Northwestern University

Human Subject Protection Program Policy Manual

Version 5.0
Modified May 1, 2007

Approved by: G. Bradley Moore — 21 May 2007
Vice President for Research — **Date**

Table of Contents

Policy for Human Subjects Research at Northwestern University

I. Preamble:

This document provides information on the policy of Northwestern University (NU, also referred to in this policy as "University" and "Northwestern") relating to human subjects research. The information is intended for use by investigators, researchers, Institutional Review Board members, members of other NU committees, NU administrators or others who are involved with NU research involving human subjects. Research that is sponsored or conducted by Northwestern University, including research conducted at the University, Northwestern Memorial Hospital (NMH), Northwestern Medical Faculty Foundation (NMFF), the Rehabilitation Institute of Chicago (RIC), the Jesse Brown Veterans Administration Medical Center (JBVAMC), Children's Memorial Hospital (CMH) or Evanston Northwestern Hospital (ENH) shall be conducted in accordance with this policy.

II. Overview of the IRB, OPRS, and the Human Subject Protection Program (HSPP)

Northwestern University operates a centralized program for the review and approval of research involving human subjects through the Office for the Protection of Research Subjects, which is established under the authority of the Office of the Vice President for Research. The overall program, which is referred to as the Human Subject Protection Program (HSPP) includes all of the offices and individuals in the University who have a role in ensuring compliance with this policy, and more importantly who participate in ensuring the safeguarding of the rights and welfare of human subjects involved in research that is supported or conducted by Northwestern University. The Office for the Protection of Research Subjects has immediate and primary responsibility for ensuring the ongoing development and maintenance of the HSPP. The IRBs have a central role in ensuring that non-exempt human subject research is planned and conducted in an ethical manner, and in compliance with federal and state regulations. Each member of the NU community who is involved in the conduct of research has a responsible role in ensuring adherence to federal regulations and state laws pertaining to human subject research, and to the requirements of this policy and the specific requirements of the IRB. When members of the NU community encounter possible non-compliance with the requirements of the HSPP, they are responsible to report the allegations to the IRB or to OPRS for investigation, with the goal of corrective actions to maintain the safeguarding of the rights and welfare of subjects. NU employees and agents who wish to file an anonymous report using a confidential web-based reporting tool (http://www.northwestern.edu/ethics/).

Before any non-exempt research project involving human subjects is initiated, it must be reviewed and approved by an Institutional Review Board (IRB). While the principal investigator has immediate and primary responsibility for protecting research subjects by following the approved research protocol procedures, the Northwestern University IRBs are responsible for ensuring that the research plan and the ongoing conduct of the research adequately protect the rights and welfare of study participants. Through this policy and its Federalwide Assurance (FWA), the University has promised to be accountable for establishing and following these guidelines for the use of human subjects in research.

The Northwestern University Office for the Protection of Research Subjects (OPRS), located at 750 N. Lake Shore Drive (Chicago), and in Hogan Hall, G100-6th Floor, 2205 Tech Drive (Evanston) has several functions:

- To provide administrative support for the NU HSPP, including its Institutional Review Boards
- To provide assistance to investigators and research staff who are preparing submissions for the HSPP
- To process submissions as efficiently as possible
- To maintain records of IRB reviews and approvals, as well as other functions of the HSPP
- To maintain documentation of the facilitated reviews of the NIH National Cancer Institute's Central IRB (CIRB).

A. Mission Statement for the Human Subject Protection Program

The mission of the NU HSPP is to ensure that the IRB process and OPRS services are effective at safeguarding the rights and welfare of human subjects involved in research when Northwestern is engaged in that research. While the protection of research subjects is a shared responsibility, with the institution, investigators, research staff, the IRBs and OPRS all working together toward accomplishing this common goal, OPRS is uniquely responsible for developing and directing the University's human subject protection program, and the NU IRBs are uniquely responsible for conducting reviews in order to maintain adequate ethical and regulatory oversight of human subjects research at the University. Both OPRS and the NU IRBs are responsible for creating and encouraging a culture of respect for human subjects in research, as well as for creating and encouraging respect from the research community for the NU HSPP.

B. University Governance

Northwestern University is a private institution governed by its Board of Trustees. The Trustees have delegated authority to the President to oversee the administration of the University, and the President has further delegated authority to the Vice President for Research for maintaining and overseeing the central administrative functions necessary for the conduct of the University's research. Under the terms of the Federalwide Assurance (an agreement between NU and the Department of Health and Human Services), the Vice President for Research is listed as the institutional signatory authority, and he assumes responsibility for ensuring the University is in compliance with the federal regulations regarding human subjects research. The University delegates this authority to the Vice president for Research because that office has sufficient authority and independence to implement and maintain a program of excellence in the NU Human Subject Protection Program. The Executive Director of OPRS is designated the Human Protections Administrator, and assumes responsibility for the daily functioning of the Human Subject Protection Program.

The University evaluates the adequacy of the resources that are provided for supporting the efforts of the human subject protection program through multiple processes. There are faculty advisory committees that provide evaluative input into the functioning and resources of the

Office for Research, but also for the Office for the Protection of Research Subjects and the IRBs. The OPRS is included in a major programmatic review by faculty committees internal to NU as well as an external faculty review committee every seven years. In addition, there is a Research Subcommittee of the General Faculty Senate which from time to time will meet with OPRS leadership to review the adequacy of resources for meeting the needs of the research community with regards to the processes in place for human subject protections. Finally, the office conducts its own self-review on an annual basis which serves as the basis for developing a strategic plan and budget for each fiscal year.

The Northwestern University Institutional Review Boards (IRBs) are independent standing committees established under University policy and federal regulations. Members of the Institutional Review Board are appointed by the Associate Vice President for Research with delegated authority from the Vice President for Research.

C. Other Administrative Offices that Participate in the Human Subject Protections Program

1. Office for Sponsored Research

At Northwestern University, all human subjects research with external support (external funding including government, foundation and industry must be processed through the Office for Sponsored Research (OSR) which has both Evanston and Chicago office locations. This office has the authority to review and approve funding award applications, as well as clinical trial agreements and other written agreement related to the sponsorship of research that is supported by or conducted by the University. In its review of funding applications for human subject research and clinical trial agreements, the office ensures and documents to the sponsor that appropriate IRB approval or approval of a claim of exemption has been obtained for the research. The Office for Sponsored Research is also responsible for promptly reporting IRB suspensions and terminations, or serious or continuing non-compliance with human subject protection regulations or the requirements of the IRB when they need to be reported to the sponsor.

2. Office for Research Safety

When human subjects research involves the use of recombinant DNA, the Institutional Biosafety Committee and the Office for Research Safety assess the facilities, procedures, practices, and training and expertise of personnel involved in the research in accordance with, and to the extent the research is subject to, the NIH Guidelines.

3. Office for Research Integrity

Research integrity is integral to academic life, and is required by University policies as well as federal regulations. Integrity in research is also foundational to human subject protections. The Office for Research Integrity coordinates with the Office for the Protection of Research Subjects to develop and provide educational opportunities and resources for the NU community. ORI partners with the research community to proactively identify and manage research compliance risks related to human subjects research as part of a comprehensive risk assessment program. In coordination with OPRS, ORI administers self-assessment questionnaires, conducts internal data assessments and facilitates discussions of research

compliance risks at the unit level. ORI works with OPRS and the research community to eliminate or manage identified risks through corrective action, operational improvements, training and education. In addition, the Office for Research Integrity works with the IRBs and OPRS in responding, on behalf of the University, to allegations of serious non-compliance with the requirements of the IRBs or with federal regulations.

III. Ethical Foundation for Human Subject Protections

The National Research Act of 1974 established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission was charged with identifying the basic ethical principles that should underlie research with human subjects. In 1979 the Commission published its report, Ethical Principles and Guidelines for the Protection of Human Subjects of Research, commonly called the Belmont Report. Today's federal regulations for the protection of human subjects are based on the ethical principles of the Belmont Report. The Belmont Report identifies three basic principles as particularly relevant to the ethics of research involving human subjects.

Northwestern University requires that all research, regardless of the source of funding, which is conducted by the University (in which the University is "engaged"), be in compliance with the ethical principles of the Belmont Report.

A. Respect for Persons

Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents (that they have the right to make decisions for themselves) and second, that persons with diminished autonomy (e.g., minors, prisoners, persons with cognitive impairment, and medically incompetent people) are entitled to additional protections. Respect for persons requires that researchers only engage human subjects under conditions of effective informed consent, except in those rare circumstances when it is not possible to obtain informed consent because of the nature of the research question (e.g., social science experiments in which deception about the nature of the study is a requirement for the research to be possible). In order to be effective, informed consent requires the provision of adequate information, the comprehension of that information by the potential study volunteer, and must include a process that is respectful of the voluntariness with which potential subjects may choose to participate.

The way in which information is provided to the volunteer is as important as the information itself. The investigator should adapt the presentation of information to the subject's level of understanding. When a subject's comprehension is limited due to immaturity or mental disability, respect for persons requires that the potential study subject be given the opportunity to choose whether or not to participate to the extent they are able. Permission from a third party who understands the subject's situation and can act in the subject's best interest further protects the subject from harm. Finally, in order to be voluntary, consent must be given under conditions that are free of coercion and undue influence.

B. Beneficence

The principle of beneficence requires that the investigator not only protect individuals from harm, but make reasonable efforts to secure their well-being. Risks to subjects must be reasonable in light of the potential for benefit either to subjects directly or to society as a whole. Risk is evaluated by considering both the probability of harm and the magnitude of the possible

harm. Risk considerations include possible psychological, physical, legal, social, and economic harms. Benefit, on the other hand, is the anticipated positive value of the research to either the subject directly or to society in terms of knowledge that may be gained.

C. Justice

The principle of justice means that the possibility for benefits and the burdens of the research are equitable. It is a violation of the principle of justice to select a class of subjects (e.g., welfare patients, an ethnic minority, institutionalized persons) simply because of easy availability rather than for reasons directly related to the problem being studied. The principle of justice requires that there be fair procedures and outcomes in the selection of research subjects.

IV. Scope and Purpose of Institutional Review Boards

A. Federal Regulatory Authority

The federal regulations require the establishment of an Institutional Review Board (IRB) to review and approve all non-exempt federally funded human subjects research prior to its initiation. These regulations also require that specific information be included in the documents that are used to facilitate the informed consent process, and that in most cases, the consent process be documented by the signature of the person volunteering to participate in the research.

Northwestern University has filed a written assurance of compliance, called a Federalwide Assurance (FWA), with the Office for Human Research Protections (OHRP) in the Department of Health and Human Services (DHHS). The University has entered freely and intentionally into this agreement because it represents a commitment to providing responsible oversight of human subjects research at the University. This written agreement is required before the institution may receive federal funding for human subjects research. In the FWA, Northwestern University obligates itself to ensure that all human subjects research at the institution will adhere to the ethical principles of the Belmont Report (regardless of the source of funding), and that all research that is funded or conducted by DHHS will comply with federal regulations for the protection of research subjects.

The federal regulations governing the protection of human subjects in research include the DHHS regulations at title 45 Code of Federal Regulations, Part 46 (45CFR46), and the FDA regulations at title 21 CFR parts 50 and 56. In addition, investigators, OPRS staff, and IRB members are required to ensure compliance with additional federal regulations when the research is conducted at the Jesse Brown Veterans Administration Medical Center, and may be subject to additional regulations or requirements when the research is funded by another federal agency with its own regulations (e.g., Department of the Navy).

The Federalwide Assurance (FWA) makes specific commitments regarding the duties of the institution, the Office of the Vice President for Research, the NU IRBs, and NU investigators and research staff. All investigators at the Northwestern University are expected to conduct research in accordance with the provisions of this policy, regardless of the source of funding for their research.

The Jesse Brown Veterans Administration Medical Center (JBVAMC) has its own FWA. Northwestern University provides IRB review and oversight for human subjects research

conducted at JBVAMC by NU faculty under an IRB Authorization Agreement and Memorandum of Understanding between NU and JBVAMC. Projects reviewed for the JBVAMC receive the same IRB review as those conducted at Northwestern University or its Affiliates.

While the Vice President for Research is the institutional official with final authority and responsibility for the Human Subject Protection Program (HSPP), the primary responsibility for protecting the rights and welfare of the individuals involved in research rests with the principal investigators and their research staff who are conducting the research. Faculty members who assign or supervise research conducted by students have an obligation to consider carefully whether those students are adequately qualified, and their research projects are adequately designed so as to safeguard the rights and welfare of subjects. The successful conduct of human subjects research relies on the public trust, and members of the NU community must ensure that the conduct of their research is consistent with maintaining that public trust.

B. What Must be Submitted to OPRS for Review

Before a research project involving human subjects is initiated, it must be reviewed and approved through a submission to OPRS. All non-exempt human subjects research must be reviewed and approved by a Northwestern University Institutional Review Board (IRB) prior to initiation of the research activity.

All research involving human subjects must be submitted to OPRS for the appropriate kind of review and approval when the activity meets the definition of human subjects research and:

- NU is conducting or supporting the research, OR
- the research is conducted by or under the direction of any employee or agent of this institution (including students) in connection with his or her institutional responsibilities, OR
- the research is conducted by or under the direction of any employee or agent of this institution using any property or facility of this institution, OR
- the activities of an employee or agent of this institution (including students) meet the criteria for "engaged in research" as defined in OHRP guidance of January 26, 1999 (www.hhs.gov/ohrp/humansubjects/assurance/engage.htm) OR
- the research involves the use of this institution's non-public information to identify or contact human subjects.

At Northwestern, "Human Subjects Research" is defined as an activity that either:

- Meets the DHHS definition of "research" and involves "human subjects" as defined by the DHHS regulations; OR
- Meets the FDA definition of "research" and involves "human subjects" as defined by FDA regulations.

1. What is Research?

a) DHHS Definition of Research

DHHS regulations define *research* as a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research even if they are a

component of a larger non-research activity (e.g., instruction, demonstration or service projects).

b) FDA Definition of Research

FDA defines research as any experiment that involves a test article and one or more human subjects and that is one of the following:

- subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or
- is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit.
- The term does not include experiments that are subject to the provision of 21CFR58, regarding non-clinical laboratory studies. (From 21 CFR 50.3(c); 21 CFR 56.102(c))

Under FDA regulations, the terms "research" and "clinical investigation" are synonymous.

c) What is a test article?

A test article means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the Federal Food, Drug & Cosmetic Act. [21CFR50.3(j)].
For drug studies, FDA defines a clinical investigation as any experiment in which a drug is administered or dispensed to, or used involving one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice. [21 CFR 312.3(b)] (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.3)
For device studies FDA defines an investigation as a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device. [21 CFR 812.3(h)]

2. Who is a Human Subject?

a) DHHS Definition of a Human Subject

DHHS regulations define a human subject as a living individual about whom an investigator (whether professional or student) conducting research obtains either:

(a) data through intervention or interaction with the individual, OR
(b) identifiable private information.

Since the definition of a human subject is a "living" individual, research that only involves autopsy materials, cadavers or death records is not considered human subjects research and therefore does not require review by the IRB, or submission of any application to OPRS. In addition, research involving composite data about institutions, or groups of people (not individually identifiable) is not human subjects research.

(1) What characterizes an intervention with an individual?

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

(2) What characterizes an interaction with an individual?

Interaction includes communication or interpersonal contact between investigator and subject.

(3) What is private information?

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

b) FDA Definition of Human Subject

FDA regulations define human subject as an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. Under this definition, a subject may be either a healthy individual or a patient. For research involving medical devices, the definition of "human subject" is extended to include an individual or a specimen taken from an individual on whom an investigational device has been used.

3. How do I know if my project is research involving human subjects?

In order to comply with the requirements related to conducting human subject research, the Northwestern University faculty, staff, and students must be able to determine whether or not an activity constitutes human subject research under the DHHS regulations, or research under the FDA regulations. When the proposed activity does not involve an FDA-regulated agent or device, the individual planning to engage in the activity may use the decision chart #1 at http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm#c1 as a guide for making the "not human subject research" determination. Many University activities are clearly not human subject research, but others are difficult to distinguish from human subject research activities. University faculty, staff, and students are encouraged to seek collaborative input from their colleagues, when needed, in order to make this determination.

In addition, the Northwestern University IRB Chairs or senior OPRS IRB staff can also provide guidance and will provide written determinations as to when an activity meets or does not meet either the DHHS definitions for human subjects research or FDA definitions for clinical investigations. Requests for determinations may be submitted to the IRB Chairs or OPRS staff either verbally or in writing and the Chairs or OPRS staff may respond either verbally or in writing with such a determination. If you have questions about whether or not your project meets the definitions of research involving human subjects and requires IRB review, call the OPRS office at (312) 503-9338 or send an email inquiry to:

irb@northwestern.edu.

C. Northwestern University Institutional Review Boards

Northwestern University has established multiple IRB panels to review research. All of the IRBs review and approve research in accordance with Department of Health and Human Services (DHHS) regulations at 45 CFR 46. In addition, for studies involving products regulated by the Food and Drug Administration (FDA), the Northwestern University IRBs comply with the requirements set forth in 21 CFR 50 and 21 CFR 56, and function with awareness of the additional requirements for sponsors and investigators under 21 CFR 312, 21 CFR 600, 21 CFR 812 and 21 CFR 814, Subpart H. When research involving products regulated by the FDA is funded, supported or conducted by FDA and/or DHHS, both the DHHS and FDA regulations apply.

Each of the NU IRBs has at least five members, with varying backgrounds in order to promote complete and adequate review of research activities commonly conducted at Northwestern. The NU IRBs are sufficiently qualified through the experience and expertise of their members, and the diversity of those members, including diversity in their racial, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for their advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the NU IRBs are able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.

The NU IRBs include persons who are knowledgeable in these areas. None of the NU IRBs may consist entirely of members of one profession, or of one gender. Each NU IRB has at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas. Each NU IRB also has at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution. The NU IRBs do not allow a member to participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. These members with a conflict of interest are required to leave the room for the discussion and voting on those submissions, unless they are asked to come into the meeting to provide additional information (after which they will again leave the room).

The NU IRBs may, at their discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the specific panel. These individuals are not permitted to vote with the NU IRB, but assist the IRB in making its determinations under 21CFR56.111 and 45CFR46.111.

D. Non-NU Institutional Review Boards

1. Children's Memorial Hospital (CMH) IRB

Under a reciprocal IRB Authorization Agreement between Northwestern University and Children's Memorial Hospital, the CMH IRB provides IRB review for pediatric clinical trials conducted by Northwestern University. In addition, the NU IRBs are authorized to provide IRB review and oversight for research at CMH involving adults. The CMH IRB becomes the

IRB of record for providing initial and continuing review of these protocols and Northwestern University is responsible to provide facilitated review of the project that has been approved by the CMH IRB. Under the facilitated review by NU's IRB, it is possible to review and approve modified consent documents (consent documents for use at NU Affiliate sites) and to provide consideration of the local context. Northwestern University remains responsible for oversight of the local performance of these clinical trials. The Northwestern University IRBs decide on a protocol-by-protocol basis whether to accept the review of the CIRB or to conduct their own convened review of the protocol. Please contact OPRS if you have any questions about whether or not your protocol is eligible for review by the CMH IRB, with facilitated review by NU's IRB.

The procedures for investigators wishing to submit projects for CMH IRB review and NU IRB facilitated review are on the OPRS website. You may still require the review and approval of other NU committees prior to obtaining NU facilitated review of the CMH IRB-approved protocol. Please refer to our procedures or call OPRS for more information.

2. Evanston Northwestern Hospital (ENH) IRB

Under a reciprocal IRB Authorization Agreement between Northwestern University and Evanston Northwestern Hospital, the ENH IRB provides IRB review for research that is conducted by Northwestern University faculty members when ENH is a performance site for the research. The ENH IRB becomes the IRB of record for providing initial and continuing review of these protocols and Northwestern University is responsible to provide facilitated review of the project that has been approved by the ENH IRB. Under the facilitated review by NUs IRB, it is possible to review and approve modified consent documents (consent documents for use at NU Affiliate sites) in order to provide consideration of the local context. Northwestern University remains responsible for oversight of the local performance of these clinical trials. The Northwestern University IRBs decide on a protocol-by-protocol basis whether to accept the review of the CIRB or to conduct their own convened review of the protocol. Please contact OPRS if you have any questions about whether or not your protocol is eligible for review by the CMH IRB, with facilitated review by NU's IRB.

The procedures for investigators wishing to submit projects for CMH IRB review and NU IRB facilitated review are on the OPRS website. You may still require the review and approval of other NU committees prior to obtaining NU facilitated review of the CMH IRB-approved protocol. Please refer to our procedures or call OPRS for more information.

V. Categories of Review for Human Subjects Research

Human Subject Research proposals are reviewed at a full board meeting unless the project qualifies for exempt status (see Section A of this chapter) or can be classified as minimal risk and meets the criteria for expedited review (see Section B of this chapter). The type of review depends on the risks posed to potential subjects.

