusion using two cylindrical threaded fusion cages: the investigational group (34 patients) who received rhBMP-2 on an absorbable collagen sponge and a control group (33 patients) who received autogenous iliac crest bone graft.

Results: The mean operative time and blood loss for the investigational rhBMP-2 group was 2.6 hours and 322.8 mL, respectively. For the autograft control group, these values were 3.0 hours and 372.7 mL. Although not statistically different, at 24 months, the investigational group's fusion rate of 92.3% was higher than the control's at 77.8%. At all postoperative intervals, the mean Oswestry, back and leg pain scores, and physical components of the SF-36 improved in both treatment groups compared with preoperative scores. A statistically significant difference in the change in back pain was found at 24 months for the investigational group. In the control group, two adverse events related to harvesting of the iliac crest graft occurred in two patients (6.1%).

Deleted: %), and, at 24 months after surgery, 3.0% of the patients still reported graft site discomfort.

Conclusions: Although not statistically different, the investigational group had shorter average operative times and less blood loss. At 24 months, this group had a fusion rate that was more than 14 percentage points greater than the control group. All clinical outcome measurements that were studied showed, on average, greater improvement in the investigational (rhBMP-2) patients with a statistically significant improvement in back pain. Overall results show that the use of rhBMP-2 can eliminate the need for harvesting iliac crest graft and may be an equivalent or better replacement for autograft for use in successful posterior lumbar interbody fusions. Further studies of the use of rhBMP-2 in PLIF cage procedures are needed.

Deleted: a positive trend for being

Deleted: 02/20/2003

Key words: posterior lumbar interbody fusion, bone morphogenetic protein, osteoinduction, radiography, interbody fusion cages

INTRODUCTION

Posterior lumbar interbody fusion (PLIF) is an effective treatment for patients with symptomatic degenerative disc disease, spondylolisthesis, and other painful discogenic syndromes. Fusion of the degenerative and unstable lumbar spinal motion segment can give significant relief from this disabling and often progressive condition.[1-4] PLIF limits the extent of posterolateral soft tissue exposure, muscle stripping, and injury. With this technique, the surgeon uses the traditional posterior approach to the lumbar spine; however, dissection is limited laterally to the facet joints. Through this approach, direct neural decompression can be completed, disc space height and sagittal balance can be restored, and intervertebral grafts can be placed in a biomechanically advantageous position.

Lumbar spine stabilization procedures that limit the extent of posterior spinal muscle exposure have some significant advantages. With PLIF surgical techniques, the fusion bed is within the disc space, which eliminates the exposure of the transverse processes. The PLIF approach to the lumbosacral spine enables the surgeon to re-establish the normal anatomic alignment and the relationships of the spinal motion segment while avoiding excessive injury to the posterior paravertebral muscles.[2-4, 13, 24.]

Cloward [1] presented his technique for this innovative procedure in 1953. In his surgical technique, he described using a wide laminectomy and facetectomies that would allow for the placement of large structural bone grafts in the denuded and meticulously prepared disc space. Later, Lin and associates [2] modified this intervertebral grafting technique of structural grafts.

Deleted: 02/20/2003

This modified PLIF technique involves filling the disc space with cancellous bone strips, allowing for preservation of a portion of the posterior elements and avoiding the complication of insertion of large structural grafts. Additional modifications of the bone graft technique and bone graft materials have been made. Kuslich et al. [3] and Ray [4] introduced the idea of using threaded interbody fusion cages inserted through a PLIF approach as a means of stabilizing the lumbar motion segment, increasing rates of fusion and improving clinical outcomes.

Recombinant human bone morphogenetic protein type 2 (rhBMP-2) [5] applied to an absorbable collagen sponge carrier has been shown to promote osteoinduction and fusion in the lumbar spine [6-9]. In a large series of patients who underwent stand-alone anterior lumbar interbody fusion with fusion cages, rhBMP-2 was shown to enhance rates of fusion, reduce surgical time, and improve clinical outcomes [10,11] To further evaluate this method of bone graft replacement, we evaluated the clinical and radiographic outcomes at 24 months of 67 patients who underwent a single level PLIF. We compared the outcomes in the investigational patients (rhBMP-2) with those in the control patients (autogenous bone).

MATERIALS AND METHODS

Study Design. Between March 1999 and December 1999, 67 patients` with degenerative disc disease underwent surgery in this prospective, randomized, non-blinded, FDA-approved study at 14 investigational sites. All sites had local Investigational Review Board approval and the

` Although the study was originally planned to enter hundreds of patients, some preliminary CT-scans at 6 months of early patients revealed bone resorbtion to the PLIF cages. Out an abundance of caution, enrollment was suspended. By the time it was determined that the radiographic finding did not affect clinical outcome, the use of stand alone PLIF cages had gone out of favor and the study was not restarted.

Deleted: 02/20/2003

patients entered into the study gave their informed consent. All patients underwent a single-level posterior lumbar interbody fusion with two paired INTER FIX™ devices (Medtronic Sofamor Danek, Memphis, TN). The interbody fusion cages were used as stand-alone construct in the disc space from L2 to S1, with the majority being L4-L5. Patients were randomly assigned in a 1:1 manner to one of two groups: the investigational group who received rhBMP-2 on an absorbable collagen sponge carrier and the control group who received autogenous iliac crest bone graft taken from the posterior approach. INFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, TN) is the trademarked name for recombinant human bone morphogenetic protein type 2 applied to an absorbable collagen sponge.

Patient Data. Preoperatively, all patients had symptomatic, single-level degenerative lumbar disc disease and symptoms of disabling low back or leg pain, or both, of at least 6-months duration that had not responded to nonoperative treatment. Patients could also have up to Grade I spondylolisthesis. The investigational, or rhBMP-2, group comprised 34 patients, and the control group comprised 33 patients. The two treatment groups were similar demographically (Table 1). No statistically significant differences ($P < 0.05$) were found for any of the preoperative variables.

Clinical and Radiographic Outcome Measurements. Patient assessments were completed preoperatively, during hospitalization, and postoperatively at 6 weeks and at 3, 6, 12, and 24 months. Clinical outcomes were assessed using back, leg, and graft-site pain questionnaires, Short Form (SF-36), Oswestry Low Back Pain Disability Questionnaire, and work status. Back and leg symptoms were assessed separately on a visual analog scale. The intensity of pain and

the duration of pain in back and leg symptoms were measured on a ten-point numeric rating scale. Adding the numeric rating scores for pain intensity and pain duration allowed examiners to derive a composite back and leg pain score, which ranged from 0 (no pain) to 20 (maximum pain).

Radiographs and computed tomography (CT) scans were used to evaluate fusion at 6, 12, and 24 months after surgery [12]. Standing lateral and flexion-extension lateral radiographic views were obtained at each follow-up interval. Thin-cut 1-mm CT scans were taken at 6, 12 and 24 months. Two independent, blinded radiologists interpreted all radiographs and CT scans. A third, independent, blinded radiologist was used to adjudicate conflicting fusion findings. Fusion was defined as an absence of radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation of less than 5° on flexion-extension radiographs, and continuous bone growth connecting the vertebral bodies. Patients who had secondary surgeries because of persistent low back symptoms and clinically suspected nonunions were considered as having failed fusions and were classified as failures in all fusion calculations, regardless of their independent radiologic assessment.

Clinical and Radiographic Follow-up. The rate of patient return for follow-up was at least 89.6% at all postoperative periods. At 12 months, the rate of patient return for both treatment groups was at least 90%. At 24 months, the follow-up rate for the investigational group was 89.6% and the control group's rate was 100%.

Surgical Technique

Deleted: 02/20/2003

An open posterior interbody fusion procedure was carried out in each patient. Preoperatively, the patient's disc space was templated to determine the appropriate intraoperative disc space distraction and cage size. Plain radiographs were reassessed to determine normal disc space height of the adjacent spinal motion segments. Axial CT scans or MR images were used to establish the anterior-posterior dimension of the disc space to ensure proper cage sizing.

The patient was placed in the prone position on padded bolsters that support the chest and pelvis and suspend the abdomen. Care was taken to extend the pelvis to ensure that lumbar lordosis was preserved. The operating room table accommodated plain radiographs or fluoroscopy.

We performed a complete laminectomy with facetectomies or extensive bilateral laminotomies and facetectomies with preservation of the midline elements in each patient. The lateral borders of the disc were exposed along with the traversing and exiting nerve roots. Bilateral annulotomies were made and a complete discectomy was carried through these annular windows. The annulotomies were placed lateral to the dural tube. The midportion of the lateral annular window was centered adjacent to the medial wall of the pedicle. The anterior and lateral walls of the annulus were preserved; the entire nucleus was removed. Cartilaginous end plates were resected using curettes.

Reduction of sagittal and frontal plane deformities was achieved through disc space height restoration and annular tensioning. Inserting progressively larger dilators into the collapsed disc restored disc space height and the normal sagittal contours of the spine.

 Deleted: 02/20/2003

The vertebral end plates were prepared with reamers that uniformly cut a channel through the adjacent bony end plates. Great care was taken to visualize and gently retract both the traversing and exiting nerve roots. A tubular reamer guide that was impacted into the disc space protected these soft tissue elements before reaming. Care was taken to ensure that the end plate cuts were made parallel and equally into each end plate.

The INTER FIX™ cages were packed with either the rhBMP-2 soaked sponges or morcellized autograft before they were inserted. The cages were inserted sequentially in the disc space and away from any soft tissue or neural elements. The cages were not routinely recessed within the disc space. The majority of the cages were left flush to the posterior cortical wall of the vertebral bodies. Their position was assessed intraoperatively with plain radiographs or fluoroscopy.

Iliac crest bone graft harvesting. The control group received autogenous iliac crest graft placed within the cages. The bone graft was harvested from the outer table of the iliac wing. The graft was morcellized using a rongeur and was tightly packed into the cages before their insertion.

RhBMP-2 preparation. The rhBMP-2 was reconstituted using sterile water and was used as a single dose of 1.5 mg/mL in all study patients. The 1.5 mg rhBMP-2/mL solution was applied to a bovine collagen sponge and allowed to bind to the sponge for 15 minutes. The dose of rhBMP-2 varied by patient depending on cage size, with the total dose ranging from 4.0 mg to 8.0 mg. The rhBMP-2 soaked sponge was then placed in the hollow central portion of the INTER FIX™

Deleted: 02/20/2003

device before its insertion into the prepared disc space. No additional sponges were placed outside of the devices. No autogenous grafts were used in the investigational group.

Postoperatively, patients were placed in a soft lumbar corset. The treating physician decided when the patient would advance in activities. Isometric strengthening and exercise programs were started at six weeks after surgery.

Statistical Methods

The data from this clinical trial were analyzed using the statistical software package SAS® version 6.12. For comparisons between the groups for continuous variables, *P*-values are from ANOVA, and for categorical variables, they are from Fisher's exact tests or chi-square tests. For changes (improvements) from the preoperative within each group, the *P*-values are from paired t-tests.

RESULTS

Surgery

The mean operative time, average blood loss, and average hospital stay were less for the investigational group than for the control group (Table 2). None of these differences between treatment groups was statistically significant, although the time of surgery approached

Deleted: 02/20/2003

significance ($P = 0.065$). No unanticipated device-related adverse events occurred in either treatment group.

Complications

Vascular events. One control patient developed deep venous thrombosis and was treated with anticoagulation medications.

Neurological events. Three investigational (8.8%) and 2 controls (6.1%) had dural tears. As far as neurological complications, in the investigational patients 16 events occurred in 14 patients, while in the control 18 events occurred in 14 patients.

Formatted

Iliac crest graft site. In the control group, adverse events related to harvesting of the iliac crest graft were identified in two patients (6.1%). These events included one case of pain and one hematoma. Neither of these patients required additional surgery. Obviously, no graft site adverse events occurred in the investigational group since the use of rhBMP-2 precluded the need to harvest bone graft.

The level of postoperative pain and morbidity associated with the iliac crest graft harvesting was measured using numeric rating scales for pain intensity and duration (Figure 1). After surgery, all of the control patients experienced hip donor site pain. The highest levels of pain were noted immediately after surgery with a mean score of 11.6 points out of 20 points. The percentage of patients experiencing pain decreased over time; however, at 24 months after surgery, 60% of the control patients still experienced pain (i.e., had scores greater than 0). At two years, the graft site

Deleted: 02/20/2003

pain scores averaged 5.5 points out of 20 and 13.3% of the patients still felt that the appearance of the graft site bothered them some.

Deleted: and 3.0% of the patients still reported graft site discomfort.

Antibody Testing

Antibody results. Antibodies to rhBMP-2, bovine Type I collagen, and human Type I collagen were evaluated preoperatively and 3 months postoperatively using enzyme-linked immunosorbent assays (ELISAs). None of the patients in either group tested positive for antibodies to rhBMP-2 or human Type I collagen. The incidence of bovine Type I collagen antibody formation in the investigational group was 13.3% whereas the incidence in the control group was 35.7%. No negative clinical consequence to the positive collagen antibody test results was evident. GELFOAM sponge was used in 15 of the 34 (44%) investigational patients. Of these 15, 2 developed antibody formations to bovine collagen. GELFOAM sponge was also used in 20 of 33 (61%) of the controls. Of these 20, 7 had antibody formation to the bovine collagen

Clinical Outcomes

Oswestry Disability Questionnaire scores. The Oswestry Low Back Pain Disability Questionnaire measured pain associated with activities. The Oswestry Questionnaire was administered preoperatively as well as at each postoperative visit. At all postoperative visits, both treatment groups demonstrated highly significant improvements as compared with the preoperative scores (Figure 2). At all postoperative time intervals after the first 6-week follow-up period, the investigational group showed greater improvements over the control group in the

 Deleted: 02/20/2003

mean overall Oswestry scores. At last follow-up at 24 months, the mean improvements in the Oswestry scores were 29.6 points in the investigational group and 24.9 points in the controls (Figure 2). In the investigational group, 69% of patients showed an improvement of at least 15 points in their disability scores at 12 months after surgery as compared with 55.6% of patients in the control group. At 24 months, the 76.0% of the investigational group was improved and compared favorably with 64.3% improved in the control group (Table 3).

Back Pain. The mean back pain scores at all postoperative periods were improved from the preoperative mean values for both treatment groups. The mean improvements in back pain scores at all five postoperative intervals studied were greater for the investigational group than for the control autograft group (Figure 4). At 24 months, the average improvement in back pain in the investigational group was almost twice that of the control group (9 point improvement vs. 4.5 point improvement). This difference was highly significant with a *P* value of 0.009.

Leg Pain. Leg pain was assessed in a similar manner using a 20-point numeric rating scale that reflects both the intensity and duration of painful symptoms. Mean leg pain scores improved significantly after surgery in each group (Figure 5). At each study interval, average leg pain scores were less (better) in the investigational group when compared with the control group. Similarly, the investigational group also showed higher average improvement scores at each interval studied. At 24 months, the average improvement in leg pain was 7.7 points in the investigational group compared to 6.5 points in the control group. This difference was not statistically significant.

 Deleted: 02/20/2003

Short Form SF-36. At all postoperative follow-up intervals, the investigational group showed greater improvement in the physical component of the short form SF-36 when compared with the controls (Figure 6).

Neurological Status. Preoperatively and at all five postoperative time points, the motor, sensory, reflexes, and straight-leg-raise measurements were essentially the same for both treatment groups and showed no statistical differences. At 24 months, using the protocol criteria for determining overall neurological success, which represents a combination of the 4 neurological measurements, both groups had 100% success. Table 3 contains the change from preoperative results at 24 months for the motor, sensory, reflex, and straight-leg-raise measurements.

Work Status. Many factors affect a patient's work status, such as the nature of the work performed and ability of the work place to accommodate work restrictions. Before surgery, only 26.5% of the investigational group was employed while more than 45.5% of the control patients were employed (Table 3). For patients who were working before surgery, the median return-to-work interval was 43 days in the investigational group and 137 days in the control group. Although marked, this difference was not statistically significant. At last follow-up, more people in the investigational treatment group were working than were working before their surgery. At 2 years after surgery, 12 patients in the investigational group were employed while only 9 were employed before surgery. In the control group, 15 were working before surgery and 14 were working at 2 years after surgery. In other words, the percent of the investigational patients working went from 26.5% before surgery to 35.3% at two years, while in the control group the rate went from 45.5% to 42.4%. Although none of these changes are statistically significant, the

trend is promising and may be reflective of the statistically significant difference of lower back pain in the investigational patients.

Patient Satisfaction. At 12 and 24 months after surgery, the results were similar in each treatment group. At 24 months, 72.4% of the investigational patients and 80.0% of the control patients were satisfied (answering definitely true or mostly true) with their surgical outcomes. In the investigational group, 69.0% said they would undergo surgery again (answering definitely true or mostly true) compared with 83.3% of the control patients who would undergo surgery again. In the investigational group, 72.4% believed that they were helped as much as they had expected to be from the surgery; 70.0% of the control group felt they had been. None of these subjective differences was statistically significant.

Radiographic Outcomes

Cage placement. Cage placement was assessed on both plain radiographs and thin-cut CT scan. The CT scans were found to reflect more accurately the position of the cage in relation to the spinal canal posteriorly and neuroforamina laterally. No differences between the two patient groups regarding cage placement were detected. Only 6% of patients in each group (2/34 in the investigational group; 2/33 in the control group) showed cages that were countersunk 3 mm or more from the posterior margin of the vertebral body. Approximately one-third of patients in each group had cages that extended into the spinal canal on postoperative CT studies (11/34 in the investigational group; 10/33 in the control group). The remainder of the cages were placed either flush to the posterior cortex of the vertebral bodies or were recessed by only 2 mm or less.

Sagittal Plane Balance. Nearly one-third of the patients (19/67; 28%) had some sagittal plane imbalance after surgery. At their last follow-up, 6 patients had some residual spondylolithesis from failure to fully reduce the deformity at the time of surgery (up to Grade I spondylolisthesis was allowed) and 2 patients developed spondylolithesis after surgery. Eleven patients had residual retrolithesis after surgery.

Intradiscal bone formation

Fusion status of the study patients was evaluated on plain radiographs and CT scans. At 6 months after surgery, 93.1% of patients in both the investigational and control groups had evidence of fusion. At 12 months, the fusion rate in the investigational group dropped to 85.2% while the control group maintained a fusion rate of 92%. This decrease in fusion rate in the investigational group at 12 months appears to be artificially low because 7 patients who were evaluated at 24 months could not be evaluated at 12 months because of the unavailability of reconstructed CT views or poor quality films.) At 24 months, the investigational group had a 92.3% fusion rate, which was more than 14 percentage points higher than that of the control group (77.8%). While this difference was not statistically significant, it does show a positive trend in favor of the investigational group.

Bone formation outside the disc space

Deleted: 02/20/2003

The thin cut 1.0 mm CT scans and plain radiographs were used by multiple reviewers to examine for new bone formation adjacent to the interbody fusion cages in 32 of 34 investigational patients and 31 of 33 controls. (The 4 missing cases were either not available because they were not taken or were too poor a quality to read.). New bone formation extending outside the disc space and into the spinal canal or neuroforamina was found in 28 patients (24 investigational and 4 control group patients). According to the Fisher's Exact Test, this difference is statistically significant (P<.0001). Despite the statistical difference, this unexpected posterior bone formation was not correlated to a recurrence or increase in leg pain from the pre-op state. In 10 investigational and 12 control patients, the leg pain at some point in the follow-up increased at least one point (on a 20 point scale) over the pre-op value. Interestingly 7 of the 12 control patients with increased leg pain had absolutely no bone formation posteriorly.

Deleted: identify

Deleted: 23

Deleted: 5

Sagittal plane balance. In the control group, 1 of the 4 patients (25%) with bone in the spinal canal had a residual unreduced spondylolithesis after surgery. New bone formation was identified in the canal posterior to the unreduced superior vertebra under the posterior longitudinal ligament and annulus. In four patients with normal segmental sagittal plane balance in the control group, new bone formation was identified extending into the spinal canal.

Deleted: 5

Deleted: 0

In the investigational group, 10 of the 23 patients (43%) with bone in the spinal canal had some residual postoperative sagittal plane imbalance. Five patients (5/23, 22%) had spondylolithesis and 5 (5/23, 22%) had retrolithesis. In each of these patients, new bone formation occurred posterior to the unreduced vertebral body under the posterior longitudinal ligament lifted off the unreduced vertebral body. Thirteen patients in the investigational group (13/34; 38%) had a

normal postoperative segmental sagittal plane balance and new bone formation in the spinal canal.

Cage placement. In the investigational group, cage placement was strongly associated with the development of bone in the spinal canal. In the investigational group, 39% of patients with cages placed at the margin or within 2 mm of the margin of the posterior vertebral cortex developed some bone in the spinal canal. Twelve percent of patients in the control group whose cages were placed within 2 mm of the vertebral margins developed bone in the spinal canal. No patient in either group whose cage had been recessed by 3 mm or more developed bone in the spinal canal.

Secondary Surgical Procedures

In the investigational group, 7 of 34 (20.6%) had some type of secondary surgical procedure. Three (8.8%) had second spinal surgery failures; 3 (8.8%) had second spinal surgeries, but not failures; and 1 (2.9%) had an unrelated second surgery (i.e., breast surgery). Of the 3 secondary surgery failures, 2 patients received supplemental fixation for presumed pseudarthrosis.

In the control group, 9 of 33 (27.3%) patients had some type of secondary surgical procedure; 3 (9.1%) had second spinal surgery failures; 3 (9.1%) had second spinal surgeries but not failures; and 3 (9.1%) had an unrelated secondary surgery (i.e., carpal tunnel, knee, coronary artery bypass graft surgery). Of the 3 secondary surgery failures, 3 control patients received supplemental fixation for presumed pseudarthrosis.

Deleted: 02/20/2003

DISCUSSION

Threaded cylindrical cages represent a new, distinct class of segmental spinal fixation devices. These devices were not designed as spacers that require segmental stabilization; rather, they were designed as stand-alone intervertebral devices that function as an "instrumented PLIF." Threaded interbody devices are biomechanically different from interbody spacers. Biomechanical studies have shown that cage size has some significance in stand-alone cage fusions; however, stand-alone cages do not significantly increase spinal stiffness in studies using human cadavers [13-18]. This finding largely explains the current clinical trend toward using posterior segmental fixation in PLIF constructs.

Larger cages improve stiffness in rotation and lateral bending in a lumbar spinal motion segment; however, reduction of motion in flexion is not significantly improved with larger cages [16,17]. Larger cages require more extensive facet joint resection or complete facetectomy, which further destabilizes the spinal motion segment. A cylindrical device increases in its medial-lateral dimension equal to its increase in height, which necessitates greater mobilization and retraction of the neural elements. Retraction and mobilization of the neural element during cylindrical cage insertion has been associated with permanent neurologic injury [19,20]. The current trend in PLIF surgery is to limit neural element retraction through the use of a transforaminal surgical approach or through the use of impacted underbody spacers.

Initial clinical studies reported high rates of fusion and clinical success in certain centers. These results have not been widely reproduced. Authors of clinical and radiographic studies on stand-

Deleted: 02/20/2003

alone interbody implants without supplemental fixation have reported fusion rates between 83% and 100% [3,4]. Hacker [21] compared two groups of patients treated for disabling back pain; one group was treated with a stand-alone PLIF using BAK implants, and the other group was treated with combined anteroposterior fusion. He found equal patient satisfaction between the two groups. Ray [4] presented a prospective series of 236 patients treated with stand-alone interbody fusion and reported a 96% fusion rate at 2 years after surgery. These fusion criteria did correlate with improved clinical outcomes. In this study group, only 65% had good-to-excellent clinical outcomes on the Prolo scale, and 14% had a poor result.

However, PLIF procedures or any other type of spinal fusion procedure that uses autograft from the iliac crest come with a price in pain for the patient. Figure 1 shows that the iliac crest graft site pain in this study was found to be similar to that measured in the same way for a larger study of the LT-CAGE device [10] with two exceptions. First, in this study, the pain at 24 months was 5.5 on a scale of 20, while in the anterior fusion LT-CAGE study, the value was 1.8. Second, in this posterior INTER FIX study, 60% of the patients had some pain at 24 months, while in the LT-CAGE study 32% had. Although these were two separate studies using different surgeons, different numbers of patients (30 versus 118), and different sizes of cages (the INTER FIX cage is cylindrical and the LT-CAGE version is a smaller volume tapered design), these results are consistent with a review of other studies that showed that a posterior approach to the iliac crest is more painful for the patients [22]. The pain associated with the posterior bone graft harvest may be secondary, in part, to the extensive stripping of the gluteus musculature, more extensive bone graft harvesting techniques, or injury to the sacroiliac joint. For whatever reason, the measured iliac crest graft site pain scores in this study suggest that, from the patient's point of view, the

need for an autograft replacement in PLIF cylindrical cage procedures is greater than in ALIF tapered cage procedures.

We found that, regardless of the source of the bone graft, extra bone formation in the spinal canal can occur after PLIF procedures with cylindrical interbody fusion cages because it occurred in both study groups (Fig. 7). Bone formation in the spinal canal appears to be a multifactorial event. It appears to be largely dependent on cage placement and sagittal balance of the instrumented vertebral motion segment. Patients with residual sagittal plane imbalance form bone behind the unreduced vertebral segment. This may be the result of lifting of a periosteal flap along the posterior cortex of the listhesed vertebral body (Fig. 8). Cages that were not recessed within the confines of the disc space margins were also associated with bone formation in the spinal canal (Fig. 9). Thin-cut CT scans were essential to determine cage placement and new bone formation postoperatively.

RhBMP-2 on an absorbable collagen sponge has been shown to induce bone formation in the intervertebral disc space [7,8,10,11]. A recent study has shown that this montage in this milieu routinely produces a fusion zone extending 3 mm around the cage [23]. It is not surprising that bone may extend into the spinal canal when cages containing rhBMP-2 are not recessed 3 mm or more within the confines of the disc space.

The PLIF procedure using threaded cylindrical fusion cages disrupts a wide channel, which includes the posterior margin of the disc, the posterior longitudinal ligament, and annular structures. This injury can result in adjacent bone formation, which can extend into the spinal

canal. This new bone formation is best visualized on CT scan. Both the control group and investigational group exhibited bone formation outside of the disc space after this procedure.

Although not desirable, bone formation in the spinal canal does not appear to have a discernable effect on patient outcomes. Therefore, bone formation in the spinal canal after the PLIF procedure with stand-alone cylindrical interbody fusion cages appears to be primarily just a radiographic finding that is not associated with any clinical outcome. This human study seems to confirm the safety results in a canine study using rhBMP-2 on a bovine collagen sponge [25]. In that laminectomy study, the sponge was placed directly on an exposed dura. Even though bone formed, no negative outcomes were found. In both the canine and now the human study, the de novo rhBMP-formed bone occurred slowly and passively, not compressing neural structures.

Because of its small size, this study should be considered a pilot study of the ability of a bone morphogenetic protein to replace autograft in a stand-alone PLIF cage procedure. Even though the number of patients was small, we found a statistically significant improvement in back pain in the rhBMP-2 investigational patients. Although the other differences were not statistically significant, assessment of just the surgical and clinical outcome data at two years (Tables 2 and 3) and the averages of all of the outcomes measured (except for 2 of the 3 subjective patient satisfaction questions) favored the investigational group. These findings suggest that a larger study would show statistical equivalence or improvement in all clinically important outcomes. Predicting such a result can be based not only on the data in the pilot study presented here but also on the large-scale human clinical trials of spinal surgery and rhBMP-2 already conducted. In a recent 679-patient analysis, the same protein used in the same concentration inside metal cages

Deleted: 02/20/2003

for the same lumbar indication but from an anterior approach was shown to be superior to autograft [11]. The direction of implantation of a cage should not affect the ability of rhBMP-2 contained inside to form bone.

In conclusion, this detailed, independent review of the results, which represents the first use of osteoinductive proteins in a PLIF procedure, are encouraging. These findings along with other studies for other indications suggest that larger PLIF studies with rhBMP-2 are needed. Currently, studies are being conducted to assess the use of rhBMP-2 in transforaminal lumbar interbody fusion procedures. Additional PLIF studies are being done to evaluate placement of the BMP-soaked sponge adjacent to the anterior annulus and away from the posterior annulotomy sites. In future studies using modified surgical techniques, such as using more recessed cages to allow for extra posterior bone formation, adding steps to minimize bleeding and surgical variables, using narrower, noncylindrical cages that would be easier to put in and cause less tissue destruction, or adding secondary instrumentation may be beneficial. Modifying patient selection, such as entering patients with less vertebral slip, could also help minimize the confounding variables. All of these changes may produce more convincing evidence that INFUSE™ Bone Graft can also be used as a substitute for autograft in PLIF cage procedures.

Until those future studies are completed, the readers should be advised that at this writing the use described in this article are not FDA approved and use with rhBMP-2 as described is not recommended by the stand alone method described. If the reader decides to use rhBMP-2 in this manner anyway, extreme caution should be taken (like countersinking the cages) and the patients should be carefully followed.

Formatted
Formatted
Formatted
Formatted
Formatted
Formatted

Deleted: 02/20/2003

ACKNOWLEDGMENTS

Special thanks to the following doctors who were principal or co-principal clinical investigators at the 14 sites for this study. These surgeons in alphabetical order are Drs.C. William Bacon, Steven Barnes, Charles Branch, Randall Dryer, Paul Geibel, Fred Geisler, Scott Graham, Peter Holiday, Timothy Holt, Zenko Hrynkiw, Dennis Maiman, David Masel, Bruce Mathern, Christopher Meyer, Phillip Tibbs, and Frank Tomecek. The work of the Clinical Research Department at Medtronic Sofamor Danek in collecting the clinical data and performing the statistical analyses is acknowledged. D. Lynn Sanders, CCRC was instrumental in sorting and organizing radiographic data for analysis.

Deleted: 02/20/2003

REFERENCES

1. Cloward RB. The treatment of ruptured intervertebral discs by vertebral body fusion. I. Indications, operative technique, after care. *J Neurosurg* 1953;10:154-168

2. Lin PM, Cautilli RA, Joyce MF. Posterior lumbar interbody fusion. *Clin Orthop* 1983;180:154-168.

3. Kuslich SD, Ulstrom CL, Griffith SL, Ahern JW, Dowdle JD. The Bagby and Kuslich method of lumbar interbody fusion. History, techniques, and 2-year follow-up results of a United States prospective, multicenter trial. *Spine* 1998;23:1267-1268.

4. Ray CD. Threaded titanium cages for lumbar interbody fusions. Spine 1997;22:667-679.

5. Urist MR. Bone: Formation by autoinduction. *Science* 1965;150:893-899.

6. Boden SD, Schimandle JH, Hutton WC. 1995 Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. *Spine* 1995;20:2633-2644.

7. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. *Spine* 2000;25:376-381.

8. Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2. A prospective study of clinical and radiographic outcomes. *Spine* 2001;26:2751-2756.

9. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. *Spine* 1995; 20:1326-1337.

10. Burkus JK, Gornet MF, Dickman C, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. *J Spinal Disord Tech* 2002; 337-349.

Deleted: 02/20/2003

Deleted: in press

11. Burkus JK, Heim SE, Gornet MF, Zdeblick TA. Is INFUSE™ Bone Graft Superior to Autograft Bone? An Integrated Analysis of Clinical Trials Using the LT-CAGE™ Lumbar Tapered Fusion Device. *J Spinal Disord Tech* 2003; 16:113-122.

12. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. *Neurosurg Focus* 2001;10:1-9.

13. Brodke DS, Dick JC, Kunz DN, McCabe R, Zbeblick TA. Posterior lumbar interbody fusion: a biomechanical comparison, including a new threaded cage. *Spine* 1997;22:26-31.

14. Dimar JR, Wang M, Beck DJ, Glassman SD, Voor MJ: Posterior lumbar interbody cages do not augment segmental biomechanical stability. *Am J Orthop* 2001;30:636-639

15. Hasegawa K, Ikeda M, Washio T, Hara T: An experimental study of porcine lumbar segmental stiffness by the distraction-compression principle using a threaded interbody cage. *J Spinal Disord* 2000;13:247-252.

16. Kettler A, Wilke HJ, Dietl R, Krammer M, Lumenta C, Claes L. Stabilizing effect of posterior lumbar interbody fusion cages before and after cyclic loading. *J Neurosurg* 2000;92:87-92

17. Lund T, Oxland TR, Jost B, Cripton P, Grassmann S, Etter C, Nolte LP. Interbody cage stabilisation in the lumbar spine: biomechanical evaluation of cage design, posterior instrumentation and bone density. *J Bone Joint Surg Br* 1998;80:351-359.

18. Rapoff AJ, Ghanayem AJ, Zdeblick TA. Biomechanical comparison of posterior lumbar interbody fusion cages. *Spine* 1997;22:2375-2379.

Deleted: 02/20/2003

19. Barnes B, Rodts GE, McLaughlin MR, Haid RW Jr. Threaded cortical bone dowels for lumbar interbody fusion: Over 1-year mean follow-up in 28 patients. *J Neurosurg* 2002;95(1 Suppl):1-4.

20. Barnes B, Rodts GE, Haid RW Jr, Subach BR, McLaughlin MR. Allograft implants for posterior lumbar interbody fusion: results comparing cylindrical dowels and impacted wedges. *Neurosurgery* 2002;51:1191-1198.

21. Hacker RJ: Comparison of interbody fusion approaches for disabling low back pain. *Spine* 1997;22:660-665

22. Polly DW, Kuklo TR. Bone graft donor site pain [Abstract]. In Program and abstracts of 39th Annual Meeting of the Scoliosis Research Society; September 18-21,2002; Seattle, WA; p. 178.

23. Burkus JK, Dorchak JD, Sanders DL. Radiographic assessment of interbody fusion using recombinant human bone morphogenetic protein type 2. *Spine* 2003; 28:372-377.

24. Palm WJ, Rosenberg WS, Keaveny TM: Load transfer mechanisms in cylindrical interbody cage constructs. *Spine* 2002;27:2101-7.

25. Meyer RA, Gruber HE, Howard BA, et al. Safety of recombinant human bone morphogenetic protein-2 after spinal laminectomy in the dog. *Spine* 1999;24:747-54.

Deleted: in press

Formatted

30 Deleted: 02/20/2003

Table 1. Patient Demographic Information.

Variable	Investigational (n=34)	Control (n=33)	*P* value *
Age (years) [mean (range)]	46.3 (25.8 – 66.1)	46.1 (28.5 – 70.9)	0.928
Weight (lb) [mean ± SD]	180.5 ± 38.4	172.8 ± 35.7	0.400
Sex [n (%)]			
Male	17 (50)	15 (45.5)	0.808
Female	17 (50)	18 (54.5)	
Workers' compensation [n (%)	8 (23.5)	9 (27.3)	0.784
Spinal litigation [n (%)]	3 (8.8)	1 (3.0)	0.614
Tobacco used [n (%)]	18 (52.9)	15(45.5)	0.628
Alcohol use [n (%)]	15 (44.1)	9 (27.3)	0.204
Preoperative work status [n (%) working]	9 (26.5)	15 (45.5)	0.131
Previous back surgery [n (%)]	12 (35.3)	13 (39.4)	0.803

For continuous variables, *P* values are from ANOVA, and for categorical variables, they are from Fisher's exact test.

Deleted: 02/20/2003

Table 2. Surgical Parameters.

Variable	Investigational group	Control group
Mean operative time	2.6 hours	3.0 hours
Average blood loss	322.8 ml	372.7 ml
Average hospital stay	3.4 days	5.2 days

Table 3. 24-Month Clinical Outcome Parameters

	Investigational	Control
Improvement Points in Oswestry Score	29.6	24.9
% Patients with ≥15 point Oswestry Improvement	69%	55.6%
% Patients with Oswestry Improvement	76.0%	64.3%
Back Pain Improvement from preop (Points)	9*	4.5
Leg Pain Average Improvement from preop (Points)	7.7	6.5
Motor change from preop	4.5	2.8
Sensory Change from preop	8.0	2.8
Reflex change from preop	7.0	5.4
Straight leg raise change from preop	48.0	39.3
Net change in % patients working	+8.8%	-3.1%
Median return to work time	83 days	137 days
Fusion rate	97.3%	77.8%

*Statistically significant difference ($P < .05$)

Deleted: 02/20/2003

LEGEND OF FIGURES

Figure 1. Mean hip pain scores.

Figure 2. Mean improvement in Oswestry scores.

Figure 3. Mean back pain scores.

Figure 4. Mean improvement in back pain scores.

Figure 5. Mean leg pain scores.

Figure 6. Mean SF-36 PCS scores.

Figure 7. **A**. Lateral radiograph of the L3-L4 interspace three months after a PLIF procedure using autogenous iliac bone graft. The disc space height has been restored anatomically and the cages are recessed by 3 mm within the disc space. There is no bone posterior to the cages. **B**. Lateral radiograph at 24 months after the PLIF with autograft shows loss of disc space height, subsidence of the implants through the vertebral endplates and new bone formation posterior to the cages (arrows). The posterior bone formation extends into the spinal canal. **C**. Sagittal CT scan reconstruction across the L3-L4 interspace at 20 months after the PLIF using autograft confirms that there is new bone formation posterior to the implants that extend into the spinal canal (arrows). **D**. Axial CT scan across the L3-L4 interspace at 24 months after surgery shows new bone formation (arrow) extending into the spinal canal.

Figure 8. Schematic illustration of an unreduced spondylolisthesis treated by a stand-alone PLIF technique. There is elevation of the posterior longitudinal ligament with a triangular subperiosteal zone behind the unreduced superior vertebral body (shaded area). This zone commonly filled in with bone following the PLIF procedure in both the BMP and autograft treated patients.

Deleted: 02/20/2003

Figure 9. **A**. Preoperative lateral radiograph shows significant disc space narrowing and radial osteophyte formation. **B**. Lateral radiograph at three months after a PLIF using rhBMP-2 on a collagen sponge carrier shows that the disc space height has been restored both anteriorly and posteriorly (arrows). The cages are recessed by less than 3 mm. **C**. Lateral radiograph at 24 months after surgery shows loss of disc space height, implant subsidence, and bone formation extending into the spinal canal (arrows). **D.** Sagittal reconstructed CT scan shows new bone formation posterior to the cages and extending into the spinal canal (arrows). **E.** Axial CT scan at 24 months after surgery shows asymmetric cage placement (arrow) within the disc space. There is also new asymmetric bone growth. There is more bone behind the more prominent centrally placed cage.

From: Treharne, Rick
Sent: Tuesday, June 3, 2003 02:27:53 PM
To: Bearcroft, Julie
Subject: FW: PLIF manuscript

Attachments: Posterior Lumbar Interbody Fusion-Revised.3.doc; Spine Journal Manuscript.1.doc

Somehow the first reviewer's comments in the letter to the journal got un-bolded. I made it bold again in the attached.

Regarding the paper itself, I think Burkus' writer (Carol Binns) will say that this journal uses a capital P instead of a lower case p to show probabilities. She will also say there should be no 0 before the decimal point since the P value can never be greater than 1.0. So maybe these could be switched back and made consistent throughout the text.

Also, what about the references? I don't know if they are in order of appearance or alphabetical, but they are currently neither. Also, look at the two references after 25 which are both Dr. Branch's. They got turned into an A and B instead of 26 & 27 and the A got made bold text for some reason. So someone needs to renumber these and fix this.

Also, I eliminated the * for the footnote after the mention of the 67 patients since the footnote was added to the text.

Also, look at the two sentences I made red. They say different things. Judy: which one is right? I think the second.

Can you find out if the word GELFOAM is a trademark of Upjohn, Inc. Whosever it is should be noted with a footnote.

Thanks for your help on this...Rick

-----Original Message-----
From: Bearcroft, Julie
Sent: Tuesday, June 03, 2003 1:23 PM
To: Treharne, Rick
Cc: Joe, Jennifer; English, Judy
Subject: PLIF manuscript

Rick -
FYI - This is the latest version of the manuscript and response to the editors after Burkus and I worked on this over the weekend at LSSG. Dr Branch has an electronic copy and will review it next.

julie

Posterior Lumbar Interbody Fusion Using rhBMP-2 with Cylindrical Interbody Cages

Regis W. Haid, Jr., MD*

Charles L. Branch, Jr., MD†

Joseph T. Alexander, MD‡

J. Kenneth Burkus, MD§

*Professor, Department of Neurosurgery, Emory University School of Medicine, Atlanta, Georgia

†Professor and Chair, Department of Neurosurgery, Wake Forest School of Medicine, Winston-Salem, North Carolina

‡Assistant Professor, Department of Neurosurgery, Wake Forest School of Medicine, Winston-Salem, North Carolina

§Spine Surgeon, The Hughston Clinic, Columbus, Georgia

Address correspondence and reprint requests to J.K. Burkus, MD, The Hughston Clinic, [redacted]

ABSTRACT

Background context: In a large series of human patients undergoing open anterior lumbar interbody fusion with a tapered titanium fusion cage, rhBMP-2 on an absorbable collagen sponge carrier has been shown to decrease operative time and blood loss, to promote osteoinduction and fusion, and to be a safe and effective substitute for iliac crest harvesting.

Purpose: The purpose of the study was to determine the clinical and radiographic outcomes in patients treated for single-level degenerative lumbar disc disease with a posterior interbody fusion using stand-alone cylindrical threaded titanium fusion cages with either autogenous bone graft or rhBMP-2 and an absorbable collagen sponge carrier.

Study design/setting: In a prospective, randomized, nonblinded, 2-year study at 14 investigational sites, 67 patients underwent posterior lumbar interbody fusion using two paired cylindrical threaded titanium fusion devices. Patients were randomly assigned to one of two groups: one received recombinant human bone morphogenetic protein-2 (rhBMP-2) on a collagen sponge carrier; the other autogenous iliac crest bone graft.

Patient sample: Between March 1999 and December 1999, 67 patients with symptomatic, single-level degenerative lumbar disc disease of at least 6 months duration underwent a single-level posterior lumbar interbody fusion.

Outcome measures: Clinical outcomes were measured using low back and leg pain numerical rating scales, the Short Form 36, Oswestry Low Back Pain Disability Questionnaire, and work status. Plain radiographs and computed tomographic scans were used to evaluate fusion at 6,12 and 24 months after surgery. For comparisons between the groups for continuous variables, *p*-values are from ANOVA, and for categorical variables, they are from Fisher's exact tests or chi-

square tests. For changes (improvements) from the preoperative within each group, the *p* values are from paired *t* tests.

Methods: In this prospective nonblinded study, 67 patients were randomized into 2 groups that underwent interbody fusion using two cylindrical threaded fusion cages: the investigational group (34 patients) who received rhBMP-2 on an absorbable collagen sponge and a control group (33 patients) who received autogenous iliac crest bone graft.

Results: The mean operative time and blood loss for the investigational rhBMP-2 group was 2.6 hours and 322.8 mL, respectively. For the autograft control group, these values were 3.0 hours and 372.7 mL. Although not statistically different, at 24 months, the investigational group's fusion rate of 92.3% was higher than the control's at 77.8%. At all postoperative intervals, the mean Oswestry, back and leg pain scores, and physical components of the SF-36 improved in both treatment groups compared with preoperative scores. A statistically significant difference in the change in back pain was found at 24 months for the investigational group. In the control group, two adverse events related to harvesting of the iliac crest graft occurred in two patients (6.1%).

Conclusions: Although not statistically different, the investigational group had shorter average operative times and less blood loss. At 24 months, this group had a fusion rate that was more than 14 percentage points greater than the control group. All clinical outcome measurements that were studied showed, on average, greater improvement in the investigational (rhBMP-2) patients with a statistically significant improvement in back pain. Overall results show that the use of rhBMP-2 can eliminate the need for harvesting iliac crest graft and may be an equivalent or better replacement for autograft for use in successful posterior lumbar interbody fusions. Further studies of the use of rhBMP-2 in PLIF cage procedures are needed.

Key words: posterior lumbar interbody fusion, bone morphogenetic protein, osteoinduction, radiography, interbody fusion cages

INTRODUCTION

Posterior lumbar interbody fusion (PLIF) is an effective treatment for patients with symptomatic degenerative disc disease, spondylolisthesis, and other painful discogenic syndromes. Fusion of the degenerative and unstable lumbar spinal motion segment can give significant relief from this disabling and often progressive condition.[1-4] PLIF limits the extent of posterolateral soft tissue exposure, muscle stripping, and injury. With this technique, the surgeon uses the traditional posterior approach to the lumbar spine; however, dissection is limited laterally to the facet joints. Through this approach, direct neural decompression can be completed, disc space height and sagittal balance can be restored [REF}, and intervertebral grafts can be placed in a biomechanically advantageous position.

