United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510–6200

March 17, 2006

Via Electronic Transmission

Dr. Andrew C. von Eschenbach
Acting Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. von Eschenbach:

Thank you for scheduling a briefing next Wednesday, March 22, 2006, for my Committee on Finance (Committee) staff regarding the clinical trial the Food and Drug Administration (FDA) approved for a blood substitute called PolyHeme, which is manufactured by Northfield Laboratories, Inc. (the PolyHeme Study).1 The PolyHeme Study was approved by local institutional review boards (IRBs) in 18 states – California, Colorado, Delaware, Georgia, Illinois, Indiana, Kansas, Kentucky, Michigan, Minnesota, New York, North Carolina, Ohio, Pennsylvania, Tennessee, Texas, Utah, and Virginia – and disapproved by an unknown number of IRBs. According to information posted at ClinicalTrials.gov, four of the thirty-one medical institutions participating in the PolyHeme Study have suspended recruiting patients, as of March 10, 2006.[1]

As chairman of the Committee, I request that the FDA officials, who will brief my Committee staff, come prepared to address in detail the issues and arguments raised in a letter published recently in *The American Journal of Bioethics* entitled, "An Open Letter to IRBs Considering Northfield Laboratories' PolyHeme Trial," among other issues related to the PolyHeme Study.

Thank you for your full attention to this urgent matter. Should you have any questions please contact

Sincerely,

Charles E. Grassley
Chairman

Attachment

[1] http://www.clinicaltrials.gov/ct/show/NCT00076648?order=1

xxxx

An Open Letter to IRBs Considering Northfield Laboratories' PolyHeme Trial

Ken Kipnis, University of Hawaii at Manoa, Honolulu
Nancy M.P. King, University of North Carolina School of Medicine, Chapel Hill
Robert M. Nelson, University of Pennsylvania School of Medicine and The Children's Hospital of Philadelphia

At this writing, a widely publicized waived consent trial is underway. Sponsored by Northfield Laboratories, it is intended to evaluate the emergency use of PolyHeme, an oxygen-carrying resuscitative fluid that might prevent deaths from uncontrolled bleeding. The protocol allows patients in hemorrhagic shock to be randomized between PolyHeme and saline in the field and, still without consent, between PolyHeme and blood after arrival at an emergency department. The Federal regulations that govern the waiver of consent restrict its applicability to circumstances where proven, satisfactory treatments are unavailable. Blood—the standard treatment for hemorrhagic shock—is not available in ambulances but is in hospitals. The authors argue that the in-hospital stage of the study fails to meet ethical and regulatory standards.

Some months ago we prepared what was essentially the letter below. Our purpose was to alert Institutional Review Boards (IRBs) to a serious ethical/regulatory error in a widely-publicized waived-consent trial sponsored by Northfield Laboratories. The product is PolyHeme, an oxygen-carrying resuscitative fluid that might prevent deaths from uncontrolled bleeding in the field. The error was the linking of an in-hospital comparison of PolyHeme and blood (which should require informed consent) with a field comparison of PolyHeme and saline, both under the emergency waiver of consent. Although the error had been caught by several IRBs, we were not able to confirm that it had been formally reported to the Food and Drug Administration (FDA)nor that other IRBs considering or approving the protocol had been alerted. Our efforts to obtain a timely list of IRB contacts did not bear fruit. Indeed, we have written a second article (Kipnis et al. 2006) setting out in some detail the barriers we uncovered in trying to correct the error characterized in the letter below.

The three of us—Kenneth Kipnis, Nancy M.P. King and Robert M. Nelson—have been doing research on the ethics of waived-consent trials that are now permitted under 21 CFR 50.24. We have been looking at the most widely publicized example to date: the Northfield PolyHeme study.