A. Exempt Human Subjects Research

The Northwestern University policy requires that all human subjects research protocols be submitted for review and approval prior to initiation of the research. However, certain types of human subjects research may be classified as exempt under the federal regulations [45 CFR 46.101(b) (DHHS) and 21 CFR 56.104 (FDA)]. Exemption means the research does not need to

comply with the rest of the regulatory requirements, but the University requires that all research (including exempt human subjects research) is conducted in compliance with the ethical principles of the Belmont Report.

The determination of exemption may not be made by an individual investigator for his or her own research, but must be made by the institution through review of a submission to OPRS or through other procedures which may be implemented with the written agreement of the Executive Director of OPRS. The Executive Director shall only approve alternative procedures when there is a plan for adequately training the individuals who would make the determinations, when there is a plan for OPRS monitoring of the procedures used and the determinations made, and when the monitoring reports will be submitted for review by the NU IRB Chairs Committee. Institutional Officials responsible for the Human subjects Protection Program may cancel any alternative procedure at any time by informing the Department Head of this decision in writing.

1. DHHS Categories of Exempt Research

When a claim of exemption is submitted for review, the reviewer must determine whether the research in its entirety fits within one or more of the exempt criteria, based on review and approval of the investigator's Application for Exemption Certification application. Exempt research projects have no requirement for continuing review. Exemptions under the DHHS regulations are limited to research activities in which the only involvement of human subjects will be in one or more on the following categories:

1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior not otherwise exempt under category 2 above, if: (i) the human subjects are elected or appointed public officials or candidates for public office; OR (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. NOTE: Existing data, documents, records, pathological or diagnostic specimens means the items must be “on the shelf” or in existence at the time the project is submitted for review.

5) Research and demonstration projects which are conducted by or subject to the approval of Department or Agency heads, and which are designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payments for benefits or services under those programs.

6) Taste and food quality evaluation and consumer acceptance studies (i) if wholesome foods without additives are consumed; or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the FDA or approved by the EPA or the Food Safety and Inspection Service of the US Department of Agriculture.

The exemption criteria above do not apply to research involving prisoners. In addition, the exemption criteria listed as #2 above, does not apply to research involving children except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

2. FDA Categories of Exempt Research

When a research activity falls under FDA jurisdiction, unless the activity falls into one of the following categories, the clinical investigation involving human participants is subject to IRB review. Exempt categories for research under the FDA regulations include:

1) Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.

2) Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.

3) Emergency use of a test article (see definition in Chapter 3, Section B1), provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. See Chapter 9, Section "Emergency Use of a Drug or Device"

4) Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

When both DHHS and FDA regulations apply to research involving human subjects, the NU IRBs apply the most restrictive regulations from each to the research being conducted to ensure the protections of the rights and welfare of the human participants.

B. Expedited IRB Review

Federal regulations recognize certain kinds of research that may be reviewed by an IRB through an expedited review procedure [45 CFR 46.110 (DHHS) and 21 CFR 56.110 (FDA)]. Expedited review means that the IRB chair, or a designee from among the experienced members of the IRB may provide the review and approval of research on behalf of the IRB without the requirement of a convened panel meeting. Expedited review does not necessarily mean that the review occurs quickly. Approval under expedited review procedures requires that the IRB member conducting the review determines and documents that the research and consent procedures meet all of the same criteria for approval as research that must be approved through a convened review procedure. Information regarding research that has been approved using expedited procedures is made available to all of the IRB members in the event that the convened panel or other members of the IRB have questions or concerns about what has been approved by a single reviewer on behalf of the IRB. The IRB member conducting expedited reviews exercises all the authority of the IRB except that she or he cannot disapprove research. Research proposals may only be disapproved by a convened panel.

The expedited review procedure may be used for approving some categories of research (requires a determination that it is no more than minimal risk and that it fits entirely into one or more approved categories), may be used for approving minor modifications of previously approved projects (revisions), and may be used for some categories of continuing review when the study previously required approval by a convened panel.

1. What is minimal risk?

The federal regulations provide two definitions of minimal risk – one for prisoners, and another for non-prisoners (general population).

For the *general population*, the federal regulations define minimal risk to mean that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. [45 CFR 46.102(i) & 21 CFR 56.102(i)]

For *prisoners*, the federal regulations define minimal risk as the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons. [45 CFR 46.303(d)]

The definition of minimal risk serves as a starting point to determine whether the study is eligible for expedited review. Risk in this context includes not only physical risk, but also psychological, emotional, legal, social, and financial or the risk of loss of privacy or breach of confidentiality. If a project meets the definition of minimal risk, and falls into one of the expedited review categories as described below, the IRB chairs or their designees alone may review and approve the project.

2. Expedited Categories for Research

The IRB is the ultimate authority for determining whether the research meets the expedited criteria, based on review and approval of the investigator's application to the IRB. The chair or designee retains the discretionary right to require full board review, even when the project appears to meet the criteria for expedited review. The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them

at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless the investigator has documented that reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal risk.

The expedited review process may be used for the initial review of projects involving a) no more than minimal risk, and b) only those procedures listed in one or more of the following categories. The activities listed are not deemed to be of minimal risk simply because they are included on the list. Inclusion on the list merely means that the activity is eligible for expedited review when the specific circumstances of the proposed research involve no more than minimal risk to human subjects. If the research project as a whole involves more than minimal risk, it must be reviewed by the full board even if the activities are limited to those listed below:

1) Research on drugs for which an investigational new drug application is not required or research on medical devices for which a) an investigational device exemption application is not required or b) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2) Collection of blood samples by finger stick, heel stick, ear stick or venipuncture as follows: (a) from healthy, nonpregnant adults, who weigh at least 110 pounds. For these subjects, amounts drawn may not exceed 550 ml in an 8 weeks period and no more than 2 times per week; OR (b) from other adults and children, considering age, weight, and health, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml/kg in an 8-week period and collection may not occur more frequently than 2 times per week.

3) Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings, in a nondisfiguring manner; (b) deciduous teeth at the time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography,

electroencelphalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight and health of the individual.

5) Research involving materials (data, documents, records or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

6) Collection of data from voice, video, digital or image recordings made for research purposes.

7) Research on individual or group characteristics or behavior (including but not limited to research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

3. Minor Modifications to Previously Approved Research

The IRB may review modifications, or revisions to previously approved projects using the expedited review procedures when the proposed changes involve only minor modifications to the approved project during the period of IRB approval. See Chapter 7, Section B below for a definition of minor modification.

4. Continuing Review

The continuing review of research may be conducted using expedited procedures in the following instances:

1) If the project was previously reviewed and approved using the expedited procedure and conditions have not changed such that the research would no longer be eligible for expedited review (e.g. protocol change, or experience shows the research to be of greater than minimal risk).

2) If continuing review of the research was previously approved by the convened IRB and conditions have changed to make the research eligible for expedited review under criteria 1 through 7 above (e.g. the research is now within those categories and experience confirms the research to be of no greater than minimal risk)

3) If continuing review of the research was previously approved by the convened IRB and the research is now: (a) permanently closed to the enrollment of new subjects, (b) all subjects have completed all research-related interventions, and (c) the research remains active only for long-term follow-up of subjects.

4) If continuing review of the research was previously approved by the convened IRB, but no subjects have been enrolled (at the local site) since the initial approval and no

additional risks have been identified.

5) If continuing review of the research was previously approved by the convened IRB, but the study interventions and data collection are now all over and the ONLY remaining research activities are limited to data analysis.

6) If continuing review of the research was previously approved by the convened IRB and a) the research is not conducted under an investigational new drug application or an investigational device exemption, and b) the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk, and c) no additional risks have been identified since IRB review at a convened meeting.

The expedited review procedure is not used for the continuing review of research where the research involves more than minimal risk (except when no subjects have been enrolled and no additional risks have been identified) or where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections are implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal (except for when no subjects have been enrolled and no additional risks have been identified). The expedited review procedure is also not used for classified research. Finally, no studies involving prisoners may be reviewed under expedited procedures regardless of whether or not they meet the criteria above EXCEPT for new studies limited in scope to retrospective review of prisoners' records and minor modifications to already approved research. In the case of these exceptions, approval of the research may only be granted after the expedited review of and comment on the proposed research or minor modifications has been provided by a prisoner advocate member of the IRB.

C. Full Board Review

Human subjects research that is not classified as exempt nor qualifies for review under expedited requires must be reviewed by the full IRB at a convened meeting. All expedited IRB approvals are reported to a convened IRB through the use of an "agenda addendum," which is either distributed with the meeting packets, or is available to IRB members online via eIRB.

1. How often does the full board meet to review applications?

Most of the NU IRBs meet once per month, with the continuing review biomedical panel meeting weekly. In order to give enough time for OPRS staff to conduct pre-review, and to give IRB members adequate time to review protocol submissions, investigators are advised to allow three to four weeks for an application to be scheduled for review at a convened meeting. There are times when a full board meeting may be canceled, or may end without completing its agenda. This can happen because of inclement weather, University holidays, faculty vacation and other travel schedules or other reasons that result in a lack of quorum or loss of quorum.

2. How is it determined when an IRB meeting is properly convened?

In order to bring a meeting of the convened IRB to order, the Chair (or designee if the Chair is absent) consults with the OPRS staff present to determine together whether or not the requirements for quorum have been met. The IRB Member Attendance sheet is completed in order to ensure that there is a simple majority of members present, including at least one non-scientific member and one scientific member. In addition, the staff have pre-reviewed the submissions on the agenda and are aware of the need for additional consultants when the research involves more than minimal risk and minors (under 16), prisoners, or pregnant women and/or fetuses. Whenever individual IRB members leave the room (after the quorum is initially declared), the Chair/designee and OPRS staff share responsibility for ensuring that the quorum has been maintained. When the quorum is lost, the IRB members may deliberate about submissions, and may request modifications or clarifications from an investigator, but those changes/clarifications must be returned for review by a convened panel. No research may be approved without a quorum present.

There must be a "Prisoner representative" present to constitute quorum for approval of any research involving prisoners. The IRB membership can determine on a case-by-case basis whether other consultants need to be present for the discussion (when additional scientific expertise is needed), or at times whether the written review of additional consultants is adequate for the panel to be sufficiently qualified to review and approve the research under the regulatory requirements at 45 CFR 46.11 and 21 CFR 56.111.

3. What is required for approval by the Convened IRB?

In order for research to be approved by a convened panel, the quorum must be established and maintained, and a motion for approval must be made and seconded. That motion must then be affirmed by the vote of a majority of the members present. If the motion does not pass (less than a majority vote for the motion), then the Chair must call for another motion, followed by discussion and then another vote. This process must continue until the panel passes a motion.

4. How are projects reviewed by the full board?

The Northwestern University IRBs use a primary reviewer system for full board reviews. One or two members are selected by OPRS staff (with input from the Administrative Chair) as the primary reviewers for a project. Application materials are normally sent to the IRB members scheduled to attend a meeting at least one week in advance of the meeting. All members attending the meeting receive the application, the Informed Consent Document, and other materials such as advertisements or recruitment letters. In addition to those materials, the primary reviewers also receive the complete grant application (when applicable) or research protocol, any sample consent documents (e.g., for Cooperative Group studies), and for investigational drug/device studies a copy of the Investigator's Brochure and/or package insert. At the discretion of the chair and/or primary reviewer, the investigator may be invited to attend the meeting for the purpose of additional clarification or discussion. If attending, the investigator will be asked to leave the meeting for the final discussion and voting. The primary reviewers lead the discussion of each project at the full board meeting.

The primary reviewers complete written review guides prior to the meeting, which serve as an outline for the regulatory determinations required for approval of the research, and which

provide a prompt for the verbal summary they will provide to the convened panel. Once the meeting is convened, they will offer their opinions as to whether or not the proposed protocol meets the regulatory criteria for IRB approval, or whether revisions to the study design or consent document are required. The Informed Consent Document is reviewed for accuracy, clarity, and inclusion of required and optional elements of consent. The primary reviewer makes a recommendation to the convened IRB to:

1) Approve the protocol as submitted;
2) Pending Modifications, including required minor revisions to study procedures, Informed Consent Document(s), or other written materials;
3) Defer approval pending major revisions to or clarifications regarding the study procedures protocol application, Informed Consent document(s) or other written materials, or
4) Disapprove the proposed protocol.

At the discretion of the chair, voting may be by written ballot or a show of hands. The members vote for, against, or abstain from voting regarding the motion presented by the primary reviewer(s). Actions are ratified whenever a majority of members present (assuming that there is a quorum constituted) vote for a motion. If a motion is voted down, the motion and votes are recorded for the minutes and the Chair must ask for another motion until an action is taken by the panel.

A "no action" vote may only be taken by the IRB when the primary reviewers were unable to attend and/or have not provided a copy of their written review of a submission, and the IRB members determine they do not possess sufficient expertise or familiarity with the research to consider another action. The IRB may not take a "no action" vote for any other reasons. Controverted issues are expected to occur during IRB deliberations, and are to be recorded, along with their resolution or lack thereof in the minutes of the meeting. When controverted issues are unresolved, this is reflected in a split vote and sometimes by registering a "minority opinion" in the minutes.

5. How are the Deliberations and Determinations of the Convened IRB Documented?

Investigators will receive written notification regarding the determinations of the IRB following convened meetings. In addition, following the meeting, OPRS staff members prepare minutes to summarize the determinations of the IRB. In those minutes, they will record:

- attendance at the meeting (including those who are present, those who recuse themselves from specific submissions and leave the room, as well as members who are not present),
- actions taken by the panel, including motions that are not seconded, and thereby fail, as well as motions that are voted down by the panel,
- the specific number of votes for, against, and the number abstaining from the motion (those who abstain from voting are named),
- protocol-specific modifications or clarifications that are required before approval may be granted,
- the basis for requiring changes in or disapproving the research when that is the action taken,
- the length of time until the next review (for initial approvals and continuation approvals--not to exceed one year),
- a summary of the discussion of any controverted issues and their resolution,

- specific comments relevant to inclusion of certain populations in the research, and
- where appropriate, information regarding discussion of expedited approvals, modifications, terminations, emergency/single patient use, unanticipated problems involving risks to subjects or others, and any other business appropriate for board meetings.

D. Special Types of Approval

1. Approval of Training, Center, or Umbrella Grant Applications

Approval under 45 CFR 46.118 allows the IRB to approve projects that support human subjects research when the activities directly funded by the applications do not involve human subjects research. For instance, a training grant, center grant, or program project grant that indirectly supports human subjects research can be approved through this mechanism. This type of approval allows the Principal Investigator and the Office for Sponsored Research to provide a single IRB approval date to the funding agency for the overall award itself. Overall approval is therefore an administrative tool, but does not indicate approval for any of the specific projects described in the grant.

Human subjects may not be enrolled in any of the specific projects described in the grant under a "118" or "Umbrella Grant" approval. This kind of approval is usually given under the expedited review procedure. To obtain approval for the individual projects described in the training grant, center grant, or program project grant, the principal investigator of each individual project should submit a Revision Submission Form (or a "New Revision" in eIRB) to modify the IRB approval previously given to a "Project Submission Form for Grants."

When completing application forms for individual research protocols that are supported by an umbrella funding award, the investigator should reference the funding source (and the IRB approved Umbrella protocol number) as the funding agency that provided the overall award. More than one funding source may be linked to a particular IRB-approved protocol, and more than one IRB-approved protocol may be linked to a funding source, but all of the applications on file with OPRS need to reflect the updated status of the research vis-à-vis the funding application(s).

2. Approval of Development-Only Grant Applications

Under the same category (45 CFR 46.118), the IRB may provide approval for a funding application where the funding application includes an initial period of time for development of the final protocol, questionnaires, data forms, or similar activities. Since the IRB may not approve "draft" protocols or Informed Consent Documents, and the final protocols or other documents or instruments are not yet in existence, "development-only" approval shows that the IRB has approved the study in concept, so that the Office for Sponsored Research can award the funds for the preliminary work. "Development only" approval is therefore an administrative tool, and it explicitly does not indicate approval for the enrollment of human subjects.

Human subjects may not be enrolled in a project given "development-only" approval, which is usually given using expedited review procedures. To obtain approval for enrolling human subjects, the investigator should submit a Revision Submission Form (or a "New Revision" in eIRB) to reflect the fact that the activities now supported by the funding award are about to

include the enrollment of subjects. If separate protocols are submitted and approved by the IRB, the protocol that previously received "development-only" approval must be revised to reflect the fact that the activities funded by the award now include IRB approved human subjects research. Investigators and research staff should contact OPRS for additional guidance if there are questions regarding this process.

VI. The Legally Effective Informed Consent Process

A. The Process of Consent and Assent

1. Consent & Assent

Obtaining informed consent is a basic ethical obligation for researchers. The process of consent should ensure that potential subjects are provided with information about the research project that is understandable and that permits them to make an informed and voluntary decision about whether or not to participate. The amount of information and the manner of presentation will vary depending on the complexity and risk involved in the research study. While the initial process is prospective and takes place prior to any research activity, informed consent is also an ongoing educational interaction between the investigator and the research subject that continues throughout the study.

If an investigator already has a relationship with potential subjects (physician-patient, instructor-student, employer-employee), then additional care should be taken to avoid recruitment methods that may be (or may appear to be) coercive because of the pre-existing relationship between the two parties.

Except in certain minimal risk studies, the Informed Consent Document:

- is typically signed after the investigator has verbally explained the purpose and procedures involved in the study, answered questions, and otherwise provided information that permits the subject to make a prospective, informed decision.
- must be signed and dated before any study data collection or research-related procedures begin.
- serves as a written source of information for the subject and documents the fact that the process of informed consent occurred.

Consent is a legal concept. Only legally competent adults can give legally effective informed consent. Children and those individuals who are not competent to provide consent should be given the opportunity to assent to participate in the research project. Assent is a knowledgeable agreement to participate in the project. Adequate provisions should be made for soliciting the independent, non-coerced assent from children or cognitively impaired persons who are capable of a knowledgeable agreement. In general, the IRB recommends that children age seven and older, and most cognitively impaired adults, be given the opportunity to assent. Children and cognitively impaired adults are usually required to document their assent by signing an assent document.

If the person from whom assent is sought declines to participate in the research, then that person should not be enrolled, even if the parent or legally authorized representative gives permission. (Please note that the IRB waives this requirement in clinical protocols involving minors with serious or life-threatening illness who are eligible for clinical investigations that

are approved by the IRB as having a direct prospect of benefit (category 405). Additionally, if the person from whom assent is sought agrees to participate, the person may not be enrolled if the parent or legally authorized representative does not give permission. In rare circumstances, depending on the nature of the study and the age and circumstances of the prospective subjects, the IRB may waive the requirement for parental or legally authorized representative permission.

The subject must affirmatively agree to participate in a research study. Northwestern University IRBs do not recognize a "passive" consent or assent (i.e. the assumption of agreement to participation in the absence of any response). For example, sending a letter home to parents telling them that the research is taking place in a school and giving them the opportunity to object if they do not want their child to participate is NOT recognized as a valid consent process by the NU IRBs. In order to utilize a passive consent procedure, an investigator must apply for and receive approval of a waiver of parental permission which will be documented in the IRB approval letter.

In cases where assent is obtained from a child or cognitively impaired subject, permission must also be obtained from a legally authorized representative. [NOTE: See Chapter 8, Section D, Vulnerable Populations, for more information about enrolling cognitively impaired subjects in research studies.] A child by DHHS definition is a person who has not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. By FDA definition, a child is a person who has not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted. For purposes of research conducted in the state of Illinois, the term "child" as used in both the DHHS and FDA definitions is analogous to a "minor" under Illinois law and is defined as any individual under eighteen years of age who is not emancipated by the courts, or under specific applicable statute.

In cases of human subjects research under the authority of the NU IRB(s) but conducted outside of the state of Illinois, the NU IRB may confer with the NU Office of General Counsel regarding the applicability of other state, national, or international laws to the particular project. These cases are usually identified in the pre-review process of an application to the IRB and the advice of counsel is sought prior to the approval of the study. In general, the NU IRB will attempt to apply the law of the state or country in which the research is being conducted. For example, if a project involves children and one of the recruitment sites is in a bordering state, the laws of the bordering state will be evaluated to which individuals meet the DHHS and FDA definition of "children" at that site.

2. Legally Authorized Representative for Consent

In research studies involving minors (an individual under the age of eighteen years), consent for participation must be obtained from the legally authorized representative, which in Illinois is:

1. the parent; or
2. the court appointed guardian.

In Illinois, when experimental treatment is being provided to an adult patient who does not have capacity to make their own medical decisions, consent may be obtained from the

following legally authorized representatives in order of priority:

1. The court appointed guardian of the person if that guardian has the right to make healthcare decisions.
2. The agent under a Durable Power of Attorney for healthcare.
3. A surrogate under the Healthcare Surrogate Act, which includes:
   - the patient's court appointed guardian of the person if that person has the right to make healthcare decisions
   - the patient's spouse
   - any adult child of the patient
   - a parent of the patient
   - any adult sibling of the patient
   - any adult grandchild of the patient

In other research studies (not experimental treatments) involving adults who do not have decisional capacity, permission must be sought from the priority list above, even if someone else is more conveniently available.