Lumbar spine stabilization procedures that limit the extent of posterior spinal muscle exposure have some significant advantages. With PLIF surgical techniques, the fusion bed is within the disc space, which eliminates the exposure of the transverse processes. The PLIF approach to the lumbosacral spine enables the surgeon to re-establish the normal anatomic alignment and the relationships of the spinal motion segment while avoiding excessive injury to the posterior paravertebral muscles.[2-4, 13, 24]

Cloward [1] presented his technique for this innovative procedure in 1953. In his surgical technique, he described using a wide laminectomy and facetectomies that would allow for the placement of large structural bone grafts in the denuded and meticulously prepared disc space. Later, Lin and associates [2] modified this intervertebral grafting technique of structural grafts. This modified PLIF technique involves filling the disc space with cancellous bone strips, allowing for preservation of a portion of the posterior elements and avoiding the complication of

insertion of large structural grafts. Additional modifications of the bone graft technique and bone graft materials have been made. Kuslich et al. [3] and Ray [4] introduced the idea of using threaded interbody fusion cages inserted through a PLIF approach as a means of stabilizing the lumbar motion segment, increasing rates of fusion and improving clinical outcomes.

Recombinant human bone morphogenetic protein type 2 (rhBMP-2) [5] applied to an absorbable collagen sponge carrier has been shown to promote osteoinduction and fusion in the lumbar spine [6-9]. In a large series of patients who underwent stand-alone anterior lumbar interbody fusion with fusion cages, rhBMP-2 was shown to enhance rates of fusion, reduce surgical time, and improve clinical outcomes [10,11] To further evaluate this method of bone graft replacement, we evaluated the clinical and radiographic outcomes at 24 months of 67 patients who underwent a single level PLIF. We compared the outcomes in the investigational patients (rhBMP-2) with those in the control patients (autogenous bone).

MATERIALS AND METHODS

Study Design. Between March 1999 and December 1999, 67 patients with degenerative disc disease underwent surgery in this prospective, randomized, non-blinded, FDA-approved study at 14 investigational sites. Although the study was originally planned to enter hundreds of patients, some preliminary CT-scans at 6 months of early patients revealed bone posterior to the PLIF cages [A,B]. Out an abundance of caution, enrollment was suspended. By the time it was determined that the radiographic finding did not affect clinical outcome, the use of stand alone PLIF cages had gone out of favor and the study was not restarted.

All sites had local Investigational Review Board approval and the patients entered into the study gave their informed consent. All patients underwent a single-level posterior lumbar

interbody fusion with two paired INTER FIX™ devices (Medtronic Sofamor Danek, Memphis, TN). The interbody fusion cages were used as stand-alone construct in the disc space from L2 to S1, with the majority being at the L4-L5 level. Patients were randomly assigned in a 1:1 manner to one of two groups: the investigational group who received rhBMP-2 on an absorbable collagen sponge carrier and the control group who received autogenous iliac crest bone graft taken from the posterior approach. INFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, TN) is the trademarked name for recombinant human bone morphogenetic protein type 2 applied to an absorbable collagen sponge.

Patient Data. Preoperatively, all patients had symptomatic, single-level degenerative lumbar disc disease and symptoms of disabling low back or leg pain, or both, of at least 6-months duration that had not responded to nonoperative treatment. Patients could also have up to Grade I spondylolisthesis. The investigational, or rhBMP-2, group comprised 34 patients, and the control group comprised 33 patients. The two treatment groups were similar demographically (Table 1). No statistically significant differences ($p < 0.05$) were found for any of the preoperative variables.

Clinical and Radiographic Outcome Measurements. Patient assessments were completed preoperatively, during hospitalization, and postoperatively at 6 weeks and at 3, 6, 12, and 24 months. Clinical outcomes were assessed using back, leg, and graft-site pain questionnaires, Short Form (SF-36), Oswestry Low Back Pain Disability Questionnaire, and work status. Back and leg symptoms were assessed separately on a visual analog scale. The intensity of pain and the duration of pain in back and leg symptoms were measured on a ten-point numeric rating scale. Adding the numeric rating scores for pain intensity and pain duration allowed examiners to

derive a composite back and leg pain score, which ranged from 0 (no pain) to 20 (maximum pain).

Radiographs and computed tomography (CT) scans were used to evaluate fusion at 6, 12, and 24 months after surgery [12]. Standing lateral and flexion-extension lateral radiographic views were obtained at each follow-up interval. Thin-cut 1-mm CT scans were taken at 6, 12 and 24 months. Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent, blinded radiologist was used to adjudicate conflicting fusion findings. Fusion was defined as an absence of radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation of less than 5° on flexion-extension radiographs, and continuous bone growth connecting the vertebral bodies. Patients who had secondary surgeries because of persistent low back symptoms and clinically suspected non-unions were considered as having failed fusions and were classified as failures in all fusion calculations, regardless of their independent radiologic assessment.

Clinical and Radiographic Follow-up. The rate of patient return for follow-up was at least 89.6% at all postoperative periods. At 12 months, the rate of patient return for both treatment groups was at least 90%. At 24 months, the follow-up rate for the investigational group was 89.6% and the control group's rate was 100%.

Surgical Technique

An open posterior interbody fusion procedure was carried out in each patient. Preoperatively, the patient's disc space was templated to determine the appropriate intraoperative disc space distraction and cage size. Plain radiographs were assessed to determine normal disc space height of the adjacent spinal motion segments. Axial CT scans or MR images were used to

establish the anterior-posterior and the transverse dimensions of the disc space to ensure proper cage sizing.

The patient was placed in the prone position on padded bolsters that support the chest and pelvis and suspend the abdomen. Care was taken to extend the pelvis to ensure that lumbar lordosis was preserved. The operating room table accommodated plain radiographs or fluoroscopy.

A complete laminectomy with facetectomies or extensive bilateral laminotomies and facetectomies with preservation of the midline elements was performed in each patient. The lateral borders of the disc were exposed along with the traversing and exiting nerve roots. Bilateral annulotomies were made and a complete discectomy was carried through these annular windows. The annulotomies were placed lateral to the dural tube. The mid-portion of the lateral annular window was centered adjacent to the medial wall of the pedicle. The anterior and lateral walls of the annulus were preserved; the entire nucleus was removed. Cartilaginous end plates were resected using curettes; the bony end plates were preserved.

Reduction of sagittal and frontal plane deformities was achieved through disc space height restoration and annular tensioning. Inserting progressively larger dilators into the collapsed disc restored disc space height and the normal sagittal contours of the spine.

The vertebral end plates were prepared with reamers that uniformly cut a channel through the adjacent bony end plates. Great care was taken to visualize and gently retract both the traversing and exiting nerve roots. Before reaming, a tubular reamer guide that was impacted into the disc space protected these soft tissue elements. Care was taken to ensure that the end plate cuts were made parallel and equally into each end plate.

The INTER FIX™ cages were packed with either the rhBMP-2 soaked sponges or morcellized autograft before they were inserted. The cages were inserted sequentially in the disc space and away from any soft tissue or neural elements. Their position was assessed intraoperatively with plain radiographs or fluoroscopy. However, cages were not routinely recessed within the disc space as determined by postoperative CT scans. The majority of the cages were left flush to the posterior cortical wall of the vertebral bodies; some cages remained partially within the spinal canal or neuroforamina.

Iliac crest bone graft harvesting. The control group received autogenous iliac crest graft placed within the cages. The bone graft was harvested from the outer table of the iliac wing. The graft was morcellized using a rongeur and was tightly packed into the cages before their insertion.

RhBMP-2 preparation. The rhBMP-2 was reconstituted using sterile water and was used as a single dose of 1.5 mg/mL in all study patients. The 1.5 mg rhBMP-2/mL solution was applied to an absorbable collagen sponge and allowed to bind to the sponge for 15 minutes. The dose of rhBMP-2 varied by patient depending on cage size, with the total dose ranging from 4.0 mg to 8.0 mg. The rhBMP-2 soaked sponge was then placed in the hollow central portion of the INTER FIX™ device before its insertion into the prepared disc space. No additional sponges were placed outside of the devices. No autogenous grafts were used in the investigational group.

Postoperatively, patients were placed in a soft lumbar corset. The treating physician decided when the patient would advance in activities. Isometric strengthening and exercise programs were started at six weeks after surgery.

Statistical Methods

The data from this clinical trial were analyzed using the statistical software package SAS® version 6.12. For comparisons between the groups for continuous variables, *p*-values are from ANOVA, and for categorical variables, they are from Fisher's exact tests or chi-square tests. For changes (improvements) from the preoperative within each group, the *p*-values are from paired t-tests.

RESULTS

Surgery

The mean operative time, average blood loss, and average hospital stay were less for the investigational group than for the control group (Table 2). None of these differences between treatment groups was statistically significant, although the time of surgery approached significance ($p = .065$). No unanticipated device-related adverse events occurred in either treatment group.

Complications:

Vascular events. One control patient developed deep venous thrombosis and was treated with anticoagulation medications.

Neurological events. Three investigational (8.8%) and 2 controls (6.1%) had dural tears. In regard to neurological complications: in the investigational patients 16 events occurred in 14 patients, while in the control 18 events occurred in 14 patients.

Iliac crest graft site. In the control group, adverse events related to harvesting of the iliac crest graft were identified in two patients (6.1%). These events included one case of pain and one hematoma. Neither of these patients required additional surgery. Obviously, no graft site adverse events occurred in the investigational group since the use of rhBMP-2 precluded the need to harvest bone graft.

The level of postoperative pain and morbidity associated with the iliac crest graft harvesting was measured using numeric rating scales for pain intensity and duration (Figure 1). After surgery, all of the control patients experienced hip donor site pain. The highest levels of pain were noted immediately after surgery with a mean score of 11.6 points out of 20 points. The percentage of patients experiencing pain decreased over time; however, at 24 months after surgery, 60% of the control patients still experienced pain (i.e., had scores greater than 0). At two years, the graft site pain scores averaged 5.5 points out of 20 and 13.3% of the patients still felt that the appearance of the graft site bothered them some.

Antibody Testing

Antibody results. Antibodies to rhBMP-2, bovine Type I collagen, and human Type I collagen were evaluated preoperatively and 3 months postoperatively using enzyme-linked immunosorbent assays (ELISAs). None of the patients in either group tested positive for antibodies to rhBMP-2 or human Type I collagen. Authentic (>3 times baseline) bovine Type I collagen antibody formation occurred in 3 investigational and 5 control patients. GELFOAM sponge was used in 15 of the 34 (44%) investigational patients. Of these 15, 2 developed antibody formations to bovine collagen. GELFOAM sponge was also used in 20 of 33 (61%) of the controls. Of these 20, 7 had antibody formation to the bovine collagen. Of the 3 investigational patients that had elevated antibodies, only one had GELFOAM sponge used. Of

the 5 control patients who had bovine collagen antibodies, only 2 had GELFOAM sponge used. Thus, there was no obvious correlation between GELFOAM sponge use and antibody formation. No negative clinical consequence to the positive bovine collagen antibody test results was evident in any of the patients; and the fact that the bovine antibody response occurred as often in the investigational group as the control shows that the bovine collagen sponge used to deliver the rhBMP-2 was not the cause of the antibody reaction. A similar result was found when the same carrier and dose of rhBMP-2 were used inside cages implanted anteriorly [7, 10].

Clinical Outcomes

Oswestry Disability Questionnaire scores. The Oswestry Low Back Pain Disability Questionnaire measured pain associated with activities. The Oswestry Questionnaire was administered preoperatively as well as at each postoperative visit. At all postoperative visits, both treatment groups demonstrated highly significant improvements as compared with the preoperative scores (Figure 2). At all postoperative time intervals after the first 6-week follow-up period, the investigational group showed greater improvements over the control group in the mean overall Oswestry scores. At last follow-up at 24 months, the mean improvements in the Oswestry scores were 29.6 points in the investigational group and 24.9 points in the controls . In the investigational group, 69% of patients showed an improvement of at least 15 points in their disability scores at 12 months after surgery as compared with 55.6% of patients in the control group. At 24 months, the 76.0% of the investigational group was improved and compared favorably with 64.3% improved in the control group (Table 3).

Back Pain. The mean back pain scores at all postoperative periods were improved from the preoperative mean values for both treatment groups (Figure 3). The mean improvements in back pain scores at all five postoperative intervals studied were greater for the investigational group than for the control autograft group (Figure 4). At 24 months, the average improvement in back pain in the investigational group was almost twice that of the control group (9 point improvement vs. 4.5 point improvement). This difference was highly significant with a p value of 0.009.

Leg Pain. Leg pain was assessed in a similar manner using a 20-point numeric rating scale that reflects both the intensity and duration of painful symptoms. Mean leg pain scores improved significantly after surgery in each group (Figure 5). At each study interval, average leg pain scores were less (better) in the investigational group when compared with the control group. Similarly, the investigational group also showed higher average improvement scores at each interval studied. At 24 months, the average improvement in leg pain was 7.7 points in the investigational group compared to 6.5 points in the control group. This difference was not statistically significant.

Short Form SF-36. At all postoperative follow-up intervals, the investigational group showed greater improvement in the physical component of the short form SF-36 when compared with the controls (Figure 6).

Neurological Status. Preoperatively and at all five postoperative time points, the motor, sensory, reflexes, and straight-leg-raise measurements were essentially the same for both treatment groups and showed no statistical differences. At 24 months, using the protocol criteria for determining overall neurological success, which represents a combination of the 4 neurological measurements, both groups had 100% success. Table 3 contains the change from preoperative results at 24 months for the motor, sensory, reflex, and straight-leg-raise measurements.

Work Status. Many factors affect a patient's work status, such as the nature of the work performed and ability of the work place to accommodate work restrictions. Before surgery, only 26.5% of the investigational group was employed while more than 45.5% of the control patients

were employed (Table 3). For patients who were working before surgery, the median return-to-work interval was 43 days in the investigational group and 137 days in the control group. Although marked, this difference was not statistically significant. At last follow-up, more people in the investigational treatment group were working than were working before their surgery. At 2 years after surgery, 12 patients in the investigational group were employed while only 9 were employed before surgery. In the control group, 15 were working before surgery and 14 were working at 2 years after surgery. In other words, the percent of the investigational patients working went from 26.5% before surgery to 35.3% at two years, while in the control group the rate went from 45.5% to 42.4%. Although none of these changes are statistically significant, the trend is promising and may be reflective of the statistically significant difference of lower back pain in the investigational patients.

Patient Satisfaction. At 12 and 24 months after surgery, the results were similar in each treatment group (Table 4). At 24 months, 72.4% of the investigational patients and 80.0% of the control patients were satisfied (answering definitely true or mostly true) with their surgical outcomes. In the investigational group, 69.0% said they would undergo surgery again (answering definitely true or mostly true) compared with 83.3% of the control patients who would undergo surgery again. In the investigational group, 72.4% believed that they were helped as much as they had expected to be from the surgery; 70.0% of the control group felt they had been. None of these subjective differences was statistically significant.

Radiographic Outcomes

Cage placement. Cage placement was assessed on both plain radiographs and thin-cut CT scans. The CT scans were found to reflect more accurately the position of the cage in relation to the spinal canal posteriorly and neuroforamina laterally. No differences between the two patient groups regarding cage placement were detected. Only 6% of patients in each group (2/34 in the investigational group; 2/33 in the control group) showed cages that were countersunk 3 mm or more from the posterior margin of the vertebral body. Approximately one-third of patients in each group had cages that marginally extended into the spinal canal or neuroforamina on postoperative CT studies (12/34 in the investigational group; 10/33 in the control group). The remainder of the cages were placed either flush to the posterior cortex of the vertebral bodies or were recessed by only 2 mm or less.

Sagittal Plane Balance. Nearly one-third of the patients (20/67; 30%) had some sagittal plane imbalance prior to surgery. At their last follow-up, 6 patients had some residual spondylolisthesis from failure to fully reduce the deformity at the time of surgery (up to Grade I spondylolisthesis was allowed) and 2 patients developed spondylolisthesis after surgery. Eleven patients had residual retrolithesis after surgery.

Intradiscal bone formation

Fusion status of the study patients was independently evaluated on plain radiographs and CT scans. At 6 months after surgery, 93.1% of patients in both the investigational and control groups had evidence of fusion. At 12 months, the fusion rate in the investigational group dropped to 85.2% while the control group maintained a fusion rate of 92%. This decrease in fusion rate in

the investigational group at 12 months appears to be artificially low because 7 patients who were evaluated at 24 months could not be evaluated at 12 months because of the unavailability of reconstructed CT views or poor quality films. At 24 months, the investigational group had a 92.3% fusion rate, which was more than 14 percentage points higher than that of the control group (77.8%). While this difference was not statistically significant, it does show a positive trend in favor of the investigational group.

Bone formation outside the disc space

The thin cut 1.0 mm CT scans and plain radiographs were used by multiple reviewers to examine for new bone formation adjacent to the interbody fusion cages in 32 of 34 investigational patients and 31 of 33 controls. (The 4 missing cases were either not available because they were not taken or were too poor a quality to read.). New bone formation extending outside the disc space and into the spinal canal or neuroforamina was found in 28 patients (24 investigational and 4 control group patients). According to the Fisher's Exact Test, this difference is statistically significant ($p < 0.0001$). Despite the statistical difference, this unexpected posterior bone formation was not correlated to a recurrence or increase in leg pain from the preoperative state. In 10 (29%) investigational and 12 (36%) control patients, the leg pain at some point in the follow-up increased at least one point (on a 20 point scale) over the preoperative value (Table 5). Interestingly, 7 of the 22 control patients with increased leg pain had absolutely no bone formation outside of the disc space. This last finding implies that bone formation extending outside of the disc space is not the only possible explanation of recurrent leg pain.

Sagittal plane balance. In the control group, 2 of the 4 patients (50%) with bone in the spinal canal had a residual unreduced spondylolisthesis after surgery. New bone formation was commonly identified in the canal posterior to the unreduced superior vertebra under the posterior longitudinal ligament and annulus. In two (2/4; 50%) patients with normal segmental sagittal plane balance in the control group, new bone formation was identified extending into the spinal canal.

In the investigational group, 12 of the 24 patients (50%) with bone in the spinal canal had some residual postoperative sagittal plane imbalance. Six patients (6/24, 25%) had spondylolisthesis and 6 (6/24, 25%) had retrolithesis. In each of these patients, new bone formation commonly occurred posterior to the unreduced vertebral body under the posterior longitudinal ligament lifted off the unreduced vertebral body. Twelve patients in the investigational group (12/32; 38%) had a normal postoperative segmental sagittal plane balance and new bone formation in the spinal canal.

Cage placement. In the investigational group, cage placement was strongly associated with the development of bone in the spinal canal. In the investigational group, 77% (23/30) of patients with cages placed at the margin or within 2 mm of the margin of the posterior vertebral cortex developed some bone in the spinal canal. Only six investigational patients with prominently placed cages did not exhibit posterior bone growth. Twelve percent of patients in the control group whose cages were placed within 2 mm of the vertebral margins developed bone in the spinal canal. No patient in either group whose cage had been recessed by 3 mm or more developed bone in the spinal canal.

Secondary Surgical Procedures

In the investigational group, 6 of 34 (17.6%) had some type of secondary spinal surgical procedure. Three (8.8%) were classified as failures because they had undergone a second spinal surgery at the same level but were not considered radiographic fusion failures.. Three additional patients underwent a spinal fusion procedure at a different spinal level. In the control group, 6 of 33 (18.2%) patients had some type of secondary spinal surgical procedure. Three (9.1%) had second spinal surgery for fusion failures. Three others (9.1%) had second spinal surgeries at a different spinal level.

DISCUSSION

Threaded cylindrical cages represent a new, distinct class of segmental spinal fixation devices. These devices were not designed as spacers that require segmental stabilization; rather, they were designed as stand-alone intervertebral devices that function as an "instrumented PLIF." Threaded interbody devices are biomechanically different from interbody spacers. Biomechanical studies have shown that cage size has some significance in stand-alone cage fusions; however, stand-alone cages do not significantly increase spinal stiffness in studies using human cadavers [13-18]. This finding largely explains the current clinical trend toward using posterior segmental fixation in PLIF constructs.

Larger cages improve stiffness in rotation and lateral bending in a lumbar spinal motion segment; however, reduction of motion in flexion is not significantly improved with larger cages [16,17]. Larger cages require more extensive facet joint resection or complete facetectomy, which further destabilizes the spinal motion segment. A cylindrical device increases in its medial-lateral dimension equal to its increase in height, which necessitates greater mobilization

and retraction of the neural elements. Retraction and mobilization of the neural element during cylindrical cage insertion has been associated with permanent neurologic injury [19,20]. The current trend in PLIF surgery is to limit neural element retraction through the use of a transforaminal surgical approach or through the use of impacted interbody spacers.

Initial clinical studies reported high rates of fusion and clinical success in certain centers. These results have not been widely reproduced. Authors of clinical and radiographic studies on stand-alone interbody implants without supplemental fixation have reported fusion rates between 83% and 100% [3,4]. Hacker [21] compared two groups of patients treated for disabling back pain; one group was treated with a stand-alone PLIF using BAK implants, and the other group was treated with combined anteroposterior fusion. He found equal patient satisfaction between the two groups. Ray [4] presented a prospective series of 236 patients treated with stand-alone interbody fusion and reported a 96% fusion rate at 2 years after surgery. These fusion criteria did correlate with improved clinical outcomes. In this study group, only 65% had good-to-excellent clinical outcomes on the Prolo scale, and 14% had a poor result.

However, PLIF procedures or any other type of spinal fusion procedure that uses autograft from the iliac crest come with a price in pain for the patient. Figure 1 shows that the iliac crest graft site pain in this study was found to be similar to that measured in the same way for a larger study on ALIF procedures [10] with two exceptions. First, in this study, the average pain at 24 months was 5.5 on a scale of 20, while in the anterior fusion study, the average pain score was 1.8. Second, in this PLIF study, 60% of the patients had some pain at 24 months, while in the ALIF study 32% had persistent pain. Although these were two separate studies using different surgeons, different numbers of patients (33 versus 134), and different volumetric sizes of cages, these results are consistent with a review of other studies that showed that a posterior

approach to the iliac crest is more painful for the patients [22]. The pain associated with the posterior bone graft harvest may be secondary, in part, to the extensive stripping of the gluteus musculature, more extensive bone graft harvesting techniques, or injury to the sacroiliac joint. For whatever reason, the measured iliac crest graft site pain scores in this study suggest that, from the patient's point of view, the need for an autograft replacement in posterior spinal procedures is greater than in anterior spinal fusion procedures.

We found that, regardless of the source of the bone graft, extra bone formation in the spinal canal can occur after PLIF procedures using stand alone cylindrical interbody fusion cages because it occurred in both study groups (Fig. 7). Bone formation in the spinal canal and neuroforamina appears to be a multifactorial event. It appears to be largely dependent on cage placement and sagittal balance of the instrumented vertebral motion segment. Patients with residual sagittal plane imbalance tend to form bone behind the unreduced vertebral segment. This may be the result of lifting of a periosteal flap along the posterior cortex of the listhesed vertebral body (Fig. 8). Cages that were not recessed 3 mm or more within the confines of the disc space margins were also associated with bone formation in the spinal canal (Fig. 9). Thin-cut CT scans were essential to determine cage placement and new bone formation postoperatively.

RhBMP-2 on an absorbable collagen sponge has been shown to induce bone formation in the intervertebral disc space [7,8,10,11]. A recent study has shown that this montage in this milieu routinely produces a fusion zone extending 3 mm around the cage [23]. It is not surprising that bone may extend into the spinal canal when cages containing rhBMP-2 are not recessed 3 mm or more within the confines of the disc space.

The PLIF procedure using threaded cylindrical fusion cages disrupts a wide channel, which includes the posterior margin of the disc, the posterior longitudinal ligament, and annular

structures. This injury can result in adjacent bone formation, which can extend into the spinal canal. This new bone formation is best visualized on CT scan. Both the control group and investigational group exhibited bone formation outside of the disc space after this procedure.

Although not desirable, bone formation in the spinal canal does not appear to have a discernable effect on patient outcomes. Therefore, bone formation in the spinal canal after the PLIF procedure with stand-alone cylindrical interbody fusion cages appears to be primarily just a radiographic finding that is not associated with any clinical outcome. This human study seems to confirm the safety results in a canine study using rhBMP-2 on a bovine collagen sponge [25]. In that laminectomy study, the sponge was placed directly on an exposed dura. Even though bone formed, no negative outcomes were found. In both the canine and now this human study, the de novo rhBMP-formed bone occurred predictability, not compressing neural structures.

Because of its small size, this study should be considered a pilot study evaluating the ability of a bone morphogenetic protein to replace autograft in a stand-alone PLIF cage procedure. Even though the number of patients was small, we found a statistically significant improvement in back pain in the rhBMP-2 investigational patients. Although the other differences were not statistically significant, assessment of just the surgical and clinical outcome data at two years (Tables 2 and 3) and the averages of all of the outcomes measured (except for 2 of the 3 subjective patient satisfaction questions) favored the investigational group. These findings suggest that a larger study would show statistical equivalence or improvement in all clinically important outcomes. Predicting such a result can be based not only on the data in the pilot study presented here but also on the large-scale human clinical trials of spinal surgery and rhBMP-2 already conducted. In a recent 679-patient analysis, the same protein used in the same concentration inside metal cages for the same lumbar indication but from an anterior approach

was shown to be superior to autograft [11]. The direction of implantation of a cage should not affect the ability of rhBMP-2 contained inside to form bone.

In conclusion, this detailed, independent review of the results, which represents the first use of osteoinductive proteins in a PLIF procedure, are encouraging. These findings along with other studies for other indications suggest that larger PLIF studies with rhBMP-2 are needed. Currently, studies are being conducted to assess the use of rhBMP-2 in transforaminal lumbar interbody fusion procedures. Additional PLIF studies are being done to evaluate placement of the BMP-soaked sponge adjacent to the anterior annulus and away from the posterior annulotomy sites. In future studies using modified surgical techniques, such as using more recessed cages to allow for extra posterior bone formation, adding steps to minimize bleeding and surgical variables, using narrower, non-cylindrical cages that would be easier to put in and cause less tissue destruction, or adding secondary instrumentation may be beneficial. Modifying patient selection, such as entering patients with less vertebral slip, could also help minimize the confounding variables. All of these changes may produce more convincing evidence that INFUSE™ Bone Graft can also be used as a substitute for autograft in PLIF cage procedures.

Until those ongoing studies are completed, the readers should be advised that at this writing the use described in this article is not FDA approved in PLIF procedures and use of rhBMP-2 as described is not recommended by the stand alone method described. If the reader decides to use rhBMP-2 in this manner anyway, caution should be taken to appropriately countersink the interbody implants and the patients should be carefully followed.

ACKNOWLEDGMENTS

Special thanks to the following doctors who were principal or co-principal clinical investigators at the 14 sites for this study. These surgeons in alphabetical order are Drs. C. William Bacon, Steven Barnes, Charles Branch, Randall Dryer, Paul Geibel, Fred Geisler, Scott Graham, Peter Holiday, Timothy Holt, Zenko Hrynkiw, Dennis Maiman, David Masel, Bruce Mathern, Christopher Meyer, Phillip Tibbs, and Frank Tomecek. The work of the Clinical Research Department at Medtronic Sofamor Danek in collecting the clinical data and performing the statistical analyses is acknowledged. D. Lynn Sanders, CCRC was instrumental in sorting and organizing radiographic data for analysis.

REFERENCES

1. Cloward RB. The treatment of ruptured intervertebral discs by vertebral body fusion. I. Indications, operative technique, after care. *J Neurosurg* 1953;10:154-168

2. Lin PM, Cautilli RA, Joyce MF. Posterior lumbar interbody fusion. *Clin Orthop* 1983;180:154-168.

3. Kuslich SD, Ulstrom CL, Griffith SL, Ahern JW, Dowdle JD. The Bagby and Kuslich method of lumbar interbody fusion. History, techniques, and 2-year follow-up results of a United States prospective, multicenter trial. *Spine* 1998;23:1267-1268.

4. Ray CD. Threaded titanium cages for lumbar interbody fusions. Spine 1997;22:667-679.

5. Urist MR. Bone: Formation by autoinduction. *Science* 1965;150:893-899.

6. Boden SD, Schimandle JH, Hutton WC. 1995 Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. *Spine* 1995;20:2633-2644.

7. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. *Spine* 2000;25:376-381.

8. Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2. A prospective study of clinical and radiographic outcomes. *Spine* 2001;26:2751-2756.

9. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. *Spine* 1995; 20:1326-1337.

10. Burkus JK, Gornet MF, Dickman C, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. *J Spinal Disord Tech* 2002; 337-349.

11. Burkus JK, Heim SE, Gornet MF, Zdeblick TA. Is INFUSE™ Bone Graft Superior to Autograft Bone? An Integrated Analysis of Clinical Trials Using the LT-CAGE™ Lumbar Tapered Fusion Device. *J Spinal Disord Tech* 2003; 16:113-122.

12. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. *Neurosurg Focus* 2001;10:1-9.

13. Brodke DS, Dick JC, Kunz DN, McCabe R, Zbeblick TA. Posterior lumbar interbody fusion: a biomechanical comparison, including a new threaded cage. *Spine* 1997;22:26-31.

14. Dimar JR, Wang M, Beck DJ, Glassman SD, Voor MJ: Posterior lumbar interbody cages do not augment segmental biomechanical stability. *Am J Orthop* 2001;30:636-639

15. Hasegawa K, Ikeda M, Washio T, Hara T: An experimental study of porcine lumbar segmental stiffness by the distraction-compression principle using a threaded interbody cage. *J Spinal Disord* 2000;13:247-252.

16. Kettler A, Wilke HJ, Dietl R, Krammer M, Lumenta C, Claes L: Stabilizing effect of posterior lumbar interbody fusion cages before and after cyclic loading. *J Neurosurg* 2000;92:87-92

17. Lund T, Oxland TR, Jost B, Cripton P, Grassmann S, Etter C, Nolte LP. Interbody cage stabilization in the lumbar spine: biomechanical evaluation of cage design, posterior instrumentation and bone density. *J Bone Joint Surg Br* 1998;80:351-359.

18. Rapoff AJ, Ghanayem AJ, Zdeblick TA: Biomechanical comparison of posterior lumbar interbody fusion cages. *Spine* 1997;22:2375-2379.

19. Barnes B, Rodts GE, McLaughlin MR, Haid RW Jr. Threaded cortical bone dowels for lumbar interbody fusion: Over 1-year mean follow-up in 28 patients. *J Neurosurg* 2002;95(1 Suppl):1-4.

20. Barnes B, Rodts GE, Haid RW Jr, Subach BR, McLaughlin MR. Allograft implants for posterior lumbar interbody fusion: results comparing cylindrical dowels and impacted wedges. *Neurosurgery* 2002;51:1191-1198.

21. Hacker RJ: Comparison of interbody fusion approaches for disabling low back pain. *Spine* 1997;22:660-665

22. Polly DW, Kuklo TR. Bone graft donor site pain [Abstract]. In Program and abstracts of 39th Annual Meeting of the Scoliosis Research Society; September 18-21,2002; Seattle, WA; p. 178.

23. Burkus JK, Dorchak JD, Sanders DL. Radiographic assessment of interbody fusion using recombinant human bone morphogenetic protein type 2. *Spine* 2003; 28:372-377..

24. Palm WJ, Rosenberg WS, Keaveny TM: Load transfer mechanisms in cylindrical interbody cage constructs. *Spine* 2002;27:2101-7.

25. Meyer RA, Gruber HE, Howard BA, et al. Safety of recombinant human bone morphogenetic protein-2 after spinal laminectomy in the dog. *Spine* 1999;24:747-54.

A. **Branch CL, Geibel PT "rhBMP-2 as a possible autograft replacement for PLIF procedures" Congress of Neurological Surgeons Scientific Program, 51st Annual Meeting, San Diego, CA, September 29 – October 4, 2001 (poster)**

B. Alexander J, Branch C "Recombinant human bone morphogenetic protein-2 in a posterior lumbar interbody fusion construct: 2-Proceedings of the NASS 17th Annual Meeting, *The Spine Journal* 2(5S): 486 (2002)

Table 1. Patient Demographic Information.

Variable	Investigational (n=34)	Control (n=33)	*p* value *
Age (years) [mean (range)]	46.3 (25.8 – 66.1)	46.1 (28.5 – 70.9)	0.928
Weight (lb) [mean ± SD]	180.5 ± 38.4	172.8 ± 35.7	0.400
Sex [n (%)]			
Male	17 (50)	15 (45.5)	0.808
Female	17 (50)	18 (54.5)	
Workers' compensation [n (%)	8 (23.5)	9 (27.3)	0.784
Spinal litigation [n (%)]	3 (8.8)	1 (3.0)	0.614
Tobacco used [n (%)]	18 (52.9)	15(45.5)	0.628
Alcohol use [n (%)]	15 (44.1)	9 (27.3)	0.204
Preoperative work status	9 (26.5)	15 (45.5)	0.131
[n (%) working]			
Previous back surgery [n (%)]	12 (35.3)	13 (39.4)	0.803

For continuous variables, *p* values are from ANOVA, and for categorical variables, they are from Fisher's exact test.

Table 2. Surgical Parameters.

Variable	Investigational group	Control group
Mean operative time	2.6 hours	3.0 hours
Average blood loss	322.8 ml	372.7 ml
Average hospital stay	3.4 days	5.2 days

Table 3. 24-Month Clinical Outcome Parameters

	Investigational	Control
Improvement Points in Oswestry Score	29.6	24.9
% Patients with ≥15 point Oswestry Improvement	69%	55.6%
% Patients with Oswestry Improvement	76.0%	64.3%
Back Pain Improvement from preop (Points)	9*	4.5
Leg Pain Average Improvement from preop (Points)	7.7	6.5
Motor change from preop	4.5	2.8
Sensory Change from preop	8.0	2.8
Reflex change from preop	7.0	5.4
Straight leg raise change from preop	48.0	39.3
Net change in % patients working	+8.8%	-3.1%
Median return to work time	43 days	137 days
Fusion rate	97.3%	77.8%

*Statistically significant difference ($p < .05$)

Table 4. Summary of Patient Satisfaction with Results of Surgery at 24 Months
[Number (%) of Patients]

Variable	Investigational	Control	*p* value*
I was satisfied with the results of my surgery.			
Definitely True	15 (51.7)	16 (53.3)	0.388
Mostly True	6 (20.7)	8 (26.7)	
Do not Know	3 (10.3)	5 (16.7)	
Mostly False	3 (10.3)	0 (0.0)	
Definitely False	2 (6.9)	1 (3.3)	
I was helped as much as I thought I would be by my surgery.			
Definitely True	13 (44.8)	16 (53.3)	0.159
Mostly True	8 (27.6)	5 (16.7)	
Do not Know	3 (10.3)	8 (26.7)	
Mostly False	3 (10.3)	0 (0.0)	
Definitely False	2 (6.9)	1 (3.3)	
All things considered I would have the surgery again for the same condition.			
Definitely True	18 (62.1)	16 (53.3)	0.196
Mostly True	2 (6.9)	9 (30.0)	
Do not Know	5 (17.2)	2 (6.7)	
Mostly False	1 (3.4)	1 (3.3)	
Definitely False	3 (10.3)	2 (6.7)	

*p values are from the Chi-square test.

TABLE 5

PLIF Patients with Bone Formation and Leg Pain Increase

Bone Formation Score	Investigational (n=32)		Control (n=31)	
	# Pts with Bone Formation Only	# Pts with Bone Formation & Leg Pain Increase	# Pts with Bone Formation Only	# Pts with Bone Formation & Leg Pain Increase
0	2	0	22	7
1	6	2	5	1
2	14	5	4	2
3a	3	1	0	0
3b	3	1	0	0
3c	4	1	0	0
Films Not Read	2	0	2	2
Total	34	10	33	12

3a * – posterior bone formation extending centrally into the spinal canal

3b * – posterolateral bone formation extending into the neuroforamina

3c * - posterior and posterolateral bone formation

*** {Reference B}**

LEGEND OF FIGURES

Figure 1. Mean hip pain scores.

Figure 2. Mean improvement in Oswestry scores.

Figure 3. Mean back pain scores.

Figure 4. Mean improvement in back pain scores.

Figure 5. Mean leg pain scores.

Figure 6. Mean SF-36 PCS scores.

Figure 7. **A**. Lateral radiograph of the L3-L4 interspace three months after a PLIF procedure using autogenous iliac bone graft. The disc space height has been restored anatomically and the cages are recessed by 3 mm within the disc space. There is no bone posterior to the cages. **B**. Lateral radiograph at 24 months after the PLIF with autograft shows loss of disc space height, subsidence of the implants through the vertebral endplates and new bone formation posterior to the cages (arrows). The posterior bone formation extends into the spinal canal. **C**. Sagittal CT scan reconstruction across the L3-L4 interspace at 20 months after the PLIF using autograft confirms that there is new bone formation posterior to the implants that extend into the spinal canal (arrows). **D**. Axial CT scan across the L3-L4 interspace at 24 months after surgery shows new bone formation (arrow) extending into the spinal canal.

Figure 8. Schematic illustration of an unreduced spondylolisthesis treated by a stand-alone PLIF technique. There is elevation of the posterior longitudinal ligament with a triangular subperiosteal zone behind the unreduced superior vertebral body (shaded area). This zone commonly filled in with bone following the PLIF procedure in both the BMP and autograft treated patients.

Figure 9. **A**. Preoperative lateral radiograph shows significant disc space narrowing and radial osteophyte formation. **B**. Lateral radiograph at three months after a PLIF using rhBMP-2 on a collagen sponge carrier shows that the disc space height has been restored both anteriorly and posteriorly (arrows). The cages are recessed by less than 3 mm. **C**. Lateral radiograph at 24 months after surgery shows loss of disc space height, implant subsidence, and bone formation extending into the spinal canal (arrows). **D.** Sagittal reconstructed CT scan shows new bone formation posterior to the cages and extending into the spinal canal (arrows). **E**. Axial CT scan at 24 months after surgery shows asymmetric cage placement (arrow) within the disc space. There is also new asymmetric bone growth. There is more bone behind the more prominent centrally placed cage.

June 2, 2003

Tom G. Mayer, M.D.
Editor-in-Chief
The Spine Journal
[redacted]
LaGrange, IL 60525

RE: MS 30023

Dear Dr. Mayer:

We have revised our manuscript, entitled "Posterior Lumbar Interbody Fusion Using rhBMP-2 with Cylindrical Interbody Cages". Enclosed are three copies. We believe we have addressed all the reviewers' comments with this revised manuscript. This paper presents data that will not be researched again for perhaps years to come. We believe this paper addresses an important issue and needs to be presented to the spinal community as soon as possible.

To demonstrate how we addressed the reviewer's comments, in the following in bold type are the reviewer's comments with our response in regular type:

This study should not be published in its current form. As noted by both Reviewer A and B, there is very little statistical significance differentiating the two groups, but the authors and/or company sponsoring this study have attempted to use any possible positive trend to promote this technique. Unless the authors can discuss the results of this study in an unbiased manner, which they have been unable to do in its present form, this data should not be published.

Formatted

We believe we have discussed the results in an unbiased, objective manner and are not quite sure what the specific problem is here, nor do we believe we are trying to promote this PLIF technique using stand-alone cylindrical cages. We believe the data speaks for itself and the readers can make up their own mind as to whether to use this technique. In our mind, we believe the article warns potential users about performing it. There will be more comments on this subject later in our response.

This is a very important study, but there are some problems with the study's execution and with the data as it is presented. First, why was this "2-year study" stopped after 9 months?

Our paper did not say that the study was stopped after 9 months. It said that all the patients were entered in a 9-month period. As the discussion says the size of this study represents in essence a pilot study. We assumed The Spine Journal would want 2-year follow-up. Nevertheless, we have added an explanation, to the text to explain why more patients were not entered into the study.

Deleted: 9 month

Deleted: footnote

The authors state that larger numbers might have helped show greater differences between the two groups, so the question remains, why stop at 67 patients after 9 months (other rhBMP-2 studies included over 300 patients)?

Performing large-scale studies is very expensive and not all studies need to be large scale. What is the reviewer suggesting as the proper alternative here? To not publish this data? We believe this information is important and should be shared with the spinal community. As was mentioned, the added text addresses this reviewer's comment.

Deleted: ;

Deleted: footnote

Also, the authors cannot talk about "greater differences" and "better outcomes" in the results unless the differences are statistically significant.

We did a search of the manuscript and cannot find the phrase "greater differences" or "better outcomes" in the text. So we do not know how to address this issue. The manuscript had the phrase "although not statistically significant" six times in the text.

They analyzed statistically almost every conceivable outcome variable, except for the one finding strongly against rhBMP-2 – that is, a higher rate of new bone growth in the spinal canal! This is the greatest fear that surgeons have regarding BMP's – uncontrolled new bone formation. It happened in 23/34 BMP patients, versus 5/33 bone graft patients. They did not do a statistical analysis of this, but I ran a Fisher's exact 2-tailed test for this data....and P<0.0001, the most significant of

all differences found in this study, yet the authors did not even run this analysis! This is very troubling, and raises the issues of commercial support of such a study leading to a biased reporting of results. I ask the authors to explain this point, and include and emphasize its importance prior to acceptance for publication.

As we understand this comment the reviewer is in essence saying that we have statistically analyzed too many outcomes parameters and then asks us to do one more. We believe the point about bone formation is obvious, but we have added the statistical analysis he has asked for in the revised manuscript.

We are not quite sure what the reviewer is saying about "commercial support" since any randomized, multicenter human study will be very expensive and require some type of commercial support in order to be performed. The reviewer seems to think that this paper is advocating the use of rhBMP-2 in PLIF procedures. Readers of this paper, once published, will see that such use, which is not FDA approved and may never be, can have unexpected radiographic findings, and surgeons will hesitate performing surgeries in the same manner as used in the study without further study or without modifying their technique. Without any publications of any kind on this subject, surgeons may have a false sense of security that rhBMP-2 can be used in PLIF procedures just as in stand alone ALIF cages.

Deleted: of recombinant proteins

As was mentioned, we do not believe our independent review of these results encourages or discourages the procedure in either the investigational or control groups. Rather we

just report the facts that until this paper gets published are only known about with rhBMP and PLIF cages through hearsay and rumor. Although we do not come out and say it (because we felt such comments would be inappropriate in a scientific publication) the use of stand alone cylindrical cages in PLIF procedures seems to have gone into disfavor in the US. We believe the net effect to the reader on the use of rhBMP inside a PLIF cage will be discouragement (which ironically will probably not be favorable to the industrial community, although some may view the posterior bone formation as proof that rhBMP-2 does form bone), as will the reader for the use of stand alone cylindrical PLIF cages with autograft.

Deleted: publicaton

Deleted: to the

Nevertheless, we have added the statistical analysis the reviewer has requested to the revised text in the results section.

They also need to specify how many patients with ectopic bone had new or persistent leg pain, not just overall average leg pain scores.

We did not ever use the term "ectopic" in the original paper. In the re-write we added the term "unexpected". We have expanded our discussion on the bone formation outside the disc space to be more descriptive and added a discussion of recurrent leg pain.

Page 16, Patient Satisfaction: Please give patient satisfaction data in tabular form, as it is given for all of the other clinical outcomes.

Table 4 has been added per this reviewer's request.

Page 18, end 1st paragraph: "Positive trend" usually refers to a P value between 0.05 and 0.10. If this is not true, then this term "positive trend" probably should not be used.

We have eliminated the term "positive trend" from the revised text.

Page 18, 2nd paragraph: Regarding bone formation outside of the disc space, it is surprising that 23 of 34 investigational patients versus 5 of 33 control patients had this problem. This appeared to me to be a statistically significant difference and in fact by Fisher's Exact Test the difference was highly significant with a P value of less than 0.0001. Why is this not stated in the text? A statistical analysis and description of these results, both in tabular format and in the text of the Results and Discussion is necessary.

This analysis was added to the text. We also found a small error (one patient was misclassified as a control) in the calculations and have corrected this error, in the revised text.