It has become evident to us that: 1) there is a serious ethical flaw in this complicated and novel study; and 2) the substance and significance of this criticism may not be reaching those who are now conducting and overseeing the research. We have learned that some IRBs have withheld approval for the reason we highlight below. All three of us have struggled with the question of what our responsibilities are when we conclude that ethically-flawed research is underway. This letter is an effort to reach the IRBs that have approved or are considering the trial.

Unlike some critics, we support the concept of waived consent trials and have contributed to the effort to improve their design and implementation. We also appreciate the dangers and limitations of blood and endorse the effort to find safer and easier-to-use alternatives. However, the commercial development of hemoglobin-based oxygen carriers has been marred by a series of visible embarrassments and there is no need for another. Our goal is not to stop the PolyHeme study but to remove a defect that needlessly threatens its promise.

We communicated our reservations to Dr. Steven A. Gould, the CEO of Northfield Laboratories. He did not agree with us. We then posted a query to the IRB Discussion Forum (http://www.irbforum.org/discussion/) where, in contrast, all four respondents (including two

The American Journal of Bioethics, 6(3): 1–4, 2006

ISSN: 1526-5161 print / 1536-0075 online
DOI: 10.1080/15265160600668644

off-list) concurred with our critique. No responses were received from IRBs that had approved the trial. Having taken those first steps, we felt the time had come to notify the FDA, Office for Human Research Protections (OHRP) and the IRBs that have approved the trial. For a variety of reasons, no resolution emerged from that effort.

The two sections that follow are intended solely to set out background. Though some concerns are briefly discussed, they are not intended as criticisms. In the third section we set out what we take to be the core objection to the Northfield trial.

BACKGROUND: THE BASIC STUDY DESIGN

The Northfield protocol provides that trial subjects—trauma patients in hemorrhagic shock who are being treated by emergency medical technicians (EMTs)—randomly receive either saline solution or PolyHeme. Enrollment occurs in the field under the waived-consent exception and before arrival at an emergency department. The waiver is properly applicable because, first, persons in hemorrhagic shock are at risk of dying unless treated promptly. Second, apart from slowing blood loss, replacing fluids and getting the patient to an emergency department, hemorrhagic shock is not treatable in the field. Finally, consent is not likely to be possible within the therapeutic window. In particular, the prospective research subject is unlikely to be capable of consent, either because of injuries or because of the gravity of the situation and the complexity of the consent process. Nor is a legally authorized representative likely to be available.

Once at the hospital, efforts will be made to secure consent for continued participation either from the patient/subject or from a legally authorized representative. However, if formal withdrawal from the study does not occur, participation continues by default in the hospital even if consent is not obtained. Patients/subjects in the control group receive standard treatment: saline and blood as needed. However, patients/subjects in the experimental group continue to receive PolyHeme instead of blood for oxygen delivery: up to six units of PolyHeme for up to twelve hours, at which point their participation in the trial ends. The study thus can be divided into two phases. The first (PolyHeme vs. saline) occurs in the field. The second phase (PolyHeme vs. blood) occurs for up to twelve hours after hospital admission.

We had wondered about the practical reason for the 12-hour clinical phase. Emergency departments like those participating in the Northfield study typically receive trauma patients less than one hour post-injury. But the trial mimics a 12-hour period without access to typed and cross-matched blood. Unlike remote areas and ships (which do not appear to be participating in this study), we expect that 12-hour field evacuation delays are either uncommon or unheard of in the communities where the studies will be conducted. Why include this troubling feature so early in a research program?

The delay reflects the circumstances of combat-wounded soldiers when evacuation to field hospitals is impossible and a safe and effective oxygen-carrying resuscitative fluid could save lives. If these well-known military constraints help to explain the design of the clinical phase, then any additional risks that might be imposed upon hospitalized civilian trauma victims would benefit neither the patients/subjects nor those subsequently injured in their communities but, rather, soldiers fighting overseas: a different population. While all of us endorse the obligation to provide the highest-quality care to injured American troops (and to others at a distance from blood banks), we think such a duty cannot justify a possible departure from ethical principles governing research on non-consenting civilian human subjects. But does the research design involve such a departure?