B. Standard Informed Consent Document

The purpose of an Informed Consent Document is to provide subjects with a written source of information for future reference and to document the fact that the process of informed consent occurred prior to the subject's participation. The form generally serves as a basis for the initial presentation of the study to the potential subject. Typically, informed consent is documented by using the written Informed Consent Document approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. The subject or the representative must always be provided adequate opportunity to read the consent document, consider their participation, and ask questions before the consent document is signed. A copy of the Informed Consent Document should be given to the subject. Unless the investigator has requested and been granted a waiver of documentation of consent, the subject's signature on an Informed Consent Document is required prior to beginning any study procedures.

Although the research study and Consent Document must be reviewed and approved by the IRB at least once per year, subjects enrolled in the study generally sign the Informed Consent Document only once, when initially enrolled. The exception to this is when the IRB or study sponsor requires subjects to sign a revised Consent Document due to a modification in the protocol or new additional information that might affect the subject's willingness to continue to participate in the study.

1. Consent Template OPRS website form

The Informed Consent Document template is available as a Word file on the OPRS website. The website also includes important information and recommended language which may be indicated for development of an informed consent document. By following the template, and the instructions, the investigator ensures that the basic and pertinent additional elements of consent as required by the federal regulations are included. In addition, OPRS has provided a copy of the review guide which is used to evaluate consent documents to ensure they include all of the required elements, and a Frequently Asked Questions document as additional guidance. Please

note that copies of the IRB approved and stamped consent documents must be used for enrolling subjects onto a study.

For all New Project applications, you must begin with the relevant consent template that is available on the "Templates" page. It is important to choose between biomedical templates (including one with HIPAA Authorization language included and one without Authorization language) and the social-behavioral consent template. Further, if your application is to be submitted through eIRB, you should choose the appropriate template for use in eIRB (both biomedical and social science templates can be found at: http://www.research.northwestern.edu/research/oprs/irb/templates/). Use of the templated language is particularly important when your research is conducted at one of Northwestern's affiliated institutions (e.g., Northwestern Memorial Hospital, Northwestern Medical Faculty Foundation, Rehabilitation Institute of Chicago) because of agreed upon language between these institutions.

The IRB expects all persons involved in the informed consent process to be individually listed, under the section "Authorized Research Personnel" on the New Project Submission Form and on subsequent continuing review applications. In order to be approved by the IRB for this role, the individuals must have met the base institutional requirement for training in human subject protections.

a) Basic Elements of Informed Consent

The basic elements of informed consent, as described in 45 CFR 46.116 (DHHS) and 21 CFR 50.25 (FDA), are as follows:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others which may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. For studies regulated by the FDA, note the possibility that the Food and Drug Administration may inspect the records.
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

b) Additional Elements of Informed Consent

The federal regulations allow that, when appropriate, additional elements of informed consent may be required by the IRB in an informed consent document. The additional elements include:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
- Any additional costs to the subject that may result from participation in the research.
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
- The approximate number of subjects who will be involved in the study.

c) Common Problems with the Written Informed Consent Document

Some common problems with the Informed Consent Document include the use of jargon, technical, or scientific terms that a lay person would not understand, and units of measure given in metric rather than the lay equivalents. Ordinary language should replace technical terms (e.g., upper extremities are better referred to as arms, hematoma as a bruise, venipuncture as taking blood from your arm with a needle, and so forth.) A website from the University of Michigan, that is helpful for converting medical terminology to lay language can be found by clicking on the following link, Medical Terminology in Lay Language.

But perhaps the most common problem with Informed Consent Documents is that they are written at a reading level several grades higher than the average subject would understand. Informed Consent Documents should be written at a reading level that potential subjects would understand. For most projects, an eighth grade reading level is suggested. Most word processing programs can determine a document's reading level.
Tips for writing a "user-friendly" Informed Consent Document:

- Write the Consent as though you were speaking to the person who will read it, using “you” and “your,” “we” and “our,” rather than third person.
- Use language that could be understood by a junior high student.
- Put technical jargon into lay terms (e.g., describe the amount of a blood draw in teaspoons rather than milliliters; use “cancer” rather than “carcinoma”).
- Clearly define complicated terms (e.g., randomization means the study treatment you’ll receive will be decided by chance, like flipping a coin).
- Don’t give a lot of technical information that participants don’t need to know (e.g., complicated methods of determining drug doses, exhaustive lists of specific lab tests).
- Use bulleted lists rather than long sentences.
- Use template headings and add subheadings as appropriate with logical and consistent formatting.
- Use tables and charts to explain when/where each procedure will take place.
- Use pictures and diagrams to help describe devices.

- Number each page of the document.
- Use hard page breaks to eliminate "widow" and "orphan" lines of text.
- Use a font with a serif (e.g., Times New Roman – easier to read).
- Use consistent and reasonable font size (e.g., 12 point, 14 point if the population may have difficulty reading).
- Do not "right justify" the text.

d) Teenage Subjects and How to Handle Wording on the Consent Document

If you plan to recruit teenage subjects (in this instance, teenage means a child older than 12 but less than 18 years of age), and the Informed Consent Document is written at an appropriate reading level, both the teenager and the parent/guardian may sign the Informed Consent. The teenager's signature on the Informed Consent Document indicates knowledgeable agreement to participate (assent), and the parent/guardian's signature indicates legal permission for the minor to be enrolled in the research.

In this situation, rather than using "you/your child," use the word "you" throughout, and insert the following statements at the very beginning of the Consent:

- . If you are the parent/guardian of a child who is being invited to be in this study, the word "you" in this document refers to your child. You will be asked to read and sign this document to give permission for your child to participate.
- If you are a teenager reading this document because you are being invited to be in this study, the word "you" in this document refers to you. You will be asked to read and sign this document to indicate your willingness to participate.

e) Signature Lines

In general, the Informed Consent Document must include signature lines for:

1. the subject AND [*See Exception #1*]
2. the person who obtained consent AND [*See Exception #2*]
3. for studies involving children or cognitively impaired individuals, a parent, guardian, or legally authorized representative.

Exceptions:

1. In some types of studies (e.g., mail-out surveys), the investigator may request a waiver of the subject's signature (see waiver of documentation of consent in Chapter 5 below) when submitting the New Project Application. In such cases, the conclusion of the Informed Consent Document (which could be formatted as a letter to the subject) should inform the subject that returning the survey will be considered evidence of consent.

2. When there is no verbal communication with potential subjects (e.g., mail-out surveys), the signature of the person who obtained consent may also be deleted. Note: the HIPAA Privacy Rule does not permit a waiver of documentation of authorization if the study data include protected health information. Thus, studies which utilize mailed surveys and wish to also obtain HIPAA authorization to access medical record information must include a process for obtaining a *signed* combined consent and HIPAA authorization.

NOTE: An auditor/witness signature line is needed only if specifically required by the IRB or the funding agency/company. However, if this line is included on the consent, the consent must *always* be witnessed and this line signed.

f) Dates

The individual providing consent, permission, or assent needs to sign and date the consent document. In addition, when using a short form of the informed consent (see section C-4 below), the witness line must also include a date.

C. Special Consenting Circumstances & Documents

1. Jesse Brown VAMC Consent Process

The Jesse Brown Veterans Affairs Medical Center requires that the standard Informed Consent Document be copied onto its own template (research applications using eIRB should use the VA template for eIRB). Detailed instructions for developing a consent document for NU IRB approval may be found on the OPRS website. In addition, OPRS has provided a copy of the review guide which is used to evaluate consent documents to ensure they include all of the required elements. Please note that copies of the IRB approved and stamped consent documents must be used for enrolling VA subjects onto a study. In addition, please note that when approved by the IRB, the stamped consent and authorization documents are directly sent by OPRS to the Jesse Brown VAMC Research Office, and will be released to the investigator (by the VA) only after R&D Committee approval.

2. Record of Consent or NU Consent Process

When a research project involves Northwestern Memorial Hospital (NMH), Northwestern Medical Faculty Foundation (NMFF), or Rehabilitation Institute of Chicago (RIC), signed copies of the Informed Consent Documents must be placed in subjects' medical records/charts. In addition, NU researchers are required to maintain their own copies of signed consent documents for all subjects enrolled in research. The investigator (or department) must retain copies of the signed informed consent documents for at least 7 (seven) years after completion and termination of the study. Investigators and departments are responsible for having procedures for maintaining confidential storage and for eventually destroying consent documents and other identifying data so as to preserve the confidentiality of subjects.

3. Assent Process

A written Assent Document shall be used when investigators recruit subjects who, by age or condition (e.g., compromised decisional capacity), are not able to give legally effective informed consent. The "assent" of the child or cognitively impaired adult subject, in addition to written permission from a parent or other legally authorized representative, must be obtained (unless this requirement is waived by the IRB) in order to enroll the subject into the research.. The parent or legally authorized representative signs the informed consent document to verify their substituted judgment giving permission for the subject to participate, and the prospective subject signs the assent document.

The Assent Form documents the child's or cognitively impaired subject's knowledgeable agreement, or assent, to participate in a research project. The investigator should respect the decision of a child or cognitively impaired subject not to participate, even when the parent or legally authorized representative gives permission, unless specifically instructed otherwise by the IRB. The NU IRBs will usually waive the requirement for obtaining assent from minors when:

I. the research has been approved as involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects (this will be communicated in the initial submission approval letters after April 15, 2007), and either:

A. when the IRB has determined that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention, or:

B. the procedures involved in the research hold out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research.

For studies involving minors, the IRB may recommend that several versions of the assent form be provided in order to provide more age-appropriate information. The OPRS website includes assent templates for children who are in the 7-12 age range, and in the 13-15 age range. In addition, an assent script is included for reading to children under 7 years of age. Minors in the 16-17 year old age range should generally be "assented" using the adult informed consent template, with modification to the signature lines (to include the minor giving assent, and the parent or legally authorized representative to sign permission), and a clarifying note should be made at the beginning of the consent/assent document (See Section VI.B.1.d above).

4. Non-English Speaking Subjects & Consent

When an investigator anticipates enrolling non-English-speaking subjects, the protocol must reflect the methods for assuring full understanding, usually with the assistance of an interpreter or by using translated Informed Consent Document(s). If the investigator intends to use a translated version of the Informed Consent Document(s), the IRB must review and approve each translated version(s) prior to use. The credentials of the person who did the translation must be provided to the IRB.

If a non-English speaking subject is unexpectedly encountered, investigators will not have a written translation of the consent document and must rely on oral translation. Investigators should carefully consider both the scientific and ethical ramifications of enrolling subjects when a language barrier exists. If investigators encounter an occasional non-English speaking subjects when there is not time to obtain an IRB approved written translation (e.g., for a clinical trial), they may use one of the translated IRB approved "short form" written consent documents (available on the OPRS website). This translated short form summarizes the elements of informed consent in language understandable to the subject as required by the regulations.

When the short form is used, an interpreter must orally interpret the information from the IRB-approved English consent document into the subject's language. *When this method is used, there must be a witness to the oral presentation.* Only the short form itself should be signed and dated by the subject or the representative. However, the witness must sign and date both the short form and a copy of the full Informed Consent Document, and the investigator who obtains consent must sign and date the full Informed Consent Document. Copies of both the full Informed Consent Document and the short form must be given to the subject or the

subjects legally authorized representative.

5. Waivers & Alterations of Informed Consent

a) Waiver of Documentation of Informed Consent

Under the DHHS regulations (45 CFR 46.117(c)), the IRB may waive the requirement for documentation of the informed consent if the IRB determines that:

- the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality; OR,
- the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

The FDA regulations (21 CFR 56.109(c)) state that a signed consent form may be waived if the IRB determines that:

- the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; OR,
- the requirements in 21 CFR 50.24 for an exception from informed consent for emergency research are met.

Waiver of documentation of consent may mean that no written document is provided to the subject at all, but the waiver of documentation of consent more often means that the subject's signature does not have to be obtained. The IRB may still require that the investigator provide the subject with a written statement about the research, even when granting a waiver of documentation.

b) Waiver or Alteration of Informed Consent (or of Elements of Informed Consent) *Not applicable to FDA-regulated research*

Some research projects would not be possible if informed consent from participants were required. The IRB may consider waiving the requirement for some or all of the elements of informed consent (45 CFR 46.116(d)) only if the study is *not* under the authority of the FDA.

The DHHS regulations state that informed consent may be waived in full or in part if the IRB determines that:

- the research involves no more than minimal risk to the subjects; AND
- the waiver or alteration will not adversely affect the rights and welfare of the subjects; AND
- the research could not practicably be carried out without the waiver or alteration; AND
- whenever appropriate, the subjects will be provided with additional pertinent information after participation.

There are certain types of studies in which some of the elements of consent can be waived. These include, but are not limited to, certain types of ethnographic research, and studies that require deception. If the investigator seeks a waiver of any or all of the elements of consent, the New Project Submission Form should describe the reasons for the request, paying particular attention to an explanation as to why the research project would be "impracticable."

The term "impracticable" means more than simple inconvenience - it means that the research could not be conducted without the waiver.

c) Emergency Exception from Informed Consent and Waiver of Informed Consent Requirements in Emergency Research

Both the FDA regulations and the DHHS regulations allow for some types of emergency research to be conducted without prior consent of the subject or their legally authorized representative. The FDA "exception from Informed Consent" regulations are found at 21 CFR 50.24. On October 2, 1996, the Secretary of DHHS announced under 45 CFR 46.101(i), a waiver of the applicability of the 45 CFR 46 requirement for obtaining and documenting informed consent for a strictly limited class of research, involving research activities that may be carried out in human subjects who are in need of emergency therapy and for whom, because of the subjects' medical condition and the unavailability of legally authorized representatives of the subjects, no legally effective informed consent can be obtained. See the guidance document on the OPRS website for additional information regarding Emergency Research.

D. Privacy and Confidentiality

Protecting the privacy of research subjects and maintaining the confidentiality of data are issues of importance. Federal regulations [45 CFR 46.111(a)(7) (DHHS) and 21 CFR 56.111(a)(7) (FDA)] require that the IRB, when appropriate, only approve research when there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. Confidentiality means the ethical or legal right that information is considered private and will be held secret unless consent is provided permitting disclosure. Privacy is the freedom from unauthorized intrusion or the state of being let alone and able to keep certain personal information to oneself.

By its nature, research may invade the privacy of individual subjects in that it may require the collection, use, or access to identifiable information that would otherwise not be shared with others. When this is required for the purposes of the research, the private information involved should be the minimum necessary to accomplish the goals of the research. The investigator must have reasonable plans to protect the subject's identity, must collect only the necessary identified information to conduct the study, and must have procedures in place to maintain the confidentiality of the research records. Care should be taken in the informed consent document and IRB application to explain the mechanisms that will be utilized to protect this information (e.g., data encryption, numbering or coding schemes, and safely locked files in private offices). Furthermore, the investigator should describe in their protocol or New Project Submission Form who has access to the data and under what circumstances a code system may be broken.

Special Circumstances for Added Protections:

1. Video/Audio tapes and/or Photographs. These media are inherently identifiable, and so it is incumbent on the Investigator to fully inform subjects of these procedures and obtain informed consent before recording the images. The consent process should include mention of plans for final disposition or eventual destruction of these records.

2. HIPAA. If a research study involves protected health information and involves consent from subjects, the consent document signed by the subject must contain the required

elements for an HIPAA Authorization. Use of the combined consent/authorization template addresses this requirement. For more information about HIPAA and protected health information, click on the link on the title of this paragraph.

3. NIH Certificate of Confidentiality and other Safeguards to prevent potential civil or criminal prosecution of the participating human subject.
(from NIH Office of External Research web site)

What is an NIH Certificate of Confidentiality?
Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect the privacy of research subjects by protecting investigators and institutions from being compelled to release information that could be used to identify subjects with a research project. Certificates of Confidentiality are issued to institutions or universities where the research is conducted. They allow the investigator and others who have access to research records to refuse to disclose identifying information in any civil, criminal, administrative, legislative, or other proceedings, whether at the federal, state, or local level. Identifying information in this context is broadly defined as any item or combination of items in the research data that could lead directly or indirectly to the identification of a research subject. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring privacy to subjects.

For what types of research might I obtain a Certificate of Confidentiality?
Certificates can be used for biomedical, behavioral, clinical or other types of research that is sensitive. Sensitive means that disclosure of identifying information could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation.

Examples of sensitive research activities include but are not limited to the following:

- Collecting genetic information;
- Collecting information on psychological well-being of subjects;
- Collecting information on subjects' sexual attitudes, preferences or practices;
- Collecting data on substance abuse or other illegal risk behaviors;
- Studies where subjects may be involved in litigation related to exposures under study (e.g., breast implants, environmental or occupational exposures).

How long is the protection afforded by the Certificate in effect?
A Certificate of Confidentiality protects personally identifiable information about subjects in the research project while the Certificate is in effect. Generally, Certificates are effective on the date of issuance or upon commencement of the research project if that occurs after the date of issuance. The expiration date should correspond to the completion of the study. The Certificate will state the date upon which it becomes effective and the date upon which it expires. A Certificate of Confidentiality protects all information identifiable to any individual who participates as a research subject (i.e., about whom the investigator maintains identifying information) during any time the Certificate is in effect. An extension of coverage must be requested if the research extends beyond the expiration date of the original Certificate. However, the protection afforded by the Certificate is permanent. All personally identifiable information maintained about participants in the project while the Certificate is in effect is protected in perpetuity.

Are there circumstances when I am allowed to disclose subject research information?
While Certificates protect against involuntary disclosure, investigators should note that research subjects might voluntarily disclose their research data or information. Subjects may disclose information to physicians or other third parties. They may also authorize in writing the investigator to release the information to insurers, employers, or other third parties. In such cases, researchers may not use the Certificate to refuse disclosure. Moreover, researchers are not prevented from the voluntary disclosure of matters such as child abuse, reportable communicable diseases, or subject's threatened violence to self or others. However, if the researcher intends to make any voluntary disclosures, the consent form must specify such disclosure.

How do I let subjects know that a Certificate of Confidentiality is in effect for the study?
In the Informed Consent Document, investigators should tell research subjects that a Certificate is in effect. Subjects should be given a fair and clear explanation of the protection that it affords, including the limitations and exceptions noted above. The Northwestern University Informed Consent Document template contains suggested language to describe the protection afforded by a Certificate of Confidentiality.

How do I apply for and obtain a Certificate of Confidentiality?
The investigator may choose to apply for a Certificate of Confidentiality on his or her own, or the IRB may require that an investigator obtain a Certificate prior to conducting the research. Investigators who intend to apply for a Certificate of Confidentiality are welcome to contact OPRS regarding procedural steps for IRB approval and communicating with NIH.

What are the procedures at NU?
Because NIH requires that the investigator submit an IRB-approved Consent Document that includes mention of the Certificate of Confidentiality, the investigator must obtain IRB approval before applying for the Certificate. This means that the investigator will have in hand a stamped, approved Informed Consent Document that describes the special protections of a Certificate, but will not yet have the Certificate itself. Therefore, in order to ensure that the Consent is not used before obtaining the Certificate, the OPRS places a "watermark" across each page of the stamped Consent that indicates it may not to be used to enroll human subjects.

The PI should apply for a Certificate following the instructions on the NIH web site (http://grants.nih.gov/grants/policy/coc/appl_extramural.htm). The application letter must be signed by a Northwestern University institutional official so the PI should bring the application letter to the Office and the OPRS will obtain the institutional official's signature and return the signed letter to the PI.
NU Procedures Summarized:

1. Submit research project application to the OPRS. Include an Informed Consent Document with the Certificate of Confidentiality Language inserted.
2. After project approval by the IRB, you will receive an IRB stamped, approved consent document with a “watermark” across each page. YOU MAY NOT USE THIS CONSENT DOCUMENT TO ENROLL SUBJECTS AT THIS TIME.
3. Apply for the Certificate following the instructions of the NIH web site (http://grants.nih.gov/grants/policy/coc/appl_extramural.htm). This involves crafting an application letter to the NIH.
4. After finalizing the application letter, bring it to OPRS. OPRS staff will obtain

the NU institutional official's signature and will return the signed letter to you.
5. Send your application to NIH and await Certificate.
6. When you receive the Certificate from the NIH, you will need to submit a revision application. Attach a copy of the certificate.
7. The IRB will review the application and upon approval the "watermark" will be removed from the approved consent document and it will be released to the PI.