Deleted: it

Page 19, 1st paragraph: Did any patients who had new bone formation have residual leg pain or new leg pain? The results describe overall average scores for leg pain, but we do not know specifically how many of the patients in each group still had leg pain or developed leg pain following surgery. This is important as this might suggest that there was a clinical impact to the new bone formation.

The revised manuscript addresses this issue. There was no correlation.

Page 19, 3rd & 4th paragraph: What are spine surgery failures? Does this mean pseudarthrosis? Does this mean the patients had recurrent or residual leg pain?

Deleted: pseudoarthrosis

Second surgery spine failures are defined as patients who have had a revision, removal, or supplemental fixation. These cases could include pseudarthrosis and included 3 controls and 3 investigational. One additional investigational patient had recurrent leg pain. We added text and a table to address this issue regarding about the recurrent leg pain.

Deleted: 2

Page 21, middle of 2nd paragraph: It is again confusing that 60% of patients had some pain in the bone graft site and yet only one patient is mentioned in the Abstract and Results section as having pain on follow-up.

A 20-point scale was used to quantify hip donor site pain. At 2 years, 60% of the patients had a score of 1 or greater. This is different from a reported complication of graft site discomfort. To make the paper more clear, we will eliminate the graft site discomfort reference from the text.

Page 22, 2nd paragraph: Here there should be a discussion regarding the greater likelihood of bone formation in the canal with rhBMP-2. Please discuss whether this new bone formation may have caused leg pain in any of the patients.

The revised manuscript addresses this point.

Page 23, 2nd paragraph: I would agree with this point of the discussion if there truly were no patients with post op leg pain and bone in the canal, whether or not the two were related.

The revised manuscript addresses this point.

Page 23, 3rd paragraph: The authors cannot state that "all the outcomes measured favored the investigational group", unless these differences were statistically significant. Since they were not, this statement is not accurate.

We have revised the text, and add the phrases "on average" and "although not statistically different".

Deleted: to tone down this sentence

General Comments:

This is described as a two-year study yet it seems that small numbers of patients were enrolled and only over a short nine-month period. Why is this? Was the study ended prematurely? If so, this should be stated at least in the body of the paper.

The revised manuscript addresses this point.

Page 3, end of 3rd paragraph: 3.0% of patients reporting graft site discomfort is one patient and should be stated as such instead of with percentage.

As was mentioned, the revised manuscript addresses this point.

Page 5, Introduction, 1st paragraph: references are needed regarding the clinical results of PLIF, as well as clinical results for DDD, spondylolisthesis, etc.

References were added to the revised text.

Page 5, Introduction: How is sagittal balance restored in the setting of stand-alone PLIF? Please reference the biomechanical studies, which demonstrate this.

Deleted: studies which

References were added to the text.

Page 5, 2nd paragraph: Can the authors reference papers describing the restoration of normal anatomic alignment with PLIF?

We added several references to this paragraph.

Deleted: , although none may specifically address the reviewer's question.

Page 12, Complications: Were there are dural tears? Were there any neuropraxic injuries, i.e. patients with postoperative weakness or postoperative numbness? These should also be cited under Complications.

Three investigational (8.8%) and 2 controls (6.1%) had dural tears. As far as neurological complications, in the investigational patients 16 events occurred in 14 patients, while in the control 18 events occurred in 14 patients. We have added these figures to the revised text.

Page 12, 2nd paragraph: It is confusing that the authors describe one patient having graft site discomfort two years out from surgery yet they in the same

paragraph state that 60% of patients who had a graft harvested had pain. They state that at two years the graft site pain scores averaged 5.5 points out of 20, yet they stated only one patient had graft site discomfort. Please explain these apparently confusing results.

This issue has been addressed in the revised text by eliminating the discussion of the graft site discomfort for the sake of clarity.

Page 13: Please discuss why there might have been such a high percentage of antibody formation to bovine type I collagen in the control group. Was this related to the use of gel foam?

GELFOAM sponge was used in 15 of the 34 (44%) investigational patients. Of these 15, 2 developed antibody formations to bovine collagen. GELFOAM sponge was also used in 20 of 33 (61%) of the controls. Of these 20, 7 had antibody formation to the bovine collagen. This result was added to the text as was a discussion on whether this was related to antibody formation.

Page 14 & 15: Throughout the Clinical Outcomes section the authors cannot describe "greater improvements", and "better" scores when there is no significant difference. For example, in the 1st paragraph of page 14 the 4th sentence should read "after the first six week follow-up the investigational group showed no significant differences over the control group in the mean overall Oswestry scores".

Deleted: significant

This can then be followed by giving the actual scores that were obtained for each group. The reader can then interpret the difference in numbers as they wish, but the fact that it is not statistically significant needs to be stated rather than stating that there were greater improvements when these differences were not statistically significant. The same is true for the results under Back Pain, Leg Pain, and Short Form SF-36.

We believe the revised paper addresses this issue.

Reviewer A

This manuscript is not worthy of publication in its current form. There are many issues, which I will develop to this end, but the most significant is that the conclusions do not support the data contained therein. I will outline the concepts for the authors. First, none of the differences, in the end, are statistically significant, yet the authors take the liberty to interject statements that there are "trends that the investigational group showed better results" when there is no evidence for this. Whenever the control group has a similar positive trend, no mention of this is made (which is appropriate, but not consistent).

Deleted: issues which

The revised manuscript addresses this point, as was previously mentioned, and we believe is now worthy of publication.

The manuscript is full of biased statements that are a reflection of the data evaluators - the company that markets the product. No mention is made in the discussion, or methods section about the introduction of bias (which is well documented in the scientific literature, I refer the authors to this months AMA News as one of many articles), which may occur when the data is collated, collected and analyzed by industry personnel. While this cannot be proven, it must at least be discussed and the potential for bias stated. We do not have disclosures of the authors or the surgeons in the multiple centers that participated, and this should have been clearly identified.

To help eliminate any potential bias, only one of the co-authors was a clinical investigator—the other three were independent reviewers of all the data. Since these data are taken from a clinical IDE study sponsored by a company, only the company would have all the data in its database—data that is reviewed by FDA auditors. We don't believe any discussion of bias is needed for the text.

Was this IRB approved at all centers? If not, why? Was consent obtained in all patients prior to inclusion into the study? All questions which should be answered via the methods section.

Of course since this study was an IDE study, IRB approval and informed consent was obtained. Text was added to the revised manuscript to state this.

There is no data given for the economic impact of the use of this product (does the cost to the insurance company or patient justify it's use at this point?) Yes, OR time

Deleted: who

is greater if a bone graft is taken, and blood loss slightly higher, but patient satisfaction was actually higher (although not statistically significant) in the control patients. This fact is very important, but glossed over and not discussed, as it should be.

An economic analysis is beyond the scope of this study and would require much more data than can be presented here. Besides, this product is not FDA approved for this surgical procedure and any economic analysis would be purely academic.

The methods section is grossly lacking. There is no control for diagnosis. What were the entry criteria? This is really a consecutive series of cases using a specific product versus autograft. The authors state that degenerative disc disease was the diagnosis in all cases, yet in the results section discuss spondylolisthesis, spondylolysis as well as degenerative disc disease, but no data is given as to the breakdown of the two groups. Did all of the investigational patients have spondylolisthesis or visa versa? This may impact the results.

The revised manuscript makes the indications section more clear and says that only low grade (Grade 1) spondylolisthesis patients could be entered into the study.

The definition of fusion is not clearly defined and the lucency of the implant data needs to be better delineated and quantified. The concept that reoperations, if felt

to be *clinically* failed fusions, were so documented is not logical, and not *scientifically* based.

The definitions used were the same as given by the FDA. We did not change the definitions.

The postoperative recovery of patients was not controlled and very well in such a small group affected the outcome. For example, if all patients in the control group were ambulated earlier than the investigational group a higher pseudo rate may have an effect.

The study protocol allowed the surgeons to decide the post-operative rehabilitation protocols.

Deleted: recovery. [NOTE: Is this true?]

This group of patients overall had a very high rate of reoperation, and is very concerning, and bears further discussion. This rate is much higher than the literature would suggest. The author's statements about the effects of isolated PLIF a procedure decreasing biomechanical stability of the motion segment is in fact true, and when the facet joints are compromised instability results. This operation is not recommended unless posterior stability is provided by supplemental instrumentation and is likely why the failure/reoperation rate was so high. The exceedingly high reoperation rate needs to be clearly discussed. Based upon these results, the authors should recommend abandonment of the procedure.

Deleted: procedures decreasing biomechanical stability of the motion segment is

We believe the revised manuscript and its closing sentence addresses this point.

IF the shortcomings and bias of this manuscript are clearly incorporated it may have benefit to the readership. As it stands it is an advertisement for a specific product without significant scientific merit.

The purpose of the paper was not to evaluate the viability of using stand-alone cylindrical PLIF cages. Instead, its purpose was to investigate the feasibility of using rhBMP-2 to replace autograft in a PLIF procedure. We feel that our comments in the discussion is appropriate—more research is needed, and if performed should be carried out making the changes in the protocol described. We do not believe the revised or original paper is an advertisement for a specific product. In general though, the data show reasons to be encouraged and cautioned about the use of rhBMP-2 in PLIF procedures. Encouraged because the need is so great and the preliminary data are trending favorably, but cautionary in nature because of the occurrence of posterior bone formation.

Deleted: in

We have modified the revised manuscript to include some language advising the reader that this use is not FDA approved In PLIF procedures and use of rhBMP-2 as described is not recommended by the stand alone method described. If the reader decides to use rhBMP-2 in this manner anyway, caution should be taken to appropriately countersink the interbody implants and the patients should be carefully followed.

Deleted: and its use is not recommended by the method described.

Deleted: If the reader decides to use BMP in this manner anyway, extreme caution should be taken (like countersinking the cages) and the patients carefully followed.

Thank you for considering this manuscript for publication.

Deleted: ¶
Please let us know if you need us to clarify anything else in this manuscript, for we feel that the changes made now make this paper acceptable for publication.¶
¶

Respectfully submitted,

Deleted: Sincerely

Deleted: ¶
¶

J. Kenneth Burkus, M.D.

From: Scott Boden [redacted]
Sent: Saturday, April 10, 2004 02:44:49 PM
To: Treharne, Rick
Subject: Re: INFUSE Complaints

Rick,
I have carefully reviewed all the information you included on your email.
I have begun hearing "concerns" out in the field about cervical swelling in BMP cases as well. While statistically your numbers do not suggest an increased incidence, I think there is a possibility that could be a misleading conclusion.

One individual that I spoke to first hand described the "swelling" as a golf ball size mass in the neck clearly visible through the skin. I have never seen that type of edema with autograft or allograft ACDF procedure at single level.

The one death reported in the literature I believe was following a multilevel corpectomy with prolonged retraction of the soft tissues at muleiple levels. These patients are clearly at higher risk of swelling, but again, it has not been my understanding that it has been described as "focal golf ball sized mass".

It would be helpful to know if the other BMP cases had visible swelling and what it looked like.

GI has some sense that it may be related to overconcentrating the BMP on the sponge or putting too much total sponge in a small area. I am not sure we have the data to support this contention either.

As far as the rate of edema formation in the c-spine, I think that is likely patient dependent and the lack of timing difference with BMP-2 does not help strengthen or weaken the potential assoociation in my opinion.

At this point, the statistics do not prove anything one way or another, but I am still concerned that there could be an association between BMP-2 and edema in these cervical cases. If it occurs in the lumbar spine or interbody space it would not be as noticeable. I think continued warning needs to be advised to surgeons about off-label use, especially in the cervical spine.

What is a bit puzzling is that the cornerstone/ACS/BMP-2 study did not have and reports of "golf ball sized swelling". Is this true that it was not seen in that pilot study?

Finally, I was at TBI yesterday and was shown a case of ALIF with peek cages filled with ACS/BMP-2 that resulted in increase leg pain 4 weeks after surgery and by 8 weeks after surgery there appears to be a fluid collection in front of the spine and in the edpidural space posteriorly. The patient does not have increase ESR and CRP suggesting it is not infection. The leg pain has resolved, but the MRI is impressive. Could this be a case of lumbar "edema" from BMP-2? Not sure, but I encouraged them to report it to you guys and I think you need to keep track of all these cases and encourage the sales force when they hear about them to report ALL cases that may involve edema so we can get a better handle on this.

Please continue to keep me updated as I will undoubtedly be asked about this issue by many sources.

Scott D. Boden, MD
Professor of Orthopaedic Surgery
Director, The Emory Orthopaedics & Spine Center

Emory University School of Medicine

>>> "Treharne, Rick" <[redacted]> 04/08/04 01:12PM >>>
I don't know if you would be interested in getting into this issue or not, but I thought as our key INFUSE consultant you may want to know about the complaints we have received so far in regard to the use of INFUSE Bone Graft. So far we have documented and registered 30 complaints on INFUSE Bone Graft. Where we have the details, which is the majority, all complaints involved off-label use, and for the ones where we don't know much we cannot confirm that the product was used on-label. In other words, after 18 months of sales we have yet to receive a confirmed complaint of an on-label use. This in a way confirms what I have heard you have say about BMP--if you change anything all bets are off. Two other points to make are that as a percentage of sales, the complaints on this product are random and one of the lowest if not the lowest of any product implant we sell.

Of the 30 complaints, at least 13 are related to cervical use. The major complaint is swelling which occurred in 7 complaints involving 17 patients. Because this is the major complaint and because of your expertise in cervical surgery and BMP, I wanted to send you the results of our analysis and investigation so far to see if you, as part of our investigation, can think of anything else we can do, know of any other references we can check, or see anything we may have missed.

Below are several icons we prepared about the issue of the use of INFUSE Bone Graft in the cervical spine. The first graph contains what we currently know. From the 7 complaining sites with 17 observations (10 from one site) we know from our investigation that at least 452 cervical cases have been performed at those sites. In the table is a rate showing these 17 cases divided by 452 as well as a rate of use estimated by our marketing group of 1000 cervical use cases, which is probably a more realistic number. These graphs are at the bottom of icon 1. At the top of icon 1 are graphs of the rates in the literature that we have been able to find as well as from three of our cervical IDE clinical trials (AFFINITY, CORNERSTONE, and PRESTIGE. All were implanted anteriorly and single level and without INFUSE material, except for a few of the patients in the CORNERSTONE trial did have some and were 2 level.) Even making the post-market rate as high as possible (by dividing by 454), the rate of cervical swelling we are hearing about is within the range in the literature and not too different from our cervical IDE database. So I guess the first question is: does a range of 1.9 to 5.5% in the literature and 1.1 to 2.8% in the cervical IDE clinical trials for cervical swelling sound right based upon your experience and knowledge of the literature? If so, does our rate of complaint (around 1.7 to 3.8%) seem to be consistent with that?
You should also know about some more evidence of all about this issue. In Wyeth's investigator brochure is a table that shows that when all the human studies from Wyeth are all combined, 208 out of 667 rhBMP-2/ACS patients (31%) had edema. In 266 controls without the use of bone graft, 114 or 43% had edema. These results were found to be a statistically lower ($p<.0008$) rate of edema in the rhBMP-2 treated patients. This fact combined with the analysis of the possible rates of occurrence of rhBMP-2 in the cervical spine being the same as in the literature and in our cervical clinical trials without rhBMP-2 implies to me that at this time there is no obvious relationship in regard to the rate of edema and use of rhBMP-2/ACS in the cervical spine. But what do you think?
In regard to timing of the edema: Icon 2 contains a "pictograph" of the timing reported in three cervical articles without rhBMP-2 and our clinical trials. On the bottom of the graph is the range we have had reported in our 17 cases. It appears to me that the timing of the edema is within the range reported in the literature and in our cervical non-rhBMP-2 IDE trials. What do you think?
In regard to severity: Icon 3 has the types of severe complications reported in the cervical literature and in our IDE cervical trials. Here too the types and rates of severity of the edema complications are apparently consistent with the literature and clinical trials, even using the 452 number for the rhBMP-2 cases as a denominator. It can be argued that the literature without rhBMP-2 has even more severe complications reported since one death out of 1183 cases is reported.
While we will keep monitoring for more cases and will investigate these matters as much as we can, does it

appear to you that there is any negative "association" between edema and the use of rhBMP-2/ACS in the cervical spine or that the onset is occurring with more severity or later than would otherwise? Since edema and the other complications occur without the use of INFUSE Bone Graft in the cervical spine, I personally would be surprised if they didn't occur with its use, but what do you think?
Please let me know what you think when you have a chance. I would value your opinion. Thanks...Rick

<<INFUSE Chart on Rate of Swelling.xls>> <<Time graft for Infuse.xls>> <<INFUSE Chart on Severity of Complications.xls>>

From: Treharne, Rick
Sent: Monday, June 14, 2004 11:44:35 AM
To: Burkus, J. Kenneth
Subject: Cervical Complaints

Attachments: INFUSE Chart on Rate of Swelling.xls; Time graft for Infuse.xls; INFUSE Chart on Severity of Complications.xls

Thank you for attending the D.C. meeting Friday and Saturday. I found it very informative and the give and take intellectually stimulating. I would have liked to have had time on the podium myself to get some feedback on some questions I have, like what I am emailing you about here. Also, I forgot to go over with you the allograft results and paper. I had brought a lot of that information with me and with everything going on forgot about it.

As our key BMP consultant I wanted to email you these confidential analyses about our No. 1 complaint (few as they are) about BMP, swelling in the cervical spine. For the sake of full disclosure, you should know that I have been told that Steve Glassman thinks there is something to all this, as apparently do a few other doctors since we have gotten some complaints/questions. But here is my analysis:

Below are 3 Icons I prepared about the issue of the use of rhBMP-2/ACS (INFUSE) in the cervical spine. In Icon 1 are what our "central complaint unit" (required by the FDA regulations) knows. Right now I have 17 cases reported of swelling in the cervical spine after the use of rhBMP-2/ACS (INFUSE). From the sites reporting these observations we know that they have used INFUSE Bone Graft in the cervical spine at least 452 times in 452 cases. In the table is a rate showing these 17 cases divided by 452 as well as a rate of use estimated by Neil Beals of 1000 cases, which is probably a conservative realistic guess of the number of uses of INFUSE Bone Graft in the cervical spine. These graphs are at the bottom of Icon 1. At the top of icon one are graphs of the rates in the cervical literature that I have been able to find as well as from three of our cervical IDE clinical trials (labeled AFFINITY, CORNERSTONE, and PRESTIGE). Even making the post-market rate as high as possible (17/452), I conclude that the rate of swelling we are hearing about is within the range in the literature without the use of INFUSE Bone Graft and is not too different from our cervical IDE database.

This analysis is consistent with what I think is the most compelling evidence of all about this issue. In Wyeth's investigator brochure is a table (5.4.1.5A) that shows that when all the human studies from Wyeth are all combined, 208 out of 667 rhBMP-2/ACS (INFUSE) patients (31%) had edema. In 266 controls without the use of bone graft, 114 or 43% had edema. These results were found to be a statistically lower ($p<.0008$) rate of edema in the rhBMP-2 (INFUSE) treated patients. This fact combined with the analysis of the possible rates of occurrence of rhBMP-2 in the cervical spine being the same as in the literature and in our cervical clinical trials without rhBMP-2 makes a compelling and convincing case that there is no issue here in regard to rates of edema. For BMP to cause cervical swelling, this statistically significant difference that Wyeth found in their human studies would not only have to be wrong, but the statistical significance would have to reverse and go the opposite direction. I can think of no case in any science where that has happened--in other words, a statistically significant negative effect turned out to be a statistically significant positive effect.

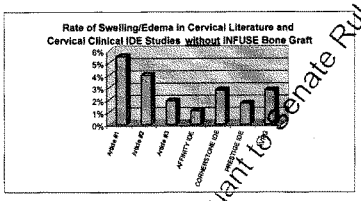
What about in regard to timing of the edema seen? Icon 2 contains a pictorograph of the timing reported in three

cervical articles without rhBMP-2 and our clinical trials. On the bottom of the graph is the range calculated for our 17 cases. I conclude that the timing of the edema is within the range reported in the literature and in our cervical non-rhBMP-2 IDE trials.

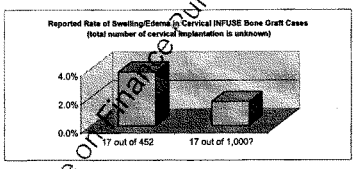
What about severity? See Icon 3. While we will keep monitoring for more cases and will investigate these matters that we know about as much as we can, I am at this time unconvinced that not only is there no negative "association" between edema and the use of rhBMP-2/ACS in the cervical spine or that the onset is occurring later than would otherwise, but the severity is no more and may be less than if the product had not been used at all. Since edema and the other complications occur without the use of rhBMP-2/ACS, why should we be surprised if they occur with its use?

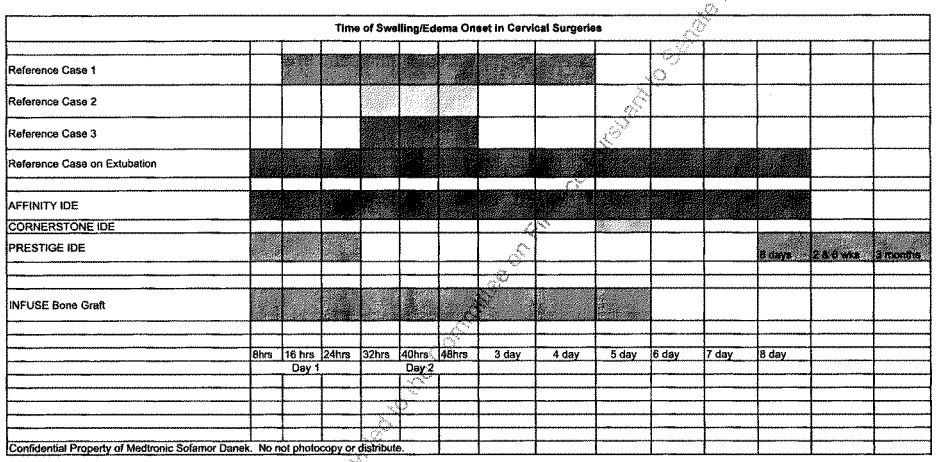
In sum, I just do not, at this time, see anything here to worry about. What do you think?

Literature Reference #1	Article #1	5.5%
Literature Reference #2	Article #2	4.0%
Literature Reference #3	Article #3	1.9%
AFFINITY IDE	AFFINITY IDE	1.1%
CORNERSTONE IDE	CORNERSTONE IDE	2.8%
PRESTIGE IDE	PRESTIGE IDE	1.7%
Average	AVRG	2.8%

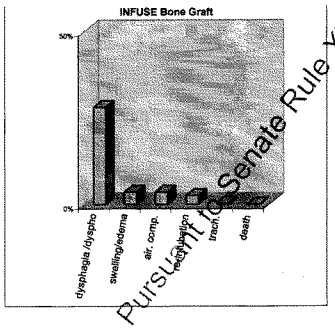


INFUSE Bone Graft Patients	
17 out of 452	3.8%
17 out of 1,000?	1.7%

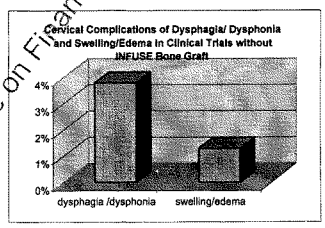




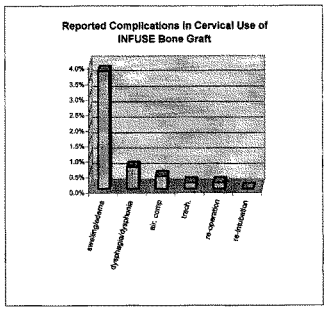
Cervical Complication	Number		Rate
Literature			
dysphagia /dysphonia	7 out of 25	dysphagia /dyspho	28.00%
swelling/edema	42 out of 1183	swelling/edema	3.60%
airway compromise	41 ot of 1134	air. comp.	3.60%
re-intubation	29 out of 1134	re-intubation	2.60%
tracheostomy / tracheotomy/ criothryroidotomy	3 out of 847	trach.	0.40%
death	1 out of 1183	death	0.08%



Clinical			
dysphagia /dysphonia	29 out of 759	dysphagia /dysphonia	3.80%
swelling/edema	10 out of 759	swelling/edema	1.30%



INFUSE			
edema / swelling	17 out of 452	swelling/edema	3.80%
dysphagia / dysphonia	3 out of 452	dysphagia/dysphonia	0.70%
respiratory /airway compromise	2 out of 452	air. comp	0.40%
tracheostomy / tracheotomy	1 out of 452	trach.	0.20%
re-operation to decompress	1 out of 452	re-operation	0.20%
re-intubation	0	re-intubation	0.00%



From: Beals, Neil
Sent: Tuesday, August 17, 2004 09:04:29 AM
To: DeMane, Michael; Wehrly, Peter
CC: Bearcroft, Julie, PhD; Cillo, Yolanda, M.D.; Treharne, Rick; Serbousek, Jon; McKay, Bill
Subject: FW: NASS BMP ACDF

reasonable position taken by Scott - action is needed on this ASAP. Julie and I will work on something.

Neil
-----Original Message-----
From: McKay, Bill
Sent: Tuesday, August 17, 2004 7:04 AM
To: Beals, Neil; Foster, Steve
Subject: FW: NASS BMP ACDF

FYI, Dr. Carl Lauyrassen is the surgeon who made this comment during the last presentation at the meeting in Los Cabos.

Bill

-----Original Message-----
From: Scott Boden [mailto:[redacted]
Sent: Monday, August 16, 2004 9:24 AM
To: MICKCH[redacted]; muehlbaue[redacted]
Subject: Re: NASS BMP ACDF

I think you ask a reasonable question. Wyeth has considered the issue in addition to Medronic.

The problem is that I have personally reviewed the data for these cases because I was concerned, they have been reported to the FDA, and there aren't enough to say for sure whether it is dose related, technique related, exposure related, or what. I think it may be premature for any "official" warning, but it should remain a topic of discussion on podium symposia and presentations until we are more sure of the mechanism, frequency, and impact.
Just my 2 cents worth.

Scott D. Boden, MD
Professor of Orthopaedic Surgery
Director, The Emory Orthopaedics & Spine Center
Emory University School of Medicine

>>> <MICKCH[redacted]> 08/16/04 10:19AM >>>
Scott,
During the meeting on new technology in Los Cabos last week, mention was made
of

eight cases reported to the FDA of side effects (local swelling with or without respiratory compromise) when BMP was used off label in association with anterior cervical discectomy and fusion.

Some manufacturers present stated they believed they were prevented by the FDA from notifying the spine community of this potential complication lest their alert in some manner be construed to be promoting off label usage.

If you are familiar with the reports, do you believe the concern raised has risen to a level that NASS, or someone, should send an alert to the membership of the potential for complications?
NASS does not wish to be alarmist or spread rumor without foundation, and yet wishs to respond responsibly if there is a chance such an alert may prevent injury.

Charlie Mick

Charles Mick, MD
Co-Director, Council on Socioeconomic Affairs
North American Spine Society

From: Wehrly, Peter [ITD Div. Pres.]
Sent: Tuesday, December 31, 2002 01:09:21 PM
To: Martin, Bill
Subject: RE: PLIF Study Manuscript

What do you think?

Pete

-----Original Message-----
From: Beals, Neil
Sent: Tuesday, December 31, 2002 10:53 AM
To: Wehrly, Peter [ITD Div. Pres.]
Cc: Bearcroft, Julie; Charlton, Clark; Martin, Bill; DeMane, Michael; Lipscomb, Bailey
Subject: RE: PLIF Study Manuscript

Julie and I will be glad to f/u on this.

As we get into this, I think we need to clarify and confirm: 1) the message delivered with this paper, 2) its timing, and 3) balanced input from all authors (Haid, Burkus, Branch/Alexander) with particular attention to positioning this with neuro community.

Ken has done a great job in getting the data into a workable manuscript form (I assume that Bailey will not have problems in filling in gaps Ken has pointed out). In its current form, the paper pretty much reports the data from the study with relatively little interpretation or comment. My recommendation would be to report the data and point out that while this study used a flawed technique that has since been modified (stand alone to instrumented PLIFs) the results, particularly with INFUSE, were quite good. The observation of bone formation should be noted and explanations provided including cage placement, construct stability, tissue disruption, and use of other exogenous materials. I think it would make great sense to include the rationale for the new INFUSE PLIF study in this paper to give these discussions some direction and purpose.

To realize this, I think we need to agree on message (INFUSE works well in PLIF with dated technique and is expected to work more consistently and with greater confidence using revised techniques), timing (get published in peer reviewed journal by year-end and try to think of new message to submit in Feb for presentations at spine meetings in the fall), and well balanced input (this must be balanced between Ken and Charley and Joe and Reg; this may be the toughest challenge and the one for which we will need support from top down (if you agree)).

We'll start cracking on more specific review and proposed revision. In meantime, any thoughts?

Neil

-----Original Message-----
From: Wehrly, Peter [ITD Div. Pres.]
Sent: Monday, December 23, 2002 8:25 AM
To: Beals, Neil; Martin, Bill
Cc: Bearcroft, Julie; Charlton, Clark
Subject: FW: PLIF Study Manuscript

Here is first draft. Neil and Julie, will you champion this?

Pete

-----Original Message-----
From: Burkus, J. Kenneth
Sent: Saturday, December 21, 2002 11:26 AM
To: DeMane, Michael; Wehrly, Peter
Subject: PLIF Study Manuscript

Mike and Pete,

Here's your Christmas present. I have attached a copy of the PLIF study manuscript. I believe this will make a significant contribution. I also think this should have a high priority to bring to completion.

I have done about all that I can do without further analysis of the PLIF study data.

In the text of the manuscript, you will find numerous areas that are in bold and underlined. I will need further analysis of this data.

The discussion and conclusions and bibliography are lacking but should be relatively easy to fix up.

I have been handicapped in writing this manuscript in that I have not had access to any of the hard numbers involving patient outcomes and x-ray interpretation with this study.
Take the cuffs off.

I am running home to pack and head off to Salt Lake City and catch up with my family. They should be spending their first day on the slopes today.

Thank you for your generosity and support and friendship throughout this past year. I am looking forward to running harder and moving the ball forward this coming year.

Merry Christmas and best regards to you and your families.

Warm regards,
Ken Burkus

From: Wehrly, Peter [ITD Div. Pres.]
Sent: Friday, January 3, 2003 07:50:38 AM
To: Beals, Neil
Subject: RE: PLIF Study Manuscript

I will talk with Bill on Monday when he returns and discuss. You may be right in that we are once again too far down the road.

Pete

-----Original Message-----
From: Beals, Neil
Sent: Thursday, January 02, 2003 8:18 AM
To: Wehrly, Peter [ITD Div. Pres.]
Cc: Bearcroft, Julie; Charlton, Clark; Martin, Bill
Subject: RE: PLIF Study Manuscript

Pete,

Based on note below from Bill, it seems that he has already covered this manuscript and its direction with Ken and all that is now needed is data from Bailey. I do not see need for Julie or I to get into this at this point. Please advise if you see things differently. Thanks. Neil

-----Original Message-----
From: Martin, Bill
Sent: Wednesday, January 01, 2003 8:06 AM
To: Beals, Neil; Wehrly, Peter [ITD Div. Pres.]
Cc: Bearcroft, Julie; Charlton, Clark; Martin, Bill; DeMane, Michael; Lipscomb, Bailey
Subject: RE: PLIF Study Manuscript

A word of caution.
I'm pretty sure that on this paper Dr. Burkus just wants us to provide him the data he requested. Dr. Burkus mentioned that his plan for this paper was to do all the work, put Drs Haid, Branch and Alexander's names first, and then he plans to route it to them "as is" for approval. If they don't agree with the data, then they may of course take their name off. Dr. Burkus has done ground work with Charlie and Reg and they have indicated initially that they seem to be fine with this - I don't anticipate any issues between them. Dr. Burkus wanted his name last (and all the neuro's first) so that it would be well accepted by the Neurosurgical community. I know that he has talked in depth with Charlie about what the paper *should*, and equally important, *should not* include.

A couple of additional thoughts:

1. Ken's intent was to purposely NOT include a lot of interpretation/explanation about radiographic observations that don't correlate to the outcomes for concern that it will confuse the issues and again look like an apology (which is part of what he hopes to clear up with this paper).
2. He's stated that the data is good and should stand on its own. His desire is to cleanly report the outcomes.
3. I'm sure that none of us believe the PLIF *technique* is going to have a resurgence from this, but we may want to steer clear of calling it a flawed technique. There are still quite a few surgeons utilizing this technique and we probably don't want to put them in that position. In the past, the way that Haid has approached this is to use verbiage such as "this technique has fallen out of favor, and many surgeons are now choosing to ____". If Reg believes that a statement like this would be necessary to add, he'll have the opportunity to add it when Dr. Burkus routes to him for approval.

Basically, let's provide Dr. Burkus with the information he requested (and I believe he's already working with Bailey on this), and just communicate with him to offer to help in any way he needs to get this done. He does have a plan already and intends to quarterback it.

Thanks,
Bill

-----Original Message-----

From: Beals, Neil [SMTP [redacted]
Sent: Tuesday, December 31, 2002 10:53 AM
To: Wehrly, Peter [ITD Div. Pres.]
Cc: Bearcroft, Julie; Charlton, Clark; Martin, Bill; DeMane, Michael; Lipscomb, Bailey
Subject: RE: PLIF Study Manuscript

Julie and I will be glad to f/u on this.

As we get into this, I think we need to clarify and confirm: 1) the message delivered with this paper, 2) its timing, and 3) balanced input from all authors (Haid, Burkus, Branch/Alexander) with particular attention to positioning this with neuro community.

Ken has done a great job in getting the data into a workable manuscript form (I assume that Bailey will not have problems in filling in gaps Ken has pointed out). In its current form, the paper pretty much reports the data from the study with relatively little interpretation or comment. My recommendation would be to report the data and point out that while this study used a flawed technique that has since been modified (stand alone to instrumented PLIFs) the results, particularly with INFUSE, were quite good. The observation of bone formation should be noted and explanations provided including cage placement, construct stability, tissue disruption, and use of other exogenous materials. I think it would make great sense to include the rationale for the new INFUSE PLIF study in this paper to give these discussions some direction and purpose.

To realize this, I think we need to agree on message (INFUSE works well in PLIF with dated technique and is expected to work more consistently and with greater confidence using revised techniques), timing (get published in peer reviewed journal by year-end and try to think of new message to submit in Feb for presentations at spine meetings in the fall), and well balanced input (this must be balanced between Ken and Charley and Joe and Reg; this may be the toughest challenge and the one for which we will need support from top down (if you agree)).

We'll start cracking on more specific review and proposed revision. In meantime, any thoughts?

Neil

-----Original Message-----
From: Wehrly, Peter [ITD Div. Pres.]
Sent: Monday, December 23, 2002 8:25 AM
To: Beals, Neil; Martin, Bill
Cc: Bearcroft, Julie; Charlton, Clark
Subject: FW: PLIF Study Manuscript

Here is first draft. Neil and Julie, will you champion this?

Pete

-----Original Message-----
From: Burkus, J. Kenneth
Sent: Saturday, December 21, 2002 11:26 AM
To: DeMane, Michael; Wehrly, Peter
Subject: PLIF Study Manuscript

Mike and Pete,

Here's your Christmas present. I have attached a copy of the PLIF study manuscript. I believe this will make a significant contribution. I also think this should have a high priority to bring to completion.

I have done about all that I can do without further analysis of the PLIF

study data.

In the text of the manuscript, you will find numerous areas that are in bold and underlined. I will need further analysis of this data.

The discussion and conclusions and bibliography are lacking but should be relatively easy to fix up.

I have been handicapped in writing this manuscript in that I have not had access to any of the hard numbers involving patient outcomes and x-ray interpretation with this study.

Take the cuffs off.

I am running home to pack and head off to Salt Lake City and catch up with my family. They should be spending their first day on the slopes today.

Thank you for your generosity and support and friendship throughout this past year. I am looking forward to running harder and moving the ball forward this coming year.

Merry Christmas and best regards to you and your families.

Warm regards,
Ken Burkus

From: Wehrly, Peter [ITD Div. Pres.]
Sent: Friday, January 3, 2003 07:53:49 AM
To: Martin, Bill
Subject: RE: PLIF Study Manuscript

Neil is out of the picture. Can you ensure Ken gets the info he needs to complete the paper?

Is it worth showing the typical results comparisons versus FDA results?

Let's make sure the paper clearly defines the issues. I want to close the door on this study!

Pete

-----Original Message-----
From: Martin, Bill
Sent: Wednesday, January 01, 2003 8:06 AM
To: Beals, Neil; Wehrly, Peter [ITD Div. Pres.]
Cc: Bearcroft, Julie; Charlton, Clark; Martin, Bill; DeMane, Michael; Lipscomb, Bailey
Subject: RE: PLIF Study Manuscript

A word of caution.
I'm pretty sure that on this paper Dr. Burkus just wants us to provide him the data he requested. Dr. Burkus mentioned that his plan for this paper was to do all the work, put Drs Haid, Branch and Alexander's names first, and then he plans to route it to them "as is" for approval. If they don't agree with the data, then they may of course take their name off. Dr. Burkus has done ground work with Charlie and Reg and they have indicated initially that they seem to be fine with this - I don't anticipate any issues between them. Dr. Burkus wanted his name last (and all the neuro's first) so that it would be well accepted by the Neurosurgical community. I know that he has talked in depth with Charlie about what the paper *should*, and equally important, *should not* include.

A couple of additional thoughts:

1. Ken's intent was to purposely NOT include a lot of interpretation/explanation about radiographic observations that don't correlate to the outcomes for concern that it will confuse the issues and again look like an apology (which is part of what he hopes to clear up with this paper).
2. He's stated that the data is good and should stand on its own. His desire is to cleanly report the outcomes.
3. I'm sure that none of us believe the PLIF *technique* is going to have a resurgence from this, but we may want to steer clear of calling it a flawed technique. There are still quite a few surgeons utilizing this technique and we probably don't want to put them in that position. In the past, the way that Haid has approached this is to use verbiage such as "this technique has fallen out of favor, and many surgeons are now choosing to ____". If Reg believes that a statement like this would be necessary to add, he'll have the opportunity to add it when Dr. Burkus routes to him for approval.

Basically, let's provide Dr. Burkus with the information he requested (and I believe he's already working with Bailey on this), and just communicate with him to offer to help in any way he needs to get this done. He does have a plan already and intends to quarterback it.

Thanks,
Bill

-----Original Message-----
From: Beals, Neil [SMTP [redacted]]
Sent: Tuesday, December 31, 2002 10:53 AM
To: Wehrly, Peter [ITD Div. Pres.]
Cc: Bearcroft, Julie; Charlton, Clark; Martin, Bill; DeMane, Michael; Lipscomb, Bailey
Subject: RE: PLIF Study Manuscript

Julie and I will be glad to f/u on this.

As we get into this, I think we need to clarify and confirm: 1) the message delivered with this paper, 2) its timing, and 3) balanced input from all authors (Haid, Burkus, Branch/Alexander) with particular attention to positioning this with neuro community.

Ken has done a great job in getting the data into a workable manuscript form (I assume that Bailey will not have problems in filling in gaps Ken has pointed out). In its current form, the paper pretty much reports the data from the study with relatively little interpretation or comment. My recommendation would be to report the data and point out that while this study used a flawed technique that has since been modified (stand alone to instrumented PLIFs) the results, particularly with INFUSE, were quite good. The observation of bone formation should be noted and explanations provided including cage placement, construct stability, tissue disruption, and use of other exogenous materials. I think it would make great sense to include the rationale for the new INFUSE PLIF study in this paper to give these discussions some direction and purpose.

To realize this, I think we need to agree on message (INFUSE works well in PLIF with dated technique and is expected to work more consistently and with greater confidence using revised techniques), timing (get published in peer reviewed journal by year-end and try to think of new message to submit in Feb for presentations at spine meetings in the fall), and well balanced input (this must be balanced between Ken and Charley and Joe and Reg: this may be the toughest challenge and the one for which we will need support from top down (if you agree)).

We'll start cracking on more specific review and proposed revision. In meantime, any thoughts?

Neil

-----Original Message-----
From: Wehrly, Peter [ITD Div. Pres.]
Sent: Monday, December 23, 2002 8:25 AM
To: Beals, Neil; Martin, Bill
Cc: Bearcroft, Julie; Charlton, Clark
Subject: FW: PLIF Study Manuscript

Here is first draft. Neil and Julie, will you champion this?

Pete

-----Original Message-----
From: Burkus, J. Kenneth
Sent: Saturday, December 21, 2002 11:26 AM
To: DeMane, Michael; Wehrly, Peter
Subject: PLIF Study Manuscript

Mike and Pete,

Here's your Christmas present. I have attached a copy of the PLIF study manuscript. I believe this will make a significant contribution. I also think this should have a high priority to bring to completion.

I have done about all that I can do without further analysis of the PLIF study data.

In the text of the manuscript, you will find numerous areas that are in bold and underlined. I will need further analysis of this data.

The discussion and conclusions and bibliography are lacking but should be relatively easy to fix up.

I have been handicapped in writing this manuscript in that I have not had access to any of the hard numbers involving patient outcomes and x-ray interpretation with this study.

Take the cuffs off.

I am running home to pack and head off to Salt Lake City and catch up with my family. They should be spending their first day on the slopes today.

Thank you for your generosity and support and friendship throughout this past year. I am looking forward to running harder and moving the ball forward this coming year.

Merry Christmas and best regards to you and your families.

Warm regards,
Ken Burkus

From: J. Kenneth Burkus[redacted]
Sent: Wednesday, November 1, 2006 06:55:09 AM
To: Yahiro, Martin, M.D.; Desrochers, Debbie; Bearcroft, Julie, PhD; Beals, Neil
Subject: Re: Draft Stopping Rules 10_30_06.doc

Martin

Thank you for you kind and thoughtful response.