MORE BACKGROUND: POLYHEME VS. BLOOD

The scientific argument for the second phase of the study places great weight on the well-known immunological problems with allogeneic blood and the suspicion that these are responsible for multiple organ failure and death. PolyHeme appears not to have that disadvantage and there is a reasonable hope that its availability would improve outcomes following hemorrhagic shock secondary to trauma. Taken together, these are good reasons for evaluating the safety and efficacy of PolyHeme in head-to-head comparisons with blood. Definitive research has not been reported and the proposed clinical studies may answer some questions.

Here are two outstanding empirical issues. There is a question whether the greater incidence of multiple organ failure in transfused trauma patients is due to the severity of the initial injuries or to the transfusions afterwards. The evidence of correlation suggests, but does not establish, causation: While the number of bandages used on a trauma patient could correlate with the probability of death, no one would conjecture that bandages cause death. Second, the absence of clotting factors in PolyHeme raises a question whether bleeding

secondary to trauma will be adequately controlled in hospitalized patients who receive it instead of blood. PolyHeme could cause deaths in this way (and possibly in other unknown ways).

We were advised that the protocol allows the use of coagulation products in the event that bleeding is a continuing problem during the 12-hour/six-unit clinical phase. Obviously there would be ethical concerns if these common treatments were to be withheld (along with blood), and patients could suffer or die as a consequence. But the clinical use of coagulation products raises a different concern. For if these products are routinely administered during the clinical phase of the trial (as needed to control bleeding), and are not available in the field, then the 12-hour post-admission phase of the trial would fail to mimic extended field evacuation times in either civilian or military settings. In particular, improved survival rates could not show that PolyHeme can be safely and effectively used in settings where those coagulation products were not also available (i.e., in the field).

Even so, it seems that PolyHeme's incompletely understood disadvantages (decreased coagulation and perhaps other unknown adverse effects) and allogeneic blood's better understood shortcomings (increased risk of inflammatory response, etc.) make it impossible to judge now which of the two is inferior in the treatment of hemorrhagic shock secondary to trauma. In that respect, clinical research may be in order. We will assume in what follows that the science behind the study is sound and that the time has come for head-to-head randomized comparisons of PolyHeme and blood. But after considerable correspondence and reflection, we have come to believe that the design of the Northfield protocol is nevertheless seriously flawed.

THE CORE OBJECTION TO THE NORTHFIELD TRIAL

Saline cannot correct hemorrhagic shock and, in consequence, patients with traumatic injuries often die of blood loss before reaching the hospital. For waived-consent trials, the patients/subjects must be in life threatening conditions and proven, satisfactory treatments must be unavailable. As the FDA has put it in its Guidance, the patients/subjects must be suffering from "diseases or conditions where the likelihood of death is high unless the course of the disease or condition is interrupted" (FDA 2005).

Blood transfusion has a good, if imperfect, record as the favored method of interrupting the natural course of hemorrhagic shock. Accordingly, the waived consent field trial of PolyHeme is justifiable just because blood is not available in the field. But blood is available in the hospital, and that salient fact rules out any head-to-head comparison of PolyHeme and blood under the waived-consent regulation. Like all medical interventions, blood has its risks and limitations, and, as suggested earlier, clinical trials should be comparing it with experimental interventions—like PolyHeme—that might be more satisfactory in some ways, but only with proper consent.