E. Recruitment and Subject Compensation Issues

1. Recruitment

Recruitment strategies in any form must be reviewed by the IRB PRIOR to their implementation, because they represent the earliest intervention in the informed consent process. There are some recruitment strategies that are either not allowed or allowed at NU. The collection of finder's fees or direct recruitment incentives, and the use of "cold calling" of potential research subjects are not permitted.

a) Finders Fees/Recruitment Incentives:

NU policy prohibits the acceptance or use of finder's fees, direct recruitment incentives, or bonuses of any type to enroll study subjects. A finder's fee or recruitment incentive may include bonuses given by sponsors to investigators or research team members (coordinators) to boost enrollment or referral fees given to physicians for referring his/her patients to another investigator's study. Any payment must be based on project-related effort consistent with the individual's salary schedule and must be made through the NU payroll system (so as not to exceed 100% effort). Payments to investigators, research team members, or subjects for recruitment that are provided to the individual outside of the NU system are NOT allowed.

b) Cold Calling:

NU policy generally restricts the use of "cold calls" to recruit subjects to research studies. An introductory letter or other informational material must first be sent or given directly to subjects prior to telephone contact. Exceptions may be made on a case-by-case basis, for example, if the potential subjects have previously agreed to be listed on a research registry for future research studies, are currently participating in a study conducted by the same investigator, or are frequently seen by or are well known to the investigator.
Acceptable strategies for recruitment of subjects for research can be varied and may include:

- Advertising to promote the study
- Direct communication with identified groups (patients, students, personnel)
- Referrals from other sources such as other physicians or disease registries

c) Advertising Materials

Recruitment materials, including brochures, flyers, advertisements, audio tapes, video tapes, and letters to potential subjects, must not contain language or incentives that are designed to create undue influence. The information in recruitment materials should be an accurate presentation of the research study purpose and/or procedures.

Any material aimed at recruiting potential subjects into a study (including the final copy of the printed advertisement, audio or video tapes or websites) must be reviewed and approved by the IRB prior to being used. Suggested guidelines for an advertisement or recruitment letter or webpage appear below:

- Include the purpose of the project and/or briefly state what is expected of the subject.
- Include the time commitment required of the subject.
- Include the investigator's University department affiliation and where the research will take place.
- List a contact name and phone number.
- Do not include the name of commercial sponsors or products.
- Avoid phrases such as "help needed" or "subjects wanted." The recommended wording is "you are invited" or "participants invited."
- If participants will be paid for their time/effort, it is recommended that the wording "Compensation Available" be used, rather than specifying a specific amount. Compensation should not be excessive to the nature of the project. If the investigator wishes to include a specific amount of compensation in an ad, the Application should include the investigator's justification as to why this is needed. Also, do not emphasize (for example, in large or bold type) the payment or the amount to be paid.
- Do not state or imply a certainty of a favorable outcome or other benefits beyond what is outlined in the consent document and protocol.
- Do not make claims that the drug, biologic or device is safe or effective for the purposes under investigation.
- Do not make claims that the drug, biologic or device is known to be equal or superior to any other drug, biologic, or device.
- Do not use terms such as “new treatment,” “new medication,” or “new drug” without explaining that it is investigational.
- Do not promise “free medical treatment,” when the intent is only to say subjects will not be charged for taking part in the investigation.

d) Use of NU staff, students or faculty as research subjects

(1) NU Students as Research Subjects

Consistent with an overall concern that no research subject should be unduly influenced to participate in research, researchers should take particular precautions to avoid the unintentional or subliminal coercion that may occur when a potential research subject is also a student. For this reason, researchers should usually avoid using their own students as research subjects. Researchers who wish to use their own students must provide a good scientific reason, rather than convenience, for selecting those students as research subjects. The research project should be relevant to the topic of the class, and participation should be part of the learning experience for the students.

In instances where investigators can provide a good reason for using their own students in their research, the IRB generally requires that someone other than the investigator (instructor) obtain informed consent and collect the data. When this is not possible, the IRB will consider other methods for obtaining consent and collecting data that would not reveal to the instructor whether or not a student participated in the research project until after final grades have been determined. The students should be informed of what these procedures are in the Informed Consent Document.

(2) Extra Credit

The IRB may approve projects that give extra credit to students who participate in a research project only when alternative means of obtaining equivalent extra credit with equivalent effort is made available to students who do not wish to volunteer as research subjects. The IRB carefully reviews the alternatives to ensure that students are not being coerced into participating. For example, if volunteering for a survey project takes 30 minutes and the student's output is not evaluated for its quality to determine whether extra credit is given, the alternative should involve 30 minutes of effort and the output should not be evaluated (beyond assurance that a good faith effort was made).

The Informed Consent Document should make clear the consequences of withdrawing from a project prior to completion (e.g., will extra credit be given despite withdrawal?). As a general matter, the IRB favors giving credit even if the subject withdraws, unless the student withdraws immediately or there is clear evidence of bad faith on the part of the student.

(3) Faculty Use of Class Assignments as Research Data

There may be circumstances when an investigator wishes to use required class assignments (e.g., journal entries in a communications study course) in his or her research. The course syllabus should clearly state that the assignments are required for the course, but that at the end of the semester, the instructor will ask the student to give permission to use the assignments for research purposes. It should be clear that participation will not affect a student's grade. The syllabus, informed consent document, and IRB-approved protocol should describe the procedure to be used to ensure that the instructor does not know who has consented until after final grades have been determined.

(4) Departmental Subject Pools

Some departments or colleges employ "subject pools" where students enrolled in introductory courses are recruited by investigators from both within and outside of the department for participation in research projects. Departments or colleges may impose their own standards for the type of research that may be conducted in this setting, and for who may have access to such subjects. Investigators who recruit from "subject pools" are still required to submit their projects to the IRB for review and approval. Beyond the considerations outlined above, academic units may impose their own additional constraints on using students as research subjects. OPRS staff or relevant IRB members are available for consultation in setting up or revising procedures related to departmental subject pools. While not required, departments may consider the departmental subject pool policy and procedures as a “recruitment and subject registry” protocol and may submit it to the IRB for review and approval.

(5) NU staff or Research Team members as Research Subjects

The recruitment of NU staff as research subjects should be undertaken with caution. It is

important that supervisors in research settings refrain from recruiting or enrolling their own employees and staff to participate in their research. Because of the power imbalance, and the perception of undue influence, these situations should be avoided. However, the recruitment of NU staff members that are unaffiliated with the research is acceptable.

(6) Referrals from other sources

Referrals from other sources can include the sending of information about ongoing research to other local sources asking that they either pass the information on to potential subjects, or obtain written permission to refer the subject to the study investigator. It can also include distributing study information to appropriate advocacy groups or student groups perhaps by giving lectures or presentations to these groups. As stated previously, this type of recruitment strategy would require review and approval by the IRB prior to implementation but is otherwise not discouraged as long as you follow the strategies as outlined in the "Advertising Materials" section above.

2. Subject Compensation

Payment for participation in research may not be offered to the subject as a means of undue influence, where it might cause someone to assume risks they would not otherwise assume. Rather, it should be a form of recognition for the investment of the subject's time, loss of wages, or other inconvenience incurred. Payments should be based on the research subject's time and/or reimbursement for reasonable expenses incurred during his/her participation in the research study. This could include payment for parking, lodging or transportation. For this reason, compensation should not usually be withheld contingent on the subject's completion of the study. In most cases involving continued participation, compensation should be given on a reasonable prorated basis to avoid the impression that the investigator is coercing the subject to continue in a study or is punishing the subject for choosing to withdraw.

VII. New Project Applications and IRB Review and Approval.

Investigators are required to submit an application for IRB review PRIOR to initiating a research project. In May, 2006, the OPRS began allowing new project applications be submitted using a new electronic database system, eIRB. This online application submission tool uses "smart form" technology to guide investigators through the application process. Instructions for completing the new project application are contained within each section of eIRB. Training sessions are held when new aspects of the system are introduced, training materials have been developed and are posted on the OPRS website, and OPRS staff are available for consultation and help using the system. For additional information, please refer our eIRB webpage. Logging into the eIRB system requires a secure network connection, which will require VPN access if you are logging in from outside of the network. The initial login screen allows you to log into the system as well as to report any technical problems you might have had in accessing or using the system.

In addition, until notified otherwise, OPRS will continue to accept initial applications from the research community using our forms which are available online on our "Forms" page.

A. Signatures

1. The Signature of the Principal Investigator

In both eIRB and paper submission processes, there is a requirement for the signature of the Principal Investigator (PI), which is required by OPRS before a submission will be forwarded for review by the IRB. While OPRS may exercise judgment to relax this requirement under extenuating circumstances, the signature of the PI on the application will be required before correspondence documenting the approval of the IRB will be provided.

The signature of the PI on an IRB submission is an important certification from the individual responsible for the conduct of the study that they are assuming responsibility for the truth and accuracy of the information contained in the submission, as well as for the overall conduct of the research. NU Investigators should pause to reflect on the implications of their signature before they sign these forms. For this reason, OPRS has included a number of bullet points on both the paper submission forms and the eIRB form which remind our researchers of their responsibilities under the federal regulations and this policy.

NU permits faculty members to be principal investigators on a research application. Among its other responsibilities, the IRB evaluates the qualifications of the investigator to determine whether or not the investigator is qualified to conduct the research proposed. If the IRB needs additional documentation of the experience or training of the investigator, the IRB may directly request access to the investigator's CV, or other evidence of their training or expertise. When individuals have both faculty and student status at NU, they will need to clarify in the application under which status they are planning to conduct the research, and they will need to follow the procedures for student research when the research is being conducted under their student role within the University. NU staff may be granted investigator privileges after a review of their credentials by the Vice President for Research or his designee. OPRS may be contacted directly for advice about this process.

2. Departmental Endorsement

In addition to endorsement by the PI, there must also be endorsement from the department or section head (usually by the Department Head or Section Chief), or their designee. Under the paper submission process, the signature of the "department approver" was specifically rendered only as official recognition that they were informed about the existence and status of the proposed research. Under eIRB, OPRS has asked for the approval of the department with this signature, reflecting a more significant rendering by the department of judgments that the investigator is capable of conducting the research proposed, and that the investigator has access to sufficient resources to adequately conduct the research as proposed. The meaning of departmental endorsement will be clarified further in future versions of this policy.

3. Faculty Sponsor for Student or Guest Research

A student or "guest" researcher may be listed as evidence that they were aware of the existence and must sign the application as the supervisor. The University requires that the faculty sponsor assume meaningful supervision of the research process, must be reasonably available to assist in the resolution of and reporting of any problems that may arise during the course of the research, must assure the IRB that only sufficiently qualified individuals will be responsible

for the conduct of the research, and ultimately must assume direct responsibility within the University for the overall conduct of the research. In order to remind faculty sponsors of their responsibilities, OPRS has included a number of bullet points before the signature line on the paper forms, and on the webpage for electronic signature in eIRB.

B. Research Team

1. Authorized Personnel

As part of your research application, you will be asked to list all members of your research team for the project. This listing should include all of the individuals who will have a significant role in the conduct of the research. At NU, we refer to these individuals as "authorized personnel." Authorized personnel includes all Principal Investigators and Co-Investigators, as well as any individuals who are named as contact persons in the informed consent documents or recruitment materials for research, who are obtaining informed consent to participate in research, or who are obtaining individually identifiable health information under an NU Business Associate Agreement. In addition, you should include any individuals who are named on a grant, contract, or other funding application (related to human subjects research), or who are listed on a FDA form 1572 (when NU or an NU faculty member is the sponsor of the research).

In the initial application for IRB approval, and in the continuing review application, you will need to include this listing of authorized personnel. We need to have their name and departmental affiliation, as well as a description of their role in the project, specific expertise as it may relate to their role in the project (e.g., certified biofeedback technician), their role in the consent process, and finally the date on which they completed the required initial training in human subject protections.

Before participating in human subjects research at or sponsored by Northwestern University, all authorized research personnel must have completed the initial training requirement in human subject protections. The principal investigator is ultimately responsible for ensuring the adequate training of his research team and must ensure that the research staff receives education appropriate to their role in the research project. Information about live and online training sessions that can meet the initial requirement is available on the OPRS website.

You will not be able to submit your application until all members of the research team have met the University's this requirement. You may submit an application without listing individuals who have not yet met the requirement, and then later submit a revision to include them, but they may not participate in the research until they have received the training and have been included in the IRB-approved study.

If your research includes personnel not affiliated with the Northwestern University (that is, they are not faculty, staff, or students of NU) who will be conducting or are engaged in research, they also need to have documentation of basic training in human subject protections. They may register with CITI to complete the online training and affiliate themselves with Northwestern University, or if they are affiliated with another institution, you may provide OPRS with documentation that they have met the training requirement at another institution. See Section X, Special Topics in this policy for additional guidance when engaging NU in Collaborative Research.

2. Other Members of the Research Team

The Principal Investigator is responsible for ensuring that the whole team of individuals who participate in the conduct of the research have adequate education in order to discharge their duties in a manner that is consistent with the federal regulations for protection of human subjects as well as with this policy and with the specific requirements of the NU IRB. If OPRS can assist you with developing or providing education for individuals who are part of the team, but not within the authorized personnel list, please feel free to contact the office and request such assistance from the IRB Manager of Training and Quality Assurance.

C. Supporting Documentation

The New Project Submission Form must be accompanied by some basic materials, when appropriate. Some of the materials that you may need to submit includes:

- Informed Consent Documentation. Depending on your study, this may include: the standard ICD, the Jesse Brown VAMC ICD, Assent documents. To create any of these documents, you will often need to start with one of the consent templates available on the OPRS website. You should download them to your computer, make the appropriate edits, and then submit them for review. Please note there are separate templates for paper submissions and eIRB, and separate templates for biomedical and social-behavioral research. Finally, there are biomedical templates with and without HIPAA authorization language.
- Recruitment materials. These may include brochures, flyers, advertisements, audio-tapes, video-tapes, or other materials used to inform people about the study.
- The complete grant proposal. This should include the budget pages and appendices.
- The study protocol & sample consent, if available. If the study involves a clinical or therapeutic intervention, this may include a pharmaceutical company protocol or investigator-initiated study protocol. Whenever the research is a DHHS Cooperative Group study, it is required that the sample consent be submitted along with your NU-specific consent documents. Whenever another sponsor-approved consent model is available, it should be included.
- Data collection materials. This would include questionnaires, surveys, stimuli, etc., that will be used as part of the procedures in the study.
- Phone or other verbal script(s). You will need to include these for situations that will involve providing information to potential participants via telephone, or obtaining consent or assent through the use of a verbal script.

For collaborations with non-NU entities:

- Letter(s) of agreement. If you are collaborating with an outside agency, company or clinic and that non-NU entity is giving you access to its clients, files, or premises, you will need to attach a letter of agreement from that agency that confirms knowledge of the project's purpose and permission for the investigator to conduct the study there. This is not required when the non-NU entity is NMH, NMFF, RIC, JBVAMC, CMH, or ENH.
- Documentation of local IRB approval at the other entity (required if the other entity is engaged in the research, See Section X. A. 2 for more information about "engagement in research")
- Individual Investigator's Agreement. See the section in Special Topics on Collaborative Research.

For studies that require review by the Pharmacy & Therapeutics Committee or involve investigational drug interventions:

- Investigator's Brochure. You will need to attach a copy of the Investigator's Brochure for the investigational drug under study.
- Investigational New Drug (IND) number documentation. If the study involves an investigational drug, you will need to attach documentation of the IND number from the sponsor (if this is not indicated on the Investigator's Brochure or protocol). In the case of investigator-held INDs, a copy of the FDA letter that informed the PI of the IND number.
- G-12 form. If the study involves an investigational drug, or if FDA-approved drugs are being used off-label, you will need to fill out and attach a G-12 form.

For studies that require review by the Radiation Safety Committee:

- The appropriate Radiation Dosimetry Form

In eIRB, there are additional instructions regarding how to attach your supporting documentation to the electronic application. OPRS staff members are also available to respond to questions by e-mail or phone. We are also available to consult individually with you on how to use the eIRB system.

D. Application Processing/Workflow

Once you have submitted your project on paper, or electronically through eIRB, it will be assigned a unique IRB study identification number. The IRB ID number remains with the study and is never reused. The IRB ID number appears on all correspondence.

1. Administrative Pre-Screening

All applications are screened by OPRS staff. At the pre-screening step, the application is being reviewed only at a superficial level to ensure that the correct form or forms appear to have been used, that all of the required questions appear to have been answered within the application, and that all required attachments appear to be present. If the application appears to be missing one of these elements, the application will be held at the administrative pre-screening stage until the attachment is received. Only complete applications will be accepted for review. OPRS will send an e-mail notification to the research team, including the PI and the submission preparer indicating what components we believe are missing from the submission.

2. OPRS Staff Review

Once an application is accepted for review, the application is assigned to an IRB Coordinator, Senior Coordinator or IRB Manager for a more in-depth review prior to being sent for IRB member expedited review or being assigned to a primary reviewer in preparation for a convened board meeting.

3. Review of Claims of Exemption

Senior members of the OPRS staff, who are also designated as alternate IRB members will review submitted claims of exemption. If they lack requisite experience or training to make a

determination as to whether or not the research falls into one or more of the exempt categories, they will have a scientific member of the IRB review the application. The review of a claim of exemption is designed to accomplish two tasks: providing a determination independent of the Investigator that the research is exempt human subject research, and that the proposed activity is consistent with the University's commitment to ensuring the principles of the Belmont report (See Section III) are adhered to in all human subject research.

4. IRB Review

OPRS staff make a pre-determination as to whether proposed research is reviewable by expedited procedures, but the IRB is the ultimate authority for making this determination. If expedited review seems to be appropriate, the chair or designated OPRS staff may correspond with the investigator with requests for additional clarification or materials prior to determining the appropriate review process. If the project requires full board review, the OPRS notifies the investigator of the meeting date at which the project will be reviewed. The OPRS distributes copies of the New Project Submission Form, Informed Consent Document, and other supporting materials to members attending the meeting at least one week in advance of the meeting. The IRBs use a primary reviewer system, in which two IRB members are assigned the role of reviewing and presenting the study to the members at the full board meeting. If there is a federal funding award connected to the research study, then the primary reviewer also reviews the grant application itself (or the pharmaceutical protocol and Investigator's Brochure). The primary reviewer IRB member may contact the investigator for clarification prior to the meeting date. Any requests for revisions will come from the full board itself after the meeting.

E. Criteria for Approval

In order for the IRB (or IRB chair or designee in the case of expedited projects) to approve a project, the following requirements must be satisfied [45 CFR 46.111 (DHHS) and 21 CFR 56.111 (FDA)]:

- Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- Risk/Benefit Ratio. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
- Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
- Informed consent sought. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to

the extent required by [45 CFR 46.116 (DHHS) or 21 CFR 50 (FDA)].

- Informed consent documented. Informed consent will be appropriately documented, in accordance with, and to the extent required by [45 CFR 46.117 (DHHS) or 21 CFR 50.27 (FDA)].
- Data safety monitoring. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- Protect privacy & maintain confidentiality. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- Vulnerable Populations. When subjects are likely to be members of a vulnerable population, there are appropriate additional safeguards in place to protect the rights and welfare of these subjects.

F. Determining the IRB Approval Period

When approving a research protocol, the IRB may assign it an approval period of up to one year (365 days). At the end of that time, IRB approval lapses unless the investigator has submitted and received approval for a continuation of the research (continuing review application).

The IRB may assign a shorter approval period, linked to either time, or subjects enrolled in the study, or other factors as the IRB may consider appropriate (there must always be a time period, but the IRB can elect to condition the approval period like in the following example: "the research is approved for up to 6 months, or until the 1st two subjects have completed the induction phase of the study."). The length of time for the approval period is to be determined based on the risk assessment of the IRB. For studies that are presumed to be of high risk, when the magnitude and frequency of possible harm are not yet known, the IRB may require submission of a continuing review application sooner than one year. When there seems to be a higher frequency or magnitude of risk than previously anticipated, possibly based on a small sample of subjects enrolled, the IRB may approve a shorter approval period in order to be in a position to do a comprehensive review of the experience gained before a full year has passed. In addition, when the IRB has concerns that investigators are conducting research in such a manner that they may not be complying with human subject protection regulations, or the requirements of this policy or of the IRB, then the IRB may assign shorter review cycles as a mechanism for providing more careful oversight over the conduct of the research with the goal of ensuring the ongoing safeguarding of the rights and welfare of subjects.

G. IRB Monitoring/Audit of Research

The NU IRBs retain the authority to monitor, or have a third party monitor the consent process and the research. The IRB requires that researchers submit copies of any monitoring reports when their studies have been monitored during a period of IRB approval. In addition, if the IRB has concerns about allegations of non-compliance, the IRB may request that the Human Protections Administrator initiate an audit of the relevant aspect of the research in question. The NU IRBs often work with other components of the Human Subject Protection Program to facilitate this monitoring or auditing function (including Office for Research Integrity, the University Auditors office, the Cancer Center and NU-CATS Institute.

When the IRB has concern that an investigator has been non-compliant with the federal regulations governing human subject protections, with the requirements of this policy or of the IRB, then the IRB shall require a process for verifying that the conduct of the research is promptly corrected. The IRB shall then also establish a mechanism for verifying that there are

not material changes to the IRB approved protocol or research materials at a level commensurate with the non-compliance and the risks involved.

H. Revisions Prior to Final Approval

For studies that are classified as exempt or expedited, the investigator must satisfactorily respond to all requests from the IRB or OPRS for revisions and/or clarification, or to provide additional information. Exempt application and expedited IRB reviews may require modifications for approval, but no research will be disapproved except by a convened panel of the IRB. When the expedited reviewer determines all revisions have been made and that the study meets all criteria for approval, s/he approves the project and for expedited studies determines the interval for the next continuing review (not to exceed one year). Exempt human subject research has no approval period, and no continuing review will be required—only revisions that might affect the category of exemption, or changes to the recruitment or consenting process.