Best regards,
Ken Burkus
----- Original Message -----
From: "Yahiro, Martin, M.D." <[redacted]>
To: <jkb[redacted]>; "Desrochers, Debbie" <[redacted]>; "Bearcroft, Julie, PhD" <[redacted]>; "Beals, Neil" <[redacted]>
Sent: Wednesday, November 01, 2006 6:24 AM
Subject: Re: Draft Stopping Rules 10_30_06.doc

> Ken,
>
> Thanks for your note. I think we're all on the same page regarding the ability to determine the exact cause of an event that could possibly be related to INFUSE (or just a result of cervical surgery). We agree it would be very difficult to pin it on INFUSE, which is exactly why we wrote the stopping rule that way. What we don't want is a rule that would have specific events with incidence rates, etc., that would stop the trial when it would be hard to say it WASN'T INFUSE. The way we wrote it, WE make the determination whether it was INFUSE-related. This way, if a patient has an AE like severe cervical swelling, we can honestly say that it is not possible to know that the cause is definitely INFUSE and therefore the study need not be stopped.
>
> I think these stopping rules allow us the ability to make good medical judgments and not stop the study unnecessarily.
>
> Am I making sense? Let me know if you have additional questions. Thanks so much for your input.
>
> Martin
> ----------
> Sent from my BlackBerry Wireless Handheld
>
>
> ----- Original Message -----
> From: J. Kenneth Burkus[redacted]>

> To: Bearcroft, Julie, PhD; kfoley@[redacted]
> Cc: Beals, Neil; Desrochers, Debbie; Yahiro, Martin, M.D.
> Sent: Wed Nov 01 04:44:15 2006
> Subject: Re: Draft Stopping Rules 10_30_06.doc
>
>
> Sirs and Ma'ams,
>
>
>
> Adverse events vary in severity with specific surgical implants and with the
> anterior cervical surgical procedure. For example, a number of patients in
> the Prestige ST study developed WHO grade 3 and 4 adverse events. In many of
> these cases if BMP-2 had been used, it would have been impossible to
> identify a single causative factor or to eliminate BMP-2 as the cause. The
> use of rhBMP-2 cannot be single out as a causative factor in clinical cases
> where the cause of an adverse event is almost always multifactorial.
>
> Overall in the Prestige ST FDA IDE study, the rate of investigational device
> patients who had at least one adverse event was very similar to the control
> group rate. This was also true for serious adverse events. There were no
> unanticipated adverse device effects reported in this study. During the
> surgery-discharge interval alone, there were 17 (5.1%) adverse events
> reported in the investigational group (Table 1) and 11 (4.2%) adverse events
> reported in the control group (Table 2). Hematoma formation, dysphagia and
> dysphonia were the most common perioperative complication in each treatment
> group. In addition, additional surgeries were higher in the fusion group
> (Table 3).
>
> Intubation alone cannot be seen as a BMP-2 related complication. I believe
> that BMP-2 would be considered as a causative factor only if its use
> exceeded the incidence in the large group of single level fusion patients
> that you have enrolled in current FDA IDE trials.
>
> I believe the rate and incidence of adverse events following all single
> level anterior cervical disc surgery should be determined from all of the
> prospective FDA IDE studies that have been conducted by Medtronic Sofamor
> Danek. Once this data has been examined. The incidence and rate of
> significant adverse events following single level anterior cervical surgery
> can be determined. The rhBMP-2 cervical study should be closed if the rate
> of significant adverse events is higher than this predetermined rate.
>

> Table 1 Investigational Operative Adverse Events

	Adverse Event Category	Event	Time Period of Occurrence
1	Neurological	Numbness/Paresthesias	Operative
2	Neurological	Back and Leg	Operative
3	Respiratory	Sleep Apnea	Operative
4	Other Pain	Bursitis	Operative
5	Anatomical/Technical Difficulty	Screw Fixation	Operative
6	Dysphagia/Dysphonia	Dysphagia	Operative
7	Other	Low Bone Density	Operative
8	Neurological		

> Shocking Sensations (Bodily)
> Operative
>
> 9
> Vascular Intra-operative (Vessel Injury)
> Hematoma
> Operative
>
> 10
> Neurological
> Paraesthesia/Pain - Arm, Cervical Radiculopathy
> Operative
>
> 11
> Vascular Intra-operative (Vessel Injury)
> Hematoma
> Operative
>
> 12
> Dysphagia/Dysphonia
> Dysphonia
> Operative
>
> 13
> Other
> Dural Leak
> Operative
>
> 14
> Infection
> UTI
> Operative
>
> 15
> Other Pain
> Headaches
> Operative
>
> 16
> Neck and/or Arm Pain
> Intrascapular Muscle Spasms
> Operative
>
> 17
> Infection
> Sinusitis
> Operative
>
>
>

Table 2 Control Operative Adverse Events

PT Adverse Event Category Event Time Period of Occurrence
1 Vascular intra-operative (vessel injury)
Venous "Ooze" Operative
2 Neurological
Numbness - Arm (Left) Operative
3 Other Pain
Headaches Operative
4 Gastrointestinal
Nausea Operative

>
> 5
> Other
>
> Dural Leak/Tear
> Operative
>
> 6
> Dysphagia/Dysphonia
>
> Dysphagia
> Operative
>
> 7
> Other Pain
>
> Headaches
> Operative
>
> 8
> Gastrointestinal
>
> Vomiting
> Operative
>
> 9
> Dysphagia/Dysphonia
>
> Dysphonia - Laryngeal Nerve Palsy
> Operative
>
> 10
> Dysphagia/Dysphonia
>
> Dysphagia
> Operative
>
> 11
> Other
>
> Dural Leak
> Operative

>
>
>
>
>
>
>
>
>
>
>
>
> Table 3. Secondary surgical procedures (total events).
>
> Procedure
> Investigational Group
> Control Group
> p value
>
> Revision
> 0
> 5
> 0.0277*
>
> Supplemental fixation
> 0
> 9
> 0.0031*
>
> Removal
> 5
> 9
> 0.2870
>
>
> *Statistically significant difference. P values calculated by Fisher's exact
> test.
>
>
>
>
>
>
>
>
>
>
>
> ----- Original Message -----
> From: "Bearcroft, Julie, PhD" <[redacted]>

> To: [redacted]JKE[redacted]>; <kfoley[redacted]
> Cc: "Beals, Neil" [redacted] "Desrochers, Debbie"
> [redacted]>; "Yahiro, Martin, M.D."
> [redacted]>
> Sent: Tuesday, October 31, 2006 3:53 PM
> Subject: FW: Draft Stopping Rules 10_30_06.doc
>
>
> Ken and Kevin -
> Please see the attached revised draft to the proposed stopping rules for
> the ACDF INFUSE IDE that were prepared by regulatory affairs. At the
> top of the page in bold, you will see the question as it was written in
> our letter from the FDA.
>
> Please review and provide comments. I apologize for the late notice but
> would very much appreciate your response tomorrow. We have a tight
> deadline to submit this response to the FDA by the end of the week.
>
> Thank you again for your support and guidance. Feel free to call me if
> you have any questions.
>
> julie
>
> _____
> From: Desrochers, Debbie
> Sent: Monday, October 30, 2006 4:32 PM
> To: Bearcroft, Julie, PhD
> Cc: Beals, Neil; Yahiro, Martin, M.D.
> Subject: Draft Stopping Rules 10_30_06.doc
>
> <<Draft Stopping Rules 10_30_06.doc>>
> Julie,
> Please forward the attached draft stopping rules to Dr. Burkus for his
> review. We will need to submit these to FDA this week, so if we could
> have a response by Wednesday it would be appreciated.
> Thanks,
> Debbie
>
>
>

From: James Larkin[redacted]ketchum.com]
Sent: Tuesday, December 11, 2001 08:20:39 PM
To: Bailey Lipscomb[redacted]
CC: Kirsten Gorsuch[redacted]@ketchum.com]
Subject: Revised Panel Speech

Attachments: Mathews Speech Version 4.doc; Mathews Speech Version 3.doc

Hello Bailey,

First, thanks for your patience. Second, we thought the speech was in very good shape and so most of changes were minor. You'll note that we did re-work some areas and re-ordered a section or two to tighten it up.

For your convenience, you'll find two versions of the speech attached. The first, labeled Version 3, was edited with the "Track Changes" function. This allows you to see exactly what we changed and also gives you the option of only accepting some of the edits. Version 4 has all of our suggested edits "accepted." Please let us know if you have any questions.

Also, we'd still like to schedule a brief call with you to discuss the schedule for this Sunday. I can make myself available nearly any time tomorrow.

Sincerely,
James

DRAFT

InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device
Panel Presentation – Clinical Results
Hallett H. Mathews, M.D.

INTRODUCTION

Good morning. My name is Dr. Hal Mathews, and I am a practicing orthopedic surgeon from Richmond, Virginia. My primary professional focus is spine care, and I am an Associate Clinical Professor of Orthopedic Surgery at Virginia Commonwealth University and the Medical College of Virginia. I have no direct financial interest in the product under review here today and am not being paid for my participation in this meeting. I participated in the open surgical approach study of the device as an investigator.

OVERVIEW OF IMPORTANT FINDINGS

I am here today to present the results of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device clinical trial. Before I discuss the details of the clinical trial, I want to report to this advisory panel and the audience the top-line findings from the open surgical approach study.

- First and foremost, the primary objective of the clinical trial as stated in the protocol was met, thus establishing the safety and effectiveness of the InFUSE Bone Graft in the treatment of degenerative disc disease.
- The InFUSE Bone Graft treatment group had a six-percent higher fusion rate than control patients who received treatment with the current gold standard, autogenous bone graft.
- InFUSE Bone Graft patients experienced shorter operative times and less blood loss than control patients.
- Patients who received the InFUSE Bone Graft avoided the complications and significant post-operative pain associated with bone graft harvests in the control group.

DRAFT

OPEN CLINICAL TRIAL

Design

I will now elaborate on the clinical trial and the results. The study examined the open surgical approach for device implantation and it had a prospective, controlled, randomized design. The investigational treatment patients received the LT-CAGE device filled with the InFUSE Bone Graft and the control patients were treated in a similar manner with LT-CAGE devices filled with autogenous bone harvested from the iliac crest. The safety and effectiveness endpoints from these two treatment groups would be compared.

The primary endpoint for the clinical trial was a derived variable termed "overall success." For a patient to be considered an overall success at a given postoperative timepoint, five criteria had to be met: (1) the treated level had to be fused, (2) the Oswestry pain/disability score had to be at least 15 points lower (better) than the preoperative value, (3) the neurological status had to be no worse than the preoperative condition, (4) no serious adverse event that was possibly device related, and (5) no second surgical procedure classified as a revision, removal, or supplemental fixation had occurred. As can be seen from this description, overall success is a comprehensive parameter that addresses both important safety and effectiveness aspects of the device treatment. It is also a very demanding variable since the criteria for success is based on successful outcomes in all five of its components.

The primary objective for the clinical trials was to determine if the overall success rate for the InFUSE Bone Graft treatment group, the investigational group, is at least as high statistically as the rate for the control group. Secondary objectives were also developed. These objectives were focused on determining if equivalency existed between the investigational and control treatment groups for the individual safety and effectiveness variables. If equivalency were demonstrated, statistical superiority for overall success and the individual

variables would also be examined. Bayesian methods were used for statistical comparisons of study outcomes.

Patients admitted to the study had single level, symptomatic degenerative disc disease as noted by back pain of discogenic origin, with or without leg pain, with degeneration of the disc confirmed by patient history and radiographic studies. There were a number of additional inclusion/exclusion criteria that had to be met prior to study participation. These criteria covered such factors as age, weight, mental competency, medical history, and existing medical condition.

Patients involved in the clinical trials were evaluated preoperatively, at surgery, and postoperatively at 6 weeks, 3, 6, 12, and 24 months.

Patient Population and Demographic Information

With this background information, I would now like to focus on the results of the prospective, randomized clinical trial evaluating the use of the InFUSE Bone Graft via an open surgical approach. The Premarket Approval application for the device is based primarily on these clinical results. A total of 143 patients received the InFUSE Bone Graft. For the sake of brevity, I will refer to this henceforth as the investigational treatment. There were 136 patients who were treated with autogenous bone graft, the control group. Patient follow-up compliance at all postoperative periods was high, with all rates exceeding 90%. Sixteen investigational centers contributed these patients.

Patients in the investigational and control groups had very similar demographic characteristics and preoperative medical conditions. This enhances one's ability to interpret the effects associated with the different treatments, since potentially confounding factors are similar for the two treatments. The scientific appeal of a prospective, randomized design is manifested in this study. The characteristics of the two treatment groups were so similar that the clinical results truly discern

the effects of the use of InFUSE Bone Graft as compared to autogenous bone graft.

Surgery Results

In terms of surgery results, the mean operative time for the investigational group was nearly a half-hour less than that for the control group and this difference was statistically different. The blood loss for the investigational group was also statistically lower than the blood loss for the control group. The mean hospital stays of patients in both treatment groups were slightly more than three days and not statistically different. The results of other surgical variables such as treated level, operative approach, type of orthosis, and outpatient/inpatient classification were very similar for both treatment groups.

Before I review the clinical results, I would like to emphasize that 24-month data are being used as primary supporting evidence of the safety and effectiveness of the treatments.

Safety Results

Overview

First, let's examine the safety information. In summary, the nature and frequency of adverse events and second surgery procedures for the investigational treatment were very similar to the control treatment and were considered typical for a patient population having anterior lumbar interbody fusion, or ALIF, procedure procedures. Antibody formation to BMP-2 was insignificant and the rates of authentic positive responses to bovine Type I collagen, the absorbable sponge material, were similar for both investigational and control treatment groups. Also, there was never a situation where a positive bovine Type I collagen antibody response triggered the body to produce antibodies to human Type I collagen. Authentic positive antibody responses appeared to be without clinical manifestations. Therefore, the InFUSE Bone Graft was found to be safe.

DRAFT

Adverse Events

Now for more details: the safety of the investigational device was evaluated based on the nature and frequency of adverse events compared to those occurring in the control group. Reported adverse events were classified by their nature, their severity according to World Health Organization criteria, and their duration. Also, Medtronic Sofamor Danek instructed investigators to report all adverse events that occurred, whether or not the event was related to the treatment or the device. This conservative approach led to the reporting of many unrelated events that were included in the analyses.

For the investigational treatment group, only 17 patients (11.9%) had an event that was possibly related to the device and in only 11 of these patients (7.7%) were the events considered "serious." Overall, a total of 113 investigational group patients (79%) had at least one adverse event, with a substantial majority not being related to the device. As you can see from the slide, these rates are very similar to those rates for the control group.

Adverse events were categorized with comparisons of the investigational and control group rates. The comparisons yielded statistical differences in only two of these categories – urogenital and graft site events. Nearly 6% of the control patients had a graft site complication. These complications included bone fractures, nerve injuries, infection, and hematoma. Obviously, there were no graft site adverse events for the investigational group. This fact clearly supports the use of InFUSE Bone Graft, since it eliminates the need to harvest bone graft.

The urogenital complication rate favored the control group. The difference in rates was mainly due to urinary retention following surgery. There were 11 reports of urinary retention in the investigational group as opposed to two in the control group. These events resolved in all patients prior to their discharge from the hospital. The reason for the difference in rates is not obvious, as the surgical procedures were the same.

There were two reported incidents of cancer in the investigational group and one case in the control group. A 79-year-old male patient was diagnosed with pancreatic cancer 11 months following surgery. This diagnosis was made more than a year ago and the patient is alive and doing well. The other cancer reported in the investigational group was a breast cancer in a 56-year-old female. The patient was approximately 24 months postoperative when the diagnosis was made and she subsequently had a lumpectomy. These are the only reported cases of cancer in more than 400 patients who received rhBMP-2 in all of our clinical trials. For comparison, a control patient was diagnosed with breast cancer approximately six months following surgery. Therefore based on these findings, tumor formation or proliferation is not a safety issue.

Second Surgeries

Another component of the safety assessment is the number and nature of additional surgical procedures performed after the initial study surgery. This slide lists the classifications of the additional surgical interventions. Revisions, removals, and supplemental fixations are considered significant procedures at the treated spinal level that affect the assessments of the treatment outcomes. Therefore, a patient having one of these procedures is considered a treatment "failure" for study purposes. On the other hand, reoperations and other surgical procedures are believed to have no affect on the treated level so, therefore, are not considered "failures."

The second surgery rates for the investigational and control groups were comparable and there were no statistically significant differences for any of the additional surgery category comparisons. There were no revisions in either treatment group. The investigational group had two implant removal procedures. Both of these occurred early postoperatively and were due to cage implantation issues. Supplemental fixations occurred at a rate of 7.0% in the investigational group, as compared to a higher 10.3% rate in the control group.

DRAFT

Antibody Results

Because of the proteinaceous nature of both the rhBMP-2 and the absorbable collagen sponge, the development of antibodies was assessed as part of the IDE clinical trial. Serum samples were taken from each patient preoperatively, to establish their baseline condition, and at three months following surgery. The samples were analyzed for the presence of antibodies specific to rhBMP-2 and to bovine Type I collagen. If a patient had a positive response to bovine Type I collagen, the serum was also tested for antibodies to human Type I collagen. Antibody levels were checked in both investigational and control patients, even though the latter group was not exposed to the InFUSE product. This slide shows the criteria for an authentic positive antibody response.

To summarize the findings, there was one investigational and one control patient who had authentic positive responses to BMP-2. The incidence rates were very low at less than 1% and the investigational group rate was no different to that of the unexposed control group. These rates essentially represent background noise. There were no adverse events that appeared to be related to these findings.

Approximately 13% of the patients in both the investigational and control treatment groups had authentic positive responses to bovine Type I collagen antibodies. This rate of authentic positive responses occurred in the control group even though the patients were not treated with the absorbable collagen sponge. Authentic positive responses to bovine Type I collagen antibodies did not appear to result in any clinical manifestations, nor impact the overall success rates for the study.

None of the patients who tested positive for bovine Type I collagen had a positive result for human Type I collagen.

These antibody findings are similar to those from other Medtronic Sofamor Danek clinical trials involving InFUSE Bone Graft.

Safety Summary

Since I have presented a lot of information, I want to briefly review the impressive safety profile of the InFUSE Bone Graft before moving to the effectiveness results. The nature and frequency of adverse events and second surgery procedures for the investigational treatment were very similar to the control treatment. The occurrences of adverse events and second surgery procedures were considered typical for a patient population having ALIF procedures and were not unanticipated. The use of the InFUSE Bone Graft also eliminated bone graft site-related adverse events for the investigational group while occurring in approximately 6% of the control patients. This finding is significant since it supports a major reason for using InFUSE Bone Graft. In addition, antibody formation to rhBMP-2 was insignificant and the rates of authentic positive responses to bovine Type I collagen, the absorbable sponge material, were similar for both investigational and control treatment groups, even though control patients did not receive the absorbable collagen sponge. Also, there was never a situation where a positive bovine Type I collagen antibody response led to the production of antibodies to human Type I collagen. Authentic positive antibody responses appeared to be without clinical manifestations. Therefore, based on the data, the InFUSE Bone Graft/LT-CAGE device is safe for its intended use in ALIF procedures to treat degenerative disc disease.

Effectiveness Results

Overview

Now I will focus on device effectiveness. In the clinical trial, effectiveness variables included fusion, Oswestry pain/disability status, neurological status, back pain, leg pain, bone graft harvest site pain, general health status, and disc height status. The results from these various measurements verify the effectiveness of the InFUSE Bone Graft. Patients receiving the treatment

experienced exceptionally high fusion rates, pain relief, maintenance or improvement in neurological status, and proper correction and maintenance of disc height. All of these benefits came without the significant amount of pain and morbidity that occurs with harvesting autograft bone from the iliac crest in conventional, gold standard, ALIF procedures.

Fusion

Let's review the effectiveness results in more detail. We consider fusion to be a primary endpoint, since the intended use of InFUSE Bone Graft is to induce bone formation in spinal fusion procedures. For this clinical trial, CT scans and radiographs were used to assess fusion and these films were evaluated at the University of California San Francisco, or UCSF, under the direction of Dr. Harry Genant, a board certified radiologist and Professor of Radiology, Medicine, Epidemiology, and Orthopedic Surgery at UCSF. There were two teams of reviewers who were masked to patient treatment, and each team worked independently of the other. If their overall fusion conclusions differed, a third reviewer at UCSF would adjudicate the findings. However, this occurred infrequently since the percent agreement between the two primary review teams exceeded 98% at all time points.

Fusion was based on evidence of bone spanning the two vertebral bodies of the treated segment using CT scans and radiographs. In addition, segmental stability and lucent line criteria also had to be met to be considered fused. Patients having second surgical procedures reported as being due to pseudarthrosis or non-unions were also considered as fusion failures regardless of the radiographic findings. This latter condition dramatically impacts the fusion rates for both treatments. For example, at 24 months postoperative, all fusion failures in the investigational group and 10 of 13 fusion failures in the control group were due to the second surgery criterion and were not radiographic non-unions.

The fusion rates for both treatment groups were high at 6, 12, and 24 months following surgery, with the investigational rate exceeding the control rate at every time period. At 24 months following surgery, the investigational treatment fusion rate was 94.5% and nearly six percentage points higher than the control group rate. Even though the clinical trial was sized for demonstrating statistical equivalence, the investigational fusion rate approached statistical superiority with a probability of 90.2%.

The reason we did not experience a perfect fusion rate with the INFUSE product can be attributed to the protocol definition of fusion that is based on a radiographic component, i.e. bridging bone, stability, and lucent line criteria, and a clinical second surgery component. These second surgeries are typically in response to pain complaints and are documented as being due to a possible non-union. However, most of the treated segments are radiographically fused according to protocol criteria. All of the investigational patients who had second surgeries for so-called non-unions after six months were actually found to be radiographically fused prior to the second surgery. This is a 100% radiographic fusion rate. A similar examination for the control group yields a radiographic fusion rate of 98.3%.

Oswestry Low Back Pain

Graft site pain will be discussed a little later but first let's examine the treatment's effects on relieving back pain. The Oswestry Low Back Pain Disability Questionnaire was used to measure the effects of back pain on a patient's ability to manage everyday life. The Oswestry questionnaire has ten questions and is self-administered. Oswestry scores are expressed as a percentage ranging from 0% to 100%, with a lower percentage indicating less pain and disability.

As seen in this slide, the mean Oswestry scores for the two treatment groups were very similar at all study time periods. Improvements from the mean preoperative scores were noted at all postoperative time points. At 24 months

following surgery, the mean improvements in Oswestry scores from preoperative were approximately 29 points for both treatments. These findings are quite gratifying and represent an approximate 55% improvement on average in both groups.

This slide illustrates the distributions of patients demonstrating preoperative to postoperative improvements in Oswestry scores of at least 15 points, a very rigorous condition mandated by FDA. This is termed Oswestry success. Like the mean Oswestry scores, the Oswestry success rates were similar for the investigational and control treatment groups. At 24 months following surgery, the Oswestry success rates for the two treatments were found to be statistically equivalent, with rates of 73% in both groups.

Neurological

The neurological status of the patients was assessed preoperatively and postoperatively at every follow-up visit and it is considered an indicator of safety as well as effectiveness. The neurological evaluations consisted of measurements of motor function, sensory, reflexes, and the degree of straight leg raise reproducing pain. An algorithm was developed to reduce the detailed scoring for each parameter into a success/failure classification. A successful outcome for each parameter was based on the postoperative condition being no worse than the preoperative condition. Overall neurological success for a patient at any given postoperative time period was based on having successful outcomes for all four neurological parameters.

This slide shows the overall neurological success rates at 12 and 24 months following surgery for the two treatment groups. The rates are very similar across time and treatments. The 24-month neurological success rates for the investigational and control groups were determined to be statistically equivalent.

Other Effectiveness Endpoints

In addition to these endpoints, which are factors that contribute to the overall success determinations, other effectiveness measurements were made during the course of the study. These measurements included back pain, leg pain, disc height maintenance, and general health status via the SF-36 survey. The 24-month results for these parameters were comparable for the two treatment groups and statistical equivalence between treatments was demonstrated for all but two comparisons, back pain and the mental component summary, or MCS, of the SF-36.

I will not focus on the MCS finding since the difference between treatment groups was less than four percentage points and this is not considered clinically significant. For back pain, the success rates were within four percentage points of each other, even though statistical equivalence could not be declared. This finding is believed to be an artifact of the assumptions of the analyses and not clinically relevant since the mean improvement in back pain scores for the investigational group was actually higher, showing more improvement, than that for the control group.

Graft Site Pain

Another very important effectiveness parameter that was assessed was graft site harvest pain. This was measured in control patients using two numerical rating scales – one for pain intensity and the other for pain duration. Each scale ranged from 0 to 10 with a lower number signifying a better outcome. The measurements from the two scales were added for a composite pain value. The composite pain score, therefore, ranged from 0 to 20. This slide shows the mean graft site pain for control patients from the time of hospital discharge to 24 months postoperative. It is evident that these patients experienced significant pain immediately following surgery.

At hospital discharge, the mean score was 12.7 out of a possible 20. Approximately 80% of the patients had total scores of at least 10 points at this time. As expected, the harvest-site pain scores improved over time. However, more than 30% of the patients at these two longer time periods reported harvest site pain. Approximately 16% of the patients indicated that they were still bothered by the appearance of the graft site at one and two years following surgery.

When these results are coupled with the nearly 6% adverse event rate associated with harvesting the bone, a very compelling case can be made for using InFUSE Bone Graft in spinal fusion procedures since it eliminates the negatives of graft-site appearance, pain and morbidity.

Overall Success

Now I will discuss the most important outcome parameter of all for PMA approval. This variable is overall success and it is the primary endpoint for the entire study. The primary objective of the study was to determine if the overall success rate for the investigational treatment was at least as high statistically as that for the control treatment. As previously mentioned, overall success is a composite variable comprised of the primary effectiveness parameters of fusion, Oswestry success, and neurological success. It also is influenced by two important safety considerations – the occurrence of a second surgical procedure classified as a failure and the occurrence of any serious adverse event possibly associated with the device. The overall success criteria are very demanding; and if a patient has met the criteria, you can be assured that he or she is doing very well clinically.

As evident from this slide, the overall success rates for the two treatment groups at 12 and 24 months following surgery are very similar and stable over time. At 24 months, the overall success rates for the two treatments were statistically equivalent with the investigational rate being 2.5 percentage points higher.

Therefore, the primary clinical trial objective has been met. Based on these findings, the InFUSE Bone Graft has been shown to be a safe and effective medical device.

LAPAROSCOPIC CLINICAL TRIAL

Overview

There is additional good news about the InFUSE Bone Graft. Another clinical trial was performed examining the laparoscopic implantation of the device and the results are just as compelling as those from the open study. The data from the laparoscopic study augment the safety profile of the device and support approval of that surgical method of cage implantation. The laparoscopic study had one treatment group – those patients treated with the InFUSE Bone Graft and the LT-CAGE device via a laparoscopic surgical approach. Other than this, the protocol was identical to that for the open study. A total of 134 patients received the investigational laparoscopic investigational treatments. Fourteen investigational sites contributed the patients. There was no overlap in surgeons between the open and laparoscopic studies.

Surgery Results

From a surgery standpoint, the mean blood loss and operative time were very similar to the control group from the open study. A very important finding was the length of hospital stay following surgery. On average, the hospital stay for the laparoscopic patients was approximately two days shorter than that for the patients in either treatment group of the open study, which was statistically significant.

Further, nearly 45% of the laparoscopic patients were treated on an outpatient basis as compared to virtually none of the patients in the open study. The laparoscopic patients also returned to work sooner than the open study patients. The results of Kaplan-Meier analyses involving the days from surgery to work return and adjusted for differences in preoperative work status yielded

statistically significant differences that favored the laparoscopic patients. The median time to work return was more than 20 days shorter than that for the open study patients. These surgery, hospital stay, and return to work advantages for the laparoscopic patients suggest that there is a synergistic effect of the use of InFUSE Bone Graft and the laparoscopic insertion of the LT-CAGE device – an effect that has potentially significant financial implications.

Safety Results

In terms of safety, the adverse event and second surgery rates were comparable for the laparoscopic investigational and open control groups. In fact, a lower percentage of patients had adverse events in the laparoscopic study as compared to the open control group. Only 3.7% of the patients had a serious adverse event that was possibly device related, as compared to an 8.8% rate for the open control group.

The occurrences of adverse events related to retrograde ejaculation were statistically higher than that for the open control group. This finding is to be expected considering the transperitoneal laparoscopic surgical approach. For perspective, the rate was lower than that noted in the earlier IDE study of the laparoscopic use of the LT-CAGE device that led to its FDA approval.

There was one patient who was found to have an authentic positive antibody response to BMP-2. The authentic positive bovine Type I collagen antibody rate was approximately 25%. This rate is believed to be artificially high due to a higher number of missing preoperative samples and the conservative position of declaring an authentic positive finding for any positive response in the absence of a preoperative sample. The authentic positive rate more closely approximates the control group rate if these patients are not included in the rates. Again, no patient with an authentic positive antibody response to bovine Type I collagen was found to have antibodies to human Type I collagen.

Effectiveness Results

The effectiveness results for the laparoscopic investigational patients were very impressive. This slide shows that statistical equivalence can be claimed for all comparisons to the control group from the open study. At 24 months, the fusion rate was virtually identical to that for the open InFUSE™ Bone Graft/LT-CAGE device treatment at approximately 94%. These compare to an 88.7% value for the control group.

Not only was across-the-board equivalence for effectiveness found, the laparoscopic investigational group was found to be statistically superior to the control group for Oswestry success and SF-36 physical component summary, or PCS, success. At 24 months following surgery, the Oswestry success rate for the laparoscopic investigational patients was 87% and 14 percentage points better than the control group rate.

Finally, the overall success rate at 24 months following surgery for the laparoscopic patients was more than 68% and nearly 12 percentage points higher than the control rate of approximately 56%. This rate was not only statistically equivalent to the control group but statistically superior – a finding that more than satisfies the primary objective of the study.

CASE HISTORY PRESENTATIONS

Since "seeing is believing", I want to spend the next few minutes showing a few slides of the CT scans from some of the study patients.

(One InFUSE patient from each study and one control.)

One question that you may be considering is "do these impressive CT scans and fusion results hold-up over longer periods of time. The answer is "yes" based on

the three- and four-year postoperative CT scans from the same InFUSE treatment that Dr. Boden previously showed.

PATIENT SATISFACTION

The scientific data I have presented have been impressive and we believe the results certainly support approval of the product. Science aside, patients need to be satisfied with their results. So, study patients were asked at their postoperative visits to respond to three questions related to satisfaction. This slide vouches for the high levels of satisfaction at both 12 and 24 months following surgery for both InFUSE Bone Graft/LT-CAGE device treatments and the control group. Generally, 75-85% of the patients offered positive responses which are very gratifying findings considering the complex nature of low back pain and degenerative disc disease.

SUMMARY AND CONCLUSIONS

In conclusion, the primary objective of the prospective, randomized study of the open surgical implantation of the investigational device was met. The overall success rate of the InFUSE Bone Graft/LT-CAGE device was found to be statistically equivalent to the control treatment. The investigational treatment was associated with shorter operative times and less blood loss than the control treatment.

Two of the primary benefits of InFUSE Bone Graft are that it induces bone formation and eliminates the need to harvest autogenous bone graft in spinal fusion procedures. The control group results attest to the need for InFUSE Bone Graft, since nearly 6% of the patients had adverse events associated with graft harvesting and there was a significant amount of post-operative graft-site pain.

Further, the laparoscopic implantation of the investigational device produced very positive clinical results, as well. The overall success rate was statistically higher than the control group. In addition, the patients had hospital stays that were two

days shorter than the control group and they returned to work some 20 days sooner.

Therefore, the results of this study of the open and laparoscopic implantation of the InFUSE Bone Graft with the LT-CAGE Lumbar Tapered Fusion Device show the device to be safe and effective in the treatment of degenerative disc disease.

Dr. Mathews' personal comments.

This concludes my presentation. Thank you for your attention. I will now turn the podium over to _____ who will discuss _____.

DRAFT

InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device
Panel Presentation – Clinical Results
Hallett H. Mathews, M.D.

INTRODUCTION

Good morning. My name is Dr. Hal Mathews, and I am a practicing orthopedic surgeon from Richmond, Virginia. My primary professional focus is spine care, and I am an Associate Clinical Professor of Orthopedic Surgery at Virginia Commonwealth University and the Medical College of Virginia. I have no direct financial interest in the product under review here today and am not being paid for my participation in this meeting. I participated in the open surgical approach study of the device as an investigator.

OVERVIEW OF IMPORTANT FINDINGS

I am here today to present the results of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device clinical trial. Before I discuss the details of the clinical trial, I want to report to this advisory panel and the audience the top-line findings from the open surgical approach study.

- First and foremost, the primary objective of the clinical trial as stated in the protocol was met, thus establishing the safety and effectiveness of the InFUSE Bone Graft in the treatment of degenerative disc disease.
- The InFUSE Bone Graft treatment group had a six-percent higher fusion rate than control patients who received treatment with the current gold standard, autogenous bone graft.
- InFUSE Bone Graft patients experienced shorter operative times and less blood loss than control patients.
- Patients who received the InFUSE Bone Graft avoided the complications and significant post-operative pain associated with bone graft harvests in the control group.

Deleted: First and foremost, the InFuse™ Bone Graft/LT-CAGE™ device was found to be safe.
Formatted: Bullets and Numbering
Deleted: ™
Deleted: age
Deleted: ™
Deleted: had
Deleted: statistically
Deleted: These benefits from InFUSE™ came without the 6% complication rate and significant postoperative pain associated with bone graft harvests as noted in the control patients.
Deleted: Finally, and important for PMA approval, the primary objective of the clinical trial as stated in the protocol was met thus establishing the safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ device in the treatment of dagenerative disc disease.
Deleted: 18
Deleted: 18
Deleted: 12/11/0112/10/01

DRAFT

OPEN CLINICAL TRIAL

Design

I will now elaborate on the clinical trial and the results. The study, examined the open surgical approach for device implantation and it had a prospective, controlled, randomized design. The investigational treatment patients received the LT-CAGE™ device filled with the InFUSE™ Bone Graft/, and the control patients were treated in a similar manner with LT-CAGE™ devices filled with autogenous bone harvested from the iliac crest. The safety and effectiveness endpoints from these two treatment groups would be compared.

The primary endpoint for the clinical trial was a derived variable termed "overall success,". For a patient to be considered an overall success at a given postoperative timepoint, five criteria had to be met: (1) the treated level had to be fused, (2) the Oswestry pain/disability score had to be at least 15 points lower (better) than the preoperative value, (3) the neurological status had to be no worse than the preoperative condition, (4) no serious adverse event that was possibly device related, and (5) no second surgical procedure classified as a revision, removal, or supplemental fixation had occurred. As can be seen from this description, overall success is a comprehensive parameter that addresses both important safety and effectiveness aspects of the device treatment. It is also a very demanding variable since the criteria for success is based on successful outcomes in all five of its components.

The primary objective for the clinical trials was to determine if the overall success rate for the InFUSE Bone Graft treatment group, the investigational group, is at least as high statistically as the rate for the control group. Secondary objectives were also developed. These objectives were focused on determining if equivalency existed between the investigational and control treatment groups for the individual safety and effectiveness variables. If equivalency were demonstrated, statistical superiority for overall success and the individual

2 of 18

Deleted: clinical trial

Deleted: LT-CAGE™ device

Deleted:

Deleted: ™

Deleted: /LT-CAGE™ device

Deleted: 18

Deleted: 18

Deleted: 12/11/0112/10/01

variables would also be examined. Bayesian methods were used for statistical comparisons of study outcomes.

Patients admitted to the study had single level, symptomatic degenerative disc disease as noted by back pain of discogenic origin, with or without leg pain, with degeneration of the disc confirmed by patient history and radiographic studies. There were a number of additional inclusion/exclusion criteria that had to be met prior to study participation. These criteria covered such factors as age, weight, mental competency, medical history, and existing medical condition.

Patients involved in the clinical trials were evaluated preoperatively, at surgery, and postoperatively at 6 weeks, 3, 6, 12, and 24 months.

Patient Population and Demographic Information

With this background information, I would now like to focus on the results of the prospective, randomized clinical trial evaluating the use of the InFUSE Bone Graft via an open surgical approach. The Premarket Approval application for the device is based primarily on these clinical results. A total of 143 patients received the InFUSE Bone Graft. For the sake of brevity, I will refer to this henceforth as the investigational treatment. There were 136 patients who were treated with autogenous bone graft, the control group. Patient follow-up compliance at all postoperative periods was high, with all rates exceeding 90%. Sixteen investigational centers contributed these patients.

Deleted:
Deleted: ™
Deleted: /LT-CAGE™ device
Deleted: PMA approval of
Deleted: ™
Deleted: /LT-CAGE™ device treatment
Deleted: the LT-CAGE™ device filled with
Deleted: were

Patients in the investigational and control groups had very similar demographic characteristics and preoperative medical conditions. This enhances one's ability to interpret the effects associated with the different treatments, since potentially confounding factors are similar for the two treatments. The scientific appeal of a prospective, randomized design is manifested in this study. The characteristics of the two treatment groups were so similar that the clinical results truly discern

Deleted: 16
Deleted: 16
Deleted: 12/11/0112/10/01

the effects of the use of InFUSE Bone Graft as compared to autogenous bone graft.

Deleted: ™

Surgery Results

In terms of surgery results, the mean operative time for the investigational group was nearly a half-hour less than that for the control group and this difference was statistically different. The blood loss for the investigational group was also statistically lower than the blood loss for the control group. The mean hospital stays of patients in both treatment groups were slightly more than three days and not statistically different. The results of other surgical variables such as treated level, operative approach, type of orthosis, and outpatient/inpatient classification were very similar for both treatment groups.

Before I review the clinical results, I would like to emphasize that 24-month data are being used as primary supporting evidence of the safety and effectiveness of the treatments.

Safety Results

Overview

First, let's examine the safety information. In summary, the nature and frequency of adverse events and second surgery procedures for the investigational treatment were very similar to the control treatment and were considered typical for a patient population having anterior lumbar interbody fusion, or ALIF, procedure procedures. Antibody formation to BMP-2 was insignificant and the rates of authentic positive responses to bovine Type I collagen, the absorbable sponge material, were similar for both investigational and control treatment groups. Also, there was never a situation where a positive bovine Type I collagen antibody response triggered the body to produce antibodies to human Type I collagen. Authentic positive antibody responses appeared to be without clinical manifestations. Therefore, the InFUSE Bone Graft was found to be safe.

Deleted: ™
Deleted: /LT-CAGE™ device
Deleted: 18
Deleted: 18
Deleted: 12/11/0112/10/01

DRAFT

Adverse Events

Now for more details, the safety of the investigational device was evaluated based on the nature and frequency of adverse events compared to those occurring in the control group. Reported adverse events were classified by their nature, their severity according to World Health Organization criteria, and their duration. Also, Medtronic Sofamor Danek instructed investigators to report all adverse events that occurred, whether or not the event was related to the treatment or the device. This conservative approach led to the reporting of many unrelated events that were included in the analyses.

For the investigational treatment group, only 17 patients (11.9%) had an event that was possibly related to the device and in only 11 of these patients (7.7%) were the events considered "serious.". Overall, a total of 113 investigational group patients (79%) had at least one adverse event, with a substantial majority not being related to the device. As you can see from the slide, these rates are very similar to those rates for the control group.

Adverse events were categorized with comparisons of the investigational and control group rates. The comparisons yielded statistical differences in only two of these categories – urogenital and graft site events. Nearly 6% of the control patients had a graft site complication. These complications included bone fractures, nerve injuries, infection, and hematoma. Obviously, there were no graft site adverse events for the investigational group. This fact clearly supports the use of InFUSE Bone Graft, since it eliminates the need to harvest bone graft.

The urogenital complication rate favored the control group. The difference in rates was mainly due to urinary retention following surgery. There were 11 reports of urinary retention in the investigational group as opposed to two in the control group. These events resolved in all patients prior to their discharge from the hospital. The reason for the difference in rates is not obvious, as the surgical procedures were the same.

5 of 18

Deleted: ,
Deleted: WHO
Deleted: .
Deleted: ing
Deleted: that significantly
Deleted: ™
Deleted: since
Deleted: 18
Deleted: 18
Deleted: 12/11/0112/10/01

DRAFT

There were two reported incidents of cancer in the investigational group and one case in the control group. A 79-year-old male patient was diagnosed with pancreatic cancer 11 months following surgery. This diagnosis was made more than a year ago and the patient is alive and doing well. The other cancer reported in the investigational group was a breast cancer in a 56-year-old female. The patient was approximately 24 months postoperative when the diagnosis was made and she subsequently had a lumpectomy. These are the only reported cases of cancer in more than 400 patients who received rhBMP-2 in all of our clinical trials. For comparison, a control patient was diagnosed with breast cancer approximately six months following surgery. Therefore based on these findings, tumor formation or proliferation is not a safety issue.

Deleted: Further, t

Deleted: over

Second Surgeries

Another component of the safety assessment is the number and nature of additional surgical procedures performed after the initial study surgery. This slide lists the classifications of the additional surgical interventions. Revisions, removals, and supplemental fixations are considered significant procedures at the treated spinal level that affect the assessments of the treatment outcomes. Therefore, a patient having one of these procedures is considered a treatment "failure" for study purposes. On the other hand, reoperations and other surgical procedures are believed to have no affect on the treated level so, therefore, are not considered "failures."

Deleted: .

The second surgery rates for the investigational and control groups were comparable and there were no statistically significant differences for any of the additional surgery category comparisons. There were no revisions in either treatment group. The investigational group had two implant removal procedures. Both of these occurred early postoperatively and were due to cage implantation issues. Supplemental fixations occurred at a rate of 7.0% in the investigational group, as compared to a higher 10.3% rate in the control group.

Deleted: 18

Deleted: 18

Deleted: 12/11/0112/10/01

6 of 18

DRAFT

Antibody Results

Because of the proteinaceous nature of both the rhBMP-2 and the absorbable collagen sponge, the development of antibodies was assessed as part of the IDE clinical trial. Serum samples were taken from each patient preoperatively, to establish their baseline condition, and at three months following surgery. The samples were analyzed for the presence of antibodies specific to rhBMP-2 and to bovine Type I collagen. If a patient had a positive response to bovine Type I collagen, the serum was also tested for antibodies to human Type I collagen. Antibody levels were checked in both investigational and control patients, even though the latter group was not exposed to the InFUSE product. This slide shows the criteria for an authentic positive antibody response.

Deleted: ™

To summarize the findings, there was one investigational and one control patient who had authentic positive responses to BMP-2. The incidence rates were very low at less than 1% and the investigational group rate was no different to that of the unexposed control group. These rates essentially represent background noise. There were no adverse events that appeared to be related to these findings.

Approximately 13% of the patients in both the investigational and control treatment groups had authentic positive responses to bovine Type I collagen antibodies. This rate of authentic positive responses occurred in the control group even though the patients were not treated with the absorbable collagen sponge. Authentic positive responses to bovine Type I collagen antibodies did not appear to result in any clinical manifestations, nor impact the overall success rates for the study.

None of the patients who tested positive for bovine Type I collagen had a positive result for human Type I collagen.

Deleted: 18
Deleted: 18
Deleted: 12/11/0112/10/01

These antibody findings are similar to those from other Medtronic Sofamor Danek clinical trials involving InFUSE Bone Graft.

Deleted: ™

Safety Summary

Since I have presented a lot of information, I want to briefly review the impressive safety profile of the InFUSE Bone Graft before moving to the effectiveness results. The nature and frequency of adverse events and second surgery procedures for the investigational treatment were very similar to the control treatment. The occurrences of adverse events and second surgery procedures were considered typical for a patient population having ALIF procedures and were not unanticipated. The use of the InFUSE Bone Graft also eliminated bone graft site-related adverse events for the investigational group while occurring in approximately 6% of the control patients. This finding is significant since it supports a major reason for using InFUSE Bone Graft. In addition, antibody formation to rhBMP-2 was insignificant and the rates of authentic positive responses to bovine Type I collagen, the absorbable sponge material, were similar for both investigational and control treatment groups, even though control patients did not receive the absorbable collagen sponge. Also, there was never a situation where a positive bovine Type I collagen antibody response led to the production of antibodies to human Type I collagen. Authentic positive antibody responses appeared to be without clinical manifestations. Therefore, based on the data, the InFUSE Bone Graft/LT-CAGE device is safe for its intended use in ALIF procedures to treat degenerative disc disease.

Deleted: ™

Deleted: ™

Deleted: /LT-CAGE™ device

Deleted: ™

Deleted: ™

Deleted: triggered the body to produce

Deleted: ™

Deleted: ™

Effectiveness Results

Overview

Now I will focus on device effectiveness. In the clinical trial, effectiveness variables included fusion, Oswestry pain/disability status, neurological status, back pain, leg pain, bone graft harvest site pain, general health status, and disc height status. The results from these various measurements verify the effectiveness of the InFUSE Bone Graft. Patients receiving the treatment

Deleted: ™

Deleted: /LT-CAGE™ device

Deleted: 18

Deleted: 18

Deleted: 12/11/0112/10/01

8 of 18

experienced exceptionally high fusion rates, pain relief, maintenance or improvement in neurological status, and proper correction and maintenance of disc height. All of these benefits came without the significant amount of pain and morbidity that occurs with harvesting autograft bone from the iliac crest in conventional, gold standard, ALIF procedures.

Fusion

Let's review the effectiveness results in more detail. We consider fusion to be a primary endpoint, since the intended use of InFUSE Bone Graft is to induce bone formation in spinal fusion procedures. For this clinical trial, CT scans and radiographs were used to assess fusion and these films were evaluated at the University of California San Francisco, or UCSF, under the direction of Dr. Harry Genant, a board certified radiologist and Professor of Radiology, Medicine, Epidemiology, and Orthopedic Surgery at UCSF. There were two teams of reviewers who were masked to patient treatment, and each team worked independently of the other. If their overall fusion conclusions differed, a third reviewer at UCSF would adjudicate the findings. However, this occurred infrequently since the percent agreement between the two primary review teams exceeded 98% at all time points.

Deleted: ™

Fusion was based on evidence of bone spanning the two vertebral bodies of the treated segment using CT scans and radiographs. In addition, segmental stability and lucent line criteria also had to be met to be considered fused. Patients having second surgical procedures reported as being due to pseudarthrosis or non-unions were also considered as fusion failures regardless of the radiographic findings. This latter condition dramatically impacts the fusion rates for both treatments. For example, at 24 months postoperative, all fusion failures in the investigational group and 10 of 13 fusion failures in the control group were due to the second surgery criterion and were not radiographic non-unions.

Deleted: 18
Deleted: 18
Deleted: 12/11/0112/10/01

The fusion rates for both treatment groups were high at 6, 12, and 24 months following surgery, with the investigational rate exceeding the control rate at every time period. At 24 months following surgery, the investigational treatment fusion rate was 94.5% and nearly six percentage points higher than the control group rate. Even though the clinical trial was sized for demonstrating statistical equivalence, the investigational fusion rate approached statistical superiority with a probability of 90.2%.