On one side are the standards that underlie the informed consent exception in 21 CFR 50.24 and its approach to the narrow category of waived consent trials, where no satisfactory treatment is available. On the other side are the more familiar baseline standards that enter into the design of ordinary clinical trials, where a possibly safer and more effective experimental treatment may be available. These must be sharply and carefully distinguished, bearing in mind the equivocation in the term "unsatisfactory." Saline is plainly an "unsatisfactory" treatment for hemorrhagic shock, but not in the same sense that blood might be. In the field, blood—the only approved and effective treatment—is unavailable, preventable deaths are common, and all EMTs can offer for hemorrhagic shock is a high-speed trip to a hospital. Under the circumstances, saline is of limited efficacy and any promising intervention that might correct hemorrhagic shock prior to admission would appear to be worth a shot, even if consent were not obtainable. In contrast, blood transfusion—the standard treatment for hemorrhagic shock—is readily available in the hospital-based clinical phase of the trial, as well as an unproven (possibly better) experimental treatment that can be approved for testing, but only on consenting patients. The amalgamation of two very different types of trial (PolyHeme vs. saline and PolyHeme vs. blood) under a single consent standard has erroneously conflated two quite different regulatory approaches.

To avoid misunderstanding, we wish to reemphasize that we are not challenging the scientific soundness of the in-house phase of the trial. We can accept the legitimacy of a head-to-head randomized clinical trial comparing blood and PolyHeme, but only with consenting patients/subjects. We don't need to be reminded of the risks associated with blood. It is enough that no one knows whether PolyHeme or blood offers a better chance to patients in hemorrhagic shock secondary to trauma. That is why a clinical trial is warranted.

What we are challenging is the extension of the 50.24 exception to an active controlled study. The regulations that create the waiver anticipate patients/subjects for whom there are only unsatisfactory options. It is therefore a mistake to stretch the regulations to include patients/subjects with options that fall short of perfect safety and efficacy. Too few patients will be left out if the phrase "unsatisfactory treatment" is given such a liberal interpretation. Accordingly, the waiver should cease to apply as soon as suitable blood is at hand. Thereafter, consent to an in-house, active-controlled trial—and not merely a good faith effort to obtain it—is plainly required before clinicians can forego the standard treatment, routine transfusion, and instead randomly substitute a promising experimental alternative. Studies like this one ought to move forward, but never under 50.24's waived consent exception.

Consider that it is inevitable that hospitalized patients/research subjects on PolyHeme will die, if only because of the severity of their initial injuries. When deaths occur during the critical 12-hour interval when available blood is medically indicated but being withheld, plaintiffs' attorneys may want to scrutinize the records carefully to ground claims of liability. Putting the point most dramatically, these men and women will have died while being denied an available treatment (blood transfusions) that is indicated by the standard of practice, following unconsented-to enrollment in a research study. Despite encouraging results in earlier trials, the use of PolyHeme is still an investigational procedure that can only be substituted for established practices with consent (except under circumstances that do not obtain in the hospital setting). Litigation flowing from this mistake would likely do damage to Northfield, to the hospitals and universities that are running what we believe to be an ethically flawed study, to the credibility of the FDA and its implementation of the 50.24 rule, to medical research in general, and to the hope of having a near-term alternative to blood.

At a minimum, we believe it is obligatory to separate the field trial and the hospital-based clinical trial. We think it is a serious and ongoing error to be piggy-backing the latter onto the former, with its waiver of consent—a narrow exception drafted for significantly different circumstances. We are in agreement with those IRBs that have thought it a mistake to enroll non-consenting subjects into a post-admission study comparing PolyHeme and blood. We believe that, once this flaw is pointed out, IRBs should revisit their earlier decisions to approve the study and— if the study is still underway— clinicians should cease administering PolyHeme to non-consenting patients/subjects as soon as cross-matched blood can be made available. Of course, if we are mistaken about the flaw in the Northfield study, we would like to learn of our error.

In the future, open letters like this one may encourage collaborative multi-site communication on questionable research, thereby increasing the likelihood of correction when protocols are seriously defective. ■

REFERENCES

Kipnis, K., N. King, and R. Nelson. 2006. Trials and errors: Barriers to oversight of emergency research. *IRB*, in press.

Food and Drug Administration Center for Drug Evaluation and Research. 2005. Guidance for industry: Information program on clinical trials for serious or life-threatening diseases and conditions. Available online at http://www.fda.gov/cder/guidance/4856fnl.htm