For studies that require full board review, the investigator receives notification of the determinations of the IRB via e-mail. This correspondence documents the IRB's determinations. If the IRB requires minor revisions prior to final approval, the letter will indicate that the study is pending modifications, meaning that it will be approved when we have received the required revisions and they have been reviewed by expedited processes to ensure they have been made as requested. Minor revisions include revisions to the protocol and/or documentation that are specifically required by the IRB. If the investigator(s) provides those modifications as requested, then a designated IRB member may review and approve the submitted revisions, giving IRB approval to the project as a whole.
If the IRB requires revisions or clarifications that impact on the IRB's determinations regarding the criteria for approval (See Section VII. F), then the letter will indicate that the study has been deferred. The investigator must respond in full to all issues raised by the IRB prior to the project being returned to the full board for further review and approval.

You may see the following actions taken by the IRB in regards to your project after it has been reviewed by the full board:

- Approved. This means the application has been approved by the IRB. The approval letter will be accompanied by approved consent documents that have been stamped by OPRS (unless your research is conducted at the Jesse Brown VAMC, in which case OPRS will forward your stamped consent document to the R&D Committee—which will release it upon R&D Committee approval).
- Modifications Required. This means that the application is approved pending minor and specific revisions and response by the PI as indicated in the letter. The PI/delegate(s)/contact persons on the research team receive an e-mail notification by OPRS of this status. The PI must respond to this letter and make the required changes before the research can receive final approval.
- Deferred. This means that the application was found to require significant changes or clarifications at the convened meeting, and that those requested changes, clarifications, or additional information will need to be provided back to the convened meeting before the research may be approved. The OPRS must receive a response from the PI prior to scheduling the protocol for re-review at a future full board meeting.
- Disapproved. This means the application was disapproved after review by the full board. The PI/delegate(s)/contact persons on the research team receive an email notification by OPRS of this determination. In that notice, the investigator will be

informed of the reasons for the disapproval, as well as an indication of what changes would be required for the research to be approved. The investigator will also be given an opportunity to respond to the disapproval determination in person or in writing.

- Withdrawn. This means the application has been withdrawn at the request of the PI.

I. Notification of Approval

Along with written notification of approval by the IRB, OPRS will provide stamped approved Informed Consent Document(s) and other materials (e.g. letters to subjects, ads) with the IRB ID number and the date of approval and approval period. Questionnaires and data collection forms are generally not stamped.

While OPRS is responsible for maintaining the IRB files and paperwork for the University, the Principal Investigator is also responsible to maintain accurate files of IRB correspondence, approvals, and research records. These records should be maintained for at least 7 (seven) years following the close of the study, or for the time specified in the specific contract supporting the research, or in accord with other university policies. With the implementation of eIRB, this requirement should be much simpler for investigators as all correspondence and IRB documentation related to the project is available electronically through the eIRB application.

The approval letter should inform the investigator of the type of review (full board, expedited, or exempt), and the date of next continuing review. This letter reminds investigators that changes in research activity may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to subjects.

The PI and research staff is required to use copies of the stamped consent documents when enrolling research subjects unless a documented exception has been granted by the IRB.

J. Limitations on IRB-Approved Projects – Rules to understand before you begin

1. Your Approval is Limited to your specified procedures

An approved project is limited in its conduct to the recruitment activities and study procedures that were described in the initial New Project Submission Form. In other words, the investigator may perform only those activities that s/he described. If the investigator wishes to change the study recruitment activities or procedures from what was initially described, s/he should submit a Revision Submission Form for IRB review and approval prior to implementation (see next chapter for more information on Modification/Update applications).

2. Your Approval is for a Limited Time Period

Each project requiring IRB approval (all non-exempt human subjects research) is approved for a specified period of time and research activity may not continue beyond that date without IRB approval of a Continuing Review application (see next chapter for more information on Continuing Review applications). The Approval documentation indicates the due date for the next continuing review. The IRB may require that review occur more frequently than annually,

for example after the first several subjects have been enrolled. Such determinations are documented in the full board meeting minutes sent to the investigator. In such cases, it is the investigator's responsibility to submit a Continuing Review application after the specified number of subjects. OPRS has in place a process for sending reminder e-mail notices, but the research retains individual responsibility for ensuring ongoing IRB approval for the research.

3. You are Approved to Enroll a Limited Number of Subjects

All projects are approved to enroll only the number of subjects indicated in the New Project Submission Form. If the investigator finds that actual enrollment is approaching that limit, and additional subjects are needed to address the scientific aims of the project, a Revision Submission Form should be submitted requesting an increase in the number of subjects to be enrolled in the study. The application must be approved before additional subjects may be enrolled beyond the originally approved number.

4. When is a subject considered enrolled?

An enrolled subject is anyone who has signed an Informed Consent Document, whether or not that individual actually completes the study. Thus, someone who signs a consent document but is determined during screening to be ineligible, or chooses not to continue, must still be counted as an enrolled subject.

5. You are Limited to the use of your Currently Approved Consenting Materials

Finally, only the current, approved Consent Document may be used for documenting informed consent. Documenting consent on a Consent Document on or after the expiration date stamped on that Document is not permitted and may not constitute valid consent. With each Continuing Review, the investigator receives newly-stamped versions with the approval notification. Even if the content is identical, you are expected to use the current, stamped version of all stamped materials.

K. Appeal of IRB Decisions

Investigators may appeal any IRB determination, including IRB requirements for specific changes in the protocol and/or consent documents(s). If the application is being reviewed under expedited procedures, the investigator should initially make an appeal to the IRB reviewer who has made the determination(s) under question. This may be done simply be responding to the IRB correspondence (usually sent to you by e-mail). If the investigator is not able to resolve the issues directly with the reviewer in this manner, the investigator may request a re-review of the application and the expedited review requirements by a convened IRB panel. Such appeals need to be made in writing to OPRS.

If the full board IRB decides to require specific changes or to disapprove a research activity, the correspondence from the IRB will provide the reasons for its decision. The investigator may appeal any of the requested changes or the disapproval. Such appeals should be submitted in writing as a response to the IRB letter, and will be reviewed by the same panel that made the initial determination under question. Such appeals will only be reviewed at a full board

meeting. The basis for an appeal must include new information that was not previously submitted to or considered by the IRB, and cannot simply be a request for re-review of the project. The investigator should provide a rationale for the appeal and copies of any other relevant supporting documentation. If the appeal requires discussion or explanation beyond what is provided to the board in written format, the investigator may be invited by the Chair to attend the full board meeting at which the appeal is presented. The investigator is invited for the purpose of answering questions and participating in a discourse with board members. The investigator will then be required to leave the room prior to the IRBs final discussion and vote on the issues. The IRB will notify the investigator in writing of the discussion and vote on the appealed issue(s).

In the case of a decision by the IRB to disapprove, suspend, or terminate a project, the decision may not be reversed by any other person or entity including the Vice President for Research, or any other officer/agency of the Northwestern University, state government, or federal government.

L. Other Committees Reviewing Human Subjects Research

1. NU Committees

The OPRS seeks to integrate the NU IRB review processes with the evaluations/reviews of other institutional committees. Although IRB review is a separate and independent review, including a review of the science (this is required in order to determine that the research meets the criteria for approval; See Section VII. F), the IRB should, whenever possible, benefit from the scientific reviews that may already have been completed for the research project, hopefully eliminating any unnecessary redundancy or variability in the complex review process.

2. External reviews

Investigators are encouraged, but not required, to provide documentation along with the IRB submission of prior external reviews. This can include copies of the study section "pink sheets," relevant FDA review documents, and documents relating to review of protocols by another IRB.

VIII. Responsibilities After Initial IRB approval.

Investigators have a variety of IRB communication and record-keeping responsibilities after their protocols are initially approved by the IRB. The section below includes many of the standard responsibilities, but investigators may have additional responsibilities from the funding agency or other regulatory agencies.

A. Modifications

Any change in the conduct of a study must be reviewed and approved by the IRB prior to implementing the change except when the change is necessary to eliminate apparent immediate hazards to subjects. Modifications to an approved project should be submitted on a Revision Submission Form. If your project was initiated in eIRB or you have transferred the project to the eIRB system via the transition/Revision process, you will need to submit any future revisions through the eIRB system. Instructions for the completion of these applications are

contained within the eIRB system.

Minor modifications are modifications to a research project and/or consent documents that pose no additional risk to subjects (e.g. changes in title, co-investigator(s), funding sources), or only minor changes to the consent document (e.g., spelling and grammar changes rather than meaningful content changes). To be considered a minor modification, it must also maintain similar or increased safeguards to protect the subject. These minor modifications may be approved by the expedited review procedure. More extensive modifications, including any change to the research that affects the IRBs determinations required for approval of the research (See Section VII. F) will require full board review if the research originally required review by a convened meeting of the IRB.

Once a PI has received a protocol amendment from a study sponsor, it is the PI's responsibility to submit the amendment in a timely manner for IRB review and approval. Based on guidance from the FDA, potential subjects who meet eligibility criteria under a pending amendment to the protocol **may not be enrolled** until after the amendment is approved by the IRB. Further, the FDA and the Sponsor will hold the PI responsible for compliance with this requirement. The sponsor does not have the authority to override this FDA regulation, and therefore it is inappropriate for the PI to request "special permission" from the sponsor to implement any aspect of the amendment before IRB approval. Rather, the PI should move as quickly as possible towards submitting the amendment for IRB approval.

B. Modifications made without prior IRB approval

The investigator is required to promptly notify the IRB of any changes made without IRB approval to eliminate apparent immediate hazards to subjects using the Protocol Deviation/Violation Form. The IRB will review these modification forms, usually at a convened meeting, in order to determine that any changes made by the investigator to eliminate apparent immediate hazards to the subjects were consistent with ensuring the subjects' continued welfare. When changes to the research need to be made (rather than a modification for a particular subject), the Protocol Deviation/Violation Form should be accompanied by a Revision Submission Form. The IRB will review for approval any accompanying revisions to the research. However, since the Protocol Deviation/Modification form represents changes that were made to the research protocol without prior IRB approval, the IRB will only acknowledge receipt and review of these submissions.

In response to a Protocol Deviation/Modification report, the IRB may simply acknowledge the report, meaning the steps taken seemed appropriate to the panel and no further action is being required. In addition, the IRB may request additional information of clarifications relating to the event and the decision to deviate from approved procedures, may request additional corrective actions be proposed by the investigator in order to minimize the likelihood of recurrence, or may propose corrective actions the investigator needs to undertake in order to minimize the likelihood of recurrence or to ensure the safeguarding of the rights and welfare of the subjects.

On occasion OPRS receives questions about whether or not "protocol violations" or "protocol deviations" need to be reported to the IRB. Please refer to Section C of this Section of the policy for more information on reporting requirements.

C. Continuing Review

The IRB is required to review and approve all non-exempt human subject research projects at intervals appropriate to the degree of risk, but not less than once a year [45 CFR 46.109(e) (DHHS) and 21 CFR 56.109(f) (FDA)]. This is called "continuing review." Continuing review for non-exempt research is required to occur as long as the research remains active for long-term follow-up of the research subject, even when the research is permanently closed to the enrollment of new subjects and all subjects have completed all research-related interventions and to occur when the remaining research activities are limited to collection of private identifiable information.

If a project initially received expedited review and risks to subjects remain no more than minimal risk, the continuing review may be expedited. If a project initially received full board review, the project generally requires full board continuing review. Investigators are encouraged to submit their continuing review applications 30-45 days before IRB approval expires.

1. Due date for submitting an application for continuing review

It is the Principal Investigator's responsibility to submit an application for continuing review in sufficient time to permit the IRB to review and approve the application **prior to its expiration date**. As a service to investigators, OPRS sends reminders to the Principal Investigator.

Since the IRB must make a substantial review of the research at the time of continuing review, it is not acceptable for an application to be made at the last minute. OPRS will try and accommodate requests for urgent reviews, but obviously this taxes the system and ultimately jeopardizes the timeliness of reviews for other continuing review applications that have been submitted in a more timely manner.

2. What if my IRB approval expires?

The IRB and investigators must work together and plan ahead to meet required continuing review dates. If an investigator has failed to provide continuing review information to the IRB or the IRB has not reviewed and approved a research study by the continuing review date specified by the IRB, the research must stop, unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. It in incumbent on the investigator to contact OPRS in order to obtain IRB approval to continue the participation of subjects already enrolled on the research. Enrollment of new subjects cannot occur after the expiration of IRB approval (please note that enrolling subjects onto a study without IRB approval constitutes serious non-compliance).

When continuing review of a research protocol does not occur prior to the end of the approval period specified by the IRB, IRB approval expires automatically. Such expiration of IRB approval does not need to be reported to OHRP as a suspension of IRB approval under HHS regulations. However, Investigators are required to notify the Sponsor if their IRB approval lapses. Repeated or very lengthy lapses in IRB approval may be deemed to be continuing non-compliance with the regulations and the requirements of this policy, and may result in requirements for corrective action in addition to notification of funding agencies and federal oversight agencies.

OPRS will send notification to the Investigator when their study has lapsed in approval, which will remind them of the requirement that research activities stop.

If studies lapse for more than 60 days, OPRS may administratively terminate the research. OPRS will send the investigator a notification via email of study termination. The investigator's department head or section chief may also receive notification of administrative termination. In cases of on-going externally funded projects, the Office for Sponsored Research also receives a copy of the termination notice and make an independent determination regarding the need to notify the sponsor. In order to resume a terminated project, the investigator must submit a Continuing Review application for IRB review and approval. The Continuing Review application has additional questions that must be answered if the project has lapsed in approval.

Procedures for expedited or full board review, criteria for approval, and revision prior to approval, are identical to those described above for New Projects. Notification of approval of a Continuing Review is made by e-mail.

D. Other Reporting Requirements for Investigators

NU investigators are required to promptly report to the IRB if there are unanticipated problems during the course of the research that involve risks to subjects or to others. These are reported using the "safety/other" tab in eIRB, or using a UPIRSO report form posted on the OPRS Forms website. NU IRBs will not review reports of adverse events, whether at NU or external sites, unless those reports constitute unanticipated problems involving risks to subjects or others. NU investigators must always report to the NU IRB any death of a NU research subject. Finally, investigators shall report promptly to the IRB whenever they discover that the conduct of the research is in serious or continuing non-compliance with the requirements of the federal regulations governing the protection of research subjects, the requirements of this policy, or the requirements of an NU IRB.

What are unanticipated problems involving risk to subjects or others?
The phrase "unanticipated problems involving risks to subjects or others" is found but not defined in the HHS regulations at 45 CFR part 46, and in the FDA regulations at 21 CFR 56. NU considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

(1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
(2) related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
(3) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

What do you mean by serious or continuing noncompliance?
Serious noncompliance refers to non-compliance with any of the following:

1. The specific requirements of the IRB,
2. The requirements of this policy,
3. Applicable state laws, and
4. Relevant federal regulations pertaining to the protection of human subjects in research,

whenever that conduct compromises the safeguarding of the rights and welfare of subjects or compromises the integrity or interpretability of the data gathered from them. Serious non-compliance may result in unexpected risks of harm to subjects. Serious non-compliance may be unintentional, or may represent intentional disregard for the requirements of the NU Human Subject Protection Program.

Continuing non-compliance refers to repeated acts of non-compliance in the conduct of human subjects research so that there appears to be a pattern indicative of a lack of understanding or attention to the safeguarding of the rights and welfare of human subjects in research. Continuing non-compliance is characterized by the frequency rather than the magnitude of the non-compliance, and may include non-compliance with applicable federal regulations pertaining to human subject protections, with the NU HSPP policy, Illinois state law relating to the research, or the specific determinations of the IRB.

1. Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs)

Investigators must report any unanticipated problem involving risk to subjects or others using the Serious Adverse Events Reporting Form or the UPIRSO Reporting Form available on the OPRS website, or the "Safety/Other" form in the eIRB system. This form includes a description of the event, the date of occurrence, whether it is a local or outside report, how the event affected the rights, safety or welfare of the subject or others, current status of NU subjects, and any planned changes or modifications to the project as a result of the event. Reports from the investigator to the IRB must be submitted no later than ten working days after the event or notification of the investigator that the event has occurred. There are additional requirements (below) for promptly reporting unanticipated deaths on study.

When a research study includes investigational drugs or devices, some unanticipated problems may also meet the definition of an unexpected adverse drug experience (serious or otherwise), or an unanticipated adverse device effect. NU investigators and research staff are expected to be familiar with the various requirements for reporting of adverse events and UPIRSOs.

When a UPIRSO report is filed with OPRS, the staff will compare the content of the report with the previously approved project materials such as applications, informed consent document(s), protocols, investigator brochures, or other supporting documents to determine whether this event appears to meet the definition of an unanticipated problem involving risk to subjects or others. This preliminary determination is forwarded to an expedited IRB reviewer.

The IRB reviews the UPIRSO report by expedited procedures in order to determine whether the criteria for approval under 45 CFR 46.111 and 21 CFR 56.111 are still met. In its review of the UPIRSO report, the IRB may determine that additional safeguards need to be developed within the protocol procedures in order to adequately minimize risks, it may require consent form modifications in order to include additional information about this new risk (already enrolled subjects may or may not need to be provided with this new information), and is responsibly to decide whether the study may continue as it was previously approved given this new information.

When very serious risks of harm, or serious harms occur, the IRB may consider suspending its approval of the research as a way of safeguarding the rights and welfare of the subjects. At times, the NU IRBs may also choose to place a "partial clinical hold" on a research protocol,

requiring an investigator to stop some aspect of the research (e.g., enrolling new subjects) as a measure to safeguard subjects, but not suspend IRB approval for the study as a whole.

All reports of unanticipated problems involving risks to subjects or others are filed with the appropriate research study. The investigator will be asked to summarize these reports for the IRB at the time of continuing review (this allows a comprehensive review of the events—including assessment of their frequency as well as magnitude).

2. UPIRSOs and Adverse Events in Biomedical Research.

FDA regulations and clinical trial agreements require the prompt reporting of Serious Adverse Drug Events and Serious Adverse Device Effects to the Sponsor and to FDA. Sponsors are responsible for reporting these events to investigators at other institutions who are conducting research under the relevant IND or IDE of these events. However, these events only need to be reported to the NU IRB (whether they occur at NU, or at an external site) when they constitute an unanticipated problem involving risks to subjects or others. While non-UPIRSO adverse events still need to be reported to the Sponsor, who must report them to FDA, they do not need to be reported to the NU IRBs and the NU IRBs will not review them. The only exception to this is the requirement that adverse device effects need to be reported by the Sponsor to the IRB. If these constitute UPIRSOs, then the NU PI will be required to submit an Adverse Event or UPIRSO report, otherwise, the reports will be acknowledged by the IRB and filed.

3. Reporting Deaths on study

All deaths of NU research subjects (deaths occurring during the time they are involved in the study) need to be reported to the NU IRB. NU investigators are required to report to the NU IRB in writing any unanticipated death of a research subject, unless the death is certainly unrelated to the research, within 24 hours of learning about the death. Investigators should phone OPRS as soon as possible in order to inform them of the written notice which may be made by e-mail, facsimile, in person using the UPIRSO form, on in eIRB using the "safety/other" tab.

Anticipated deaths (e.g., due to disease progression) may be reported at the time of continuing review, and do not need to be reported promptly. Unrelated, or probably unrelated and unanticipated deaths (e.g., death due to a motor vehicle accident) should be promptly reported to the NU IRB when the subject was enrolled by NU and the research involves FDA regulated products or test articles. If the research is not FDA-regulated (e.g., social behavioral research), then unrelated, or probably unrelated deaths may be reported at the time of continuing review.

4. Receipt of new information (including risk or benefit) that may impact the willingness of subjects to participate or continue participation in the research study

During the course of a study, researchers may become aware of new information that would impact a subject's decision to participate, or continue participating in the research study. For example, interim analyses of data may identify a trend which impacts the safety of subjects, or may identify early efficacy (benefit) of one of the interventions under study. In addition, results from other research studies or changes in standards of practice or care may affect conduct of a study and would need to be communicated to research subjects.

Investigators must report any new information that may impact the willingness of subjects to participate to the IRB along with a Revision Submission Form, in which the investigator includes modifications that need to be made to the consent process, and possibly to the protocol in order to integrate this new information.

Reports and modifications related to new information are reviewed by the IRB to determine if the method and information provided to subjects is appropriate. If the IRB determines that the proposed modifications address this new information adequately, then the revision will be approved. These Revisions may be considered for expedited review if the study is no more than minimal risk and was initially approved under expedited procedures.

5. Noncompliance with Federal Regulations or the Requirements or Determinations of the IRB

Investigators who are self-reporting noncompliance with federal regulations or the requirements or determinations of the IRB to NU IRBs use the Protocol Deviation/Violation Form. This form includes a description of the noncompliance and description of impact on the rights, safety, or welfare of subjects or others. Reports from the Investigator to the IRB must be submitted within ten working days of the event or notification to the investigator of the event, whichever is earlier.