The reason we did not experience a perfect fusion rate with the InFUSE product can be attributed to the protocol definition of fusion that is based on a radiographic component, i.e. bridging bone, stability, and lucent line criteria, and a clinical second surgery component. These second surgeries are typically in response to pain complaints and are documented as being due to a possible non-union. However, most of the treated segments are radiographically fused according to protocol criteria. All of the investigational patients who had second surgeries for so-called non-unions after six months were actually found to be radiographically fused prior to the second surgery. This is a 100% radiographic fusion rate. A similar examination for the control group yields a radiographic fusion rate of 98.3%.

Deleted: At this point, you may be wondering why the fusion rate for the InFUSE™ treatment is not 100%.

Oswestry Low Back Pain

Graft site pain will be discussed a little later but first let's examine the treatment's effects on relieving back pain. The Oswestry Low Back Pain Disability Questionnaire was used to measure the effects of back pain on a patient's ability to manage everyday life. The Oswestry questionnaire has ten questions and is self-administered. Oswestry scores are expressed as a percentage ranging from 0% to 100%, with a lower percentage indicating less pain and disability.

As seen in this slide, the mean Oswestry scores for the two treatment groups were very similar at all study time periods. Improvements from the mean preoperative scores were noted at all postoperative time points. At 24 months

Deleted: 18
Deleted: 18
Deleted: 12/11/0112/10/01

10 of 18

following surgery, the mean improvements in Oswestry scores from preoperative were approximately 29 points for both treatments. These findings are quite gratifying and represent an approximate 55% improvement on average in both groups.

This slide illustrates the distributions of patients demonstrating preoperative to postoperative improvements in Oswestry scores of at least 15 points - a very rigorous condition mandated by FDA. This is termed Oswestry success. Like the mean Oswestry scores, the Oswestry success rates were similar for the investigational and control treatment groups. At 24 months following surgery, the Oswestry success rates for the two treatments were found to be statistically equivalent, with rates of 73% in both groups.

Deleted: shows

Deleted: the

Neurological

The neurological status of the patients was assessed preoperatively and postoperatively at every follow-up visit and it is considered an indicator of safety as well as effectiveness. The neurological evaluations consisted of measurements of motor function, sensory, reflexes, and the degree of straight leg raise reproducing pain. An algorithm was developed to reduce the detailed scoring for each parameter into a success/failure classification. A successful outcome for each parameter was based on the postoperative condition being no worse than the preoperative condition. Overall neurological success for a patient at any given postoperative time period was based on having successful outcomes for all four neurological parameters.

This slide shows the overall neurological success rates at 12 and 24 months following surgery for the two treatment groups. The rates are very similar across time and treatments. The 24-month neurological success rates for the investigational and control groups were determined to be statistically equivalent.

Deleted: 18

Deleted: 18

Deleted: 12/11/0112/10/01

11 of 18

Other Effectiveness Endpoints

In addition to these endpoints, which are factors that contribute to the overall success determinations, other effectiveness measurements were made during the course of the study. These measurements included back pain, leg pain, disc height maintenance, and general health status via the SF-36 survey. The 24-month results for these parameters were comparable for the two treatment groups and statistical equivalence between treatments was demonstrated for all but two comparisons, back pain and the mental component summary, or MCS, of the SF-36.

I will not focus on the MCS finding since the difference between treatment groups was less than four percentage points and this is not considered clinically significant. For back pain, the success rates were within four percentage points of each other, even though statistical equivalence could not be declared. This finding is believed to be an artifact of the assumptions of the analyses and not clinically relevant since the mean improvement in back pain scores for the investigational group was actually higher, showing more improvement, than that for the control group.

Graft Site Pain

Another very important effectiveness parameter that was assessed was graft site harvest pain. This was measured in control patients using two numerical rating scales – one for pain intensity and the other for pain duration. Each scale ranged from 0 to 10 with a lower number signifying a better outcome. The measurements from the two scales were added for a composite pain value. The composite pain score, therefore, ranged from 0 to 20. This slide shows the mean graft site pain for control patients from the time of hospital discharge to 24 months postoperative. It is evident that these patients experienced significant pain immediately following surgery.

Deleted: 18

Deleted: 18

Deleted: 12/11/0112/10/01

DRAFT

At hospital discharge, the mean score was 12.7 out of a possible 20. Approximately 80% of the patients had total scores of at least 10 points at this time. As expected, the harvest-site pain scores improved over time. However, more than 30% of the patients at these two longer time periods reported harvest site pain. Approximately 16% of the patients indicated that they were still bothered by the appearance of the graft site at one and two years following surgery.

When these results are coupled with the nearly 6% adverse event rate associated with harvesting the bone, a very compelling case can be made for using InFUSE Bone Graft in spinal fusion procedures since it eliminates the negatives of graft-site appearance, pain and morbidity.

Overall Success

Now I will discuss the most important outcome parameter of all for PMA approval. This variable is overall success and it is the primary endpoint for the entire study. The primary objective of the study was to determine if the overall success rate for the investigational treatment was at least as high statistically as that for the control treatment. As previously mentioned, overall success is a composite variable comprised of the primary effectiveness parameters of fusion, Oswestry success, and neurological success. It also is influenced by two important safety considerations – the occurrence of a second surgical procedure classified as a failure and the occurrence of any serious adverse event possibly associated with the device. The overall success criteria are very demanding; and if a patient has met the criteria, you can be assured that he or she is doing very well clinically.

As evident from this slide, the overall success rates for the two treatment groups at 12 and 24 months following surgery are very similar and stable over time. At 24 months, the overall success rates for the two treatments were statistically equivalent with the investigational rate being 2.5 percentage points higher.

13 of 18

Deleted:
Deleted: over
Deleted:
Deleted: ™
Deleted: ,
Deleted: The use of the InFUSE™ Bone Graft will preserve the iliac crest.
Deleted: purposes
Deleted: treatment
Deleted: 18
Deleted: 18
Deleted: 12/11/0112/10/01

Therefore, the primary clinical trial objective has been met. Based on these findings, the InFUSE Bone Graft has been shown to be a safe and effective medical device.

LAPAROSCOPIC CLINICAL TRIAL

Overview

There is additional good news about the InFUSE Bone Graft. Another clinical trial was performed examining the laparoscopic implantation of the device and the results are just as compelling as those from the open study. The data from the laparoscopic study augment the safety profile of the device and support approval of that surgical method of cage implantation. The laparoscopic study had one treatment group – those patients treated with the InFUSE Bone Graft and the LT-CAGE device via a laparoscopic surgical approach. Other than this, the protocol was identical to that for the open study. A total of 134 patients received the investigational laparoscopic investigational treatments. Fourteen investigational sites contributed the patients. There was no overlap in surgeons between the open and laparoscopic studies.

Surgery Results

From a surgery standpoint, the mean blood loss and operative time were very similar to the control group from the open study. A very important finding was the length of hospital stay following surgery. On average, the hospital stay for the laparoscopic patients was approximately two days shorter than that for the patients in either treatment group of the open study, which was statistically significant. Further, nearly 45% of the laparoscopic patients were treated on an outpatient basis as compared to virtually none of the patients in the open study. The laparoscopic patients also returned to work sooner than the open study patients. The results of Kaplan-Meier analyses involving the days from surgery to work return and adjusted for differences in preoperative work status yielded statistically significant differences that favored the laparoscopic patients. The

Deleted: ™
Deleted: /LT-CAGE™ device
Deleted: ™
Deleted: /LT-CAGE™ device
Deleted: are
Deleted: ™
Deleted: /
Deleted: ™
Deleted:
Deleted: It
Deleted: different
Deleted:
Deleted: quicker
Deleted: 18
Deleted: 18
Deleted: 12/11/0112/10/01

median time to work return was more than 20 days shorter than that for the open study patients. These surgery, hospital stay, and return to work advantages for the laparoscopic patients suggest that there is a synergistic effect of the use of InFUSE Bone Graft and the laparoscopic insertion of the LT-CAGE device – an effect that has potentially significant financial implications.

Deleted: over

Deleted: ™

Deleted: ™

Safety Results

In terms of safety, the adverse event and second surgery rates were comparable for the laparoscopic investigational and open control groups. In fact, a lower percentage of patients had adverse events in the laparoscopic study as compared to the open control group. Only 3.7% of the patients had a serious adverse event that was possibly device related, as compared to an 8.8% rate for the open control group.

The occurrences of adverse events related to retrograde ejaculation were statistically higher than that for the open control group. This finding is to be expected considering the transperitoneal laparoscopic surgical approach. For perspective, the rate was lower than that noted in the earlier IDE study of the laparoscopic use of the LT-CAGE device that led to its FDA approval.

Deleted: ™

There was one patient who was found to have an authentic positive antibody response to BMP-2. The authentic positive bovine Type I collagen antibody rate was approximately 25%. This rate is believed to be artificially high due to a higher number of missing preoperative samples and the conservative position of declaring an authentic positive finding for any positive response in the absence of a preoperative sample. The authentic positive rate more closely approximates the control group rate if these patients are not included in the rates. Again, no patient with an authentic positive antibody response to bovine Type I collagen was found to have antibodies to human Type I collagen.

Deleted: 18

Deleted: 18

Deleted: 12/11/0112/10/01

DRAFT

Effectiveness Results

The effectiveness results for the laparoscopic investigational patients were very impressive. This slide shows that statistical equivalence can be claimed for all comparisons to the control group from the open study. At 24 months, the fusion rate was virtually identical to that for the open InFUSE™ Bone Graft/LT-CAGE device treatment at approximately 94%. These compare to an 88.7% value for the control group.

Not only was across-the-board equivalence for effectiveness found, the laparoscopic investigational group was found to be statistically superior to the control group for Oswestry success and SF-36 physical component summary, or PCS, success. At 24 months following surgery, the Oswestry success rate for the laparoscopic investigational patients was 87% and 14 percentage points better than the control group rate.

Finally, the overall success rate at 24 months following surgery for the laparoscopic patients was more than 68% and nearly 12 percentage points higher than the control rate of approximately 56%. This rate was not only statistically equivalent to the control group but statistically superior – a finding that more than satisfies the primary objective of the study.

CASE HISTORY PRESENTATIONS

Since "seeing is believing", I want to spend the next few minutes showing a few slides of the CT scans from some of the study patients.

(One InFUSE patient from each study and one control).

Deleted: one

One question that you may be considering is "do these impressive CT scans and fusion results hold-up over longer periods of time. The answer is "yes" based on

Deleted: 18

Deleted: 18

Deleted: 12/11/0112/10/01

16 of 18

the three- and four-year postoperative CT scans from the same InFUSE™ treatment that Dr. Boden previously showed.

PATIENT SATISFACTION

The scientific data I have presented have been impressive and we believe the results certainly support approval of the product. Science aside, patients need to be satisfied with their results. So, study patients were asked at their postoperative visits to respond to three questions related to satisfaction. This slide vouches for the high levels of satisfaction at both 12 and 24 months following surgery for both InFUSE™ Bone Graft/LT-CAGE™ device treatments and the control group. Generally, 75-85% of the patients offered positive responses which are very gratifying findings considering the complex nature of low back pain and degenerative disc disease.

SUMMARY AND CONCLUSIONS

In conclusion, the primary objective of the prospective, randomized study of the open surgical implantation of the investigational device was met. The overall success rate of the InFUSE™ Bone Graft/LT-CAGE™ device was found to be statistically equivalent to the control treatment. The investigational treatment was associated with shorter operative times and less blood loss than the control treatment.

Two of the primary benefits of InFUSE™ Bone Graft are that it induces bone formation and eliminates the need to harvest autogenous bone graft in spinal fusion procedures. The control group results attest to the need for InFUSE Bone Graft, since nearly 6% of the patients had adverse events associated with graft harvesting and there was a significant amount of post-operative graft-site pain.

Further, the laparoscopic implantation of the investigational device produced very positive clinical results, as well. The overall success rate was statistically higher than the control group. In addition, the patients had hospital stays that were two

17 of 18

Deleted:

Deleted: you may be wondering if these

Deleted: are

Deleted: One of the envisioned

Deleted: is

Deleted: ™

Deleted: 18

Deleted: 18

Deleted: 12/11/0112/10/01

DRAFT

days shorter than the control group and they returned to work some 20 days sooner.

Deleted: faster

Therefore, the results of this study of the open and laparoscopic implantation of the InFUSE Bone Graft with the LT-CAGE Lumbar Tapered Fusion Device show the device to be safe and effective in the treatment of degenerative disc disease.

Deleted: [illegible]
Deleted: [illegible]
Deleted: [illegible]

Dr. Mathews' personal comments.

This concludes my presentation. Thank you for your attention. I will now turn the podium over to _____ who will discuss _____.

Deleted: 18
Deleted: 18
Deleted: 12/11/0112/10/01

18 of 18

From: Neil Beals
Sent: Friday, March 8, 2002 04:04:43 PM
To: J. Kenneth Burkus
CC: Tom Zdeblick M.D.; Tara Hood; Bailey Lipscomb; Pete Wehrly; Bill Martin; Clark Charlton; Julie Bearcroft; [redacted]
Subject: FW: Open LT BMP manuscript

Attachments: Final revisions OPEN LTCAGE BMP.1.doc

Ken,

I read over manuscript and I think it looks great. I have only a few comments. I will get with Tara and see if we can get answers to your questions in bold.

My comments:

- would it be appropriate to make bigger deal out of donor site pain and include more discussion and references?
- would it be helpful to add in verbiage on advantages of cage design versus previous generations (page18)? this could help address reaction from those who felt results would be better
- maybe a little more emphasis on the high quality of the study - not sure a prospective randomized study of this magnitude has ever been conducted before, particularly for spine?
- LT CAGE name is used in discussion; it may be best to use generic descriptors and limit tradenames to materials and methods
- is FDA criteria of success for back and leg pain (3 point reduction) accepted?
- I didn't see mention of antibody results - should that be included for completeness? also other potential safety issues? not sure of how much to put out there
- 15 point reduction is mentioned on pg 21 - is this FDA Oswestry reference?
- not sure last sentence is needed

Again, it looks great - thanks, Ken.

Neil

-----Original Message-----
From: [redacted] JKB[redacted]
Sent: Friday, March 08, 2002 7:32 AM
To: Tom Zdeblick; Peter Wehrly; Bill Martin; Neil Beals; Clark Charlton
Subject: Open LT BMP manuscript

Sirs.

Here is the latest edition of the OPEN LT BMP Manuscript.

I have questions **written in BOLD** in the text regarding: Tables 5, 7, 9 and 11. Also the text on page 15 (radiographic assessment) with be altered when I get the table questions answered. Please give me some feedback - cannot find my red book (LT data Book) here at home - I will get into the office later today.

The manuscript will be ready for submission in 24 hours.

Best.
Ken

A Prospective, Randomized Lumbar Fusion Study using rhBMP-2 with Tapered Interbody Cages

J. Kenneth Burkus MD [†]

Matthew F. Gornet MD*

Curtis Dickman, MD[‡]

Thomas A. Zdeblick MD[§]

[†]Staff Physician, Spine Service, The Hughston Clinic, P.C., Columbus, Georgia

*Staff Physician, Missouri Bone and Joint Institute, St. Louis, Missouri

[‡]Barrows Institute, Phoenix, Arizona

[§]Chairman, Department of Orthopaedic Surgery, University of Wisconsin, Madison, Wisconsin

Address correspondence and reprint requests to J.K. Burkus, MD, The Hughston Clinic, [redacted]

ABSTRACT

Study Design. In a multi-center, prospective, randomized, nonblinded, 2-year study, 279 patients who underwent a single-level anterior lumbar interbody fusion with tapered threaded titanium fusion device were randomized into two groups: one received autogenous iliac crest bone graft, the other, recombinant human bone morphogenetic protein-2 (rhBMP-2) on a collagen sponge carrier.

Objectives. The objective of the study was to determine the clinical and radiographic outcomes in patients treated for single-level degenerative lumbar disc disease with a stand-alone anterior interbody fusion using tapered threaded titanium fusion cages with autogenous bone graft or rhBMP-2 and an absorbable collagen sponge carrier.

Summary of Background Data. In a small series of human patients undergoing anterior lumbar interbody fusion with a tapered titanium fusion cage, rhBMP-2 has been shown to promote osteoinduction and fusion.

Methods. In this prospective nonblinded study, 279 patients were randomly divided into 2 groups that underwent interbody fusion using two tapered threaded fusion cages: the investigational group (143 patients) that received rhBMP-2 on an absorbable collagen sponge and a control group (136 patients) that received autogenous iliac crest bone graft. Assessment of a patient's clinical outcome was based on neurologic status, work status, and Oswestry Low Back Pain Disability scores and back and leg pain questionnaires. Plain radiographs and computed tomographic scans were used to evaluate fusion at 6,12 and 24 months postoperatively.

Results. Mean operative time (1.6 hours) and blood loss (109.8 mL) was less in the investigational rhBMP-2 group than in the autograft control group (2.0 hours and 153.1

mL). At 24 months, the investigational group's fusion rate of 94.5% remained higher than the control's at 88.7%. New bone formation occurred in all patients treated with rhBMP-2. At all postoperative intervals, the mean Oswestry, back pain, and leg pain scores and neurologic status improved in both treatment groups compared with the preoperative scores and were similar in both groups. In the control group, 8 adverse events related to harvesting of the iliac crest graft occurred in 8 patients (5.9%), and, at 24 months after surgery, 32% patients still reported graft site discomfort and 16% were bothered by the appearance of graft site.

Conclusions. The investigational group had shorter operative times and less blood loss. At 24 months, this group had a fusion rate that was nearly 6 percentage points greater than the control group with a probability of superiority of 90.2%. Overall results show that the use of rhBMP-2 can eliminate the need for harvesting iliac crest graft for successful lumbar fusions.

Key words: anterior lumbar interbody fusion, bone morphogenetic protein, osteoinduction, radiography, interbody fusion cages

Key points:

- Fusion rates for both treatment groups were high at all studied intervals. At 24 months, the average rate of fusion for patients treated with rhBMP-2 was nearly 6 percentage points higher (94.5% vs. 88.7%) than for patients treated with autograft with a probability of superiority of 90.2 percent.
- The average operative time was1.6 hours for patients treated with rhBMP-2 compared with 2.0 hours in the autograft group. This difference was statistically significant.
- Blood loss was less for patients treated with rhBMP-2 than for patients who underwent iliac crest bone graft harvesting.
- At all postoperative assessment intervals, patients in both treatment groups showed improvement in Oswestry disability scores, in neurologic status, and in back and leg pain outcomes.
- The use of rhBMP-2 in anterior lumbar interbody fusion procedures eliminates the complications of iliac crest bone harvesting including postoperative pain and scarring.

Précis

In a 2-year prospective randomized study of 279 patients, the investigational group that received rhBMP-2 with the tapered cage device had a higher rate of fusion, reduced operative times, and decreased blood loss when compared with the control group that received autogenous bone graft with the LT-CAGE™ device. The rhBMP-2 group avoided the complications that can arise from an iliac crest bone harvesting procedure.

INTRODUCTION

Degenerative changes within a lumbar spinal motion segment are, in part, evidenced by the presence of radial tears or fissures in the annulus fibrosus, disc space desiccation and collapse, and the formation of radial osteophytes. These morphologic changes within the spinal motion segment can lead to loss of the intervertebral disc's ability to accommodate normal biomechanical stresses and can cause pain. Fusion of the degenerative and unstable spinal motion segment can give significant relief from this disabling and often progressive condition (2,7,9).

Anterior lumbar interbody fusion (ALIF) is an effective treatment for patients with symptomatic degenerative disc disease. Lumbar spine stabilization procedures that do not interfere with the posterior spinal muscles have some significant advantages (9,10,14-16,19). The anterior approach to the lumbosacral spine enables the surgeon to expand the disc space and re-establish the normal anatomic alignment and relationships of the spinal motion segment while avoiding injury to the posterior paravertebral muscles. The anterior approach also retains all posterior stabilizing structures and avoids epidural scarring and perineural fibrosis. Adjacent segment degeneration in the lumbar spine after anterior interbody fusion can also be reduced (17).

Stand-alone ALIF procedures using autogenous bone grafts alone have been associated with high rates of pseudarthrosis, graft subsidence, and graft extrusion (8,23). Supplemental posterior segmental spinal instrumentation has been advocated to stabilize interbody grafts and increase rates of fusion. Recently, cylindrical threaded

intervertebral devices with autogenous bone grafts have been shown to stabilize a lumbar motion segment after anterior discectomy. Their use has lead to high rates of fusion and to improved clinical outcomes (4).

In non-human primate animal models, recombinant human bone morphogenetic protein 2 (rhBMP-2) applied to an absorbable collagen sponge carrier has been shown to promote osteoinduction and fusion after ALIF (11). Recently, this technique was used in a small series of human patients who underwent stand-alone ALIF with tapered fusion cages. In these patients, the use of rhBMP-2 applied to a collagen sponge was also shown to promote osteoinduction and fusion (4). To further evaluate this method, we evaluated the clinical and radiographic outcomes at 24 months of 279 patients who underwent a single level ALIF. We compared the outcomes in the investigational patients (rhBMP-2) with those in the control patients (autogenous bone).

MATERIALS AND METHODS

Study Design. Between August 1998 and July 1999, 279 patients completed surgery in this prospective, randomized, nonblinded, FDA approved study at 16 investigational sites. All patients underwent a single-level anterior lumbar fusion with the LT-CAGE™ device (Medtronic Sofamor Danek, Memphis, TN). Patients were randomly assigned in a 1:1 manner to one of two groups: the investigational group received rhBMP-2 on an absorbable collagen sponge carrier and the control group received autogenous iliac crest bone graft. InFUSE Bone Graft™ (Medtronic Sofamor Danek, Memphis, TN) is the

trademarked name for recombinant human bone morphogenetic protein 2 applied to an absorbable collagen sponge.

Patient Data. Preoperatively, all patients had symptomatic, single-level degenerative lumbar disc disease and symptoms of disabling low back or leg pain, or both, of at least 6 months' duration that had not responded to nonoperative treatments. The two treatment groups were very similar demographically, and there were no statistically significant differences ($P < 0.05$) for any of the variables (Table 1). The rhBMP-2 group consisted of 143 patients and the control group consisted of 136 patients. The average age at surgery was 43.3 years for the rhBMP-2 group and 42.3 years for the control group. In the rhBMP-2 group, 47 patients (32.9%) had used tobacco within 6 months before surgery compared with 49 patients (36%) in the control group. The percentage of patients with pending litigation was 12.6% and 16.2% in the rhBMP-2 and control groups, respectively. The percentage of patients seeking worker's compensation was 32.9% in the rhBMP-2 group and 34.6% in the control group.

Clinical and Radiographic Outcome Measurements. Patient assessments were completed preoperatively, during hospitalization, and postoperatively at 6 weeks and at 3, 6, 12, and 24 months. Clinical outcomes were assessed using neurologic status, work status, patient satisfaction, and Oswestry Low Back Pain Disability, back, leg, and graft site pain questionnaires.

Radiographs and computed tomography (CT) scans were used to evaluate fusion at 6, 12, and 24 months after surgery. Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent, blinded radiologist was used to adjudicate conflicting fusion findings. Fusion was defined as an absence of

radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation less than 5° on flexion-extension radiographs, and continuous trabecular bone growth connecting the vertebral bodies (6). There was good agreement between the radiologists reviewing the studies. At 6, 12, and 24 months after surgery, agreement between the independent reviewers was more than 98%. Patients who had secondary surgeries because of persistent low back symptoms and clinically suspected nonunions were considered as having failed fusions and were classified as failures in all fusion calculations, regardless of their independent radiological assessment.

Clinical and Radiographic Follow-up. The rate of patient return for follow-up was high at all postoperative periods (Table 2). At 12 months, the rate of patient return for both treatment groups exceeded 96%. At 24 months, the follow-up rate for the investigational group was 92.5% and the control group rate was 90.8%.

Surgical Technique. All patients underwent the ALIF procedure through an open approach. Patients were placed in the supine position on the operating room table. Fluoroscopy was used throughout the surgical procedure. A vertical or transverse incision was made over the lumbosacral spine. A retroperitoneal exposure was carried out in 81% (226/279) of patients, and a transperitoneal exposure was used in 19% (53/279) of patients. The parasympathetic nerve complex was bluntly mobilized and retracted from the surgical field: electrocautery was not used during this portion of the surgical procedure. Segmental vessels were sequentially identified, ligated, and divided. The great vessels were mobilized exposing the anterior surface and lateral borders of the disc space. The midpoint of the disc space was identified with radiographic markers and fluoroscopy.

An incision was made in the anterior portion of the annulus, removing the anterior longitudinal ligament and the anteriolateral borders of the annulus fibrosus. Under direct visualization the entire contents of the disc space were removed including the nucleus pulposis and the cartilaginous endplates. Great care was taken to protect and preserve the bony vertebral endplates. The disc space was sequentially distracted to the height of normal adjacent disc space height. A double barrel guide was inserted into the disc space and the bony endplates were precisely prepared with a reamer.

In the investigational group, each cage was filled with a rhBMP-2 soaked collagen sponge. No autogenous bone grafts or local reamings were used in this group. The cages were sequentially inserted through the guide tube into the prepared intervertebral disc space. Cage placement was evaluated with fluoroscopy in both the anteroposterior and lateral dimensions. In the control group, two cage devices were packed with morcellized autogenous bone graft harvested from the iliac crest.

Postoperatively, patients were placed in a soft lumbar corset. Activities were advanced by the treating physician. Isometric strengthening and exercise program were started at six weeks postoperatively.

Statistical Methods. The data from this clinical trial were analyzed using the statistical software package SAS® version 6.12. For continuous variables, *P* values are from ANOVA, and for categorical variables, they are from Fisher's exact test or chi-square test.

RESULTS

Surgery

The mean operative time in the investigational rhBMP-2 group (1.6 hours) was less than in the control group (2.0 hours) (Table 3). The average blood loss in the rhBMP-2 group was 109.3 ml as compared with 153.8 ml in the control group. The operative time and blood loss was less in the investigational group despite the fact that the more technically demanding and time consuming approach to the L4-L5 level was performed more frequently in the investigational group (25.9%, 37/143) than in the control group (23.5%, 32/136). The average hospital stay was similar in both groups (3.1 days for the investigational group vs. 3.3 days for the control group). There were no unanticipated device-related adverse events in either treatment group.

Complications

Vascular events. Eleven intraoperative vascular events occurred: 6 were in the rhBMP-2 group (4.2%) and 5, in the autograft group (3.7%). The most common injury (6/11) was a laceration of the iliac vein. Two control group patients developed deep venous thrombosis and were treated with anticoagulation medications.

Retrograde ejaculation. Six male patients (4.1%, 6/146) complained of retrograde ejaculation after surgery. In these patients, the L5-S1 disc space was approached 5 times (83.3%, 5/6). A transperitoneal approach was used in 4 of the 6 patients (66.6%). This complication occurred in 13.3% (4/30) of the men who underwent a transperitoneal approach and occurred in only 1.8% (2/116) of men who underwent a retroperitoneal approach. In two patients, the retrograde ejaculation resolved by 12 months after

surgery; one patient underwent a retroperitoneal approach, the other a transperitoneal approach.

Iliac crest graft site. In the control group, 8 adverse events related to harvesting of the iliac crest graft were identified in 8 patients (5.9%). These events included 3 injuries to the lateral femoral cutaneous nerve, 2 avulsion fractures of the anterior superior iliac spine, 1 infection and 1 hematoma. None required an additional surgery. There were no graft site adverse events in the investigational group since the use of rhBMP-2 precluded the need to harvest bone graft.

The level of postoperative pain and morbidity associated with the iliac crest graft harvesting was measured using numeric rating scales for pain intensity and duration (Table 4). After surgery, all of the control patients experienced hip donor site pain. The highest levels of pain were noted immediately after surgery with a mean score of 12.7 points out of 20 points. The percentage of patients experiencing pain decreased over time; however, at 24 months after surgery, nearly one-third of the control patients (32%) still experienced pain. At two years, the graft site pain scores averaged 1.8 points, and 16% of the control patients were bothered by the appearance of the graft site.

Clinical Outcomes

Oswestry Disability Questionnaire scores. The Oswestry Low Back Pain Disability Questionnaire measured pain associated with activities. The Oswestry Questionnaire was administered preoperatively as well as at each postoperative visit. At all postoperative time periods for both the investigational and the control treatment groups, the mean overall Oswestry scores were similar at the time periods for both treatment groups. At all postoperative visits, both treatment groups demonstrated

statistical improvements as compared with the preoperative scores that were maintained through two years (Table 5). At 24 months, the mean improvements in the Oswestry scores were 29.0 points in the investigational group and 29.5 points in the controls. In the rhBMP-2 group, 84.6% of patients showed an improvement of at least 15% in their disability scores at 12 months after surgery and compared favorably with 85.6% of patients in the control group. (At 24 months, the 84.4% of the investigational group was improved compared with 82.4% of the control group.)

Neurologic Status. Neurologic status of the patients was determined by evaluating four neurologic measurements: motor function, sensory function, deep tendon reflexes and sciatic tension signs. Values for each of the 4 subsets of objective findings were totaled and expressed as a percentage of the maximum possible score. Each measurement was compared with the patient's preoperative score. Neurologic success was based on demonstrating maintenance of or improvement in all four neurologic measurements. At 12 and 24 months after surgery, the overall neurologic success rates for the investigational group were 81.8% and 82.8% respectively compared with 84.7% and 83.3% rates for the control group (Table 6).

Back Pain. Back pain intensity and duration were assessed using a 20-point numeric rating scale. Adding the numeric rating scores for back pain intensity and pain duration allowed examiners to derive a composite back pain score (Table 7). The mean back pain scores at all postoperative periods were improved from the preoperative mean values for both treatment groups. The mean improvements in back pain scores at both 12 and 24 months were greater for the investigational group than for the control autograft group.

Back pain success was determined for each patient by comparing the postoperative score with the preoperative score. Success was based on the patient's having at least a 3-point improvement in back pain score after surgery (Table 8). At 12 and 24 months after surgery, the investigational group had back pain success rates of 79.1% and 74.6%, respectively. These rates were similar to the respective rates in the control group of 72.8% and 78.7%.

Leg Pain. Leg pain was assessed in a similar manner using a numeric rating scale for both the intensity and duration of painful symptoms. Mean leg pain scores improved significantly after surgery (Table 9). Outcomes were similar in both treatment groups. Leg pain success was defined as a function of the patient's preoperative complaints. If a patient had a preoperative pain score of 10 points or more, success was defined as a 3-point improvement in his or her postoperative scores. In patients who had preoperative leg pain scores of less than 10 points, success was defined as maintenance of or improvement in scores when compared with their preoperative condition. At 12 months after surgery, the leg pain success rates were similar in both treatment groups. The investigational group had a success rate of 72.1% and the control group had success rate of 72.8%. At 24 months, the success rate in the investigational group improved to 80.3% and was higher than the 74.1% result in the control group.

Work Status. Many factors affect a patient's work status, such as the nature of the work performed and ability of the work place to accommodate work restrictions. The work status of the investigational patients was better than that of the control patients at most postoperative follow-up intervals (Table 10). For patients who were working before

surgery, the median return to work time was 63.5 days in the investigational group and 64.5 days in the control group. More people in both treatment groups were working at the two-year follow-up than were working before their surgery. At last follow-up, in the investigational group, 80 patients were employed while only 54 were employed before surgery. Similarly, in the control group, 38 were working before surgery and 60 were working at two years after surgery.

Patient Satisfaction. At 12 and 24 months after surgery, the results were similar in each treatment group. At 24 months, 81.2% of the investigational patients and 80.4% of the controls were satisfied with their surgical outcomes. In the investigational group, 82% said they would undergo surgery again compared with 76.7% of the control patients who would undergo surgery again. In the investigational group, 74.6% believed that they were helped as much as they had expected to be from the surgery; 76.6% of the control group felt they had been.

Radiographic Outcomes

Fusion status of the study patients was evaluated on plain radiographs and CT scans (Figs. 1-3). At six months after surgery, 97.0% of patients in the investigational group had evidence of interbody fusion compared with 115 patients (95.8 %) in the control group (Table 11). **QQ AU: Data in table do not agree with data in text. XQQ** At 12 months, 125 patients (96.9 %) in the investigational group showed evidence of fusion. **QQ AU: Table 11 says 127 pts. XQQ** In the control group, 111 patients (92.5%) showed evidence of fusion at one year. **QQ AU: Table 11 says 112 pts. XQQ** At 24 months, the investigational group had a 94.5% fusion rate, which was approximately six percentage points higher than that of the control group (88.7%).

Secondary Surgical Procedures

In the investigational group, 11 patients (7.0%) had a second surgery and 14 patients (10.3%) in the control group had second surgeries. In the investigational group, 2 patients had implant removals: One removal occurred at 5 days after surgery, and the other at 4months. The removal at 5 days was due to a vertebral bon fracture and implant displacement. The removal at 4 months was due to implant displacement and possible failed fusion. Seven investigational patients underwent supplemental fixation for presumed pseudarthrosis, 1 underwent supplemental fixation after posterior decompression for persistent radicular symptoms after the initial surgery, and 1 underwent a panlumbar fusion for discogenic back pain. Two of the supplemental fixations for presumed pseudarthrosis occurred before the 6-month follow-up evaluation. Fusion was not evaluated until 6 months after surgery; therefore, these patients cannot be classified as fusion failures. They are second surgery failures.

In the control group, 12 patients underwent supplemental posterior fixation for a presumed pseudarthrosis and 2 underwent supplemental posterior fixation for persistent discogenic pain. One patient underwent supplemental fixation for presumed pseudarthrosis before the 6-month follow up.

In 90% (18/20) of these patients (7/7 in the investigational group and 11/13 in the control group) the fusion was radiographically solid at the visit prior to the supplemental fixation, but posterior instrumentation was inserted by the treating physician based on clinical symptoms of persistent pain. In 53.3% of these patients, pain improved after the secondary posterior surgical procedure.

DISCUSSION

Spinal fusions can be performed anteriorly, posteriorly, or posterolaterally. Instrumentation can also be used to stabilize the spinal motion segment and to promote fusion. Traditionally, fusions in the lumbar spine have been performed through a posterior approach. After a successful posterolateral lumbar spinal fusion, patients often have significant relief of their painful symptoms. However, the posterolateral approach and the lateral exposure of the transverse processes of the lumbar spine can compromise the patient's functional outcome (13). The paraspinal muscles must be detached from the posterior spinal elements and transverse processes during the surgical exposure for the lateral fusion. This injury to the spinal muscles of the lumbar spine limits the patient's ultimate rehabilitation potential (1). Several studies have demonstrated significant loss of paraspinal muscle strength and muscle atrophy in patients with persistent back pain after posterolateral lumbar spinal fusion (12,18,22). The surgeon strips the paraspinal muscles from their anatomic attachments to the spine and then reattaches them to the midline fascia and retained spinal elements. However, postoperative healing and scar tissue formation interferes with the normal independent function of the paravertebral muscle groups. The loss of their normal anatomic attachment sites, formation of scar tissue, and loss of independent muscle function compromise the paravertebral muscles.

Stand-alone anterior lumbar interbody fusion allows the complications of posterior "fusion disease" to be avoided. The anterior approach retains all posterior-stabilizing structures and avoids epidural scarring and perineural fibrosis. There is no need for paraspinal muscle stripping, retraction, or denervation of the adjacent facet

joint. The muscle-splitting approach is one that does not compromise existing posterior spinal elements, and it allows the surgeon to reestablish normal disc space height and restore the normal sagittal contours of the lumbar spine. This technique allows a faster and often a more complete functional recovery of the patient. Long-term follow-up studies have not shown significant rates of adjacent segment degeneration after anterior interbody fusion (17).

Numerous clinical studies have documented the efficacy and improved outcomes with this procedure. Femoral ring allografts have been widely used; however, these intradiscal spacers alone do not provide enough stability to promote fusion consistently, and they have been associated with high rates of postoperative subsidence (2). Anterior femoral ring allografts often require an additional instrumented posterior spinal fusion to stabilize the spinal motion segment. Recent advances in metallic interbody fusion devices have been introduced to stabilize intervertebral grafts and have been used to encourage fusion and prevent disc space collapse during the healing process (5).

This study is one of the largest prospective clinical evaluations of stand alone ALIF procedures. The randomized patient groups had no statistically significant differences in the variables assessed. Clinical and radiographic follow-up exceeded 90% at all intervals.

Because the investigational, or rhBMP-2, group did not undergo an autogenous bone graft harvesting procedure, there was a statistically significant reduction in operative time and in decreased blood loss during the procedure in these patients. In our patients, retrograde ejaculation was associated with the transabdominal approach to the lumbosacral spine.

The difficulty in achieving anterior interbody fusion through the use of fusion cages lies in the preparation of the endplate. The endplate must be partially removed to allow healing of the vertebral bodies. However, if resection of the endplate is excessive, subsidence can occur and, ultimately, pseudarthrosis. The procedure used in our study patients helps to enhance this fusion in two separate ways. With the LT-CAGE™ device, there is minimal endplate resection, thus preserving the weight-bearing portions of the endplate, which allows greater restoration of lordosis and prevents subsidence. The use of recombinant human bone morphogenetic protein has been shown to accelerate fusion in animal models (3,20,21). Its use should also allow the fusion procedure to more rapidly and more thoroughly occur in humans, as well. Indeed, from a radiographic standpoint this was true in our patients: 97% of patients with the LT-CAGE™ device and rhBMP-2 had radiographic evidence of a solid fusion at one year.

Our study's fusion assessment protocol is one of the first to use thin-cut CT scans to evaluate new bone formation (6). The thin-walled second-generation LT-CAGE™ device reduced imaging artifact in the instrumented disc space, and new bone formation was identified reliably inside and outside of the intervertebral cages on these CT scans. New bone formation was identified in all patients who received cages filled with rhBMP-2 that remained implanted for more than 6 months. Fusion failure was documented in the rhBMP-2 treated group because of a secondary surgical procedure not because of lack of new bone formation. All new bone formation was found within the instrumented disc space. There was no ectopic bone formation outside of the annular confines of the disc space, and there was no bone formation extending posteriorly into the spinal canal or laterally into the neuroforamina.

Recombinant human bone morphogenetic protein is an osteoinductive growth factor that stimulates pleuripotential cells to form bone (24). We believe that exposure of bleeding cancellous bone allowed influx of pleuripotential cells that were affected by the rhBMP-2 bound to the collagen carrier sponge. The investigational, or rhBMP-2, group had a 96.9% fusion rate at 12 months compared with 92.6% in the control group. At 24 months, the investigational group had a 94.5% fusion rate, which was almost six percentage points higher than the fusion rate of the control group (88.7%) with a probability of superiority of 90.2 %. This range of effect was essentially limited to the disc space. Areas between the cages, lateral to the cages, and anterior and posterior to the cages did ossify, but in no case did this ossification extend outside of the confines of the vertebral column. No heterotopic ossification occurred in the epidural space or within the peritoneal cavity or retroperitoneal space. No metastatic calcifications were seen in these study patients.

The final assessment of a successful interbody fusion is difficult. Independent radiologists carefully scrutinized the plain x-rays, flexion-extension films, and CT scans of each patient. The reconstructed CT scans proved to be the most useful method of determining the success of the arthrodesis. Bridging trabecular bone seen on the coronal and sagittal reconstructed images was the final arbiter for determining whether a successful fusion had occurred. Only gross motion from a pseudarthrosis could be seen on the flexion-extension films and was seen best as a change in lucency between vertebral body and cage during the flexion-extension sequence. Finally, the question of how a patient with an arthrodesis that appears solid radiographically but who has persistent pain should be treated remains undetermined. In several instances in this

study, the treating surgeon elected to proceed with a posterior instrumented fusion in the face of persistent pain and a successful arthrodesis. By the treating clinician's statement, these patients were noted to have pseudarthrosis. However, there is no accurate way to determine whether these were true radiographic pseudarthroses. In fact, only approximately half of the patients who went on to have posterior instrumentation for a presumed pseudarthrosis achieved significant pain relief. Less than half (40%) achieved pain improvement of 15 points or greater. Despite these rigorous criteria for determining successful fusion, we were able to obtain a very high rate of radiographic success.

The mean improvements in Oswestry score (29.0 and 29.5 points) are among the highest improvements reported in the literature. We believe this is due in part to the successful combination of anterior approach, threaded tapered titanium fusion cages, and a high degree of successful arthrodesis.

RhBMP-2 is a promising method of facilitating anterior intervertebral spinal fusion and of decreasing pain and improving clinical outcomes after anterior lumbar fusion when used with the LT-CAGE™ device. The use of rhBMP-2 is associated with high fusion rates without the need for harvesting bone from the iliac crest and exposing the patient to the adverse effects associated with that procedure. The combination of the threaded tapered fusion cage and rhBMP-2 may be efficacious in the treatment of challenging patients, such as smokers and those with associated medical disabilities.

REFERENCES

1. Beimborn DS, Morrissey MC: A review of the literature related to trunk muscle performance. *Spine* 13:655-660, 1988.

2. Blumenthal SL, Baker J, Dossett A, Selby DK. The role of anterior lumbar fusion for internal disc disruption. Spine 1988;13:566-9.

3. Boden SD, Schimandle JH, Hutton WC. 1995 Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 1995;20:2633-44.

4. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25:376-81.

5. Boyd, L.M.; Estes, B.T. and Liu M. "Biomechanics of Lumbar Interbody Constructs, *Effect of Design and Materials*." Chirurgie Endoscopique et Mini-invasive du Rachis. Ed. Husson JL, LeHuec JC. Sauramps Médical. Montpelier, France. pp 181-92, 1999.

6. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. Neurosurg Focus 2001;10:1-9.

7. Crock HV. Anterior lumbar interbody fusion: indications for its use and notes on surgical technique. Clin Orthop 1982;165:157-63.

8. Flynn JC, Hoque MA. Anterior fusion of the lumbar spine. End result study with long-term follow-up. J Bone Joint Surg 1979;61A:1143-50.

9. Goldner JL, Urbaniak JR, McCollom DE: Anterior excision and interbody spinal fusion for chronic low back pain. *Orthop Clin North Am* 2:543-568, 1971

10. Harmon PH. Anterior excision and vertebral fusion operation for intervertebral disc syndromes of the lower lumbar spine: three to five year results in 244 cases. Clin Orthop 1963;26:107-27.

11. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999;24:629-36.

12. Jonsson B: The functions of individual muscles in the lumbar part of the spinae muscle. *Electromyography* 10:5-21, 1970.

13. Kahanovitz N, Viola K, Gallagher M: Long term strength assessment of postoperative diskectomy patients. *Spine* 14:402-403,1989.

14. Lane JD, Moore ES. Transperitoneal approach to the intervertebral disc in the lumbar area. Annals of Surgery 1948;127:537-51.

15. Loguidice VA, Johnson RG, Guyer RD, Stith WJ, Ohnmeiss DD, Hochschuler SH, Rashbaum RF. Anterior lumbar interbody fusion. Spine 1988;13:366-9.

16. Leong JC, Chun SY, Grange WJ, Fang D: Long-term results of lumbar intervertebral disc prolapse. Spine 1983;8:793-9.

17. Penta M, Sandhu A, Fraser RD: Magnetic resonance imaging assessment of disc degeneration 10 years after anterior lumbar interbody fusion. *Spine* 20: 743-747, 1995.

18. Rantanen J, Hurme M, Falck B, Alaranta H, Nykvist F, Lehto M, Einola S, Kalimo H: The lumbar multifidus muscle five years after surgery for a lumbar intervertebral disc herniation. *Spine* 18:568-574, 1993.

19. Sacks S. Anterior interbody fusion of the lumbar spine. J Bone Joint Surg [Br] 1965;47:211-23.

20. Sandhu HS, Kanim LEA, Toth JM, et al. Experimental spinal fusion with recombinant human bone morphogenetic protein-2 without decortication of osseous elements. Spine 1997;22:1171-80.

21. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995; 20:1326-37.

22. Sihvonen T, Herno A, Paljarvi L, Airaksinen O, Partanen J, Tapaninaho A: Local denervation atrophy of paraspinal muscles in postoperative failed back syndrome. *Spine* 18:575-581, 1993.