Others may report noncompliance as described in Section XI of this policy. All reports of noncompliance, regardless of the source are reviewed by the IRB Chairs Committee and/or a convened IRB panel according to the procedures described in Section XI of this Guide.

6. IRB Actions in Response to UPIRSOs and Reports of Non-Compliance

The NU IRBs expect that researchers will submit these reports promptly, and that in their report, that researchers will consider the reasons why either risk of harm or non-compliance has occurred. In making these considerations, investigators need to propose to the IRB possible corrective actions that will reduce or eliminate the likelihood of the risk of harm or non-compliance occurring again. These actions can involve protocol modifications, consent document changes, additional educational interventions, or additional monitoring of the study procedures or study staff.

The NU IRBs are responsible for reviewing these reports and determining whether or not the research continues to meet the requirements for approval (See Section VII.F of this policy) with this new information. If the NU IRB concurs with the plan of the researcher, then no additional changes are required, and the investigator's report will be acknowledged by the IRB. If the IRB believes that additional information is required for its deliberations, then the researcher will be asked to provide additional information. If additional modifications to the protocol or to the consent document or process are required, then the IRB will require those modifications.

The IRB may suspend or terminate IRB approval based on UPIRSOs or findings of serious or continuing non-compliance. If this is done, then appropriate institutional officials and federal oversight agencies will also be promptly notified.

The IRB may also elect to enact a "partial clinical hold" on the study during which some component of the research must stop. This is to allow the ongoing protection of research subjects when the IRB determines that is a necessary safeguard but suspension of the entire study is not warranted. In this event, the researcher might be required to stop enrolling new subjects onto the study, or halt one arm of a study, until such time as the issues have been resolved and the IRB is satisfied that the corrective actions are adequate and the study is re-approved (in writing). In the case of a "partial clinical hold," institutional officials will be promptly notified, but federal oversight agencies will not.

E. Post-Approval Monitoring Program

Additional monitoring of approved projects at NU occurs on a continual basis, and under numerous different programs. Included among other groups are IRB monitors, who are full-time OPRS staff who conduct random, study initiation, and directed monitoring visits of research. The HSPP will seek to obtain reports from other units within the University who are engaged in monitoring activities (including the University Auditors, the Cancer Center, DSMB, etc.). The main goal of this program is to assess and enhance the protection of human subjects involved in research, which is accomplished by providing education to investigators and their research team and determining, from a source other than the investigator's continuing review report, that no material changes have occurred in the project since the previous IRB review. In addition to the regular monitoring staff, IRB members, or other professional staff in OPRS or the Office for Research Integrity acting on behalf of the IRB, may conduct monitoring activities.

Reason(s) for an on-site review may include, for example:

1. random selections,
2. complex projects involving unusual levels or types of risks to subjects,
3. projects involving vulnerable populations,
4. projects conducted by an investigator who previously failed to comply with IRB determinations,
5. projects where continuing review or reports from other sources have indicated that changes without IRB approval may have occurred.

For random and study initiation reviews, the research monitors meet with research team members to review and assess the following areas:

- Research team composition
- Recruitment and consent procedures
- Study procedures and expected study end
- Study reports from outside monitoring entities such as Data Safety Monitoring Boards, Contract Research Organizations
- Publications from the study
- Current enrollment and verification of signed consent
- Reporting of unanticipated problems involving risks to subjects or others, receipt of new information, and issues of noncompliance
- Storage of study documents and data
- Privacy and confidentiality issues
- Data analysis
- Drug/Device accountability
- Staff training and communication
- Subject payment

The conduct of an on-site review may include any or all of the following:

(1) requests for progress reports from investigators,
(2) examinations of research records, including signed Informed Consent Documents, protocol amendments, and serious and/or unexpected adverse experience reports,
(3) contacts with research subjects,
(4) observation of the consent process.

Examples of when observation of the consent process could occur are: 1) the full board IRB determines during review of a project that a conflict of interest exists such that the informed consent process should be observed by a neutral party; 2) the IRB is made aware of a complaint or concern with regard to the informed consent process; or 3) the IRB determines as a result of the monitoring process that the consent process is insufficient and education/training is required for conduct of consent.

A draft report of the findings of random monitoring visits is written by the monitor and e-mailed to the PI and copied to other research team members as appropriate within 10 working days of the monitoring visit. The PI is asked to reply regarding any comments or on the accuracy of issues described in the report within 2 weeks of receipt. If the PI does not reply in this time frame, the report is considered to be accurate and it is forwarded to the IRB Chairs Committee for review. Any responses from the PI will be incorporated into a final report to the IRB Chairs Committee of the monitoring visit. The IRB Chairs Committee (ICC) reviews and approves the report or requests changes to the suggested corrective actions based on the information provided. If any of the findings require full board review, the report is referred to the next available full board meeting for review. If none of the items require full board review, the final approved report is e-mailed to the PI and research team and the matter is either closed, or a response is required within 30 days. If a response is required, but the PI does not respond in this timeframe, the PI is sent a letter by e-mail indicating they must respond within 2 weeks or the report will be sent to the Vice President for Research for consideration of study suspension (suspension of institutional approval) until the issue is resolved. A copy of that correspondence will be forwarded to a convened IRB, which may also elect to suspend IRB approval for the research. Correspondence regarding non-compliance will also be copied to the Department Chair or Division Chief as applicable.

A written record of these monitoring activities is maintained in the study file and separately in the OPRS office.

F. Project Closure

1. When should I close my project with the IRB?

When a study ends, is closed, or canceled for any reason, you must complete a Project Termination/Closure Form. This form serves as notification to OPRS that IRB continuing review of the study is no longer needed. If no subjects have been enrolled in a study for a period of three or more years, the IRB may require that the project be closed, unless there are extenuating circumstances or justification for keeping the project open (e.g., the study is about a rarely-seen condition).

Take care not to close the project too soon! Once a Project Closure Form is submitted, no more data may be collected about any of the subjects in the study and no more contact with

subjects for research purposes is allowed.

If an investigator is still collecting follow-up data about subjects (either directly from subjects or indirectly from existing records), the project should remain open until all data have been collected, even if new subjects are no longer being enrolled. On a sponsored project, it is prudent to delay protocol termination/closure until after the "closure" visit by the Monitor.

2. How do I submit a project closure?

If your project was started in the eIRB system or has been transferred to the eIRB system, you should use eIRB to close the project. If not, the Project Termination/Closure Form on the OPRS website should be completed and submitted.

IX. Vulnerable Populations

Federal regulations involving human subjects in research include specific protections for children, pregnant women and fetuses, and prisoners. In addition, the IRB expects the investigator to provide additional protections for cognitively impaired individuals in research as well as indicate in the application whenever there are other populations that the investigator might consider to be particularly vulnerable in a research setting. Examples of these additional types of vulnerable populations include those persons who are educationally or economically disadvantaged, students (see Section VI. E. 1. D of this policy for more information regarding students in research), or other groups that may require special consideration.

A. Pregnant Women, Human Fetuses and Neonates

Federal regulations direct that IRBs require additional safeguards before approving research involving fetuses, pregnant women, or neonates (45 CFR 46, Subpart B).

1. Pregnant Women and Fetuses

The IRB may approve research involving pregnant women or fetuses if all of the following conditions are met:

a) where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

b) the risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means;

c) any risk is the least possible for achieving the objectives of the research;

d) if the research holds out the prospect of direct benefit to the pregnant woman, the prospect of direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, the woman's consent is obtained OR

e) if the research holds out the prospect of direct benefit solely to the fetus, then

the consent of the pregnant woman and the father is obtained except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest;

f) each individual providing consent under (d) or (e) is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

g) for children who are pregnant, assent and permission are obtained in accord with the regulations for children in research;

h) no inducements, monetary or otherwise, will be offered to terminate a pregnancy;

i) individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

j) individuals engaged in the research will have no part in determining the viability of the neonate.

2. Neonates

Neonates, neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

a) where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates;

b) each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate;

c) individuals engaged in the research will have no part in determining the viability of the neonate;

d) the requirements regarding neonates of uncertain viability (see below) or nonviable neonates (see below) have been met as applicable.

a) *Neonates of uncertain viability.*

Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research unless the following additional conditions have been met:

(1) The IRB determines that:

(i) the research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective; or

(ii) the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research.

AND

(2) The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained (except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest).

b) *Nonviable neonates*.

After delivery nonviable neonates may not be involved in research unless all of the following additional conditions are met:

(1) vital functions of the neonate will not be artificially maintained;
(2) the research will not terminate the heartbeat or respiration of the neonate;
(3) there will be no added risk to the neonate resulting from the research;
(4) the purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
(5) the legally effective informed consent of both parents of the neonate Is obtained (note: waiver or alteration of the consent does not apply here) If either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements except that the consent of the father need not be obtained if the pregnancy resulted form rape or incest. The consent of the legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements.

c) *Viable neonates*.

A neonate, after delivery, that has been determined to be viable may be included in the research only to the extent permitted by and in accord with the requirements for children involved in research (see Section C below).

Research not otherwise approvable will only be allowed in this vulnerable population if:

(a) the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates; AND

(b) the Secretary of DHHS, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following an opportunity for public review and comment, including a public meeting announced in the Federal Register has determined that the research may take place.

Research involving human fetal tissue (placenta, or tissue from a spontaneous or induced abortion or from a still birth) is evaluated as tissue specimen research, using the guidelines for research involving specimens. Studies using human fetal tissue for transplantation research and studies of human embryos involve very explicit regulations concerning consent and study procedures. Investigators wishing to conduct transplantation research with human fetal tissue should contact OPRS well in advance of IRB application submission in order to schedule one or more meetings with representatives from the IRB, and General Counsel's office to discuss applicable federal and state regulations.

B. Prisoners

Because incarceration could affect a person's ability to make a truly voluntary decision whether or not to participate in research, the federal regulations provide additional safeguards for the protection of prisoners (45 CFR 46, Subpart C). A prisoner is defined as any individual involuntarily confined or detained in a penal institution. This definition includes individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal

prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

At Northwestern University, any project that recruits prisoners must be reviewed at a full IRB meeting with a prisoner advocate present. If the project was not initially approved to recruit prisoners, then the investigator may not enroll a prisoner (e.g., a prisoner who is brought to NMH for treatment who happens to be eligible for a research study may not be enrolled unless the "prisoner box" was checked on the initial application face page and the project was reviewed at a full board meeting with a prisoner advocate present.)

The prisoner rules also apply for a subject who at a later date becomes a prisoner, because it is unlikely that the IRB review of the research project contemplated the constraints imposed by incarceration. Therefore, if an investigator determines that a subject has become a prisoner at some later date after enrollment, and the study involves additional research interventions or interactions with that subject, the subject must either be dropped from follow-up, or a modification application must be submitted requesting review for inclusion of prisoners as subjects.

When a prisoner is a subject, in addition to the usual criteria for approval, the IRB must find that:

1) the research under review represents one of the categories of research permissible under 45 CFR 46.306(a)(2);

2) any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

3) the risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;

4) procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;

5) the information is presented in language which is understandable to the subject population;

6) adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

7) where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

Four categories of research involving prisoners are permitted under the federal regulations. They are:

1) studies of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

2) studies of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

3) research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere); and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults; or

4) research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject.

The Informed Consent Document must include additional information for potential subjects regarding the fact that participation or non-participation will have no effect on the duration of incarceration or terms of parole. Suggested language is in the Appendix of the Informed Consent Document template.

C. Children

Categories of Research Involving Children

Federal regulations permit IRBs to approve a research project involving children only after determining which of the following categories applies, and only if the project satisfies all of the conditions in the applicable category [45 CFR 46, Subpart D (DHHS) and 21 CFR 50 Subpart D (FDA)]:

1) Research that does not involve greater than minimal risk may be approved if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians. The IRB may determine that permission of one parent or guardian is sufficient.

2) Research involving greater than minimal risk, but presenting the prospect of direct benefit to an individual subject, or a monitoring procedure that is likely to contribute to the subject's well-being, may be approved if the IRB finds that:

- the risk is justified by the anticipated benefit to the subject;
- the relationship of anticipated benefit to risk is at least as favorable as that presented by available alternative approaches; and
- adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

The IRB may determine that permission of one parent or guardian is sufficient.

3) Research involving greater than minimal risk with no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition, may be approved if the IRB finds that:

- the risk represents a minor increase over minimal risk;
- the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected

medical, dental, psychological, social, or educational situations;
- the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the subject's disorder or condition; and
- adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.

The IRB requires that permission of both parents is obtained, unless one parent is deceased, unknown, incompetent, or not reasonably available, or unless only one parent has legal responsibility for the care and custody of the child.

4) Research that is not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children may be approved if the IRB and the Secretary of DHHS, after consultation with a panel of experts in pertinent disciplines and following an opportunity for public review and comment, find that:
- the research in fact satisfies one of the above three conditions; or
- the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
- the research will be conducted in accordance with sound ethical principles; and
- adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.

In this case, the permission of both parents is required, unless one parent is deceased, unknown, incompetent, or not reasonably available, or unless only one parent has legal responsibility for the care and custody of the child.

5 The regulations also indicate that children who are wards of the state, or any other agency, institution, or entity can only be included in research in this category if the research is related to their status as wards or conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards. If one of these criteria is met and the research is approved, the IRB must require appointment of an advocate for each child who is a ward in addition to the person acting as guardian or in loco parentis. One person may serve as the advocate for multiple wards, however this advocate must have the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and cannot be associated in any way (except as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization. Unless these additional determinations have been made, in response to the initial submission and a clear statement that the research may involve Wards of the State, NU investigators are not to enroll a Ward of the State onto a research project without first obtaining approval for a revision to the protocol. The IRB approved consent documents will include provisions for the signature of the advocate for the children.

Assent

When children are involved in research, the IRB may require the assent (knowledgeable agreement) of the child, in addition to the permission of the parent(s). (See also Section VI. C. 3, for more information about assent.) Children should be asked whether or not they wish to participate in the research. The regulations do not specify a certain age at which assent must be sought, but for most studies, the IRB suggests obtaining assent beginning at about age seven. In certain studies involving treatment for an illness or condition that is

available only in the context of research study, the IRB may determine that the assent of the child is not necessary. The IRB must determine and document whether assent is required of all children in the research, some of the children in the research or that assent is not required of any of the children in the research.

D. Cognitively Impaired Persons

Individuals in a wide variety of situations may have impaired decision-making capacity. For example, impairment may occur at times of great stress. Impaired capacity is not limited to individuals with neurologic, psychiatric, or substance abuse problems; conversely, individuals with neurologic, psychiatric, or substance abuse problems should not be presumed to be decisionally impaired. Some research questions may be answered only by research that involves persons with impaired decision making capacity; precluding this research would contribute to needless suffering. The most severely impaired individuals have the greatest need for the benefits of research on etiology and treatment. While this area is controversial, limiting research to the least impaired individuals would hamper research on the underlying causes and potential therapies of many disorders. Not all research will directly benefit the individual participant but may offer future benefits to others who have or will develop the condition or disorder. For example, genetic studies, biochemical measures, or other non therapeutic approaches may benefit subsequent generations.

While limited decision-making capacity should not prevent participation in research, it is important to keep in mind that additional protections are warranted for research involving this population. The NIH offers the following Points to Consider to assist IRBs and clinical investigators in their effort to protect participants in research who are, or may be, or may become decisionally impaired:

1. Conflicting Roles and Potential Conflicts of Interest

Potential and actual research participants, especially those with permanent or transient cognitive impairments, may find it difficult to understand the difference between research and treatment, and to understand researchers' multiple roles, making "therapeutic misconceptions" particularly problematic, and possibly creating confusion among participants and their families. It is essential that the consent process (including consent documents) clearly indicate differences both between individualized treatment and research and between clinician and clinical investigator.

2. Assessing Capacity to Consent

Individual's capacities, impairments, and needs must be taken into account in order to develop practical and ethical approaches to enable them to participate in research. A clear understanding of the implications of various cognitive impairments, along with a careful consideration of proposed clinical research methodology, is required. Assessment is complex; simply answering a certain number of factual questions about a protocol may not be an adequate assessment. A key factor in participants' decision making is their appreciation of how the risks, benefits, and alternatives to participation in the study apply to them personally.

Limited decision making capacity covers a broad spectrum. A healthy person in shock may be temporarily decisionally impaired. Another may have been severely mentally retarded since birth, while yet a third who has schizophrenia may have fluctuating capacity. Researchers

should be sensitive to the differing levels of capacity and use assessment methods tailored to the specific situation. Further, researchers should carefully consider the timing of assessment to avoid periods of heightened vulnerability when individuals may not be able to provide valid informed consent.

Both IRBs and clinical investigators must keep in mind that decision making capacity may fluctuate, requiring ongoing assessment during the course of the research. The consent process should be ongoing. The IRB, at its discretion, may require an outside witness to observe the consent process.

Because no generally accepted criteria for determining competence to consent to research exists for persons whose mental status is uncertain or fluctuating, the role of the IRB in assessing the criteria proposed by the investigator is of major importance. The selection of an appropriate representative to consent on behalf of those unable to consent for themselves must be accomplished without clear guidance from statutes, case law, or regulations.

3. Comprehension

The determination of a subject's ability to understand the implications of the decision to participate in research is best made by the clinician/investigator. In most cases, it will be the clinician/investigator who is in the ideal position to evaluate the subject's ability to understand the implications of the research and whether the subject is making a rational decision to participate. Likewise, in most studies it is the clinician/investigator who can best make a judgment of the subject's ability to understand and follow the protocol.
In developing the consenting process, the investigator is obligated to incorporate any special accommodations necessary to assure that the subject population or their surrogates comprehend the nature and purpose of the study. Useful techniques may include simplified consent documents, supplemental summary sheets, formal Q&A sessions for the subject and family or friends, and waiting periods after the initial discussion before the prospective subject actually enrolls.

There is no universally accepted test or standard for making a determination of comprehension. This process should operate in research studies in much the same manner as the informed consent process in clinical treatment that does not involve research.
The American Journal of Psychiatry, 155:11, November 1998, published "Guidelines for Assessing the Decision-Making Capacities of Potential Research Subjects with Cognitive Impairment." Investigators are encouraged to review this article.

4. Voluntary Agreement

Closely related to the determination of the ability to comprehend the nature of the study is the importance of ensuring that subjects' participation is completely voluntary. Some knowledge and assessment of the subject's competence is relevant to a determination of whether voluntary participation is evidenced by a written consent, or in the case of persons lacking legal capacity to consent, their assent. Research should not be conducted against the wishes of the subject, and making certain that the written documents are indeed a reflection of reality is the function of the individual researcher and the IRB.

5. Second Signature on the Consent Document

There are many situations in which a subject should be encouraged to authorize the involvement of family members. However, the permission of another party will be required only when the subject is determined to lack the legal ability to provide an informed consent. This would include children (when research is conducted in the state of Illinois, this would include persons under the age of 18 who have not been emancipated by the court) and persons adjudicated incompetent. This also includes persons who are not capable of understanding the nature of their illness or the risks, benefits, and natural consequences of participation. Also see Section VI. A. 2 of this policy, for more information about who may provide permission for an incompetent adult to participate in a research study.

In conclusion, in all human research, varied degrees of research risk and decisional impairment call for varied levels of scrutiny and safeguards; additional protections may be highly advisable in certain circumstances. But treating all individuals who have cognitive deficits as incapable of understanding research is inaccurate and disrespectful of their autonomy. Many individuals, adequately informed, may be willing to undertake certain risks so that they, or others, may benefit in the future. Researchers and IRBs must strive for a balance that maximizes potential benefits and opportunities, recognizes and extends individual autonomy, and minimizes risks associated with scientific inquiry.

X. Special Topics

A. Collaborative Research

NU IRBs may approve human subject research activities at locations for which the IRB has an understanding of the local research context or the University is assured that there is appropriate oversight for the conduct of human subjects research. The HSPP allows the NU IRBs to approve collaborative projects with other institutions, and ensures there are mechanisms in place to assure appropriate oversight of collaborative research with non-NU entities.

1. With other NU Personnel

The NU encourages collaborative research projects across departments. Research team members can be from any department on the NU campus. There are some projects that may develop into the sharing of information with other researchers who are not members of the research team. Research team members should not share data or specimens with investigators outside of the research team for the project unless permission for this sharing has been obtained through the informed consent/authorization document(s).

2. With non-NU entities

In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with any applicable regulations. Federal regulations from DHHS and FDA [45 CFR 46.114 & 21 CFR 56.114] allow for cooperative research projects which involve more than one institution to avoid duplication of review efforts by IRBs. Under these rules, institutions can choose to conduct joint IRB reviews, rely on one or the other institution's IRB oversight or rely upon the review of another qualified IRB. In each of these cases, there is often the need for institutions to have agreements in place to document the process for IRB review and both IRB and institutional oversight.

3. When is an institution "engaged" in research?

Discussion of how best to ensure effective and efficient IRB review for research at each institution involved in the research usually begins with an evaluation of which institutions are "engaged" in human subject research. An institution becomes "engaged" when its employees or agents (agents include all individuals performing institutionally designated activities or exercising institutionally delegated authority or responsibility):

i) intervene or interact with living individuals for research purposes OR
ii) obtain individually identifiable private information for research purposes

An institution is automatically "engaged" in human subject research whenever it receives a direct DHHS award to support human subject research. The awardee institution bears ultimate responsibility for protecting human subjects under the award.

OHRP has provided guidance and examples for when institutions are considered to be "engaged" in research and examples of when institutions are NOT "engaged" in research. If NU is not "engaged" in the research, and the research does not involve the use or disclosure of PHI, then there is likely no need for NU IRB review or approval of the research. Likewise, OPRS, or the NU IRB may make a determination that an outside institution is not engaged in human subjects research, and that there is no need for IRB oversight of the activities at that institution. Please call OPRS for more information if there is any question about the involvement of outside institutions in human subjects research.

Once the determination is made that the outside institution is engaged in human subjects research, the following are the NU IRB policies with regard to IRB oversight at those institutions.

1) When the outside institution is receiving federal funds through a subcontract with NU, the NU Office for Sponsored Research requires documentation that the outside institution holds an FWA through the subcontract process. If the outside institution does not hold its own FWA, NU requires that they obtain one prior to finalization of the subcontract. If this is the case, and the other institution obtains its own FWA, there are a few methods of IRB oversight that the NU IRB would consider acceptable based on the circumstances of the project and the role of the other institution. The NU IRB could either

- accept a concurrent review of the research project with the other institution's own IRB (the most frequent arrangement), or
- the NU IRB could be the IRB of record for the other institution. This agreement is formalized through the use of an IRB Authorization Agreement, or
- NU can accept the other institution's IRB as the IRB of record for the project. This would be in cases where the NU determines that the outside institution's IRB review will provide more appropriate expertise, oversight, and/or knowledge of local context for the NU role in the study. This agreement is formalized using an IRB Authorization Agreement or other equivalent agreement. The outside IRB is then added to the NU FWA.
- Under limited circumstances, when the NU is able to assure understanding of the local context in relation to the proposed research and has sufficient resources to provide appropriate oversight during the conduct of the research, and an individual investigator outside of NU does not have an institutional affiliation that would be an appropriate FWA institution, NU may choose to extend its FWA to cover the outside investigator's role in the individual project. This agreement is formalized using an Individual Investigator's Agreement. This mechanism will NOT be allowed:

a. If the non-assured institution is the primary awardee for an DHHS-funded project OR
b. If the non-assured institution routinely engages in the conduct of human subjects research.

If either of the above conditions apply to the cooperating institution or investigator, the non-assured institution will be required to obtain its own OHRP-approved FWA.

2) When the outside institution is not receiving federal funding for the study through a subcontract with NU, the NU IRB requires that the research be conducted under either the other institution's IRB oversight or the NU IRB takes on oversight of the research. In the former instance, the IRB will require documentation that the outside IRB has approved the research. In the latter instance, this agreement is documented through a formal IRB Authorization Agreement.

The NU IRB will oversee research for an outside institution only when the NU IRB is able to assure understanding of local context in relation to the proposed research and has sufficient resources and a written agreement with that institution to provide appropriate oversight during the conduct of the research.

For each of these mechanisms of collaborative research oversight, you must have the approval of the designated IRB(s) of record PRIOR to conducting any research that involves human subjects. In addition, when one institution relies on the IRB approval of another, this requires a written agreement between the two institutions. Northwestern is careful about its choice to enter into such an agreement. The final determination to enter into any agreements described in this section is made by the NU Institutional Official.

For projects that involve international sites, please see the section below on International Research.

B. Conflict of Interest –

For the purposes of this policy, we are almost exclusively referring to financial conflict of interest as it relates to real or apparent conflicts when they impact or possibly impact on human subject protections. It is important to note that the goal of this process is not to eliminate real or apparent conflicts of interest, but to ensure they are adequately managed. Oversight of financial conflicts of interest for NU faculty and staff, including members of the IRBs and OPRS is managed through multiple mechanisms including the NU IRB review process, Office for Sponsored Research reporting and review (OSR-1 form), and departmental or school review mechanisms. In addition, there are annual University processes for all faculty and staff which require reporting and management of conflicts of interest and commitment.

1. Investigator and research team

Financial conflict of interest in research involves situations in which an investigator or research team member, or an investigator or research team member's immediate family has a ***significant financial interest*** that may compromise, or have the appearance of compromising, professional judgment in the design, conduct, or reporting of research. Significant financial

interest does not include ownership interests such as mutual funds that are managed by an independent third party. "Significant financial interest" means a financial interest in a sponsor of research, or intellectual property (patents, copyrights, or trade secrets) held by an investigator or research team member or the investigator or research team member's immediate family (spouse or domestic partner and dependent children) individually or in aggregate including:

1. Payments in excess of $10,000 including salary, consulting fees, royalty or licensing payments from intellectual property, honoraria and/or gifts received within the past 12 months or anticipated for the next 12 months (excluding salary and other payments received from the University);

2. Equity interest worth more than $10,000 or more than 5% of the business entity as determined by reference to its publicly listed price (excluding mutual funds):

3. Any equity interest if the value cannot be determined by reference to publicly listed prices (e.g., start-up companies);

4. A position as director, officer, partner, trustee, employee, or any other position of management with the Sponsor; or

5. Patent rights or royalties from such rights whose value may be affected by the outcome of the research, including royalties under any royalty-sharing agreements involving the University.

Personal agreements between sponsors and investigators or members of the research team, or their immediate family members where the amount of compensation (consulting, board honoraria, or any other kind) could change depending on the outcome of a study or any other activity the investigator/research team member/immediate family member performs as part of their University service are prohibited by this policy.

In the New Project Submission Forms, and in eIRB, investigators are asked to provide information about possible financial conflict of interest for themselves and their research team. When a project is submitted for review, and the investigator has indicated that there is a financial conflict of interest, they need to provide additional information for review by the IRB. Any NU investigator holding a significant financial interest as defined above must disclose this interest ***in writing prior to submission of a grant or contract application or, for non-sponsored research, prior to initiation of the activity.***

When there is disclosure of a conflict, the NU IRBs will ask the investigator to undergo review of the conflict within the jurisdiction of their School, Department, or other institutional affiliation. The IRB is to be provided with a summary of the management plan, and will not approve a study until reported conflicts of interest have been managed. If a new significant financial interest is created or if a new investigator with a significant financial interest is hired to work on the research project, that interest must be disclosed within 60 days by way of a revision to the approved protocol. In addition, the continuing review application requires the investigator to answer the same questions again on at least an annual basis.

2. IRB Members

Conflict of interest involves situations where an IRB member has some personal “stake” in a

particular outcome regarding a panel deliberation and action so that their objective decision making might be influenced, or might appear to be influenced by the conflict of interest. When an IRB member is an investigator, co-investigator, or is otherwise directly associated with a research study, that individual must not participate in the IRBs deliberations or voting on submissions that are related to that study. At other times, an IRB member might identify themselves as conflicted because of a close or conflicted relationship with either the investigator whose study is under deliberation, or because of a financial conflict of interest (see below). They are required to identify their conflict of interest, to disclose it to the panel members present, and to leave the room. If called back into the room by the IRB for informational purposes, the conflicted IRB member must again absent the room for the final discussion and voting by the IRB.

Financial conflict of interest for IRB members involves situations in which an IRB member, or an IRB member's immediate family has a ***significant financial interest*** that may compromise, or have the appearance of compromising, objective judgment in the IRB member's review, approval and ongoing oversight of research. Significant financial interest does not include ownership interests such as mutual funds that are managed by an independent third party. "***Significant financial interest***" means a financial interest in a sponsor of research, or intellectual property (patents, copyrights, or trade secrets) held by an IRB member or IRB member's immediate family (spouse or domestic partner and dependent children) individually or in aggregate including:

1. Payments in excess of $10,000 including salary, consulting fees, royalty or licensing payments from intellectual property, honoraria and/or gifts received within the past 12 months or anticipated for the next 12 months (excluding salary and other payments received from the University);

2. Equity interest worth more than $10,000 or more than 5% of the business entity as determined by reference to its publicly listed price (excluding mutual funds):

3. Any equity interest if the value cannot be determined by reference to publicly listed prices (e.g., start-up companies);

4. A position as director, officer, partner, trustee, employee, or any other position of management with the Sponsor; or

5. Patent rights or royalties from such rights whose value may be affected by the outcome of the research, including royalties under any royalty-sharing agreements involving the University.

Personal agreements between IRB members or their immediate family members where the amount of compensation (consulting, board honoraria, or any other kind) could change depending on the outcome of a particular study or any other activity the IRB member reviews, approves, or has ongoing oversight responsibility for as part of their University service are prohibited by this policy.

IRB members are required to complete a financial conflict of interest disclosure form at least once annually. The disclosures are reviewed by the IRB Chairs Committee, and then recommendations for the management of the conflicts are made in writing to the Vice President for Research. When IRB members have a significant financial interest in any protocol or submission under review, they must recuse themselves and absent the room for the

duration of the IRBs deliberation and voting.

3. OPRS Staff

Conflict of interest involves situations where an OPRS staff member has some personal "stake" in a particular outcome regarding a panel deliberation and action so that their objective decision making might be influenced, or might appear to be influenced by the conflict of interest. When an OPRS staff member is an investigator, co-investigator, or is otherwise directly associated with a research study, that individual must not participate in the IRBs deliberations or voting on submissions that are related to that study. At other times, an OPRS staff member might identify themselves as conflicted because of a close or conflicted relationship with either the investigator whose study is under deliberation, or because of a financial conflict of interest (see below). They are required to identify their conflict of interest, to disclose it to the panel members present, and to leave the room. If called back into the room by the IRB for informational purposes, the conflicted OPRS staff member must again absent the room for the final discussion and voting by the IRB.

Financial conflict of interest for OPRS staff involves situations in which an OPRS staff member, or a staff member's immediate family has a ***significant financial interest*** that may compromise, or have the appearance of compromising, objective judgment in the OPRS staff member's involvement in the IRBs review, approval and ongoing oversight of research. Significant financial interest does not include ownership interests such as mutual funds that are managed by an independent third party. "***Significant financial interest***" means a financial interest in a sponsor of research, or intellectual property (patents, copyrights, or trade secrets) held by an OPRS staff member or OPRS staff member's immediate family (spouse or domestic partner and dependent children) individually or in aggregate including:

1. Payments in excess of $10,000 including salary, consulting fees, royalty or licensing payments from intellectual property, honoraria and/or gifts received within the past 12 months or anticipated for the next 12 months (excluding salary and other payments received from the University);

2. Equity interest worth more than $10,000 or more than 5% of the business entity as determined by reference to its publicly listed price (excluding mutual funds):

3. Any equity interest if the value cannot be determined by reference to publicly listed prices (e.g., start-up companies);

4. A position as director, officer, partner, trustee, employee, or any other position of management with the Sponsor; or

5. Patent rights or royalties from such rights whose value may be affected by the outcome of the research, including royalties under any royalty-sharing agreements involving the University.

Personal agreements between OPRS staff members or their immediate family members where the amount of compensation (consulting, board honoraria, or any other kind) could change depending on the outcome of a particular study or any other activity the OPRS staff member reviews, approves, or has any oversight responsibility for as part of their University service are prohibited by this policy.

OPRS staff members are required to complete a financial conflict of interest disclosure form at least once annually. The disclosures are reviewed by the IRB Chairs Committee, and then recommendations for the management of the conflicts are made in writing to the Vice President for Research. When OPRS staff members have a significant financial interest in any protocol or submission under review, they must recuse themselves and absent the room for the duration of the IRBs deliberation and voting.

C. Course-Related Student Projects

All research meeting the definitions of human subjects research that is carried out at the Northwestern University or under its auspices must be reviewed and approved by an Institutional Review Board (IRB) prior to the start of the research. Accordingly, honors theses, research practica, and Master's or Doctoral theses involving human subjects research must be submitted for IRB review.

The University recognizes that some student projects conducted to fulfill course requirements involve activities that, in a different context, might meet the definition of human subjects research. As a general rule, when those activities are conducted solely to fulfill a course requirement, an element of the definition of research (the intent to develop or contribute to generalizable knowledge) is usually lacking. However, it is also the case that some classroom assignments could place people at risk.

The Northwestern University has determined that some classroom assignments may require review by the appropriate IRB. The University considers classroom assignments to be educational in nature, and not subject to IRB review, when all of the following criteria are true. If any one of these criteria is not true, or if the project extends beyond these limitations, then the project must be sent to the appropriate IRB for review or for a determination that the activity is not human subjects research.

1. The classroom assignment or activity is not designed to develop or contribute to generalizable knowledge. The only purpose of the assignment or activity is to teach research methodology.
2. The results of the assignment do not develop or contribute to generalizable knowledge because either:
    a) The results of the project are not at any time presented or published outside of the University, or,
    b) The project involves gathering data from or about a company, agency, or organization and the data/results are shared only with that company, agency, or organization to be used internally for internal quality assurance or quality improvement purposes).
3. The project is limited to surveys/questionnaires/interview procedures, observation of public behavior, or standard educational exercises directly related to the topic(s) being studied in an official University course.
4. Surveys/questionnaires/interviews, if used, contain no sensitive personal questions (e.g., no questions about alcohol/drug use, sexual behavior/attitudes, criminal activity, medical history, grades/test scores) or other personal information that could "label" or "stigmatize" an individual.
5. The project does not include a special population that requires extra protections (pregnant women, prisoners, children, cognitively impaired individuals).
6. EITHER - information is recorded without any direct or indirect (code number) identifier linking anyone to his/her data - OR - if a direct or indirect identifier is used when recording the data, then the questions being asked could not reasonably harm a

person's reputation, employability, financial standing, or place a person at risk of criminal or civil liability.
7. No Northwestern University faculty, staff or student is receiving monetary compensation or any type of support from an external company/organization/agency for collecting, analyzing or reporting the results of this project.
8. This project is not conducted on VA premises and does not use VA resources, and is not otherwise subject to oversight by a federal regulatory body.

1. Faculty Responsibilities

It is the responsibility of faculty to determine whether an assigned project involving humans can be classified as a course-related student project under the 8 criteria above. Faculty should contact the OPRS if assistance in making this determination is needed. It is the responsibility of faculty to discuss general principles of ethics with the class prior to the initiation of the project.

2. Disclosure

All surveys/questionnaires/interviews should be preceded by a disclosure of the following points to the respondent. If an information sheet is used, consider including these points in that document.

1. The student identifies him/herself as an NU student who is performing the activity to fulfill a course requirement, and the course is specifically identified.
2. The name of the supervising faculty member to contact for questions is provided.
3. The persons who have access to the individual data and/or summarized results are specified (e.g., instructor only, company/organization/agency).
4. Respondents are informed that their participation is completely voluntary.

D. Data and/or Specimens

Most research involves the collection of data and/or specimens. This section outlines some issues with regards to data and/or specimen collection.

1. Existing Data or Specimens

a) Case Reports

Case reports (i.e. write-up of a single patient case) do not need prospective review by the IRB. Publishing a case report does not meet the federal regulatory definition of human subjects research. The IRB will review and provide approval for case reports when they are being submitted to a journal that requires IRB approval as a condition of publication – this is the journal's requirement and not an IRB requirement.

b) Chart/Record Reviews

A human subject is defined, in part, as a living individual about whom an investigator conducting research obtains identifiable private information. Therefore, medical chart or other kinds of record review research (e.g., student records) require IRB review and approval. The IRB chair may authorize a waiver of informed consent for chart/record review

research studies if the study is minimal risk, the rights and welfare of the subjects are not adversely affected, the research could not practicably be carried out without the waiver, and, when appropriate, subjects are provided with pertinent information after participation.

Generally, a waiver of consent is granted when all of the chart/record information that will be used in the research study exists in the original records prior to the date of the IRB application -- such studies are considered retrospective chart/record reviews. However, if some or all of the information that will be used in the research will be taken from charts/records dated some time in the future (i.e., after the date of the IRB application), then consent from some or all subjects may be required.

In order to assist the IRB in making the determination for waiver of consent, the investigator should provide the inclusive dates of chart/record information that will be used in the study. In addition to describing the purpose or hypothesis being studied, and the types of analyses that will be done, the investigator should provide the IRB a list of specific variables that will be used from the original source. This could be done in the application itself, or by including the data collection forms that will be used for compiling the chart/record data.

If the research study involves gathering data from medical records at NMH, NMFF, or RIC, then the researcher must be aware of their policies and procedures for obtaining medical record information for NU research. Guidance may be located on the OPRS website in the HIPAA policies and guidance.

c) Existing Specimens

Research on completely de-identified, existing specimens, where the researcher does not need to access any identifiable data (e.g., the medical record) in order to conduct the research is not human subjects research.

Research involving existing specimens (e.g., all specimens are "on the shelf" on the date the application for IRB review is submitted) may be classified as exempt if the researcher accessing identifiable data (e.g., the medical record) is only recording de-identified data (18 HIPAA identifiers have been removed) for research purposes. There may be no link in the investigator's records, linking the specimen back to the identity of the subject.

Research involving specimens, all of which have already been obtained at the time of the IRB application, may be eligible for a waiver of consent.

E. Secondary Analysis of Existing Data

Any research that involves secondary use of data where the data includes individually identifiable private information requires IRB review. For example, an investigator who plans to analyze an existing data set obtained from another source that includes private identifiable information should submit an application for IRB review. If the data set contains no identifiers (either direct or linked code numbers), and the results will not be submitted to the FDA, the project is not human subjects research. Otherwise, the project may be eligible for expedited review. If you have questions about whether or not your project requires IRB review, please contact OPRS at (312) 503-9338 or by email at irb@northwestern.edu .

The IRB chair may waive informed consent for research involving secondary analusis of existing data when research is minimal risk, the rights and welfare of the subjects are not

adversely affected, the research could not practicably be carried out without the waiver, and, when appropriate, subjects are provided with pertinent information after participation.

Secondary analysis of already aggregated data sets (e.g., meta analysis) never requires IRB review, since the investigator does not obtain individually identifiable private information.

F. Prospectively Collected Data or Specimens

1. Specimens

If the study involves the collection of extra tissue or specimens beyond what is needed for a clinical procedure, IRB review and approval and an Informed Consent Document is required. In such cases, the subject should be informed as to the purpose for obtaining the specimen. If the specimen is going to be retained for future use beyond the purpose of the study for which it was obtained, the subject should be informed regarding who might have future access, for what purposes the specimen might be used, how to request destruction or removal of the specimen from future research use, and whether there are plans to compensate the subject should a product be developed.

Specimens (e.g., blood, tissue, other bodily fluids) collected as part of standard clinical procedures that are unused at the completion of the diagnostic or treatment process and are destined for disposal are often referred to as discarded specimens. Although a surgical consent form might notify patients that such discarded materials may be used in research, this is a surgical consent form and is intended for patients to consent to a surgical procedure. It is not intended for or adequate as an Informed Consent Document to participate in research. Therefore, studies involving discarded specimens obtained prospectively may require an Informed Consent Document. One ideal way to do this is with an IRB-approved tissue repository, with an IRB-approved informed consent document. As a general rule, if the study requires obtaining identifiable information about the patient (demographic, diagnostic) for use in the analysis, consent may be required. The IRB may consider waiving informed consent only if the requirements for waiving informed consent are met.

2. Data Registry

A research registry is defined as the collection and maintenance of data in which:

(1) the individuals in the registry have a common condition,
(2) the individuals in the registry may be contacted for future studies, and/or
(3) the names/data of the individuals may be used by investigators other than the original research team.

If a registry is being created, the investigator should include the name of the registry, the method of data storage, how subjects are informed of their inclusion in the registry, and how subject identity and information is protected in the New Project Submission Form. The Informed Consent Document should inform a potential subject that if s/he decides to participate, his/her name will be stored in a registry and s/he may be contacted in the future by investigators other than the current research team.

Not all compilations of individuals' names and associated data constitute a research registry. A database is not necessarily a registry. *The key element in a registry* is that names and other identifying information are being stored so that people other than the original research team may access the registry information in the future to contact individuals for other studies. For

further guidance, please contact the OPRS.

3. Specimen/Data Repositories

If a Northwestern University researcher stores human specimens for the specific purpose of providing specimens and/or associated data to others who are not members of the original "specimen collection" research team, the IRB may require that the researcher provide additional information to the IRB for establishing a formal repository.

Purpose for Establishing a Formal Repository:

- to give the "collector investigator" authority and responsibility for distributing specimens or data from the repository if certain pre-determined guidelines are met
- to minimize the paperwork burden on "recipient investigators" (those individuals with whom the PI intends to share the specimens or data)

Features of a Formalized Repository:

- Repository PI ("collector") obtains IRB approval for establishing and maintaining the repository
- Repository PI obtains informed consent from subjects in order to add their data and tissues to the registry
- Repository PI determines the conditions under which s/he will share specimens or data from the repository with Recipient Investigators
- Repository PI develops a "Usage Agreement" that describes those conditions
- Repository PI is responsible for maintaining a copy of the signed Usage Agreements

If Recipient Investigator agrees to those conditions, and the Repository PI and Recipient Investigator both sign the Usage Agreement, the Recipient Investigator does NOT need IRB approval or informed consent – the Repository PI may provide the specimens or data based on the signed Usage Agreement alone.