23. Stauffer RN, Coventry MB. Anterior interbody lumbar spine fusion. J Bone Joint Surg [Am]1972;54:756-68.

24. Urist MR. Bone: Formation by autoinduction. Science 1965;150:893-9.

Table 1. Patient Data

Variable	Investigational (n=143)	Control (n=136)	P value *
Age (yrs.)			
n	143	136	0.369
Mean	43.3	42.3	
Weight (lbs.)			
n	143	134	0.639
Mean	179.1	181.1	
Sex [n (%)]			
Male	78 (54.5)	68 (50.0)	0.473
Female	65 (45.5)	68 (50.0)	
Workers' Compensation [n (%)]	47 (32.9)	47 (34.6)	0.801
Spinal Litigation [n (%)]	18 (12.6)	22 (16.2)	0.400
Tobacco Used [n (%)]	47 (32.9)	49 (36.0)	0.615
Preop Work Status [n (%)]	68 (47.6)	50 (36.8)	0.071
Working			

*For continuous variables, P values are from ANOVA. For categorical variables, P values are from Fisher's exact test or chi-square test.

Table 2. Patient Accountability

Investigational Group

	Preop	Surgery	6 Weeks	3 Months	6 Months	12 Months	24 Months
Theoretical							
Follow-up[1]	143	143	143	143	143	143	143
Deaths	0	0	0	0	0	0	0
(Cumulative)							
Failures[2]	0	0	1 (1)	0 (1)	3 (4)	1 (5)	4 (9)
(Cumulative)							
Expected[3]	143	143	142	142	139	138	133
Number Evaluated	143	143	141	141	137	133	123
Percent Follow-up	100.0%	100.0%	99.3%	99.3%	98.6%	96.4%	92.5%

Control Group

	Preop	Surgery	6 Weeks	3 Months	6 Months	12 Months	24 Months
Theoretical							
Follow-up[1]	136	136	136	136	136	136	136
Deaths	0	0	0	0	0	1	1
(Cumulative)							
Failures[2]	0	0	0	0	1 (1)	4 (5)	7 (12)
(Cumulative)							
Expected[3]	136	136	136	136	135	130	120
Number Evaluated	136	136	134	134	133	126	109
Percent Follow-up	100.0%	100.0%	98.5%	98.5%	98.5%	96.9%	90.8%

[1] Theoretical = Patients who have entered the follow-up window.
[2] Failures include device removals, revisions and supplemental fixations.
[3] Expected = Theoretical – Cumulative Deaths – Cumulative Failures

Table 3. Surgery Information

Variable	Investigational (n=143)	Control (n=136)
Operative Time (hrs)		
n	143	136
Mean	1.6	2.0
Blood Loss (ml)		
n	142	136
Mean	109.8	153.1
Hospital Stay (days)		
n	143	136
Mean	3.1	3.3
Treatment Levels [n (%)]		
L4-L5	37 (25.9)	32 (23.5)
L5-S1	106 (74.1)	103 (75.7)
L5-L6	0 (0.0)	1 (0.7)
Operative Approach [n (%)]		
Retroperitoneal	116 (81.1)	110 (80.1)
Transperitoneal	27 (18.9)	26 (19.1)

Table 4. Iliac Crest Graft Site Pain and Appearance Scores

Period	Variable	Control
Discharge	Pain Score	
	n	134
	Mean	12.7
	P value[1]	<0.001
	Appearance of Graft Site	
	Poor[2]	13 (9.8)
6 Weeks	Pain Score	
	n	132
	Mean	6.7
	P value	<0.001
	Appearance of Graft Site	
	Poor	5 (3.8)
3 Months	Pain Score	
	n	134
	Mean	3.5
	P value	<0.001
	Appearance of Graft Site	
	Poor	3 (2.3)
6 Months	Pain Score	
	n	132
	Mean	2.6
	P value	<0.001
	Appearance of Graft Site	
	Poor	5 (3.8)
12 Months	Pain Score	
	n	130
	Mean	2.1
	P value	<0.001
	Appearance of Graft Site	
	Poor	5 (3.8)
24 Months	Pain Score	
	n	117
	Mean	1.8
	P value	<0.001
	Appearance of Graft Site	
	Poor	3 (2.6)

[1] P values are from Student's *t* test comparing mean with zero.
[2] Poor= "It bothers me very much."

Table 5 – Oswestry Low Back Pain Disability Scores

Period	Variable	Investigational	Control
Preoperative			
	n	143	136
	Mean	53.7	55.1
6 Weeks			
	n	140	131
	Mean	42.1	41.4
Improvement from Preoperative			
	Mean	11.4	13.6
	P value[1]	<0.001	<0.001
3 Months			
	n	141	134
	Mean	33.5	34.2
Improvement from Preoperative			
	Mean	19.9	20.8
	P value	<0.001	<0.001
6 Months			
	n	136	131
	Mean	29.3	29.4
Improvement from Preoperative			
	Mean	24.4	25.4
	P value	<0.001	<0.001
12 Months			
	n	130	125
	Mean	25.5	25.6
Improvement from Preoperative			
	Mean	27.7	28.9
	P value	<0.001	<0.001
24 Months			
	n	122	108
	Mean	23.9	23.8
Improvement from Preoperative			
	Mean	29.0	29.5
	P value	<0.001	<0.001

[1] **QQ AU: What does the footnote symbol by P value indicate? XQQ**

Table 6. Neurologic Outcomes

Period	Variable	Investigational (n=143) n (%)	Control (n=136) n (%)
6 Weeks	Overall		
	Success	110 (80.3)	108 (83.7)
	Failure	27 (19.7)	21 (16.3)
3 Months	Overall		
	Success	119 (84.4)	103 (77.4)
	Failure	22 (15.6)	30 (22.6)
6 Months	Overall		
	Success	106 (77.9)	106 (80.9)
	Failure	30 (22.1)	25 (19.1)
12 Months	Overall		
	Success	108 (81.8)	105 (84.7)
	Failure	24 (18.2)	19 (15.3)
24 Months	Overall		
	Success	101 (82.8)	90 (83.3)
	Failure	21 (17.2)	18 (16.7)

Table 7. Back Pain Outcomes

Period	Variable	Investigational	Control
Preoperative	n	143	136
	Mean	15.8	16.1
6 Weeks	n	139	132
	Mean	9.3	8.8
Improvement from Preoperative	Mean	6.5	7.4
	P value[1]	<0.001	<0.001
3 Months	n	140	134
	Mean	8.7	9.0
Improvement from Preoperative	Mean	7.1	7.1
	P value	<0.001	<0.001
6 Months	n	136	131
	Mean	8.6	8.9
Improvement from Preoperative	Mean	7.3	7.1
	P value	<0.001	<0.001
12 Months	n	129	125
	Mean	8.0	8.4
Improvement from Preoperative	Mean	7.8	7.6
	P value	<0.001	<0.001
24 Months	n	122	108
	Mean	7.3	7.9
Improvement from Preoperative	Mean	8.4	8.1
	P value	<0.001	<0.001

[1] **QQ AU: What does the footnote symbol by P value indicate? XQQ**

Table 8. Back Pain Success Rates

Variable	Investigational n (%)	Control n (%)
6 Weeks		
Success	107/139 (77.0)	101/132 (76.5)
Failure	32/139 (23.0)	31/132 (23.5)
3 Months		
Success	103/140 (73.6)	105/134 (78.4)
Failure	37/140 (26.4)	29/134 (21.6)
6 Months		
Success	106/136 (77.9)	94/131 (71.8)
Failure	30/136 (22.1)	37/131 (28.2)
12 Months		
Success	102/129 (79.1)	91/125 (72.8)
Failure	27/129 (20.9)	34/125 (27.2)
24 Months		
Success	91/122 (74.6)	85/108 (78.7)
Failure	31/122 (25.4)	23/108 (21.3)

Table 9. Leg Pain Scores

Period	Variable	Investigational n = 143	Control n = 136
Preoperative			
	n	143	136
	Mean	12.5	12.5
6 Weeks			
	n	139	132
	Mean	7.5	8.4
Improvement from Preoperative	n	139	132
	Mean	5.1	4.1
	P value[1]	<0.001	<0.001
3 Months			
	n	140	134
	Mean	6.8	6.8
Improvement from Preoperative	n	140	134
	Mean	5.6	5.6
	P value	<0.001	<0.001
6 Months			
	n	136	131
	Mean	6.3	6.3
Improvement from Preoperative	n	136	131
	Mean	6.4	6.3

	P value	<0.001	<0.001
12 Months			
	n	129	125
	Mean	6.3	6.6
Improvement from Preoperative	n	129	125
	Mean	6.4	6.6
	P value	<0.001	<0.001
24 Months			
	n	122	108
	Mean	6.3	6.3
Improvement from Preoperative	n	122	108
	Mean	6.5	5.9
	P value	<0.001	<0.001

[1] P values for change from preoperative in each group are from paired test.
QQ AU: Should this be "paired tests" or "paired *t* tests"?

Table 10. Return-To-Work Status

Period	Variable	Investigational n (%)	Control n (%)
3 Months	Working	54 (38.3)	38 (28.4)
	Not Working	42 (29.8)	43 (32.1)
	Was Not Working Before Surgery	45 (31.9)	53 (39.6)
6 Months	Working	69 (50.7)	60 (45.5)
	Not Working	25 (18.4)	29 (22.0)
	Was Not Working Before Surgery	42 (30.9)	43 (32.6)
12 Months	Working	72 (55.0)	63 (50.4)
	Not Working	20 (15.3)	19 (15.2)
	Was Not Working Before Surgery	39 (29.8)	43 (34.4)
24 Months	Working	80 (66.1)	60 (56.1)
	Not Working	11 (9.1)	13 (12.1)
	Was Not Working Before Surgery	30 (24.8)	34 (31.8)

Table 11. Rates of Radiographic Fusion [Number (%) of Patients]
QQ AU: Text says at 12 months there are 125 investigational pts., which would be 95.4% and 111 control pts., which would be 91.7%. Which is correct? Check accuracy of fusion data given in Discussion section.

Variable	Investigational (n=143) n (%)	Control (n=136) n (%)
6 Months		
Success	128/132 (97.0)	115/120 (95.8)
Failure	4/132 (3.0)	5/120 (4.2)
12 Months		
Success	127/131 (96.9)	112/121 (92.6)
Failure	4/131 (3.1)	9/121 (7.4)
24 Months		
Success	120/127 (94.5)	102/115 (88.7)
Failure	7/127 (5.5)	13/115 (11.3)

LEGEND OF FIGURES

Figure 1: Standing lateral radiograph of the lumbosacral spine shows disc space collapse at L5-S1 and early radial osteophyte formation. There is loss of segmental lordosis at the disc space to 15°.

Figure 2: Standing lateral radiograph at 24 months after surgery shows restoration of anatomic disc space height at the L5-S1 interspace and improvement of segmental lordosis to 27°. New bone formation can be seen anterior to the cages.

Figure 3: Thin-cut 1-mm CT scan sagittal reconstruction at 24 months after surgery shows new bone formation within the LT-CAGE™ device and new bone formation anterior to the cage but within the confines of the disc space.

From: Tara Hood
Sent: Friday, March 8, 2002 04:21:39 PM
To: Neil Beals; J. Kenneth Burkus
CC: Tom Zdeblick M.D.; Bailey Lipscomb; Pete Wehrly; Bill Martin; Clark Charlton; Julie Bearcroft; [redacted]
Subject: RE: Open LT BMP manuscript

Dr. Burkus,
I wanted to clarify some of the remaining questions/numbers that were identified in bold by you.

Page 15/Table 11 - fusion data in table is correct, numbers in text should be changed to 127 investigational patients at 12 months, 112 control patients at 12 months.

Table 5 - footnote = "P-values for change from preoperative in each group are from paired t-test." (this applies to all p-values in table)

Table 7 - footnote = "P-values for change from preoperative in each group are from paired t-test." (this applies to all p-values in table)

Table 9 - footnote should read "paired t-test"

Hope this helps. Thanks for everything.
Tara

-----Original Message-----
From: Neil Beals
Sent: Friday, March 08, 2002 4:05 PM
To: J. Kenneth Burkus
Cc: Tom Zdeblick M.D.; Tara Hood; Bailey Lipscomb; Pete Wehrly; Bill Martin; Clark Charlton; Julie Bearcroft; [redacted]

Subject: FW: Open LT BMP manuscript

Ken,

I read over manuscript and I think it looks great. I have only a few comments. I will get with Tara and see if we can get answers to your questions in bold.

My comments:

- would it be appropriate to make bigger deal out of donor site pain and include more discussion and references?
- would it be helpful to add in verbiage on advantages of cage design versus previous generations (page18)? this could help address reaction from those who felt results would be better
- maybe a little more emphasis on the high quality of the study - not sure a prospective randomized study of this magnitude has ever been conducted before, particularly for spine?
- LT CAGE name is used in discussion; it may be best to use generic descriptors and limit tradenames to materials and methods
- is FDA criteria of success for back and leg pain (3 point reduction) accepted?
- I didn't see mention of antibody results - should that be included for completeness? also other potential safety issues? not sure of how much to put out there
- 15 point reduction is mentioned on pg 21 - is this FDA Oswestry reference?
- not sure last sentence is needed

Again, it looks great - thanks, Ken.

Neil

-----Original Message-----
From: JKE[redacted]
Sent: Friday, March 08, 2002 7:32 AM
To: Tom Zdeblick; Peter Wehrly; Bill Martin; Neil Beals; Clark Charlton
Subject: Open LT BMP manuscript

Sirs.

Here is the latest edition of the OPEN LT BMP Manuscript.

I have questions **written in BOLD** in the text regarding: Tables 5, 7, 9 and 11. Also the text on page 15 (radiographic assessment) with be altered when I get the table questions answered. Please give me some feedback - cannot find my red book (LT data Book) here at home - I will get into the office later today.

The manuscript will be ready for submission in 24 hours.

Best.
Ken << File: Final revisions OPEN LTCAGE BMP.1.doc >>

From: Martin, Bill
Sent: Wednesday, January 1, 2003 08:05:31 AM
To: Beals, Neil; Wehrly, Peter [ITD Div. Pres.]
CC: Bearcroft, Julie; Charlton, Clark; Martin, Bill; DeMane, Michael; Lipscomb, Bailey
Subject: RE: PLIF Study Manuscript

A word of caution.
I'm pretty sure that on this paper Dr. Burkus just wants us to provide him the data he requested. Dr. Burkus mentioned that his plan for this paper was to do all the work, put Drs Haid, Branch and Alexander's names first, and then he plans to route it to them "as is" for approval. If they don't agree with the data, then they may of course take their name off. Dr. Burkus has done ground work with Charlie and Reg and they have indicated initially that they seem to be fine with this – I don't anticipate any issues between them. Dr. Burkus wanted his name last (and all the neuro's first) so that it would be well accepted by the Neurosurgical community. I know that he has talked in depth with Charlie about what the paper *should*, and equally important, *should not* include.

A couple of additional thoughts:

1. Ken's intent was to purposely NOT include a lot of interpretation/explanation about radiographic observations that don't correlate to the outcomes for concern that it will confuse the issues and again look like an apology (which is part of what he hopes to clear up with this paper).
2. He's stated that the data is good and should stand on its own. His desire is to cleanly report the outcomes.
3. I'm sure that none of us believe the PLIF *technique* is going to have a resurgence from this, but we may want to steer clear of calling it a flawed technique. There are still quite a few surgeons utilizing this technique and we probably don't want to put them in that position. In the past, the way that Haid has approached this is to use verbiage such as "this technique has fallen out of favor, and many surgeons are now choosing to ____". If Reg believes that a statement like this would be necessary to add, he'll have the opportunity to add it when Dr. Burkus routes to him for approval.

Basically, let's provide Dr. Burkus with the information he requested (and I believe he's already working with Bailey on this), and just communicate with him to offer to help in any way he needs to get this done. He does have a plan already and intends to quarterback it.

Thanks,
Bill

—Original Message—
From: Beals, Neil [SMTP [redacted]
Sent: Tuesday, December 31, 2002 10:53 AM
To: Wehrly, Peter [ITD Div. Pres.]
Cc: Bearcroft, Julie; Charlton, Clark; Martin, Bill; DeMane, Michael; Lipscomb, Bailey
Subject: RE: PLIF Study Manuscript

Julie and I will be glad to f/u on this.

As we get into this, I think we need to clarify and confirm: 1) the message delivered with this paper, 2) its timing, and 3) balanced input from all authors (Haid, Burkus, Branch/Alexander) with particular attention to positioning this with neuro community.

Ken has done a great job in getting the data into a workable manuscript form (I assume that Bailey will not have problems in filling in gaps Ken has pointed out). In its current form, the paper pretty much reports the data from the study with relatively little interpretation or comment. My recommendation would be to report the data and point out that while this study used a flawed technique that has since been modified (stand alone to instrumented PLIFs) the results, particularly with INFUSE, were quite good. The observation of bone formation should be noted and explanations provided including cage placement, construct stability, tissue disruption, and use of other exogenous materials. I think it would make great sense to include the rationale for the new INFUSE PLIF study in this paper to give these discussions some direction and purpose.

To realize this, I think we need to agree on message (INFUSE works well in PLIF with dated

technique and is expected to work more consistently and with greater confidence using revised techniques), timing (get published in peer reviewed journal by year-end and try to think of new message to submit in Feb for presentations at spine meetings in the fall), and well balanced input (this must be balanced between Ken and Charley and Joe and Reg; this may be the toughest challenge and the one for which we will need support from top down (if you agree)).

We'll start cracking on more specific review and proposed revision. In meantime, any thoughts?

Neil

-----Original Message-----
From: Wehrly, Peter [ITD Div. Pres.]
Sent: Monday, December 23, 2002 8:25 AM
To: Beals, Neil; Martin, Bill
Cc: Bearcroft, Julie; Charlton, Clark
Subject: FW: PLIF Study Manuscript

Here is first draft. Neil and Julie, will you champion this?

Pete

-----Original Message-----
From: Burkus, J. Kenneth
Sent: Saturday, December 21, 2002 11:26 AM
To: DeMane, Michael; Wehrly, Peter
Subject: PLIF Study Manuscript

Mike and Pete,

Here's your Christmas present. I have attached a copy of the PLIF study manuscript. I believe this will make a significant contribution. I also think this should have a high priority to bring to completion.

I have done about all that I can do without further analysis of the PLIF study data.

In the text of the manuscript, you will find numerous areas that are in bold and underlined. I will need further analysis of this data.

The discussion and conclusions and bibliography are lacking but should be relatively easy to fix up.

I have been handicapped in writing this manuscript in that I have not had access to any of the hard numbers involving patient outcomes and x-ray interpretation with this study.

Take the cuffs off.

I am running home to pack and head off to Salt Lake City and catch up with my family. They should be spending their first day on the slopes today.

Thank you for your generosity and support and friendship throughout this past year. I am looking forward to running harder and moving the ball forward this coming year.

Merry Christmas and best regards to you and your families.

Warm regards,
Ken Burkus

From: Martin, Bill
Sent: Wednesday, January 1, 2003 08:34:36 AM
To: Wehrly, Peter [ITD Div. Pres.]
Subject: FW: PLIF Study Manuscript

CONFIDENTIAL

Pete,
Sent this because:

1. Sounds like he wants to rewrite, but it isn't clear what value that will add to the work the surgeon has already done.
2. Sounds like he wants to get "happy consensus" with all four docs doing the work – ain't happening.
3. Deciding it needs all this rework and stuff without talking to Burkus, well……
4. I didn't want to embarrass him by saying this, but Julie knows all this too as she's been in the loop. In addition to hearing it from Ken, I've heard much of his intended plan from her too. I'm pretty darn sure that Neil's heard most of this too, but maybe he just hasn't listened to it or *accepted* it.
5. I sent the response to all the people he brought into the loop, but I'm still not sure why DeMane needs to see all the gory details. Sometimes I feel like we write all this crap just to try and impress him.

Sending this to you in hope that you'll help him understand that "championing" doesn't always mean redoing it. It can simply mean offering a comment, a small suggestion, or talking to our surgeon customer and finding out what they need to get it published. As a general rule, it would be far more helpful for the primary focus to be on proliferation of papers from a broad group of authors versus perfecting the "style" of those from the most prolific publishers.

Yes I feel better now,
Thanks,
Bill

-----Original Message-----
From: Martin, Bill
Sent: Wednesday, January 01, 2003 8:06 AM
To: Beals, Neil; Wehrly, Peter [ITD Div. Pres.]
Cc: Bearcroft, Julie; Charlton, Clark; Martin, Bill; DeMane, Michael; Lipscomb, Bailey
Subject: RE: PLIF Study Manuscript

A word of caution.
I'm pretty sure that on this paper Dr. Burkus just wants us to provide him the data he requested. Dr. Burkus mentioned that his plan for this paper was to do all the work, put Drs Haid, Branch and Alexander's names first, and then he plans to route it to them "as is" for approval. If they don't agree with the data, then they may of course take their name off. Dr. Burkus has done ground work with Charlie and Reg and they have indicated initially that they seem to be fine with this – I don't anticipate any issues between them. Dr. Burkus wanted his name last (and all the neuro's first) so that it would be well accepted by the Neurosurgical community. I know that he has talked in depth with Charlie about what the paper *should*, and equally important, *should not* include.

A couple of additional thoughts:

1. Ken's intent was to purposely NOT include a lot of interpretation/explanation about radiographic observations that don't correlate to the outcomes for concern that it will confuse the issues and again look like an apology (which is part of what he hopes to clear up with this paper).
2. He's stated that the data is good and should stand on its own. His desire is to cleanly report the outcomes.
3. I'm sure that none of us believe the PLIF *technique* is going to have a resurgence from this, but we may want to steer clear of calling it a flawed technique. There are still quite a few surgeons utilizing this technique and we probably don't want to put them in that position. In the past, the way that Haid has approached this is to use verbiage such as "this technique has fallen out of favor, and many surgeons are now choosing to ____". If Reg believes that a statement like this would be necessary to add, he'll have the opportunity to add it when Dr. Burkus routes to him for approval.

Basically, let's provide Dr. Burkus with the information he requested (and I believe he's already working

with Bailey on this), and just communicate with him to offer to help in any way he needs to get this done. He does have a plan already and intends to quarterback it.

Thanks,
Bill

-----Original Message-----
From: **Beals, Neil [SMTP[redacted]**
Sent: Tuesday, December 31, 2002 10:53 AM
To: Wehrly, Peter [ITD Div. Pres.]
Cc: Bearcroft, Julie; Charlton, Clark; Martin, Bill; DeMane, Michael; Lipscomb, Bailey
Subject: RE: PLIF Study Manuscript

Julie and I will be glad to f/u on this.

As we get into this, I think we need to clarify and confirm: 1) the message delivered with this paper, 2) its timing, and 3) balanced input from all authors (Haid, Burkus, Branch/Alexander) with particular attention to positioning this with neuro community.

Ken has done a great job in getting the data into a workable manuscript form (I assume that Bailey will not have problems in filling in gaps Ken has pointed out). In its current form, the paper pretty much reports the data from the study with relatively little interpretation or comment. My recommendation would be to report the data and point out that while this study used a flawed technique that has since been modified (stand alone to instrumented PLIFs) the results, particularly with INFUSE, were quite good. The observation of bone formation should be noted and explanations provided including cage placement, construct stability, tissue disruption, and use of other exogenous materials. I think it would make great sense to include the rationale for the new INFUSE PLIF study in this paper to give these discussions some direction and purpose.

To realize this, I think we need to agree on message (INFUSE works well in PLIF with dated technique and is expected to work more consistently and with greater confidence using revised techniques), timing (get published in peer reviewed journal by year-end and try to think of new message to submit in Feb for presentations at spine meetings in the fall), and well balanced input (this must be balanced between Ken and Charley and Joe and Reg; this may be the toughest challenge and the one for which we will need support from top down (if you agree)).

We'll start cracking on more specific review and proposed revision. In meantime, any thoughts?

Neil

-----Original Message-----
From: Wehrly, Peter [ITD Div. Pres.]
Sent: Monday, December 23, 2002 8:25 AM
To: Beals, Neil; Martin, Bill
Cc: Bearcroft, Julie; Charlton, Clark
Subject: FW: PLIF Study Manuscript

Here is first draft. Neil and Julie, will you champion this?

Pete

-----Original Message-----
From: Burkus, J. Kenneth
Sent: Saturday, December 21, 2002 11:26 AM
To: DeMane, Michael; Wehrly, Peter
Subject: PLIF Study Manuscript

Mike and Pete,

Here's your Christmas present. I have attached a copy of the PLIF study manuscript. I believe this will make a significant contribution. I also think this should have a high priority to bring to completion.

I have done about all that I can do without further analysis of the PLIF study data.

In the text of the manuscript, you will find numerous areas that are in bold and underlined. I will need further analysis of this data.

The discussion and conclusions and bibliography are lacking but should be relatively easy to fix up.

I have been handicapped in writing this manuscript in that I have not had access to any of the hard numbers involving patient outcomes and x-ray interpretation with this study.

Take the cuffs off.

I am running home to pack and head off to Salt Lake City and catch up with my family. They should be spending their first day on the slopes today.

Thank you for your generosity and support and friendship throughout this past year. I am looking forward to running harder and moving the ball forward this coming year.

Merry Christmas and best regards to you and your families.

Warm regards,
Ken Burkus

From: Martin, Bill
Sent: Friday, January 3, 2003 12:08:51 PM
To: Wehrly, Peter [ITD Div. Pres.]
BCC: Martin, Bill
Subject: RE: PLIF Study Manuscript

Will do,
I really don't think they should be out of it totally, we just need a more appropriate response (ie. NOT "this is a major undertaking and we're gonna completely re-do it").

Julie has been/is involved at the appropriate level right now, I'll plan to keep her (and Neil) engaged in *assisting* Dr. Burkus' effort.

I'll follow up to make sure he is getting the needed info.

Thanks,
Bill

-----Original Message-----
From: Wehrly, Peter [ITD Div. Pres.] [SMTP[redacted]m]
Sent: Friday, January 03, 2003 7:54 AM
To: Martin, Bill
Subject: RE: PLIF Study Manuscript

Neil is out of the picture. Can you ensure Ken gets the info he needs to complete the paper?

Is it worth showing the typical results comparisons versus FDA results?

Let's make sure the paper clearly defines the issues. I want to close the door on this study!

Pete

-----Original Message-----
From: Martin, Bill
Sent: Wednesday, January 01, 2003 8:06 AM
To: Beals, Neil; Wehrly, Peter [ITD Div. Pres.]
Cc: Bearcroft, Julie; Charlton, Clark; Martin, Bill; DeMane, Michael; Lipscomb, Bailey
Subject: RE: PLIF Study Manuscript

A word of caution.
I'm pretty sure that on this paper Dr. Burkus just wants us to provide him the data he requested. Dr. Burkus mentioned that his plan for this paper was to do all the work, put Drs Haid, Branch and Alexander's names first, and then he plans to route it to them "as is" for approval. If they don't agree with the data, then they may of course take their name off. Dr. Burkus has done ground work with Charlie and Reg and they have indicated initially that they seem to be fine with this - I don't anticipate any issues between them. Dr. Burkus wanted his name last (and all the neuro's first) so that it would be well accepted by the Neurosurgical community. I know that he has talked in depth with Charlie about what the paper *should*, and equally important, *should not* include.

A couple of additional thoughts:

1. Ken's intent was to purposely NOT include a lot of interpretation/explanation about radiographic observations that don't correlate to the outcomes for concern that it will confuse the issues and again look like an apology (which is part of what he hopes to clear up with this paper).
2. He's stated that the data is good and should stand on its own. His desire is to cleanly report the outcomes.
3. I'm sure that none of us believe the PLIF *technique* is going to have a resurgence from this, but we may want to steer clear of calling it a flawed technique. There are still quite a few surgeons utilizing this technique and we probably don't want to put them in that position. In the past, the way that Haid has approached this is to use verbiage such as "this technique has fallen out of favor, and many surgeons are now choosing to ____". If Reg believes that a statement like this would be necessary to

add, he'll have the opportunity to add it when Dr. Burkus routes to him for approval.

Basically, let's provide Dr. Burkus with the information he requested (and I believe he's already working with Bailey on this), and just communicate with him to offer to help in any way he needs to get this done. He does have a plan already and intends to quarterback it.

Thanks,
Bill

-----Original Message-----
From: **Beals, Neil [SMTP:** [redacted]
Sent: Tuesday, December 31, 2002 10:53 AM
To: Wehrly, Peter [ITD Div. Pres.]
Cc: Bearcroft, Julie; Charlton, Clark; Martin, Bill; DeMane, Michael; Lipscomb, Bailey
Subject: RE: PLIF Study Manuscript

Julie and I will be glad to f/u on this.

As we get into this, I think we need to clarify and confirm: 1) the message delivered with this paper, 2) its timing, and 3) balanced input from all authors (Haid, Burkus, Branch/Alexander) with particular attention to positioning this with neuro community.

Ken has done a great job in getting the data into a workable manuscript form (I assume that Bailey will not have problems in filling in gaps Ken has pointed out). In its current form, the paper pretty much reports the data from the study with relatively little interpretation or comment. My recommendation would be to report the data and point out that while this study used a flawed technique that has since been modified (stand alone to instrumented PLIFs) the results, particularly with INFUSE, were quite good. The observation of bone formation should be noted and explanations provided including cage placement, construct stability, tissue disruption, and use of other exogenous materials. I think it would make great sense to include the rationale for the new INFUSE PLIF study in this paper to give these discussions some direction and purpose.

To realize this, I think we need to agree on message (INFUSE works well in PLIF with dated technique and is expected to work more consistently and with greater confidence using revised techniques), timing (get published in peer reviewed journal by year-end and try to think of new message to submit in Feb for presentations at spine meetings in the fall), and well balanced input (this must be balanced between Ken and Charley and Joe and Reg; this may be the toughest challenge and the one for which we will need support from top down (if you agree)).

We'll start cracking on more specific review and proposed revision. In meantime, any thoughts?

Neil

-----Original Message-----
From: Wehrly, Peter [ITD Div. Pres.]
Sent: Monday, December 23, 2002 8:25 AM
To: Beals, Neil; Martin, Bill
Cc: Bearcroft, Julie; Charlton, Clark
Subject: FW: PLIF Study Manuscript

Here is first draft. Neil and Julie, will you champion this?

Pete

-----Original Message-----
From: Burkus, J. Kenneth
Sent: Saturday, December 21, 2002 11:26 AM

To: DeMane, Michael; Wehrly, Peter
Subject: PLIF Study Manuscript

Mike and Pete,

Here's your Christmas present. I have attached a copy of the PLIF study manuscript. I believe this will make a significant contribution. I also think this should have a high priority to bring to completion.

I have done about all that I can do without further analysis of the PLIF study data.

In the text of the manuscript, you will find numerous areas that are in bold and underlined. I will need further analysis of this data.

The discussion and conclusions and bibliography are lacking but should be relatively easy to fix up.

I have been handicapped in writing this manuscript in that I have not had access to any of the hard numbers involving patient outcomes and x-ray interpretation with this study.

Take the cuffs off.

I am running home to pack and head off to Salt Lake City and catch up with my family. They should be spending their first day on the slopes today.

Thank you for your generosity and support and friendship throughout this past year. I am looking forward to running harder and moving the ball forward this coming year.

Merry Christmas and best regards to you and your families.

Warm regards,
Ken Burkus

From: Martin, Bill
Sent: Sunday, January 5, 2003 02:24:10 PM
To: Beals, Neil; Wehrly, Peter [ITD Div. Pres.]
CC: Bearcroft, Julie; Charlton, Clark; Martin, Bill
Subject: RE: PLIF Study Manuscript

Neil,
Understand your point, however, I would strongly prefer that you and Julie not be *completely* out of it. Just realize that we are definitely and clearly in a "supporting cast" role in this situation. I'll follow up with Bailey to make sure we're getting all the info that Dr. B needs.

Thanks,
Bill

-----Original Message-----
From: Beals, Neil [SMTP [redacted]
Sent: Thursday, January 02, 2003 8:18 AM
To: Wehrly, Peter [ITD Div. Pres.]
Cc: Bearcroft, Julie; Charlton, Clark; Martin, Bill
Subject: RE: PLIF Study Manuscript

Pete,

Based on note below from Bill, it seems that he has already covered this manuscript and its direction with Ken and all that is now needed is data from Bailey. I do not see need for Julie or I to get into this at this point. Please advise if you see things differently. Thanks. Neil

-----Original Message-----
From: Martin, Bill
Sent: Wednesday, January 01, 2003 8:06 AM
To: Beals, Neil; Wehrly, Peter [ITD Div. Pres.]
Cc: Bearcroft, Julie; Charlton, Clark; Martin, Bill; DeMane, Michael; Lipscomb, Bailey
Subject: RE: PLIF Study Manuscript

A word of caution.
I'm pretty sure that on this paper Dr. Burkus just wants us to provide him the data he requested. Dr. Burkus mentioned that his plan for this paper was to do all the work, put Drs Haid, Branch and Alexander's names first, and then he plans to route it to them "as is" for approval. If they don't agree with the data, then they may of course take their name off. Dr. Burkus has done ground work with Charlie and Reg and they have indicated initially that they seem to be fine with this - I don't anticipate any issues between them. Dr. Burkus wanted his name last (and all the neuro's first) so that it would be well accepted by the Neurosurgical community. I know that he has talked in depth with Charlie about what the paper *should*, and equally important, *should not* include.

A couple of additional thoughts:

1. Ken's intent was to purposely NOT include a lot of interpretation/explanation about radiographic observations that don't correlate to the outcomes for concern that it will confuse the issues and again look like an apology (which is part of what he hopes to clear up with this paper).
2. He's stated that the data is good and should stand on its own. His desire is to cleanly report the outcomes.
3. I'm sure that none of us believe the PLIF *technique* is going to have a resurgence from this, but we may want to steer clear of calling it a flawed technique. There are still quite a few surgeons utilizing this technique and we probably don't want to put them in that position. In the past, the way that Haid has approached this is to use verbiage such as "this technique has fallen out of favor, and many surgeons are now choosing to ____". If Reg believes that a statement like this would be necessary to add, he'll have the opportunity to add it when Dr. Burkus routes to him for approval.

Basically, let's provide Dr. Burkus with the information he requested (and I believe he's already working with Bailey on this), and just communicate with him to offer to help in any way he needs to get this done. He does have a plan already and intends to quarterback it.

Thanks,

Bill

—Original Message—
From: **Beals, Neil [SMTP** [redacted]
Sent: Tuesday, December 31, 2002 10:53 AM
To: Wehrly, Peter [ITD Div. Pres.]
Cc: Bearcroft, Julie; Charlton, Clark; Martin, Bill; DeMane, Michael; Lipscomb, Bailey
Subject: RE: PLIF Study Manuscript

Julie and I will be glad to f/u on this.

As we get into this, I think we need to clarify and confirm: 1) the message delivered with this paper, 2) its timing, and 3) balanced input from all authors (Haid, Burkus, Branch/Alexander) with particular attention to positioning this with neuro community.

Ken has done a great job in getting the data into a workable manuscript form (I assume that Bailey will not have problems in filling in gaps Ken has pointed out). In its current form, the paper pretty much reports the data from the study with relatively little interpretation or comment. My recommendation would be to report the data and point out that while this study used a flawed technique that has since been modified (stand alone to instrumented PLIFs) the results, particularly with INFUSE, were quite good. The observation of bone formation should be noted and explanations provided including cage placement, construct stability, tissue disruption, and use of other exogenous materials. I think it would make great sense to include the rationale for the new INFUSE PLIF study in this paper to give these discussions some direction and purpose.

To realize this, I think we need to agree on message (INFUSE works well in PLIF with dated technique and is expected to work more consistently and with greater confidence using revised techniques), timing (get published in peer reviewed journal by year-end and try to think of new message to submit in Feb for presentations at spine meetings in the fall), and well balanced input (this must be balanced between Ken and Charley and Joe and Reg; this may be the toughest challenge and the one for which we will need support from top down (if you agree)).

We'll start cracking on more specific review and proposed revision. In meantime, any thoughts?

Neil

-----Original Message-----
From: Wehrly, Peter [ITD Div. Pres.]
Sent: Monday, December 23, 2002 8:25 AM
To: Beals, Neil; Martin, Bill
Cc: Bearcroft, Julie; Charlton, Clark
Subject: FW: PLIF Study Manuscript

Here is first draft. Neil and Julie, will you champion this?

Pete

-----Original Message-----
From: Burkus, J. Kenneth
Sent: Saturday, December 21, 2002 11:26 AM
To: DeMane, Michael; Wehrly, Peter
Subject: PLIF Study Manuscript

Mike and Pete,

Here's your Christmas present. I have attached a copy of the PLIF study manuscript. I believe this will make a significant contribution. I

also think this should have a high priority to bring to completion.

I have done about all that I can do without further analysis of the PLIF study data.

In the text of the manuscript, you will find numerous areas that are in bold and underlined. I will need further analysis of this data.

The discussion and conclusions and bibliography are lacking but should be relatively easy to fix up.

I have been handicapped in writing this manuscript in that I have not had access to any of the hard numbers involving patient outcomes and x-ray interpretation with this study.

Take the cuffs off.

I am running home to pack and head off to Salt Lake City and catch up with my family. They should be spending their first day on the slopes today.

Thank you for your generosity and support and friendship throughout this past year. I am looking forward to running harder and moving the ball forward this coming year.

Merry Christmas and best regards to you and your families.

Warm regards,
Ken Burkus

From: Martin, Bill
Sent: Tuesday, March 9, 2004 06:32:18 AM
To: DeMane, Michael
Subject: RE: Editorial comment for MS30023

Michael,
You're probably right, however considering it presents favorable data from the study I can't imagine that it could make the perception of this study worse. The understanding of virtually every surgeon on the street is that the study was stopped "due to exuberant bone growth in the canal". Many of the ones that I talk to mistakenly think that FDA stopped it.
Should prove interesting to see how it is received.
-----Original Message-----
From: DeMane, Michael
Sent: Monday, March 08, 2004 1:07 PM
To: Martin, Bill
Subject: RE: Editorial comment for MS30023

as I expected...this is going to hurt more than help because of the reviewers comments. Too late to turn back tho. thanks

M -----Original Message-----
From: Martin, Bill
Sent: Saturday, March 06, 2004 7:16 AM
To: Branch, Charles
Subject: RE: Editorial comment for MS30023

CB,
Just wanted to say thanks one more time for keeping me posted! Agree with your approach and I look forward to seeing the publication.
Best,
-Bill

-----Original Message-----
From: Charles Branch [mailto:[redacted]
Sent: Monday, March 01, 2004 9:14 AM
To: Martin, Bill
Subject: FW: Editorial comment for MS30023

Bill
The PLIF BMP paper has been accepted for publication. One Deputy Editor has submitted a commentry that was somewhat disparaging. I was give the opportunity to respond. Attached is my response. Ken should have forwarded the final version to you back in October or sometime! We hope to see this in print in 2 months or so!
CB
-----Original Message-----
From: Charles Branch
Sent: Saturday, February 28, 2004 7:09 PM
To: rhai[redacted]
Cc: Joseph Alexander; jkl[redacted]
Subject: Editorial comment for MS30023

Reg
Our PLIF BMP paper is in the home stretch. You might want to write Joy Kenyon at The Spine Journal[redacted] and give her your new title and address. The original manuscript of which you are the lead author came when you were still at Emory.
Reg, Ken and Joe
As you know, this paper had a rather critical review, some of which was merited, some of which was pure competitive bias. But, it has been accepted, and the deal was that Neal Kahanovitz would add an editorial commentary, and that I would get to respond. He has essentially accused us of biased reporting and overwhelming enthusiasm for rhBMP and a cylindrical cage through a posterior approach among other things. He obviously didn't read the paper! I can't send you his comments, but I am attaching my response for your preview. My approach is to take the high road of

measured calm. I hope to see this in print by June or so. There will be a TLIF - BMP paper in the Neurosurgical Focus next month that is "encouraging" as well. Be sure to check that issue out as we received a good collection of manuscripts documenting clinical and preclinical experience with bioasorbables.
CB

From: JKB[redacted]
Sent: Thursday, July 4, 2002 07:11:41 PM
To: Peter Wehrly[redacted] Bill Martin[redacted]; Neil Beals[redacted] Tara Hood[redacted] Joseph Pizzurro[redacted]com]; Clark Charlton[redacted]
Subject: Revised Open LT BMP manuscript

Attachments: JSD&T revison OPEN LTCAGE BMP.1.doc

Sirs and Ma'am:

I have attached the revised Open LT BMP paper.

Don't even think about making **any** more changes - just kidding.

Get in touch with Carol Binns for any last minute changes.

If you guys think the Big Guy in the corner office wants this thing on the way to the printer - you can imagine how I feel.

Best regards to all my friends.

I greatly appreciate the opportunity to participate in this study.

Ken Burkus

Anterior Lumbar Interbody Fusion Using rhBMP-2 with Tapered Interbody Cages

J. Kenneth Burkus MD*

Matthew F. Gornet MD†

Curtis Dickman, MD‡

Thomas A. Zdeblick MD§

*Staff Physician, Spine Service, The Hughston Clinic, P.C., Columbus, Georgia

†Staff Physician, Missouri Bone and Joint Institute, St. Louis, Missouri

‡Barrows Institute, Phoenix, Arizona

§Chairman, Department of Orthopedics and Rehabilitation, University of Wisconsin, Madison, Wisconsin

Address correspondence and reprint requests to J.K. Burkus, MD, The Hughston Clinic, [redacted]

ABSTRACT

Study Design. A multi-center, prospective, randomized, nonblinded, 2-year study of 279 patients who underwent a single-level anterior lumbar interbody fusion with a tapered threaded titanium fusion device and received either autogenous iliac crest bone graft or bone morphogenetic protein (rhBMP-2) on a collagen sponge carrier.

Objectives. To compare the outcomes in patients treated for degenerative disc disease with interbody fusion using tapered threaded titanium fusion cages with either autogenous bone graft or rhBMP-2.

Summary of Background Data. In a small series of human patients undergoing anterior lumbar interbody fusion, rhBMP-2 has been shown to promote osteoinduction and fusion.

Methods. Two hundred seventy-nine patients were randomly divided into 2 groups that underwent interbody fusion using two tapered threaded fusion cages: the investigational group (143 patients) received rhBMP-2 on an absorbable collagen sponge and a control group (136 patients) received autogenous iliac crest bone graft. Clinical outcome assessment was based on neurologic status, work status, Oswestry Low Back Pain Disability scores, and back and leg pain questionnaires. Plain radiographs and computed tomographic scans were used to evaluate fusion at 6, 12, and 24 months postoperatively.

Results. Mean operative time (1.6 hours) and blood loss (109.8 mL) were less in the investigational rhBMP-2 group than in the autograft control group (2.0 hours and 153.1 mL). At 24 months, the investigational group's fusion rate (94.5%) remained higher than

the control's (88.7%). New bone formation occurred in all investigational patients. At all intervals, mean postoperative Oswestry, back pain, and leg pain scores and neurologic status improved in both treatment groups with similar outcomes. In the control group, 8 adverse events related to the iliac crest graft harvest occurred in 8 patients (5.9%), and, at 24 months, 32% of patients still reported graft site discomfort and 16% were bothered by its appearance.

Conclusions. Lumbar fusion using rhBMP-2 and a tapered titanium fusion cage can yield a solid union and eliminate the need for harvesting iliac crest bone graft.

Key words: anterior lumbar interbody fusion, interbody fusion cage, bone morphogenetic protein

Key points:

- Fusion rates for both treatment groups were high at all follow-up intervals. At 24 months, the average rate of fusion for patients treated with rhBMP-2 was nearly 6 percentage points higher (94.5% versus 88.7%) than for patients treated with autograft with a probability of superiority of 90.2 percent.
- The average operative time was 1.6 hours for patients treated with rhBMP-2 compared with 2.0 hours in the autograft group. This difference was statistically significant.
- Blood loss was less for patients treated with rhBMP-2 than for patients who underwent iliac crest bone graft harvesting.
- At all postoperative assessment intervals, patients in both treatment groups showed improvement in Oswestry disability scores, in neurologic status, and in back and leg pain outcomes.

- The use of rhBMP-2 in anterior lumbar interbody fusion procedures eliminates the complications of postoperative pain and scarring associated with iliac crest bone harvesting.

Deleted: 07/04/02

Précis

In a 2-year prospective randomized study of 279 patients, the investigational group that received rhBMP-2 with the LT-CAGE™ device had a higher rate of fusion, reduced operative times, and decreased blood loss when compared with the control group that received autogenous bone graft with the same tapered cage device. The rhBMP-2 group avoided the complications that can arise from an iliac crest bone harvesting procedure.

INTRODUCTION

Degenerative changes within a lumbar spinal motion segment are, in part, evidenced by the presence of radial tears or fissures in the annulus fibrosus, disc space desiccation and collapse, and the formation of radial osteophytes. These morphologic changes within the spinal motion segment can lead to loss of the intervertebral disc's ability to accommodate normal biomechanical stresses and can cause pain. Fusion of the degenerative and unstable spinal motion segment can give significant relief from this disabling and often progressive condition.[2,7,9]

Anterior lumbar interbody fusion (ALIF) is an effective treatment for patients with symptomatic degenerative disc disease. Lumbar spine stabilization procedures that do not interfere with the posterior spinal muscles have some significant advantages.[9,10,14-16,19] The anterior approach to the lumbosacral spine enables the surgeon to expand the disc space and re-establish the normal anatomic alignment and relationships of the spinal motion segment while avoiding injury to the posterior paravertebral muscles. The anterior approach also retains all posterior stabilizing structures and avoids epidural scarring and perineural fibrosis. Adjacent segment degeneration in the lumbar spine after ALIF can also be reduced.[17]

Stand-alone ALIF procedures using autogenous bone grafts alone have been associated with high rates of pseudarthrosis, graft subsidence, and graft extrusion.[8,23] Supplemental posterior segmental spinal instrumentation has been used to stabilize interbody grafts and increase rates of fusion. Recently, cylindrical threaded intervertebral devices with autogenous bone grafts have been shown to stabilize a

lumbar motion segment after anterior discectomy, and their use has lead to high rates of fusion and to improved clinical outcomes.[4]

In non-human primate models, recombinant human bone morphogenetic protein 2 (rhBMP-2) applied to an absorbable collagen sponge carrier has been shown to promote osteoinduction and fusion after ALIF.[11] Recently, this technique was used in a small series of human patients who underwent stand-alone ALIF with tapered fusion cages. In these patients, the use of rhBMP-2 applied to a collagen sponge was also shown to promote osteoinduction and fusion.[4] To further evaluate this method, we compared the clinical and radiographic outcomes at 24 months of 279 patients who underwent a single-level ALIF with a tapered fusion device and either rhBMP-2 or autogenous bone.

MATERIALS AND METHODS

Study Design. Between August 1998 and July 1999, 279 patients had surgery in this prospective, randomized, nonblinded, FDA approved study at 16 investigational sites. All patients underwent a single-level anterior lumbar fusion with the LT-CAGE™ Lumbar Tapered Fusion Device (Medtronic Sofamor Danek, Memphis, TN). Patients were randomly assigned in a 1:1 manner to one of two groups: the investigational group received rhBMP-2 on an absorbable collagen sponge carrier and the control group received autogenous iliac crest bone graft. InFUSE Bone Graft™ (Medtronic Sofamor Danek, Memphis, TN) is the trademarked name for recombinant human bone morphogenetic protein-2 applied to an absorbable collagen sponge.

Patient Data. Preoperatively, all patients had symptomatic, single-level degenerative lumbar disc disease and symptoms of disabling low back or leg pain, or both, of at least 6 months' duration that had not responded to nonoperative treatments. The two treatment groups were very similar demographically, and there were no statistically significant differences ($P < 0.05$) for any of the variables (Table 1). The rhBMP-2 group consisted of 143 patients and the control group consisted of 136 patients. The average age at surgery was 43.3 years for the rhBMP-2 group and 42.3 years for the control group. In the rhBMP-2 group, 47 patients (32.9%) had used tobacco within 6 months before surgery compared with 49 patients (36%) in the control group. The percentage of patients with pending litigation was 12.6% and 16.2% in the rhBMP-2 and control groups, respectively. The percentage of patients seeking worker's compensation was 32.9% in the rhBMP-2 group and 34.6% in the control group.

Clinical and Radiographic Outcome Measurements. Patient assessments were completed preoperatively, during hospitalization, and postoperatively at 6 weeks and at 3, 6, 12, and 24 months. Clinical outcomes were assessed using neurologic status, work status, patient satisfaction, and Oswestry Low Back Pain Disability, back, leg, and graft site pain questionnaires.

Radiographs and computed tomography (CT) scans were used to evaluate fusion at 6, 12, and 24 months after surgery. Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent, blinded radiologist was used to adjudicate conflicting fusion findings. Fusion was defined as an absence of radiolucent lines covering more than 50% of either implant, translation of 3 mm or less and angulation less than 5° on flexion-extension radiographs, and continuous trabecular

bone growth connecting the vertebral bodies on CT scan.[6] There was good agreement between the radiologists reviewing the studies. At 6, 12, and 24 months after surgery, agreement among the independent reviewers was greater than 98%. In order to take a very critical and conservative approach to fusion assessment, fusion success was based on both clinical symptoms and radiographic findings. Patients who had secondary surgeries because of persistent low back symptoms and clinically suspected nonunions were considered as having failed fusions and were classified as failures in all fusion calculations, regardless of their independent radiological assessment.

Clinical and Radiographic Follow-up. The rate of return for follow-up in our patients was high at all postoperative periods (Table 2). At 12 months, the rate of patient return for both treatment groups exceeded 96%. At 24 months, the follow-up rate for the investigational group was 92.5% and the control group rate was 90.8%.

Surgical Technique. All patients underwent the ALIF procedure through an open approach. Patients were placed in the supine position on the operating room table. Fluoroscopy was used throughout the surgical procedure. A vertical or transverse incision was made over the lumbosacral spine. A retroperitoneal exposure was carried out in 81% (226/279) of patients, and a transperitoneal exposure was used in 19% (53/279) of patients. The parasympathetic nerve complex was bluntly mobilized and retracted from the surgical field; electrocautery was not used during this portion of the surgical procedure. Segmental vessels were sequentially identified, ligated, and divided. The great vessels were mobilized exposing the anterior surface and lateral borders of the disc space. The midpoint of the disc space was identified with radiographic markers and fluoroscopy.

Deleted: 07/04/02

An incision was made in the anterior portion of the annulus, removing the anterior longitudinal ligament and the anteriolateral borders of the annulus fibrosus. Under direct visualization the entire contents of the disc space were removed including the nucleus pulposis and the cartilaginous endplates. Great care was taken to protect and preserve the bony vertebral endplates. The disc space was sequentially distracted to the height of normal adjacent disc space height. Intraoperative distraction was, in part, determined by the preoperative use of templates assessing the disc space height of normal adjacent discs. Similarly, appropriate cage size was preoperatively estimated through the use of templates on axial scans (MRI or CT) studies. Ultimately, the final amount of intradiscal distraction and cage size was determined by intraoperative assessment of annular tension and direct visualization of the disc space dimensions. A double barrel guide was inserted into the disc space and the bony endplates were precisely prepared with a reamer.

In the investigational group, each cage was filled with an rhBMP-2 soaked collagen sponge. No autogenous bone grafts or local reamings were used in this group. The cages were sequentially inserted through the guide tube into the prepared intervertebral disc space. Cage placement was evaluated with fluoroscopy in both the anteroposterior and lateral dimensions. In the control group, two cage devices were packed with morcellized autogenous bone graft harvested from the iliac crest.

Deleted: usind

The rhBMP-2 was reconstituted using sterile water and was used as a single dose of 1.5 mg/mL in all study patients. The 1.5-mg rhBMP-2/mL solution was applied to a bovine collagen sponge and allowed to bind to the sponge for 15 minutes. The absorbable collagen sponge (Integra LifeSciences) is a bovine tendon Type 1 collagen.

The FDA initially approved it as an implantable hemostatic agent. Its manufacturing process meets or exceeds all U.S. guidance. In addition, there is extensive clinical experience of safe use with this product since it became commercially available in 1981.The total dose of rhBMP-2 ranged from 4.2 to 8.4 mg depending on the size of the cage required in each patient. The rhBMP-2 soaked sponge was then placed in the hollow central portion of the cage device before its insertion into the prepared disc space. No additional sponges were placed outside the devices. No autogenous grafts were used in the investigational group.

Patients in the investigational group did have prior posterior annulotomies from prior posterior discectomy surgery. Many patients in this group had posterior annular tears document on MR imaging or discography. Two patients underwent anterior lumbar disc removal with an annulotomy of the posterior annulus at the time of the investigational surgery. The rhBMP protein is bound by the collagen carrier and does not egress into the spinal canal.

The control group received morcellized autogenous iliac crest graft placed within the cages. The bone graft was harvested from the inner table of the right iliac wing. Cortical and cancellous bone graft was obtained using osteotomes and gouges. The graft was morcellized using a rongeur and was tightly packed into the cages before their insertion.

Postoperatively, patients were placed in a soft lumbar corset. Activities were advanced by the treating physician. Isometric strengthening and an exercise program were started at six weeks after surgery.

Deleted: 07/04/02

Statistical Methods. The data from this clinical trial were analyzed using the statistical software package SAS® version 6.12. For continuous variables, *P* values are from ANOVA, and for categorical variables, they are from Fisher's exact test or chi-square test.

RESULTS

Surgery

The mean operative time in the investigational rhBMP-2 group (1.6 hours) was less than in the control group (2.0 hours) (Table 3). The average blood loss in the rhBMP-2 group was 109.3 ml as compared with 153.8 ml in the control group. The operative time and blood loss was less in the investigational group despite the fact that the more technically demanding and time consuming approach to the L4-L5 level was performed more frequently in the investigational group (25.9%, 37/143) than in the control group (23.5%, 32/136). The average hospital stay was similar in both groups (3.1 days for the investigational group versus 3.3 days for the control group). Discharge from the hospital was based upon the treating surgeons standard fro discharge criteria. No objective discharge parameters were used in this study. There were no unanticipated device-related adverse events in either treatment group.

Complications

Vascular events. Eleven intraoperative vascular events occurred: 6 were in the rhBMP-2 group (4.2%) and 5, in the autograft group (3.7%). The most common injury (6/11) was a laceration of the iliac vein. Two control group patients developed deep venous thrombosis and were treated with anticoagulation medications. No patients in

Deleted: 07/04/02

the investigational group developed a deep venous thrombosis. This may, in part, be secondary to the reduced surgical times.

Deleted: In the investigational group and reduction in time the great vessels were manipulated and retracted during the surgical procedure.

Retrograde ejaculation. Six male patients (4.1%, 6/146) complained of retrograde ejaculation after surgery. In these patients, the L5-S1 disc space was approached 5 times (83.3%, 5/6). A transperitoneal approach was used in 4 of the 6 patients (66.6%). This complication occurred in 13.3% (4/30) of the men who underwent a transperitoneal approach and occurred in only 1.8% (2/116) of men who underwent a retroperitoneal approach. This difference is statistically significant using Fisher's Exact Test (p=0.017). In two patients, the retrograde ejaculation resolved by 12 months after surgery; one patient underwent a retroperitoneal approach, the other a transperitoneal approach. At the final 2-year postoperative interval, 4 males had permanent retrograde ejaculation: One in the retroperitoneal group (0.86%), and 3 in the transperitoneal group (10%) and all had an L5-S1 Fusion. The difference in these two groups with permanent retrograde ejaculation is also statistically significant using Fisher's Exact Test (p=0.027).*Iliac crest graft site.* In the control group, 8 adverse events related to harvesting of the iliac crest graft were identified in 8 patients (5.9%). These events included 3 injuries to the lateral femoral cutaneous nerve, 2 avulsion fractures of the anterior superior iliac spine, 1 infection and 1 hematoma. None required an additional surgery. The graft site infection was superficial and required a course of oral antibiotics. Obviously, there were no graft site adverse events in the investigational group because the use of rhBMP-2 precluded the need to harvest bone graft.

Deleted: ¶

The level of postoperative pain and morbidity associated with the iliac crest graft harvesting was measured using numeric rating scales for pain intensity and duration

(Fig. 1 and Table 4). After surgery, all of the control patients experienced hip donor site pain. The highest levels of pain were noted immediately after surgery with a mean score of 12.7 points out of 20 points. The percentage of patients experiencing pain decreased over time; however, at 24 months after surgery, nearly one-third of the control patients (32%) still experienced pain (Fig. 2). At two years, the graft site pain scores averaged 1.8 points, and 16% of the control patients were bothered by the appearance of the graft site.

Antibody Testing

Antibodies to rhBMP-2 were evaluated preoperatively and at 3 months after surgery using enzyme-linked immunosorbent assays (ELISAs). The results were similar between the investigational and control groups (0.7% and 0.8%, respectively). There appeared to be no negative consequence to positive antibody test results.

Clinical Outcomes

Oswestry Disability Questionnaire scores. The Oswestry Low Back Pain Disability Questionnaire measures pain associated with activities. The Oswestry Questionnaire was administered preoperatively and at each postoperative visit. The mean overall Oswestry scores for both treatment groups were similar at each of the time periods. At all postoperative visits, average scores in both treatment groups showed statistical improvement compared with their preoperative scores (Fig. 3). At 24 months, the mean improvements in the Oswestry scores were 29.0 points in the investigational group and 29.5 points in the control group (Table 5). In the rhBMP-2 group, 84.6% of patients showed an improvement of at least 15% in their disability scores at 12 months after surgery compared with 85.6% of patients in the control group.

At 24 months, 84.4% of the investigational group was improved and compared favorably with 82.4% improved in the control group.

Neurologic Status. Neurologic status of the patients was determined by evaluating four neurologic measurements: motor function, sensory function, deep tendon reflexes, and sciatic tension signs. Values for each of the 4 subsets of objective findings were totaled and expressed as a percentage of the maximum possible score. Each measurement was compared with the patient's preoperative score. Neurologic success was based on demonstrating maintenance of or improvement in all four neurologic measurements. At 12 and 24 months after surgery, the overall neurologic success rates for the investigational group were 81.8% and 82.8%, respectively, compared with 84.7% and 83.3% rates for the control group (Table 6).

Back Pain. Back pain intensity and duration were assessed using a 20-point numeric rating scale. Adding the numeric rating scores for back pain intensity and pain duration allowed examiners to derive a composite back pain score. The mean back pain scores at all postoperative periods were improved from the preoperative mean values in both treatment groups (Fig. 4). The mean improvements in back pain scores at both 12 and 24 months were greater for the investigational group than for the control autograft group (Table 7).

Back pain success was determined for each patient by comparing their postoperative score with their preoperative score. Success was based on the patient's having had at least a 3-point improvement in his or her back pain score after surgery (Table 8). At 12 and 24 months after surgery, the investigational group had back pain

success rates of 79.1% and 74.6%, respectively. These rates were similar to the respective rates in the control group of 72.8% and 78.7%.

Leg Pain. Leg pain was assessed in a similar manner using a numeric rating scale for both the intensity and duration of painful symptoms. Mean leg pain scores improved significantly after surgery (Table 9). Outcomes were similar in both treatment groups (Fig. 5). Leg pain success was defined as a function of the patient's preoperative complaints. If a patient had a preoperative pain score of 10 points or more, success was defined as a 3-point improvement in his or her postoperative scores. In patients who had preoperative leg pain scores of less than 10 points, success was defined as maintenance of or improvement in scores when compared with their preoperative condition. At 12 months after surgery, the leg pain success rates were similar in both treatment groups. The investigational group had a success rate of 72.1% and the control group had success rate of 72.8%. At 24 months, the success rate in the investigational group improved to 80.3% and was higher than the 74.1% result in the control group.

Work Status. Many factors affect a patient's work status, such as the nature of the work performed and ability of the work place to accommodate work restrictions. The work status of the investigational patients was similar to that of the control patients at most postoperative follow-up intervals (Fig. 6). For patients who were working before surgery, the median return to work time was 63.5 days in the investigational group and 64.5 days in the control group. More people in both treatment groups were working at the two-year follow-up than were working before their surgery. At last follow-up, in the investigational group, 80 patients were employed while only 54 were employed before

surgery. Similarly, in the control group, 38 were working before surgery and 60 were working at two years after surgery (Table 10).

Patient Satisfaction. At 12 and 24 months after surgery, the results were similar in each treatment group. At 24 months, 81.2% of the investigational patients and 80.4% of the controls were satisfied with their surgical outcomes. In the investigational group, 82% said they would undergo surgery again compared with 76.7% of the control patients who would undergo surgery again. In the investigational group, 74.6% believed that they were helped as much as they had expected to be from the surgery; 76.6% of the control group felt they had been.

Radiographic Outcomes

Fusion status of the study patients was evaluated on plain radiographs and CT scans. At 6 months after surgery, 97.0% of patients in the investigational group had evidence of interbody fusion compared with 115 patients (95.8 %) in the control group (Table 11). At 12 months, 127 patients (96.9 %) in the investigational group showed evidence of fusion. In the control group, 112 patients (92.5%) showed evidence of fusion at 1 year. At 24 months, the investigational group had a 94.5% fusion rate, which was approximately 6 percentage points higher than that of the control group (88.7%) (Fig. 7). Fusion rates decreased over time for two reasons. Over time, radiolucencies from micromotion at the implant host bone interface were identified. Autogenous bone grafts also become atrophic over time. Fusion success was based upon both radiographic criteria and clinical symptoms. Those patients that had radiographic evidence of fusion but who persistent low back symptoms to warrant addition posterior

stabilizing surgery by their attending physician were also considered fusion failure. This was a truly very conservative and critical approach to assessing fusion.

Secondary Surgical Procedures

In the investigational group, 11 patients (7.0%) had a second surgery and 14 patients (10.3%) in the control group had second surgeries. In the investigational group, 2 patients had implant removals: One removal occurred 5 days after surgery, and the other, at 4 months. The removal at 5 days was due to a vertebral bone fracture and implant displacement. The removal at 4 months was due to implant displacement and possible failed fusion. Seven investigational patients underwent supplemental fixation for presumed pseudarthrosis, 1 underwent supplemental fixation after posterior decompression for persistent radicular symptoms after the initial surgery, and 1 underwent a panlumbar fusion for discogenic back pain. Two of the supplemental fixations for presumed pseudarthrosis occurred before the 6-month follow-up evaluation. Fusion was not evaluated until 6 months after surgery; therefore, these patients cannot be classified as fusion failures. They are second surgery failures.

In the control group, 12 patients underwent supplemental posterior fixation for a presumed pseudarthrosis and 2 underwent supplemental posterior fixation for persistent discogenic pain. One patient underwent supplemental fixation for presumed pseudarthrosis before the 6-month follow up.

In 90% (18/20) of these patients (7/7 in the investigational group; 11/13 in the control group), the fusion was radiographically solid at the visit prior to the supplemental fixation, but posterior instrumentation was inserted by the treating physician based on

clinical symptoms of persistent pain. In 53.3% of these patients, pain improved after the secondary posterior surgical procedure.

DISCUSSION

Spinal fusions can be performed anteriorly, posteriorly, or posterolaterally. Instrumentation can also be used to stabilize the spinal motion segment and to promote fusion. Traditionally, fusions in the lumbar spine have been performed through a posterior approach. After a successful posterolateral lumbar spinal fusion, patients often have significant relief of their painful symptoms. However, the posterolateral approach and the lateral exposure of the transverse processes of the lumbar spine can compromise the patient's functional outcome.[13] The paraspinal muscles must be detached from the posterior spinal elements and transverse processes during the surgical exposure for the lateral fusion. This injury to the spinal muscles of the lumbar spine limits the patient's ultimate rehabilitation potential.[1] Several studies have demonstrated significant loss of paraspinal muscle strength and muscle atrophy in patients with persistent back pain after posterolateral lumbar spinal fusion.[12,18,22] The surgeon strips the paraspinal muscles from their anatomic attachments to the spine and then reattaches them to the midline fascia and retained spinal elements. However, postoperative healing and scar tissue formation interferes with the normal independent function of the paravertebral muscle groups. The loss of their normal anatomic attachment sites, formation of scar tissue, and loss of independent muscle function compromise the paravertebral muscles.

Deleted: 07/04/02

Stand-alone anterior lumbar interbody fusion allows the complications of posterior "fusion disease" (25) to be avoided. The anterior approach retains all posterior-stabilizing structures and avoids epidural scarring and perineural fibrosis. There is no need for paraspinal muscle stripping, retraction, or denervation of the adjacent facet joint. The "mini-open" approach is muscle-splitting approach that does not compromise existing posterior spinal elements. This approach bluntly mobilizes the abdominal wall musculature and allows for quicker rehabilitation of the patient. The anterior approach also allows the surgeon to reestablish normal disc space height and restore the normal sagittal contours of the lumbar spine without entering the spinal canal. This technique allows a faster and often a more complete functional recovery of the patient. Complications associated with this procedure are injures to the inferior vena cava or left iliac vein. Careful dissection and new reaming tube designs help to reduce this complication. In a long-term follow-up study, Penta et al. found no significant rates of adjacent segment degeneration after anterior interbody fusion.[17]

Deleted: The

Deleted: is one

Deleted: ,

Deleted: and it

Numerous clinical studies have documented the efficacy and improved outcomes with the anterior lumbar interbody fusion procedure.[7,8,10,14-16,19] Femoral ring allografts have been widely used; however, these intradiscal spacers alone do not provide enough stability to promote fusion consistently, and they have been associated with high rates of postoperative subsidence.[2] Anterior femoral ring allografts often require an additional instrumented posterior spinal fusion to stabilize the spinal motion segment. Recent advances in metallic interbody fusion devices have been introduced to stabilize intervertebral grafts and have been used to encourage fusion and prevent disc space collapse during the healing process.[5] The LT-CAGE™ Lumbar Tapered Fusion Device

represents a significant technological advance over first generation cylindrical cages. The insertional torque on implantation of the fusion device is greater, there is less scatter and artifact on postoperative imaging, and achieves segmental lordosis without asymmetric endplate reaming.

Our study is one of the largest prospective clinical studies of stand-alone ALIF procedures. Clinical and radiographic follow-up exceeded 90% at all intervals. The randomized patient groups showed no statistically significant differences in the variables assessed. However, because the investigational, or rhBMP-2, group did not undergo an autogenous bone graft harvesting procedure, there was a statistically significant reduction in operative time and in decreased blood loss during the procedure in these patients. Retrograde ejaculation was associated with the transabdominal approach to the lumbosacral spine.

The difficulty in achieving anterior interbody fusion through the use of fusion cages lies in the preparation of the endplate. The endplate must be partially removed to allow healing of the vertebral bodies. However, if resection of the endplate is excessive, subsidence can occur and, ultimately, pseudarthrosis. The procedure used in our study patients helps to enhance this fusion in two separate ways. With the LT-CAGE™ device, there is minimal endplate resection, thus preserving the weight-bearing portions of the endplate, which allows greater restoration of lordosis and prevents subsidence. The use of recombinant human bone morphogenetic protein has been shown to accelerate fusion in animal models.[3,20,21] Its use should also allow the fusion procedure to more rapidly and more thoroughly occur in humans. Indeed, from a radiographic

standpoint this was true in our patients; 97% of patients who received the LT-CAGE™ device and rhBMP-2 had radiographic evidence of a solid fusion at one year.

Our study's fusion assessment protocol is one of the first to use thin-cut CT scans to evaluate new bone formation.[6] The thin-walled second-generation LT-CAGE™ device reduced imaging artifact in the instrumented disc space, and new bone formation was identified reliably inside and outside of the intervertebral cages on these CT scans. New bone formation was identified in all patients who received cages filled with rhBMP-2 that remained implanted for more than 6 months. Fusion failure was documented in the rhBMP-2 treated group because of a secondary surgical procedure, not because of lack of new bone formation. All new bone formation was found within the instrumented disc space. Areas between the cages, lateral to the cages, and anterior and posterior to the cages did often ossify (Figs. 8 and 9). However, there was no ectopic bone formation outside of the annular confines of the disc space, and there was no bone formation extending posteriorly into the spinal canal or laterally into the neuroforamina.

Recombinant human bone morphogenetic protein is an osteoinductive growth factor that stimulates pleuripotential cells to form bone.[24] We believe that exposure of bleeding cancellous bone allowed influx of pleuripotential cells that were affected by the rhBMP-2 bound to the collagen carrier sponge. The investigational, or rhBMP-2, group had a 96.9% fusion rate at 12 months compared with a 92.6% rate in the control group. At 24 months, the investigational group had a 94.5% fusion rate, which was almost six percentage points higher than the fusion rate of the control group (88.7%). This range of effect was essentially limited to the disc space. Areas between the cages, lateral to the cages, and anterior and posterior to the cages did ossify, but in no case did this

Deleted: 07/04/02

Deleted: No heterotopic ossification occurred in the epidural space or within the peritoneal cavity or retroperitoneal space.

ossification extend outside of the confines of the vertebral column. No metastatic calcifications were seen in these study patients.

The final assessment of a successful interbody fusion is difficult. Independent radiologists carefully scrutinized the plain radiographs, flexion-extension films, and CT scans of each patient. The reconstructed CT scans proved to be the most useful method of determining the success of the arthrodesis. Bridging trabecular bone seen on the coronal and sagittal reconstructed images was the final arbiter for determining whether a successful fusion had occurred (Figs. 10 and 11). Only gross motion from a pseudarthrosis could be seen on the flexion-extension films and was seen best as a change in lucency between vertebral body and cage during the flexion-extension sequence. Finally, the question of how a patient with an arthrodesis that appears solid radiographically but who has persistent pain should be treated remains undetermined. In several instances in this study, the treating surgeon elected to proceed with a posterior instrumented fusion in the face of persistent pain and a successful arthrodesis. By the treating clinician's statement, these patients were noted to have pseudarthrosis. However, there is no accurate way to determine whether these were true radiographic pseudarthroses. In fact, only approximately half of the patients who went on to have posterior instrumentation for a presumed pseudarthrosis achieved significant pain relief. Less than half (40%) achieved pain improvement of 15 points or greater. Despite these rigorous criteria for determining successful fusion, we were able to obtain a very high rate of radiographic success.

The mean improvements in Oswestry score (29.0 and 29.5 points) are among the highest improvements reported. We believe this is due, in part, to the successful

combination of anterior approach, threaded tapered titanium fusion cages, and a high degree of successful arthrodesis.

rhBMP-2 is a promising method of facilitating anterior intervertebral spinal fusion and of decreasing pain and improving clinical outcomes after anterior lumbar fusion when used with the LT-CAGE™ device. The use of rhBMP-2 is associated with high fusion rates without the need for harvesting bone from the iliac crest and exposing the patient to the adverse effects associated with that procedure. The combination of the threaded tapered fusion cage and rhBMP-2 may be efficacious in the treatment of challenging patients, such as smokers and those with associated medical disabilities. The use of rhBMP-2 is associated with high fusion rates without the need for harvesting bone graft from the iliac crest and exposing the patient t the adverse effects associated with that procedure.

REFERENCES

1. Beimborn DS, Morrissey MC: A review of the literature related to trunk muscle performance. *Spine* 13:655-660, 1988.

2. Blumenthal SL, Baker J, Dossett A, Selby DK. The role of anterior lumbar fusion for internal disc disruption. Spine 1988;13:566-9.

3. Boden SD, Schimandle JH, Hutton WC. 1995 Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 1995;20:2633-44.

4. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25:376-81.

5. Boyd, L.M.; Estes, B.T. and Liu M. "Biomechanics of Lumbar Interbody Constructs, *Effect of Design and Materials*." Chirurgie Endoscopique et Mini-invasive du Rachis. Ed. Husson JL, LeHuec JC. Sauramps Médical. Montpelier, France. pp 181-92, 1999.

6. Burkus JK, Foley K, Haid R, LeHuec JC. Surgical Interbody Research Group – radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. Neurosurg Focus 2001;10:1-9.

7. Crock HV. Anterior lumbar interbody fusion: indications for its use and notes on surgical technique. Clin Orthop 1982;165:157-63.

8. Flynn JC, Hoque MA. Anterior fusion of the lumbar spine. End result study with long-term follow-up. J Bone Joint Surg 1979;61A:1143-50.

9. Goldner JL, Urbaniak JR, McCollom DE: Anterior excision and interbody spinal fusion for chronic low back pain. *Orthop Clin North Am* 2:543-568, 1971

10. Harmon PH. Anterior excision and vertebral fusion operation for intervertebral disc syndromes of the lower lumbar spine: three to five year results in 244 cases. Clin Orthop 1963;26:107-27.

11. Hecht BP, Fischgrund JS, Herkowitz HN, Penman L, Toth JM, Shirkhoda A. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999;24:629-36.

12. Jonsson B: The functions of individual muscles in the lumbar part of the spinae muscle. *Electromyography* 10:5-21, 1970.

13. Kahanovitz N, Viola K, Gallagher M: Long term strength assessment of postoperative diskectomy patients. *Spine* 14:402-403,1989.

14. Lane JD, Moore ES. Transperitoneal approach to the intervertebral disc in the lumbar area. Annals of Surgery 1948;127:537-51.

15. Loguidice VA, Johnson RG, Guyer RD, Stith WJ, Ohnmeiss DD, Hochschuler SH, Rashbaum RF. Anterior lumbar interbody fusion. Spine 1988;13:366-9.

16. Leong JC, Chun SY, Grange WJ, Fang D: Long-term results of lumbar intervertebral disc prolapse. Spine 1983;8:793-9.

17. Penta M, Sandhu A, Fraser RD: Magnetic resonance imaging assessment of disc degeneration 10 years after anterior lumbar interbody fusion. *Spine* 20: 743-747, 1995.

18. Rantanen J, Hurme M, Falck B, Alaranta H, Nykvist F, Lehto M, Einola S, Kalimo H: The lumbar multifidus muscle five years after surgery for a lumbar intervertebral disc herniation. *Spine* 18:568-574, 1993.

19. Sacks S. Anterior interbody fusion of the lumbar spine. J Bone Joint Surg [Br] 1965;47:211-23.

20. Sandhu HS, Kanim LEA, Toth JM, et al. Experimental spinal fusion with recombinant human bone morphogenetic protein-2 without decortication of osseous elements. Spine 1997;22:1171-80.

21. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995; 20:1326-37.

22. Sihvonen T, Herno A, Paljarvi L, Airaksinen O, Partanen J, Tapaninaho A: Local denervation atrophy of paraspinal muscles in postoperative failed back syndrome. *Spine* 18:575-581, 1993.

23. Stauffer RN, Coventry MB. Anterior interbody lumbar spine fusion. J Bone Joint Surg [Am]1972;54:756-68.

24. Urist MR. Bone: Formation by autoinduction. Science 1965;150:893-9.

25. Zdeblick TA: personal communication.

Table 1. Data obtained in 279 patients undergoing ALIF for degenerative disc disease.

Variable	Investigational (n=143)	Control (n=136)	*P* value *
Age (yrs.)			
n	143	136	0.369
Mean	43.3	42.3	
Weight (lbs.)			
n	143	134	0.639
Mean	179.1	181.1	
Sex [n (%)]			
Male	78 (54.5)	68 (50.0)	0.473
Female	65 (45.5)	68 (50.0)	
Workers' Compensation [n (%)]			
	47 (32.9)	47 (34.6)	0.801
Spinal Litigation [n (%)]	18 (12.6)	22 (16.2)	0.400
Tobacco Used [n (%)]	47 (32.9)	49 (36.0)	0.615
Preop Work Status [n (%)]	68 (47.6)	50 (36.8)	0.071
Working			

*For continuous variables, *P* values are from ANOVA. For categorical variables, *P* values are from Fisher's exact test or chi-square test.

 Deleted: 07/04/02

Table 2. Patient accountability in investigational and control group patients at intervals in the follow-up period.

Investigational (rhBMP-2) Group

	Preop	Surgery	6 Weeks	3 Months	6 Months	12 Months	24 Months
Theoretical Follow-up[1]	143	143	143	143	143	143	143
Deaths (Cumulative)	0	0	0	0	0	0	0
Failures[2] (Cumulative)	0	0	1 (1)	0 (1)	3 (4)	1 (5)	4 (9)
Expected[3]	143	143	142	142	139	138	133
Number Evaluated	143	143	141	141	137	133	123
Percent Follow-up	100.0%	100.0%	99.3%	99.3%	98.6%	96.4%	92.5%

Control (autograft) Group

	Preop	Surgery	6 Weeks	3 Months	6 Months	12 Months	24 Months
Theoretical Follow-up[1]	136	136	136	136	136	136	136
Deaths (Cumulative)	0	0	0	0	0	1	1
Failures[2] (Cumulative)	0	0	0	0	1 (1)	4 (5)	7 (12)
Expected[3]	136	136	136	136	135	130	120
Number Evaluated	136	136	134	134	133	126	109
Percent Follow-up	100.0%	100.0%	98.5%	98.5%	98.5%	96.9%	90.8%

[1] Theoretical = Patients who have entered the follow-up window.
[2] Failures include device removals, revisions and supplemental fixations.
[3] Expected = Theoretical – Cumulative Deaths – Cumulative Failures

Deleted: 07/04/02

Table 3. Comparison of surgical data between groups.

Variable	Investigational (n=143)	Control (n=136)
Operative Time (hrs)		
n	143	136
Mean	1.6	2.0
Blood Loss (mL)		
n	142	136
Mean	109.8	153.1
Hospital Stay (days)		
n	143	136
Mean	3.1	3.3
Treatment Levels [n (%)]		
L4-L5	37 (25.9)	32 (23.5)
L5-S1	106 (74.1)	103 (75.7)
L5-L6	0 (0.0)	1 (0.7)
Operative Approach [n (%)]		
Retroperitoneal	116 (81.1)	110 (80.1)
Transperitoneal	27 (18.9)	26 (19.1)

Deleted: 07/04/02

Table 4. Comparison of mean iliac crest graft site pain and appearance scores between groups.

Period	Variable	Control
Discharge	Pain Score	
	n	134
	Mean	12.7
	P value[1]	<0.001
	Appearance of Graft Site	
	Poor[2]	13 (9.8)
6 Weeks	Pain Score	
	n	132
	Mean	6.7
	P value	<0.001
	Appearance of Graft Site	
	Poor	5 (3.8)
3 Months	Pain Score	
	n	134
	Mean	3.5
	P value	<0.001
	Appearance of Graft Site	
	Poor	3 (2.3)
6 Months	Pain Score	
	n	132
	Mean	2.6
	P value	<0.001
	Appearance of Graft Site	
	Poor	5 (3.8)
12 Months	Pain Score	
	n	130
	Mean	2.1
	P value	<0.001
	Appearance of Graft Site	
	Poor	5 (3.8)
24 Months	Pain Score	
	n	117
	Mean	1.8
	P value	<0.001
	Appearance of Graft Site	
	Poor	3 (2.6)

[1] *P* values are from Student's *t* test comparing mean with zero.

Deleted: 07/04/02

[2] Poor= "It bothers me very much."

Table 5. Comparison of mean Oswestry low back pain disability scores between groups.

Period	Variable	Investigational	Control
Preoperative			
	n	143	136
	Mean	53.7	55.1
6 Weeks			
	n	140	131
	Mean	42.1	41.4
Improvement from Preoperative			
	Mean	11.4	13.6
	P value[1]	<0.001	<0.001
3 Months			
	n	141	134
	Mean	33.5	34.2
Improvement from Preoperative			
	Mean	19.9	20.8
	P value	<0.001	<0.001
6 Months			
	n	136	131
	Mean	29.3	29.4
Improvement from Preoperative			
	Mean	24.4	25.4
	P value	<0.001	<0.001
12 Months			
	n	130	125
	Mean	25.5	25.6
Improvement from Preoperative			
	Mean	27.7	28.9
	P value	<0.001	<0.001
24 Months			
	n	122	108
	Mean	23.9	23.8
Improvement from Preoperative			
	Mean	29.0	29.5
	P value	<0.001	<0.001

[1] *P* values for change from preoperative in each group are from paired t-test

Deleted: 07/04/02

Table 6. Comparison of neurologic outcomes between groups.

Period	Variable	Investigational (n=143) n (%)	Control (n=136) n (%)
6 Weeks	Overall		
	Success	110 (80.3)	108 (83.7)
	Failure	27 (19.7)	21 (16.3)
3 Months	Overall		
	Success	119 (84.4)	103 (77.4)
	Failure	22 (15.6)	30 (22.6)
6 Months	Overall		
	Success	106 (77.9)	106 (80.9)
	Failure	30 (22.1)	25 (19.1)
12 Months	Overall		
	Success	108 (81.8)	105 (84.7)
	Failure	24 (18.2)	19 (15.3)
24 Months	Overall		
	Success	101 (82.8)	90 (83.3)
	Failure	21 (17.2)	18 (16.7)

Table 7. Comparison of mean back pain scores between groups.

Period	Variable	Investigational	Control
Preoperative	n	143	136
	Mean	15.8	16.1
6 Weeks	n	139	132
	Mean	9.3	8.8
Improvement from Preoperative	Mean	6.5	7.4
	P value[1]	<0.001	<0.001
3 Months	n	140	134
	Mean	8.7	9.0
Improvement from Preoperative	Mean	7.1	7.1
	P value	<0.001	<0.001
6 Months	n	136	131
	Mean	8.6	8.9
Improvement from Preoperative	Mean	7.3	7.1
	P value	<0.001	<0.001
12 Months	n	129	125
	Mean	8.0	8.4
Improvement from Preoperative	Mean	7.8	7.6
	P value	<0.001	<0.001
24 Months	n	122	108
	Mean	7.3	7.9
Improvement from Preoperative	Mean	8.4	8.1
	P value	<0.001	<0.001

[1] *P* values for change from preoperative in each group are from paired t-test

Table 8. Comparison of back pain success rates between groups.

Variable	Investigational n (%)	Control n (%)
6 Weeks		
Success	107/139 (77.0)	101/132 (76.5)
Failure	32/139 (23.0)	31/132 (23.5)
3 Months		
Success	103/140 (73.6)	105/134 (78.4)
Failure	37/140 (26.4)	29/134 (21.6)
6 Months		
Success	106/136 (77.9)	94/131 (71.8)
Failure	30/136 (22.1)	37/131 (28.2)
12 Months		
Success	102/129 (79.1)	91/125 (72.8)
Failure	27/129 (20.9)	34/125 (27.2)
24 Months		
Success	91/122 (74.6)	85/108 (78.7)
Failure	31/122 (25.4)	23/108 (21.3)

Table 9. Comparison of mean leg pain scores between groups.

Period	Variable	Investigational n = 143	Control n = 136
Preoperative			
	n	143	136
	Mean	12.5	12.5
6 Weeks			
	n	139	132
	Mean	7.5	8.4
Improvement from Preoperative	n	139	132
	Mean	5.1	4.1
	P value[1]	<0.001	<0.001
3 Months			
	n	140	134
	Mean	6.8	6.8
Improvement from Preoperative	n	140	134
	Mean	5.6	5.6
	P value	<0.001	<0.001
6 Months			
	n	136	131
	Mean	6.3	6.3
Improvement from Preoperative	n	136	131
	Mean	6.4	6.3
	P value	<0.001	<0.001
12 Months			

	n	129	125
	Mean	6.3	6.6
Improvement from Preoperative	n	129	125
	Mean	6.4	5.6
	P value	<0.001	<0.001
24 Months			
	n	122	108
	Mean	6.3	6.3
Improvement from Preoperative	n	122	108
	Mean	6.5	5.9
	P value	<0.001	<0.001

[1] *P* values for change from preoperative in each group are from paired t-test.

Deleted: 07/04/02

Table 10. Comparison of work status between groups.

Period	Variable	Investigational n (%)	Control n (%)
3 Months	Working	54 (38.3)	38 (28.4)
	Not Working	42 (29.8)	43 (32.1)
	Was Not Working Before Surgery	45 (31.9)	53 (39.6)
6 Months	Working	69 (50.7)	60 (45.5)
	Not Working	25 (18.4)	29 (22.0)
	Was Not Working Before Surgery	42 (30.9)	43 (32.6)
12 Months	Working	72 (55.0)	63 (50.4)
	Not Working	20 (15.3)	19 (15.2)
	Was Not Working Before Surgery	39 (29.8)	43 (34.4)
24 Months	Working	80 (66.1)	60 (56.1)
	Not Working	11 (9.1)	13 (12.1)
	Was Not Working Before Surgery	30 (24.8)	34 (31.8)

Table 11. Comparison of radiographic fusion rates between groups.

Variable	Investigational (n=143) n (%)	Control (n=136) n (%)
6 Months		
Success	128/132 (97.0)	115/120 (95.8)
Failure	4/132 (3.0)	5/120 (4.2)
12 Months		
Success	127/131 (96.9)	112/121 (92.6)
Failure	4/131 (3.1)	9/121 (7.4)
24 Months		
Success	120/127 (94.5)	102/115 (88.7)
Failure	7/127 (5.5)	13/115 (11.3)

LEGEND OF FIGURES

Figure 1: Comparison of average donor site hip pain scores between groups.

Figure 2: Percentage of control group patients with donor site hip pain.

Figure 3: Comparison of average Oswestry scores between groups.

Figure 4: Comparison of average low back pain scores between groups.

Figure 5. Comparison of average leg pain scores between groups.

Figure 6. Comparison of work status between groups.

Figure 7. Comparison of fusion rates between groups.

Figure 8: Postoperative standing lateral radiograph shows centrally placed LT-CAGE™ fusion devices in the L5-S1 disc space and restoration of disc space height.

Figure 9: Standing lateral radiograph at 24 months after surgery shows anatomic disc space height at the L5-S1 interspace with no evidence of subsidence of the implants. New bone formation is seen anterior to the implants (arrows).

Figure 10: Thin-cut 1-mm CT scan sagittal reconstruction immediately following surgery shows no bone formation within the LT-CAGE™.

Figure 11: Thin-cut 1-mm CT scan sagittal reconstruction at 24 months after surgery shows new bone formation within the LT-CAGE™ device and new bone formation anterior and posterior to the cage but within the confines of the disc space.

From: Ken Burkus[redacted]
Sent: Tuesday, October 1, 2002 11:59:32 AM
To: Rick Treham[redacted] Joseph Pizzurro[redacted]
Subject: ALL BMP Outcome manuscript

Attachments: Tables in question.doc

Rick and Joe,

Thank you for all of your help and support.

The final changes to the TABLES for the "All BMP Outcomes" can go directly to **Carol Binns**.

Once those issues are behind us, we can submit the manuscript straight away.

Best regards,
Ken Burkus

----- Original Message -----
From: Carol Binns
To: JKB[redacted]
Cc: Sanders, Lynn ; Earnest, Vicki
Sent: Tuesday, October 01, 2002 12:12 PM
Subject: Re: Medscape chapters

Dr. Burkus,
I'm thankful we found Donna Siegfried to use in a freelance capacity. She may save my sanity. She pays careful attention to detail (a nit-picker) and has good experience with the publication process. When one of our staff physicians (who shall remain nameless) threw her revision full of author queries back at me and said, "Carol, I don't want to do all that. You just fix it like you always do," I knew she could be of help on some of your papers. I will be checking her work closely, but she will be able to do more on her own with experience. I passed along your appreciation...and mine...to her.

All I am waiting on before sending the "All BMP Outcomes" paper in is the answers to my questions regarding the tables from you and the figures, which are on the way from Carol Capers.

> ---- Original Message ----
> **From:** JKB[redacted]
> **To:** Carol Binns
> **Sent:** Tuesday, October 01, 2002 1:04 AM
> **Subject:** Medscape chapters
>
> Carol,
>
> Thanks for all of your help. Give my regards to Donna.
>
> I am working on the Medscape chapter 1 that you sent me.
>
> I have **already redone** the Fusion Assessment Chapter. I believe that is Chapter 6. So do not work on that one. I will send it to you when I find again - I think it is on my office computer.
>
> I greatly appreciate all of the help that you are providing the remaining chapters.
>
> Best regards,
> Ken Burkus

Table 2. Demographic information.

QQ AU: Asterisk must have a footnote. ANOVA? XQQ

Variable [n(%)]	InFUSE™ Open (N=143)	InFUSE™ Lap (N=134)	InFUSE™ Total (N=277)	Autograft Open (N=136)	Autograft Lap (N=266)	Autograft Total (N=402)	*p*-value* InFUSE vs Autograft
Age (yrs.)							
n	143	134	277	136	266	402	.007
Mean	43.3	42.4	42.9	42.3	40.0	40.8	
SD	9.8	10.5	10.2	9.7	9.6	9.7	
Height (in.)							
n	143	134	277	135	262	397	.216
Mean	68.1	67.5	67.8	68.0	68.3	68.2	
SD	4.2	4.0	4.1	4.2	3.9	4.0	
Weight (lbs.)							
n	143	134	277	134	264	398	.146
Mean	179.1	169.8	174.6	181.1	177.6	178.8	
SD	33.1	38.3	36.0	37.0	37.9	37.6	
Sex [n(%)]							
Male	78 (54.5)	57 (42.5)	135 (48.7)	68 (50.0)	142 (53.4)	210 (52.2)	.391
Female	65 (45.5)	77 (57.5)	142 (51.3)	68 (50.0)	124 (46.6)	192 (47.8)	
Marital Status [n(%)]							
Single	24 (16.8)	24 (17.9)	48 (17.3)	18 (13.2)	52 (19.5)	70 (17.4)	.983
Married	95 (66.4)	91 (67.9)	186 (67.1)	91 (66.9)	177 (66.5)	268 (66.7)	
Divorced	18 (2.6)	14 (10.4)	32 (11.6)	20 (14.7)	30 (11.3)	50 (12.4)	
Separated	5 (3.5)	2 (1.5)	7 (2.5)	5 (3.7)	5 (1.9)	10 (2.5)	
Widowed	1 (0.7)	3 (2.2)	4 (1.4)	2 (1.5)	2 (0.8)	4 (1.0)	
Education Level [n(%)]							
< High School	13 (9.1)	7 (5.2)	20 (7.2)	17 (12.6)	25 (9.5)	42 (10.6)	.277
High School	45 (31.5)	39 (29.1)	84 (30.3)	39 (28.9)	86 (32.7)	125 (31.4)	
> High School	85 (59.4)	88 (65.7)	173 (62.5)	79 (58.5)	152 (57.8)	231 (58.0)	
Workers' Compensation [n(%)]							
Yes	47 (32.9)	42 (31.3)	89 (32.1)	47 (34.6)	89 (33.7)	136 (34.0)	.620
No	96 (67.1)	92 (68.7)	188 (67.9)	89 (65.4)	175 (66.3)	264 (66.0)	
Spinal Litigation [n(%)]							
Yes	18 (12.6)	11 (8.2)	29 (10.5)	22 (16.2)	29 (11.1)	51 (12.8)	.398
No	125 (87.4)	123 (91.8)	248 (89.5)	114 (83.8)	233 (88.9)	347 (87.2)	
Tobacco Used [n(%)]							
Yes	47 (32.9)	40 (29.9)	87 (31.4)	49 (36.0)	83 (31.2)	132 (32.8)	.738
No	96 (67.1)	94 (70.1)	190 (68.6)	87 (64.0)	183 (68.8)	270 (67.2)	
Alcohol Use [n(%)]							
Yes	39 (27.3)	66 (49.3)	105 (37.9)	43 (31.6)	94 (35.3)	137 (34.1)	.328
No	104 (72.7)	68 (50.7)	172 (62.1)	93 (68.4)	172 (64.7)	265 (65.9)	
Preop Work Status [n(%)]							
Working	68 (47.6)	70 (52.2)	138 (49.8)	50 (36.8)	118 (44.5)	168 (41.9)	.050
Not Working	75 (52.4)	64 (47.8)	139 (50.2)	86 (63.2)	147 (55.5)	233 (58.1)	

Table 7. Summary of Oswestry Low Back Pain Disability scores

		InFUSE™			Autograft			*p*-value*
Period	Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	INFUSE vs Autograft
Preoperative	Pain Score							
	n	143	134	277	136	264	400	
	Mean	53.7	52.3	53.0	55.1	46.5	49.4	
	SD	12.7	11.7	12.2	11.8	15.6	15.0	
3 Months	Pain Score							
	n	141	127	268	134	252	386	.0041
	Mean	33.5	30.2	32.0	34.2	33.7	33.9	
	SD	17.6	19.9	18.8	18.5	19.7	19.3	
6 Months	Pain Score							
	n	136	120	256	131	239	370	.0053
	Mean	29.3	25.1	27.3	29.4	29.0	29.1	
	SD	18.8	20.4	19.6	18.2	20.1	19.4	
12 Months	Pain Score							
	n	130	114	244	125	224	349	.0013
	Mean	25.5	20.4	23.1	25.6	25.7	25.7	
	SD	18.2	19.8	19.1	19.1	20.5	20.0	
24 Months	Pain Score							
	n	122	93	215	108	177	285	.0023
	Mean	23.9	18.7	21.7	23.8	22.7	23.1	
	SD	18.8	19.3	19.2	20.7	20.9	20.8	

** One-sided *p*-values are from analysis of covariance with the model including bone graft type, surgical approach, and their interaction, adjusting the seven prognostic covariates. **QQ AU: Should this be a single asterisk? XQQ**

Table 8. Summary of SF-36 Health Survey scores

		InFUSE™			Autograft			*p*-value*
Period	Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	INFUSE vs Autograft
Preoperative	PCS							
	n	142	134	276	136	263	399	
	Mean	27.7	28.3	28.0	29.4	29.5	29.5	
	SD	5.7	6.1	5.9	6.2	7.3	6.9	
	Pain Index							
	n	143	134	277	136	263	399	
	Mean	21.8	22.6	22.2	22.7	24.7	24.1	
	SD	11.1	13.4	12.2	13.6	14.7	14.3	
3 Months	PCS							
	n	140	127	267	133	249	382	.0015
	Mean	36.6	37.3	36.9	35.9	35.1	35.4	
	SD	9.7	10.2	10.0	9.4	9.8	9.7	
	Pain Index							
	n	141	127	268	134	250	384	.0002
	Mean	47.4	50.4	48.8	44.1	43.4	43.6	
	SD	23.8	22.5	23.2	23.3	22.3	22.6	
6 Months	PCS							
	n	136	119	255	131	234	365	.0004
	Mean	39.4	41.0	40.1	38.6	37.8	38.1	
	SD	11.3	11.8	11.5	10.9	11.2	11.1	
	Pain Index							
	n	136	120	256	131	236	367	.0002
	Mean	53.0	54.8	53.8	50.5	46.3	47.8	
	SD	27.8	25.4	26.7	24.4	23.8	24.1	
12 Months	PCS							
	n	131	113	244	125	223	348	.0003
	Mean	41.3	43.4	42.3	40.8	40.0	40.3	
	SD	11.0	11.9	11.5	12.1	12.1	12.1	
	Pain Index							
	n	131	113	244	125	223	348	.0002
	Mean	55.0	60.8	57.7	53.5	52.1	52.6	
	SD	26.6	27.8	27.3	26.0	26.0	26.0	
24 Months	PCS							
	n	122	94	216	108	177	285	.0007
	Mean	42.4	45.0	43.6	42.1	42.5	42.4	
	SD	11.9	11.5	11.8	12.8	12.3	12.4	
	Pain Index							
	n	122	95	217	108	177	285	.0008
	Mean	58.5	63.9	60.9	56.4	57.1	56.8	
	SD	27.6	26.2	27.1	28.9	27.4	27.9	

** One-sided *p*-values are from analysis of covariance with the model including bone graft type, surgical approach, and their interaction, adjusting the seven prognostic covariates. **QQ AU: Should this be a single asterisk? XQQ**

PCS = Physical component score

Table 10. Summary of time-to-event analysis for days to return to work (mean in days).

QQ AU: Why are there no entries under Preoperative Work Status? XQQ

QQ AU: Why are there 2 asterisks in the body of the table and 1 in the footnote? Mistake or am I missing something? XQQ

Preoperative Work Status	InFUSE™			Autograft			*p*-value** INFUSE vs Autograft
	Open	Lap	Total	Open	Lap	Total	
	165.0	89.0	116.0	386.5	154.0	170.5	0.0156

* One-sided *p*-value is from the proportional hazard regression (PHREG) procedure with the model including bone graft type and surgical approach, adjusting preoperative work status and the seven prognostic covariates. The interaction term between bone graft type and surgical approach is not significant and thus is not included.

From: Ken Burkus[redacted]
Sent: Wednesday, December 4, 2002 04:53:54 PM
To: Michael DeMane[redacted]; Peter Wehrly[redacted]; Rick Treharne[redacted]
CC: Bill Martin[redacted]; Joseph Pizzurro[redacted]; Clark Charlton[redacted]; Neil Beals[redacted]; Julie Bearcroft[redacted]
Subject: All BMP Outcomes revised manuscript

Attachments: All BMP Outcomes paper.8.doc

Sirs and Ma'am:

I have attached the revised "All BMP Pooled Data" paper.

The manuscript will be resubmitted in the morning to *The Journal of Spinal Disorders and Techniques.*

Respectfully yours,
J Kenneth Burkus, MD

Is INFUSE™ Bone Graft Superior to Autograft Bone? An Integrated Analysis of Clinical Trials Using the LT-CAGE™ Lumbar Tapered Fusion Device

J. Kenneth Burkus, M.D.*

Stephen E. Heim MD†

Matthew F. Gornet MD‡

Thomas A. Zdeblick MD§

* Staff Physician, Spine Service, The Hughston Clinic, P.C., [redacted]

† Staff Physician, Orthopaedic Associates of DuPage, Warrenville, Illinois

‡Staff Physician, Orthopaedic Center of St. Louis, St. Louis, Missouri

§Chairman, Department of Orthopaedics and Rehabilitation, University of Wisconsin, Madison, Wisconsin

FDA device/drug status: Approved for this indication.

Statement of Financial Relationship: The authors are consultants and clinical investigators for the company distributing the device studied.

Address correspondence and reprint requests to: J. K. Burkus, M.D., The Hughston Clinic, [redacted] Columbus, Georgia 31908-9517

SUMMARY

Multicenter human clinical studies of patients undergoing anterior lumbar fusion have been conducted using recombinant bone morphogenetic protein, or rhBMP-2 on an absorbable collagen sponge, marketed as INFUSE™ Bone Graft, or autograft implanted in the LT-CAGE™ Lumbar Tapered Fusion device. An integrated analysis of multiple clinical studies was performed using an analysis of covariance to adjust for preoperative variables in a total of 679 patients. Of these patients, 277 had their cages implanted with rhBMP-2 on an absorbable collagen sponge, and 402 received autograft transferred from the iliac crest. The patients treated with rhBMP-2 had statistically superior outcomes with regard to length of surgery, blood loss, hospital stay, reoperation rate, median time to return to work, and fusion rates at 6, 12, and 24 months. Oswestry Disability Index scores and the Physical Component Scores and Pain Index of the SF-36 scale at 3, 6, 12, and 24 months showed statistically superior outcomes in the rhBMP-2 group.

Keywords: Anterior lumbar interbody fusion—INFUSE™ Bone Graft—Bone morphogenetic protein—Fusion cage—Degenerative disc disease—Lumbar spine, rhBMP-2

INTRODUCTION

The surgical technique and indications for implanting the LT-CAGE™ Lumbar Tapered Fusion Device (Medtronic Sofamor Danek, Memphis, Tennessee) and reports of outcome measurements in patients in whom it has been implanted have been reported in the literature (1-3). The history, development, and method of use of the protein product, called rhBMP-2 (recombinant human bone morphogenetic protein), used in our study have also been reviewed (4-7). The prospective, randomized trial that lead to the product's approval by showing equivalency in outcome between the INFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, Tennessee) and autograft was published in 2002 (2). INFUSE™ Bone Graft is composed of rhBMP-2 and an absorbable collagen sponge. The advantages to the patient and to the surgeon of not having to create a second surgical site and the complications and pain of iliac crest harvesting have also been reviewed (8).

The purpose of our analysis was to investigate the potential statistical superiority of INFUSE™ Bone Graft to autograft used inside the LT-CAGE™ Lumbar Tapered Fusion Device in surgical parameters, hospital stay, and clinical outcome in single-level spinal fusions. We integrated, or pooled, the results from similar large-scale clinical trials of the same device used for the same indication and measured in the same manner to check for statistical superiority. These data came from both published (2,3) and unpublished studies.

INFUSE™ Bone Graft with the LT-CAGE™ device was approved by the U.S. Food and Drug Administration on July 2, 2002, for treating patients with degenerative

disc disease and up to grade I spondylolisthesis using a single-level anterior spinal fusion procedure. The approval was based primarily on the clinical data from a prospective, randomized, controlled clinical trial that is discussed in detail elsewhere (2). That study used the INFUSE™ Bone Graft with the LT-CAGE™ Tapered Lumbar Fusion Device in the investigational group patients and compared their results with those of the control group patients who received autograft inside the LT-CAGE™ device in open surgical procedures. Wyeth BioPharma, Cambridge, MA, genetically engineered the rhBMP-2 component. The absorbable collagen sponge component is manufactured by Integra LifeSciences, Plainsboro, NJ. Together, the components are distributed commercially under the trade name INFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, TN).

The clinical trial was designed to establish statistical equivalence (noninferiority) between the INFUSE group and autograft group. The fusion success rate in the INFUSE group was 94.5% at 24 months after surgery compared with 88.7% in the autograft group. The probability of noninferiority of INFUSE Bone Graft to autograft was shown to be essentially 100%. The probability of superiority was 90.2%, which, albeit high, did not meet the minimum superiority criterion of 95% predefined in the prospective, randomized protocol. Fusion superiority was not shown probably because of insufficient sample size and, therefore, insufficient statistical power because that clinical trial was designed and sized only to show equivalence. Because the number of patients enrolled in that single study was not adequate to demonstrate statistical superiority, we combined the patient data from that randomized study with two additional studies to assess the statistical superiority of the results in the INFUSE patients over those in the autograft controls.

METHODS

Our analysis combines data sets from a published randomized trial (2) that had two arms with those from two additional clinical trials to increase the sample size and statistical power. Patients who were included in the open trials were randomly assigned in **a 1 : 1 manner** to one of two groups: the investigational group, which received INFUSE, or the control group, which received autogenous iliac crest bone graft. These two additional patient data sets were from studies in which the fusion cage was implanted laparoscopically. One of these two patient data sets is from the clinical trial in which INFUSE™ Bone Graft was used with the LT-CAGE™ Tapered Lumbar Fusion Device and implanted laparoscopically. This study used the identical inclusion-exclusion criteria and procedures as the prospective randomized open study. A portion of the results of this study from one site has been published (3). The second set of additional patient data comes from another clinical trial in which autograft and the LT-CAGE™ device were inserted using a laparoscopic surgical approach to treat single-level degenerative disc disease. The main inclusion-exclusion criteria for these patients were identical to those for the patients in the randomized trial and the other laparoscopic arm of the study with the minor exception of not having a minimum Oswestry low back pain disability score for entry as was required for the other three sets of patients. These four prospective, multi-center clinical studies are summarized in Table 1. All patients were entered into these studies between 1996 and 1999.

Surgical Techniques

All open surgical procedures were performed using a mini-ALIF approach. A retroperitoneal or a transperitoneal approach to the lumbosacral spine was carried out

through a left paramedian abdominal incision. The anterior portion of the L4-5 or L5-S1 disc space was exposed after mobilization of the great vessels. A box incision of the annulus fibrosus was completed, and a complete lumbar discectomy was carried out under direct visualization. Great care was taken to remove the cartilaginous end plates while preserving the bone end plates. Dilators were used for sequential distraction of the interspace. The vertebral end plates were reamed symmetrically to a depth of 1.5mm. The tapered fusion devices were placed symmetrically in the disc space, and the cages were packed with either autogenous bone graft or InFUSE.

In the laparoscopic groups, the lumbosacral spine was approached through a transperitoneal portal. Channel discectomies were followed by disc space distraction. Using a method similar to that in the open mini-ALIF approach, the vertebral end plates were reamed symmetrically to a depth of 1.5mm. The tapered fusion devices were packed with autogenous graft or InFUSE and were inserted sequentially into the disc space.

Clinical Studies

The two treatment factors in these four patient data sets are bone graft type (INFUSE™ Bone Graft or autograft) and the surgical approach (open or laparoscopic). Our goal was to compare and analyze the results in the patients who received INFUSE™ Bone Graft with those in the patients who received autograft. The results from the two surgical approaches were pooled and the effects of surgical approach, if any, such as at early time points, were statistically adjusted so as not to affect the comparison between the graft types. Thus, our analysis compared the results of 277 INFUSE™ Bone Graft patients with 402 autograft patients. All of the 679 patients had degenerative disc disease with up to grade 1 spondylolisthesis. All patients had two LT-CAGE devices implanted

anteriorly at one lumbar level, and all were included in prospective, multi-centered studies using the same outcome measurement tools and methodology of analysis (Figure 1). More than 60 surgeons at 36 different sites enrolled the 679 patients. No single surgeon performed more than 10% of the cases. Hence, the outcomes represent typical results from a wide variety of surgeons with different degrees of experience.

Because not all of the four prospectively studied groups had a randomized control, the patients' demographic characteristics and prognostic factors could be different among the groups. Tables 2, 3, and 4 summarize demographic information, preoperative medical condition and medication usage, and preoperative measurements of several clinical endpoints, respectively. Among approximately 20 summarized variables, seven were found to be significantly different between the combined INFUSE group and the combined autograft group.

Statistical Analysis

The seven variables that were found to have statistically significant differences were age, previous back surgery, preoperative non-narcotic medication use, weak-narcotic medication use, muscle relaxant medication use, preoperative low back pain score on the Oswestry Disability Index, and preoperative SF-36 Physical Component Score. Because these seven prognostic factors could potentially affect the clinical outcomes and therefore confound the analysis of a study between the INFUSE and autograft groups, a statistical technique called analysis of covariance (ANCOVA) was performed. With the use of this statistical methodology, the influences of these prognostic factors were adjusted for, and comparisons could then be made between the INFUSE and autograft results. In essence, this statistical method makes it possible to have both groups

start at the same level statistically for these seven factors before any differences in outcome are compared.

RESULTS

The statistical analyses of operative time, blood loss, and hospital stay for the INFUSE and autograft groups are shown in Table 5. These analyses reveal superior ($p<$ .05) benefits of the combined INFUSE group compared with the autograft group for all three variables. The INFUSE group had an average of 0.9 hours (54 minutes) shorter surgery time, lost an average of 66 mL less blood (probably because of the shorter surgery time and not having a second surgery site), and, on average, left the hospital nearly a day (0.9) earlier than the autograft group. No differences were found between the L4-5 and L5-S1 treated patients.

The fusion success rate in the combined INFUSE group was 94.4% (201/213) at 24 months after surgery compared with 89.4% (252/282) in the autograft group (Table 6). No differences were found between the L4-5 and L5-S1 treated patients. This 5-percentage point difference was shown to be statistically significant by an analysis of covariance, with an adjusted p-value of .022. In short, fusion, the primary goal of performing the original surgery, was found to be statistically superior for the INFUSE patients.

In the combined INFUSE group, preoperative low back pain scores on the validated Oswestry Disability Index improved significantly over those in the autograft group for all time points—3, 6, 12, and 24 months—in the study (Table 7). No differences were found between the L4-5 and L5-S1 treated patients. The adjusted p-values were all highly significant.

The Physical Component and Pain Index scores of the SF-36 Health Survey, which measures a patient's physical well being after surgery, are shown in Table 8. As with the Oswestry Disability Index low back pain scores, the results showed the statistical superiority of the combined INFUSE group to the autograft group for all time points after surgery.

Additional surgical events in the study patients are summarized in Table 9. Simple Fisher's exact tests show that the combined INFUSE groups had statistically fewer reoperations than patients who were implanted with autograft (p=.0036). At the two-year time point used in the study, the revision rate in INFUSE patients approached statistical superiority (p=.0631). No differences were found between the L4-5 and L5-S1 treated patients.

Although the difference was not statistically significant, 103 (74.6%) of the INFUSE patients who were working before surgery, returned to work after surgery compared with 109 (64.9%) patients in the autograft group. Again although not statistically significant, 49 (35.3%) of the INFUSE patients who were not working before surgery returned to work after surgery compared with 73 (31.3%) of the autograft patients. The difference that was found to be statistically significant was the time it took for the patients to return to work. A summary of time-to-event type analysis of return to work is contained in Table 10. The statistical comparison between the INFUSE and autograft groups was adjusted by the preoperative work status, the seven prognostic covariates, and the surgical approach. The median days to return to work was 54.5 days shorter for the LT-CAGE patients implanted with INFUSE Bone Graft. This finding was statistically significant in favor of the INFUSE patients (adjusted p-value = .0156).

DISCUSSION

Surgeons have long sought to find the best way to fuse two bones. Although allograft bone has been used with some degree of success, transplanting living bone from one part of the body to another has become the "gold standard" by which all other procedures are measured (8). Disadvantages to autogenous bone graft harvesting are well known. Clinical trials have shown there is increased operative time, increased blood loss, cosmetic disfigurement, and pain associated with iliac crest bone graft **harvesting (1,2,3,8).** Finding a substitute for human tissue has also been a noble goal of researchers for decades, and finding a bone graft substitute to replace autogenous bone seemed at times an impossible task. What material could researchers develop that would be better than a naturally occurring material?

Since the discovery of bone morphogenetic proteins (BMP) by Dr. Marshall Urist in 1965 (9), his dream, and those of many others, was to have BMP available in operating rooms as a safe and effective replacement for autograft. In July 2002, his dream became a reality in the United States with the FDA approval of rhBMP-2, a recombinant version of one of the family of BMPs. His goal, and the goal of other researchers like him, was for the substitute to be equal to autograft so harvesting of autograft bone from other parts of the body would no longer be necessary. Preclinical studies (5,6,10-14) have indicated the possibility that osteoinductive protein-containing materials may be superior to autograft in some applications and for some outcome measurements. Wozney (7) suggests that BMP can result in direct intramembranous ossification because in some animal models direct bone formation is observed after administration of the protein. Because chips of transferred autogenous graft may need to be resorbed or be remodeled before fusing and

rhBMP-formed bone does not, this feature may explain why some animal studies had superior results with rhBMP-containing grafts when compared with autograft.

INFUSE must be used with a cage or some type of supportive structure within the vertebral interspace. The rhBMP-2 protein is applied to an absorbable collagen sponge. For this reason, it cannot resist compressive or shear forces within a vertebral motion segment. A supportive biomechanical environment is required for bone formation in the disc space. InFUSE cannot be used as a "stand-alone" device within the disc space.

The question remains: Can any recombinant BMP on any carrier ever be superior to autograft—the gold standard—with regard to operative parameters and clinical outcome in humans? Pilot study results of the LT-CAGE™ Lumbar Tapered Fusion Device in humans (1) and the results from a prospective, randomized study (2) showed a trend toward faster fusion with the INFUSE™ Bone Graft and other data that were comparable with that in the patients who received autograft. We hypothesized that this trend would become a superior outcome in a larger study.

We used the ANCOVA method for an integrated analysis of four, large-scale multicenter sets of patient data. This analysis of prospectively gathered data has answered the question of the superiority of INFUSE™ Bone Graft over autograft for one particular human clinical use. This analysis of 679 patients represents the largest prospective combined study of a single-level anterior procedure using a single device for a single indication in the spinal literature. Because all patients received the same LT-CAGE implants, we had, for the first time, a data set large enough to determine whether INFUSE™ Bone Graft is equivalent to or superior to autograft bone. Because of the large sample size used in this analysis and its subsequent statistical power, the answer is an

unequivocal "yes." The INFUSE patients had statistically superior outcomes in the following categories: shortened surgery time, reduced blood loss, shortened hospital stay, higher fusion rate, better Oswestry Low Back Pain Disability Questionnaire scores at all follow-up intervals, better Physical Component Scores and Pain Index scores on the SF-36 Health Survey at all follow-up intervals, fewer reoperations, and an earlier return to work.

As can be calculated from Table 7, for all postoperative time points, the change from preoperative scores for INFUSE patients was approximately 5 points better than for the autograft control patients, about a 7% to 10% greater improvement from the preoperative score in favor of the INFUSE patients. As can be calculated from Table 8, the PCS scores on the SF-36 scale also had approximately a 12% to 15% greater improvement from the preoperative values in favor of the INFUSE patients than the control patients. Obviously, any statistical decrease in pain at any time point would be considered significant and desirable by the patient. The statistically significant decrease in the INFUSE patients' low back pain must be at least part of the explanation for their returning to work nearly two months earlier than the autograft patients.

The INFUSE patients obviously had none of the pain or problems associated with iliac crest graft harvesting. The elimination of these complications would explain why, in spite of a solid fusion, patients in the autograft group have poor outcomes when compared with those in the INFUSE group. Persistent pain in the autograft groups would also explain reduced outcomes. In one study, iliac crest graft site pain was recorded on a separate 20-point numeric rating scale by the patients who discriminated low back pain from iliac crest harvest site pain(2). In the autograft open group, nearly a third (32%) of

the patients continued to have some pain at their harvest site two years after the surgery. In addition to pain, the 402 autograft patients treated with open and laparoscopic surgery, also had a 3.0% chance of a significant graft site complication: 5 (1.25%) had infections at their harvest site, 2 (0.5%) had fractures at the graft site, and 5 (1.25%) had other adverse events related to their harvest site.

We believe these analyses demonstrate the superiority of using INFUSE™ Bone Graft. In fact, we found no disadvantage to using INFUSE™ Bone Graft for the surgical, hospital discharge, and major postoperative outcome measurements discussed. In addition, the INFUSE patients did not have the pain, morbidity, or complications associated with the second surgery of iliac crest graft harvest. The results of this integrated analysis coupled with the comprehensive safety profile for the recombinant human bone morphogenetic protein (rhBMP-2) material used in the study (15) indicates that the use of INFUSE Bone Graft is an effective replacment for autograft bone inside the LT-CAGE device for lumbar spinal fusions.

With its superiority, INFUSE™ Bone Graft may now become the new gold standard for replacing autograft bone inside the LT-CAGE™ device when used for lumbar spinal fusions. INFUSE Bone Graft is now used exclusively for this purpose in our institutions.

ACKNOWLEDGMENTS

The authors thank the more than 60 clinical investigators who provided patients for this study and the Clinical Research group at Medtronic Sofamor Danek for their help in data collection and the statistical analyses.

REFERENCES

1. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25:376-81.
2. Burkus JK, Gornet MF, Dickman C, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. J Spinal Disord **2002;15:337-349**.
3. Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2. A prospective study of clinical and radiographic outcomes. Spine 2001;26:2751-6.
4. Boden SD. Overview of the biology of lumbar spine fusion and principles for selecting a bone graft substitute. Spine 2002;27:S26-31.
5. McKay B, Sandhu HS. Use of recombinant human bone morphogenetic protein-2 in spinal fusion applications. Spine 2002;27(16 Suppl 1):S66-85.
6. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995;20:1326-37.
7. Wozney JM. Overview of bone morphogenetic proteins. Spine 2002;27(16 Suppl 1):S2-8.
8. Vaccaro AR, Kazuhiro C, Heller JG, Patel TC, Thalgott JS, Truumees E, Fischgrund JS, Craig MR, Berta SC, Wang JC. Bone grafting alternatives in spinal surgery. The Spine Journal 2002;2:206-15.
9. Urist MR. Bone: formation by autoinduction. Science 1965;150:893-9.

10. David SM, MD, Gruber HE, Meyer RA, Murakami T, Tabor OB, Howard BA, Wozney JM, Hanley EN. Lumbar spinal fusion using recombinant human bone morphogenetic protein in the canine. A comparison of three dosages and two carriers. Spine 1999;24:1973 –9.

11. Boden SD, Schimandle JH, Hutton WC. The 1995 Volvo award in basic sciences. The use of an osteoconductive growth factor for lumbar spinal fusion. Part II: study of dose, carrier, and species. Spine 1995;20:2633-44.

12. Sandhu HS, Kanim LE, Kabo JM, Toth JM, Zeegen EN, Liu D, Delamarter RB, Dawson EG. Effective doses of recombinant human bone morphogenetic protein-2 in experimental spinal fusion. Spine 1996;21:2115-22.

13. Sandhu HS, Toth JM, Diwan AD, Seim HB, Kanim LE, Kabo JM, Turner AS. Histologic evaluation of the efficacy of rhBMP-2 compared with autograft bone in sheep spinal anterior interbody fusion. Spine 2002;27:567-75.

14. Zdeblick TA, Ghanayem AJ, Rapoff AJ, Swain CS, Bassett T, Cooke ME, Markel M. Cervical interbody fusion cages. An animal model with and without bone morphogenetic protein. Spine 1998;23:758-65.

15. Poynton AR, Lane JM. Safety profile for the clinical use of bone morphogenetic proteins in the spine. Spine 2002;27(16 Suppl 1):S40-8.

Table 1. Summary of study groups analyzed.

Study group	Graft type	Surgical approach	Randomized	Prospective	Number of patients
INFUSE™ Open	INFUSE™	Open	Yes	Yes	143
INFUSE™ Lap	INFUSE™	Laparoscopic	No	Yes	134
Autograft Open	Autograft	Open	Yes	Yes	136
Autograft Lap	Autograft	Laparoscopic	No	Yes	266

Table 2. Demographic information.

Variable [n(%)]	INFUSE™ Open (N=143)	INFUSE™ Lap (N=134)	INFUSE™ Total (N=277)	Autograft Open (N=136)	Autograft Lap (N=266)	Autograft Total (N=402)	*p*-value* INFUSE vs Autograft
Age (yrs.)							
n	143	134	277	136	266	402	.907
Mean	43.3	42.4	42.9	42.3	40.0	40.8	
SD	9.8	10.5	10.2	9.7	9.6	9.7	
Height (in.)							
n	143	134	277	135	262	397	.216
Mean	68.1	67.5	67.8	68.0	68.3	68.2	
SD	4.2	4.0	4.1	4.2	3.9	4.0	
Weight (lbs.)							
n	143	134	277	134	264	398	.146
Mean	179.1	169.8	174.6	181.1	177.6	178.8	
SD	33.1	38.3	36.0	37.0	37.9	37.6	
Sex [n(%)]							
Male	78 (54.5)	57 (42.5)	135 (48.7)	68 (50.0)	142 (53.4)	210 (52.2)	.391
Female	65 (45.5)	77 (57.5)	142 (51.3)	68 (50.0)	124 (46.6)	192 (47.8)	
Marital Status [n(%)]							
Single	24 (16.8)	24 (17.9)	48 (17.3)	18 (13.2)	52 (19.5)	70 (17.4)	.983
Married	95 (66.4)	91 (67.9)	186 (67.1)	91 (66.9)	177 (66.5)	268 (66.7)	
Divorced	18 (2.6)	14 (10.4)	32 (11.6)	20 (14.7)	30 (11.3)	50 (12.4)	
Separated	5 (3.5)	2 (1.5)	7 (2.5)	5 (3.7)	5 (1.9)	10 (2.5)	
Widowed	1 (0.7)	3 (2.2)	4 (1.4)	2 (1.5)	2 (0.8)	4 (1.0)	
Education Level [n(%)]							
< High School	13 (9.1)	7 (5.2)	20 (7.2)	17 (12.6)	25 (9.5)	42 (10.6)	.277
High School	45 (31.5)	39 (29.1)	84 (30.3)	39 (28.9)	86 (32.7)	125 (31.4)	
> High School	85 (59.4)	88 (65.7)	173 (62.5)	79 (58.5)	152 (57.8)	231 (58.0)	
Workers' Compensation [n(%)]							
Yes	47 (32.9)	42 (31.3)	89 (32.1)	47 (34.6)	89 (33.7)	136 (34.0)	.620
No	96 (67.1)	92 (68.7)	188 (67.9)	89 (65.4)	175 (66.3)	264 (66.0)	
Spinal Litigation [n(%)]							
Yes	18 (12.6)	11 (8.2)	29 (10.5)	22 (16.2)	29 (11.1)	51 (12.8)	.398
No	125 (87.4)	123 (91.8)	248 (89.5)	114 (83.8)	233 (88.9)	347 (87.2)	
Tobacco Used [n(%)]							
Yes	47 (32.9)	40 (29.9)	87 (31.4)	49 (36.0)	83 (31.2)	132 (32.8)	.738
No	96 (67.1)	94 (70.1)	190 (68.6)	87 (64.0)	183 (68.8)	270 (67.2)	
Alcohol Use [n(%)]							
Yes	39 (27.3)	66 (49.3)	105 (37.9)	43 (31.6)	94 (35.3)	137 (34.1)	.328
No	104 (72.7)	68 (50.7)	172 (62.1)	93 (68.4)	172 (64.7)	265 (65.9)	
Preop Work Status [n(%)]							
Working	68 (47.6)	70 (52.2)	138 (49.8)	50 (36.8)	118 (44.5)	168 (41.9)	.050
Not Working	75 (52.4)	64 (47.8)	139 (50.2)	86 (63.2)	147 (55.5)	233 (58.1)	

* For continuous variables, *p*-values are from ANOVA, and for categorical variables, they are from Fisher's exact test or the chi-square test.

Table 3. Preoperative medical condition and medication usage [Number (%) of patients]

	INFUSE™			Autograft			*p*-value*
Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	INFUSE vs Autograft
Previous Back Surgery							
Yes	54 (37.8)	33 (24.6)	87 (31.4)	55 (40.4)	110 (41.4)	165 (41.0)	.012
No	89 (62.2)	101 (75.4)	190 (68.6)	81 (59.6)	156 (58.6)	237 (59.0)	
Previous Back Surgery							
1	39 (72.2)	16 (50.0)	55 (64.0)	34 (61.8)	78 (70.9)	112 (67.9)	.574
>1	15 (27.8)	16 (50.0)	31 (36.0)	21 (38.2)	32 (29.1)	53 (32.1)	
Non-narcotic Medications							
Yes	80 (55.9)	97 (72.4)	177 (63.9)	75 (55.1)	109 (41.0)	184 (45.8)	<.001
No	63 (44.1)	37 (27.6)	100 (36.1)	61 (44.9)	157 (59.0)	218 (54.2)	
Weak Narcotic Medications							
Yes	77 (53.8)	61 (45.5)	138 (49.8)	67 (49.3)	90 (33.8)	157 (39.1)	.006
No	66 (46.2)	73 (54.5)	139 (50.2)	69 (50.7)	176 (66.2)	245 (60.9)	
Strong Narcotic Medications							
Yes	31 (21.7)	17 (12.7)	48 (17.3)	33 (24.3)	42 (15.8)	75 (18.7)	.686
No	112 (78.3)	117 (87.3)	229 (82.7)	103 (75.7)	224 (84.2)	327 (81.3)	
Muscle Relaxant Medications							
Yes	45 (31.5)	49 (36.6)	94 (33.9)	37 (27.2)	39 (14.7)	76 (18.9)	<.001
No	98 (68.5)	85 (63.4)	183 (66.1)	99 (72.8)	227 (85.3)	326 (81.1)	

*p-values are from Fisher's exact test.

Table 4. Preoperative evaluations of clinical endpoints

	INFUSE™			Autograft			*p*-value*
Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	INFUSE vs Autograft
Oswestry Pain Score							
n	143	134	277	136	264	400	.001
Mean	53.7	52.3	53.0	55.1	46.5	49.4	
SD	12.7	11.7	12.2	11.8	15.6	15.0	
SF-36 PCS							
n	142	134	276	136	263	399	.004
Mean	27.7	28.3	28.0	29.4	29.5	29.5	
SD	5.7	6.1	5.9	6.2	7.3	6.9	
SF-36 Pain Index							
n	143	134	277	136	263	399	.077
Mean	21.8	22.6	22.2	22.7	24.7	24.1	
SD	11.1	13.4	12.2	13.6	14.7	14.3	

*p-values are from analysis of variance.

Table 5. Surgery information.

Variable	INFUSE™ Open (N=143)	INFUSE™ Lap (N=134)	INFUSE™ Total (N=277)	Autograft Open (N=136)	Autograft Lap (N=266)	Autograft Total (N=402)	p-value* INFUSE vs Autograft
Operative Time (hrs)							
n	143	134	277	136	265	401	<.001
Mean	1.6	1.9	1.8	2.0	3.1	2.7	
SD	0.6	0.9	0.8	0.7	1.4	1.3	
Blood Loss (mL)							
n	142	134	276	136	263	399	.024
Mean	109.8	146.1	127.4	153.1	213.6	192.9	
SD	117.3	406.2	295.3	179.1	493.0	414.4	
Hospital Stay (days)							
n	143	134	277	136	266	402	<.001
Mean	3.1	1.2	2.2	3.3	3.0	3.1	
SD	1.6	1.1	1.7	1.3	3.8	3.2	
Treatment Levels [n (%)]							
L2-L3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	
L3-L4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	2 (0.5)	
L4-L5	37 (25.9)	21 (15.7)	58 (20.9)	32 (23.5)	21 (7.9)	53 (13.2)	
L5-L6	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	2 (0.8)	3 (0.7)	
L5-S1	106 (74.1)	113 (84.3)	219 (79.1)	103 (75.7)	240 (90.2)	343 (85.3)	
Operative Approach [n (%)]							
Retroperitoneal	116 (81.1)	28 (20.9)	144 (52.0)	109 (80.1)	9 (3.4)	118 (29.4)	
Transperitoneal	27 (18.9)	106 (79.1)	133 (48.0)	26 (19.1)	256 (96.2)	282 (70.1)	
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.4)	2 (0.5)	

*p-values are from analysis of variance.

Table 6. Summary of success rates of radiographic fusion [Number (%) of Patients]

	INFUSE™						Autograft						*p*-value*
Variable	Open (N=143)		Lap (N=134)		Total (N=277)		Open (N=136)		Lap (N=266)		Total (N=402)		INFUSE vs Autograft
6 Months													
Success	128	(97.0)	88	(92.6)	216	(95.2)	115	(95.8)	192	(95.5)	307	(95.6)	.633
Failure	4	(3.0)	7	(7.4)	11	(4.8)	5	(4.2)	9	(4.5)	14	(4.4)	
12 Months													
Success	127	(96.9)	95	(94.1)	222	(95.7)	112	(92.6)	202	(93.1)	314	(92.9)	.131
Failure	4	(3.1)	6	(5.9)	10	(4.3)	9	(7.4)	15	(6.9)	24	(7.1)	
24 Months													
Success	120	(94.5)	81	(94.2)	201	(94.4)	102	(88.7)	150	(89.8)	252	(89.4)	.022
Failure	7	(5.5)	5	(5.8)	12	(5.6)	13	(11.3)	17	(10.2)	30	(10.6)	

*One-sided *p*-values are from logistic regression analysis with the model including bone graft type and surgical approach, adjusting the seven prognostic covariates. The interaction term between bone graft type and surgical approach is not significant and thus is not included.

Table 7. Summary of Oswestry Low Back Pain Disability scores

		INFUSE™			Autograft			*p*-value*
Period	Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	INFUSE vs Autograft
Preoperative	Pain Score							
	n	143	134	277	136	264	400	
	Mean	53.7	52.3	53.0	55.1	46.5	49.4	
	SD	12.7	11.7	12.2	11.8	15.6	15.0	
3 Months	Pain Score							
	n	141	127	268	134	252	386	.0041
	Mean	33.5	30.2	32.0	34.2	33.7	33.9	
	SD	17.6	19.9	18.8	18.5	19.7	19.3	
6 Months	Pain Score							
	n	136	120	256	131	239	370	.0053
	Mean	29.3	25.1	27.3	29.4	29.0	29.1	
	SD	18.8	20.4	19.6	18.2	20.1	19.4	
12 Months	Pain Score							
	n	130	114	244	125	224	349	.0013
	Mean	25.5	20.4	23.1	25.6	25.7	25.7	
	SD	18.2	19.8	19.1	19.1	20.5	20.0	
24 Months	Pain Score							
	n	122	93	215	108	177	285	.0023
	Mean	23.9	18.7	21.7	23.8	22.7	23.1	
	SD	18.8	19.3	19.2	20.7	20.9	20.8	

* One-sided *p*-values are from analysis of covariance with the model including bone graft type, surgical approach, and their interaction, adjusting the seven prognostic covariates.

Table 8. Summary of SF-36 Health Survey scores.

		INFUSE™			Autograft			*p*-value*
Period	Variable	Open (N=143)	Lap (N=134)	Total (N=277)	Open (N=136)	Lap (N=266)	Total (N=402)	INFUSE vs Autograft
Preoperative	PCS							
	n	142	134	276	136	263	399	
	Mean	27.7	28.3	28.0	29.4	29.5	29.5	
	SD	5.7	6.1	5.9	6.2	7.3	6.9	
	Pain Index							
	n	143	134	277	136	263	399	
	Mean	21.8	22.6	22.2	22.7	24.7	24.1	
	SD	11.1	13.4	12.2	13.6	14.7	14.3	
3 Months	PCS							
	n	140	127	267	133	249	382	.0015
	Mean	36.6	37.3	36.9	35.9	35.1	35.4	
	SD	9.7	10.2	10.0	9.4	9.8	9.7	
	Pain Index							
	n	141	127	268	134	250	384	.0002
	Mean	47.4	50.4	48.8	44.1	43.4	43.6	
	SD	23.8	22.5	23.2	23.3	22.3	22.6	
6 Months	PCS							
	n	136	119	255	131	234	365	.0004
	Mean	39.4	41.0	40.1	38.6	37.8	38.1	
	SD	11.3	11.8	11.5	10.9	11.2	11.1	
	Pain Index							
	n	136	120	256	131	236	367	.0002
	Mean	53.0	54.8	53.8	50.5	46.3	47.8	
	SD	27.8	25.4	26.7	24.4	23.8	24.1	
12 Months	PCS							
	n	131	113	244	125	223	348	.0003
	Mean	41.3	43.4	42.3	40.8	40.0	40.3	
	SD	11.0	11.9	11.5	12.1	12.1	12.1	
	Pain Index							
	n	131	113	244	125	223	348	.0002
	Mean	55.0	60.8	57.7	53.5	52.2	52.6	
	SD	26.6	27.8	27.3	26.0	26.0	26.0	
24 Months	PCS							
	n	122	94	216	108	177	285	.0007
	Mean	42.4	45.0	43.6	42.1	42.5	42.4	
	SD	11.9	11.5	11.8	12.8	12.3	12.4	
	Pain Index							
	n	122	95	217	108	177	285	.0008
	Mean	58.5	63.9	60.9	56.4	57.1	56.8	
	SD	27.6	26.2	27.1	28.9	27.4	27.9	

* One-sided *p*-values are from analysis of covariance with the model including bone graft type, surgical approach, and their interaction, adjusting the seven prognostic covariates.
PCS = Physical component score

Table 9. Summary of second surgeries.

Type of second surgery	INFUSE™			Autograft			*p*-value* INFUSE™ vs Autograft
	Open	Lap	Total (%)	Open	Lap	Total (%)	
Revisions	0/143	1/134	1/277 (0.36)	0/136	8/266	8/402 (1.99)	.0631
Removals	2/143	2/134	4/277 (1.44)	0/136	7/266	7/402 (1.74)	.5106
Supplemental Fixations	10/143	7/134	17/277 (6.14)	14/136	14/266	28/402 (6.97)	.3970
Reoperations	6/143	2/134	8/277 (2.89)	4/136	28/266	32/402 (7.96)	.0036

*One-sided *p*-values are from Fisher's exact test.

Table 10. Summary of time-to-event analysis for days to return to work (median in days).

INFUSE™			Autograft			*p*-value* INFUSE vs Autograft
Open	Lap	Total	Open	Lap	Total	
165.0	89.0	116.0	386.5	154.0	170.5	0.0156

* One-sided *p*-value is from the proportional hazard regression (PHREG) procedure with the model including bone graft type and surgical approach, adjusting preoperative work status and the seven prognostic covariates. The interaction term between bone graft type and surgical approach is not significant and thus is not included.

LEGEND OF FIGURES

Figure 1. A. Preoperative lateral radiograph shows isolated disc space collapse with radial osteophyte formation at the L5-S1 level. B. Postoperative anteroposterior radiograph and C, lateral radiograph shows the tapered fusion cage in place. Normal disc space height segmental lordosis has been restored at the L5-S1 vertebral interspace.

Figure 2. A. An immediate postoperative (48 hours) sagittal plane, thin-cut (1mm) CT scan reconstruction through the central portion of the LT-CAGE shows the rhBMP-2 soaked collage sponge present in the cage. B. Coronal plain CT scan reconstructions show the cages well placed centrally in the disc space. No autogenous grafts were placed in the interspace.

Figure 3. At 12 months after surgeryy, thin-cut CT scans were repeated. A. Sagittal reconstruction 12 months after surgery through the midportion of the LT-CAGE shows abundant new bone formation throughout the central portion of the cage. B. Coronal reconstructions shows new bone formation through the cages and lateral to the cages. This new bone formation connects the adjacent vertebral end plates.