The Recipient Investigator DOES need IRB approval in the following circumstances:

a) If the Recipient Investigator wants to use the specimens or data in a manner that goes beyond what is described in the Usage Agreement (e.g., get subject identifiers so that additional data items can be obtained from medical records), the Recipient Investigator must submit an IRB application for review and approval. The IRB application should specifically describe why the Recipient Investigator cannot do his/her study without going beyond the terms of use in the Usage Agreement.

b) If the Recipient Investigator is being funded by a funding source that requires evidence of IRB approval (e.g., NIH), the Recipient Investigator should submit an IRB application for review and approval. The Recipient Investigator should include with his/her IRB application a copy of the funding agency grant, and a copy of the signed Usage Agreement so that the IRB knows that the terms of the Usage Agreement will be followed. OPRS will provide documentation of a review of the proposed research as constituting "not human subjects research."

Investigators are encouraged to contact the OPRS for assistance before submitting an application to establish a formal registry.

G. Emergency Settings: Research in the Emergency Setting

(Planned Emergency Research)

The federal regulations for the protection of human subjects in research require informed consent, with a few narrow exceptions. FDA regulations in 21 CFR 50.24 provides a narrow exception to the requirement for informed consent from each human subject, or his or her legally authorized representative, prior to initiation of an experimental intervention. The Department of Health and Human Services (DHHS) also outlines waiver criteria for DHHS funded research so that there is a single standard for this class of research.

The exception to the requirement for informed consent would apply to a limited class of research activities involving human subjects who are in need of emergency medical intervention but who cannot give informed consent because of their life-threatening medical condition. The intent of the regulation is to allow research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent, while establishing additional protections to provide for safe and ethical studies.

Persons with life-threatening conditions who can neither give informed consent nor refuse enrollment are a vulnerable population. FDA recognizes that the lack of autonomy and inability of subjects to give informed consent requires additional protective procedures in the review, approval, and operation of this research. The exception from the informed consent requirement permitted by the rule is conditional upon documented findings by the IRB. Because these projects almost certainly represent situations of more than minimal risk and certain requirements are necessary to conduct this research at NU, call the OPRS for guidance if you receive funding to or wish to conduct this type of research project.

H. Emergency Use of an Investigational Drug or Device

From the FDA Information Sheets, Guidance for Institutional Review Boards and Clinical Investigators, 1998 Update.
*FDA defines that **emergency use** means the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval. [21 CFR 56.102(d)]*

1. Obtaining an Emergency IND

The emergency use of an unapproved investigational drug or biologic requires an IND. If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND.

The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means.

2. Exemption from Prospective IRB Approval

Emergency use is defined as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)].

The emergency use provision in the FDA regulations [21 CFR 56.104(c)] is an exemption from prior review and approval by the IRB. The exemption allows for one emergency use (per institution) of a test article without prospective IRB review. Life-threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible. Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Not all emergency use requires an exemption from prospective IRB review. When there is time for prospective IRB approval, the Northwestern University IRB expects the investigator to complete a New Project Submission Form describing the emergency use. With notification to OPRS of the urgent nature of the submission, the application can be scheduled for review at the next IRB meeting (usually within one week). The FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. [21 CFR 56.104(c)] Therefore, if the first use does not have prospective review, the clinical investigator should seriously consider whether subsequent use of the agent may be needed. If so, a New Project Submission Form should be submitted for IRB review promptly following the first emergency use. The FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

The investigator should notify the IRB, when possible, prior to the emergency use. This notification, or written acknowledgement of the notification should not be construed as IRB approval. The investigator is required to file a written report to the IRB within five working days, and notifying the chair is used to initiate tracking to ensure that the investigator files this report as required by 21 CFR 56.104(c). There are not provisions for expedited IRB approval in emergency situations. An IRB must either convene and give "full board" approval of the emergency use or, if the conditions of 21 CFR 56.102(d) are met and it is not possible to convene a quorum within the time available, the emergency use may proceed without any IRB approval.

Some manufacturers will agree to allow the use of the test article, but their policy requires "an IRB approval letter" before the test article will be shipped. If it is not possible to convene a quorum of the IRB within the time available, the OPRS will provide for the sponsor a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). Although this is not an "IRB approval," the acknowledgment letter is generally acceptable to manufacturers and has allowed the shipment to proceed.

3. Exception From Informed Consent Requirement

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:
(1) The subject is confronted by a life-threatening situation necessitating the use of the test

article.
(2) Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
(3) Time is not sufficient to obtain consent from the subject's legal representative.
(4) No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within five working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB in writing of this use within 5 working days after the use of the test article.

I. Genetic Research

DNA projects, by nature of their subject matter, are reviewed for the following information in addition to the standard required review. Genetic information is uniquely personal information and has the potential to influence employment, insurance, finance, education and possibly self perception. Therefore, genetic information must be carefully maintained in order to protect against stigmatization, discrimination, or significant psychological harm to the subject.

IRB review considers the following issues in both the application and the Informed Consent Document, as applicable:

- Information that can be obtained from DNA samples in general, and the specific questions to be addressed in this study.
- The extent of subject and sample confidentiality if the sample and subsequent information will be part of a registry or database.
- The rights and limitations of those rights if subjects request destruction of their sample and/or associated data at a future date.
- The rights and limitations of subjects to subsequently request that their sample and or associated data be stripped of any identifying information.
- Identifying information available to other researchers if their sample and/or associated data are part of a registry or database.
- Mechanisms for maintaining confidentiality in long-term studies, registries, or databases.
- Potential for commercial profit by the institution, investigator or sponsor from information gathered in this study.
- The availability or access to genetic counseling in cases where a study may reveal genetically important information (i.e., possessing genetic defects which could be passed on). Please note that subjects must also have the right to decline receiving genetic information.

Before involving children in DNA research, the parent(s) or legal guardian(s) must review and sign the Informed Consent Document. The Informed Consent Document must give parents/guardians the option of whether or not they want the results (if available) of the genetic analysis disclosed to them. Whenever appropriate, the child's assent should be solicited. Upon reaching the age of majority, if the subject may request his or her information be disclosed that should be included in the Consent Document. Investigators must follow the appropriate

measures with regard to releasing such information (e.g., counseling, etc.). In some cases it may be possible to determine that some members of the family are not genetic relatives. Issues of genetic relationships (paternity or maternity, as could be hidden by adoption or donor fertilization) and other incidental information should not be revealed. The standard Informed Consent Document template contains suggested language for genetic research and for storing tissue or specimens for future use.

J. HIPAA

The Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA) provides standards for maintaining the privacy of individually identifiable health information. It applies only to individually identifiable health information that is created or maintained by a covered entity, which makes the data "protected health information" or PHI.

Most of the research use or disclosure of PHI related to research at Northwestern University involves individually identifiable health information that is created or maintained by one of our Affiliate Institutions (NMH, NMFF, and RIC). With this in mind, a separate Northwestern University HIPAA Research Policy has been developed which covers the use and disclosure of PHI from those institutions for NU research. This policy and other guidance documents can be accessed on the OPRS HIPAA website.

K. International Research

The cultural norms and legal considerations for human subjects research that is conducted outside the United States may differ from those set forth in federal and University policies. These may result from differences in language, cultural and social history, and social mores. In addition, national policies such as the availability of national health insurance, philosophically different legal systems, and social policies may make U.S. forms and procedures inappropriate.

In federally funded research, research activities in a foreign country may be approved by the IRB if the human subject protections in place are at least equivalent to those required in the U.S. The federal Office for Human Research Protections provides a "compilation" of existing laws, regulations, and guidelines that govern human subjects research in many countries around the world.

Requests to review and waive some standard requirements for domestic research may be considered. However, protections afforded subjects must approximate those provided to subjects in the United States.

L. Investigational Drugs or Biologics

1. IND – Investigational New Drug

Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer) having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.

There are three IND types:

- An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
- Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
- Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

Once the IND is submitted to FDA, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk. For more information on IND's, refer to the following link: FDA (CDER) website. NU investigators conducting studies with an IND are required to submit documentation from the sponsor (either as a letter from the FDA or sponsor, email from the FDA or sponsor or indication on the commercial sponsor's protocol) of the IND number assigned by the FDA. This documentation must be attached to the new project application in EIRB. IRB staff will check for this documentation and return protocols with inadequate documentation of the IND number.

2. Promotion and Charging for Investigational New Drugs

[Taken from 21 CFR 312.7]

Promotion. A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context (e.g in advertisements, brochures or any recruitment media) that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including the dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

A sponsor or investigator shall not commercially distribute or test market an investigational new drug. In addition, a investigator should be aware that a sponsor cannot unduly prolong an investigation after finding that the results of the investigation appear to establish sufficient data to support a marketing application.

a) Charging.

Charging for an investigational drug in a clinical trial under an IND is NOT permitted without the prior written approval of FDA. In requesting such approval, the sponsor shall provide a full written explanation of why charging is necessary in order for the sponsor to undertake or continue the clinical trial, e.g., why distribution of the drug to test subjects should not be considered by the sponsor to be part of the normal cost of doing business.

Investigators should include in the "Costs" section of the Informed Consent Document a statement that there will be no charges for the investigational new drug(s) used in the study. If this statement is not included in the informed consent document, the NU IRB will only allow its absence if the investigator attaches the prior written approval of the FDA to the sponsor to allow for test subject charges. This authorization to charge for an investigational drug under this section may be withdrawn by FDA if the agency finds that the conditions underlying the authorization are no longer satisfied. In this instance, it is the responsibility of the investigator to submit a modification to the informed consent document inserting the required statement as indicated above. In such cases where charges are allowed, sponsors are not allowed to commercialize the investigational new drug by charging a price larger than that necessary to recover costs of manufacture, research, development, and handling of the investigational drug. The investigator must be cognizant of this rule when participating in a clinical trial of an investigational new drug.

Treatment protocol or treatment IND. A sponsor or investigator may charge for an investigational drug for a treatment used under a treatment protocol or treatment IND provided:

1. There is adequate enrollment in the ongoing clinical investigations under the authorized IND;
2. Charging does not constitute commercial marketing of a new drug for which a marketing application has not been approved;
3. The drug is not being commercially promoted or advertised; AND
4. The sponsor of the drug is actively pursuing marketing approval with due diligence.

FDA must be notified in writing in advance of commencing any such charges, in an information amendment. Authorization for charging goes into effect automatically 30 days after receipt by FDA of the information amendment, unless the sponsor is notified to the contrary.

3. Investigational Use of FDA-approved Drugs or Biologics

The investigational use of approved, marketed products differs from the situation described above. "Investigational use" suggests the use of an approved product in the context of a clinical study protocol [see 21 CFR 312.3(b)]. When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, submission

of an IND or IDE may be required. However, according to 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug or biologic does not require submission of an IND if all six of the following conditions are met:

(i) it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
(ii) it is not intended to support a significant change in the advertising for the product;
(iii) it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
(iv) it is conducted in compliance with the requirements for IRB review and informed consent;
(v) it is conducted in compliance with the requirements concerning the promotion and sale of drugs; and
(vi) it does not intend to invoke the exception for informed consent requirements [21 CFR 50.24].

4. Sponsor-Investigator (Investigator-Initiated) Research with Drugs or Biologics

The following information is intended to provide sponsor-investigators with information to guide them through the FDA requirements for sponsor-investigators who hold an IND. The federal regulations for INDs are found under 21 CFR 312. Responsibilities of sponsors and investigators are also contained in the International Conference on Harmonisation (ICH) Guidance for Industry, E6 Good Clinical Practice. For more information, review the FDA's Center for Drug Evaluation and Research (CDER) web site www.fda.gov/cder.
This text is a synopsis of requirements specific to sponsor-investigators who hold INDs. It is intended to be a guide, but does not include the complete text of the regulations. Hyperlinks are included throughout the following text so that you may read the corresponding regulations. Sponsor-investigators must review and be familiar with the federal regulations before undertaking these responsibilities.

Sponsor-investigators are also required to follow all federal regulations and Northwestern University policies and guidance for Human Subjects research. Federal regulations are found in 45 CFR 46, and are available on the Office for Human Research Protections web site. Northwestern University policies and guidance for human subjects research are available in this Investigator's Guide.

a) What is a Sponsor-Investigator?

When an Investigator holds an IND for the product being tested in a particular research study, he/she must also assume the role of the Sponsor, and is called a "Sponsor-Investigator." The FDA defines a Sponsor-Investigator as "means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor." [21 CFR 312.3]

b) What must the Sponsor-Investigator report to the FDA?

Sponsor-investigators have extensive reporting requirements under FDA regulations.

1. New protocol 21 CFR 312.30a

Once the IND has been approved by the FDA, the sponsor-investigator must submit a new protocol for any study not contained in the IND application. The protocol can be submitted before or after IRB approval. The study may not begin until the protocol has been reviewed by the FDA and approved by the IRB.

2. Changes in the protocol 21 CFR 312.30b

The following protocol changes must be submitted to the FDA.

- For *Phase 1 studies*, any change that significantly affects the safety of subjects.
- For *Phase 2 and 3 studies*, any change that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study.

3. New investigator 21 CFR 312.30c

The addition of a new investigator must be reported to the FDA within 30 days of the investigator being added. The IND may not be shipped to the new investigator until the FDA has been notified.

4. Information amendments 21 CFR 312.31

Any essential information that is not included in a protocol amendment, IND safety report, or annual report must be submitted to the FDA. Examples of essential information include new toxicology, chemistry, or other technical information. Information amendments should be submitted as necessary, but not more than every 30 days.

5. IND safety/adverse events reports 21 CFR 312.32

An investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, *or probably caused by*, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately. [21 CFR 312.64]. Guides to adverse event reporting are indicated below:

- ***Unexpected fatal or life-threatening*** experiences that are associated with the investigational drug must be reported to the FDA *by fax or telephone as soon as possible*, but no later than 7 days after the sponsor-investigator initially receives the information.
- ***Serious and unexpected adverse events*** associated with the use of the drug that are not fatal or life-threatening must be submitted to the FDA as soon as possible, but no later than 15 days after the sponsor-investigator initially receives the information.

6. Annual reports 21 CFR 312.33

The sponsor-investigator must submit a progress report to the FDA within 60 days of the anniversary date that the IND went into effect. **The sponsor is also required under** 21 CFR 312.33 **to submit annual reports to the FDA on the progress of the clinical investigations.** [21 CFR 312.64]. The expected contents of the progress report are included in 21 CFR 312.33**.**

7. Withdrawal of an IND 21 CFR 312.38

Sponsor-investigators must inform the FDA of desire to withdraw an IND.

8. Discontinuation of an investigation 21 CFR 312.31(a)2
If the sponsor-investigator determines that an investigation drug presents an unreasonable and significant risk to subjects, she/he must discontinue the investigation within 5 working days after determining that the investigation should be discontinued. A report of the discontinuation of the investigation should be submitted to the FDA within 5 working days of the discontinuance.

9. Financial disclosure reports 21 CFR 312.57d
Any changes to financial disclosure information must be promptly reported to the FDA during the investigation and for 1 year following completion of the study.

c) What records must a sponsor-investigator maintain?

The sponsor-investigator is responsible for maintaining the following records during and for 2 years after the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such an indication, the sponsor-investigator is responsible for maintaining the following records until 2 years after the investigation is discontinued and FDA is notified. [21 CFR 312.62] The sponsor-investigator must make these available to FDA inspectors at their request.

1. Drug accountability 21 CFR 312.57a
The sponsor-investigator must maintain records showing receipt, shipment, or other disposition of the investigational drug.

2. Financial interest 21 CFR 312.57b
The sponsor-investigator must maintain records showing any financial interests of any of the clinical investigators involved in the study (see also 21 CFR 54). The clinical investigator shall provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements. The clinical investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study [21 CFR 312.64].

3. Case Histories 21 CFR 312.62b
The sponsor-investigator must maintain accurate case histories that record all observations and other data pertinent to the investigation on each subject who received the investigational drug and each subject who was employed as a control in the investigation. [21 CFR 312.62]. Case histories include the case report forms and supporting data such as signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

4. Essential documents ICH E6 S8
The sponsor-investigator must maintain documents included in ICH E6 S8. These documents are considered essential to conducting a clinical trial and are subject to audit by regulatory authorities. The investigator shall furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained. Examples of essential documents are signed protocol and amendments, informed consent documents,

IRB approval notices, and signed, dated, and completed case report forms (CRFs). For a complete list of essential documents, see ICH E6 S8

d) What are the sponsor-investigator's responsibilities as a sponsor?

The sponsor-investigator carries all responsibilities toward co-investigators that are normally assigned to the sponsor.

1. General responsibilities of sponsors 21 CFR 312.50

The sponsor-investigator is responsible for

- selecting qualified investigators and providing them with the information they need to conduct an investigation properly.
- ensuring proper monitoring of the investigation. For more information on monitoring guidelines, see Section 5.18 of the ICH Guidance.
- ensuring that the investigation is conducted in accordance with the general investigational plan and protocols contained in the IND.
- maintaining an effective IND with respect to the investigations.
- complying with FDA regulations with regard to the promotion and charging for investigational new drugs. See Chapter 9, Section IND – Investigational Drugs or Biologics, Sub-section Promotion and Charging for Investigational New Drugs above.
- ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug.

2. Selection and monitoring of investigators 21 CFR 312.53 – 312.56

The sponsor-investigator is responsible for

- selecting qualified investigators and monitors.
- ensuring that the study drug is shipped only to participating investigators.
- informing co-investigators of new observations with regard to the investigational drug and progress of the study.
- reviewing on-going investigations, including assuring compliance of all investigators with the protocol, reviewing and evaluating safety and efficacy data of the investigational drug, and discontinuing studies that are deemed to pose an unreasonable and significant risk to subjects.

3. Recordkeeping and record retention 21 CFR 312.57

The sponsor-investigator is responsible for maintaining study records, as described above.

4. Inspection of sponsor's records and reports 21 CFR 312.58

The sponsor-investigator must allow FDA employees access to all records and reports at their request. Drug Enforcement Administration and Department of Justice employees must be given access to records and reports involving controlled substances at their request.

5. Disposition of unused supply of investigational drug 21 CFR 312.59

If the investigation is terminated, suspended, discontinued, or completed, the sponsor-investigator is responsible for assuring that all co-investigators return any unused supplies of the investigational drug **to the sponsor**, or **otherwise provide for disposition of the unused supplies of the drug under** 21 CFR 312.59 [21 CFR 312.62] The

sponsor-investigator must maintain records of the disposition of the drug as described above.

e) What are the sponsor-investigator's responsibilities as an investigator?

As an investigator, the sponsor-investigator has all the responsibilities of investigators in any clinical trial.

1. General responsibilities of investigators 21 CFR 312.60
The sponsor-investigator is responsible for

- ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations.
- protecting the rights, safety, and welfare of subjects under the investigator's care
- ensuring the control of drugs under investigation.

2. Control of the investigational drug 21 CFR 312.61
The sponsor-investigator must administer the investigational drug only to subjects under his/her direct supervision, or under the supervision of a sub-investigator responsible to the investigator. The sponsor-investigator must also ensure that the investigational drug is not given to any person not authorized to receive it.

3. Investigator recordkeeping and record retention 21 CFR 312.62
The sponsor-investigator is responsible for maintaining adequate records of the disposition of the drug, including dates, quantity, and use by subjects. This is described above.

4. Investigator reports 21 CFR 312.64
The sponsor-investigator must provide reports to the FDA as described above.

5. Assurance of IRB review 21 CFR 312.66
The sponsor-investigator is responsible for

- assuring that a qualified IRB will be responsible for initial and continuing review and approval of the investigation.
- providing a letter or email from the FDA (as an attachment to the EIRB new project application) giving the IND number assigned by the FDA.
- assuring that he/she will report to the IRB all changes and unanticipated problems involving risk to human subjects or others.
- assuring that he/she will not make any changes in the investigation without prior IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

6. Inspection of investigator's records and reports 21 CFR 312.68
The sponsor-investigator must allow FDA employees access to all records and reports at their request. An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to 21 CFR 312.62 [21 CFR 312.68]. The investigator is not required to divulge participant names unless the records of particular individuals require a more detailed study of the cases, or

unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

7. Handling of controlled substances 21 CFR 312.69
The sponsor-investigator must take adequate precautions to ensure the safe and secure handling of controlled substances. The investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

M. Investigational Medical Devices

1. IDE – Investigational Device Exemption

An investigational device is a medical device which is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. Clinical investigations undertaken to develop safety and effectiveness data for medical devices must be conducted according to the requirements of the IDE regulations. An IDE study may not necessarily commence 30 days after an IDE submission to FDA. Certain clinical investigations of devices (e.g., certain studies of lawfully marketed devices) may be exempt from the IDE regulations. Unless exempt from the IDE regulations, an investigational device must be categorized as either "significant risk" (SR) or "nonsignificant risk" (NSR) – see the section below for more information. The determination that a device presents a nonsignificant or significant risk is initially made by the sponsor. The proposed study is then submitted either to FDA (for SR studies) or to an IRB (for NSR studies).

The IRB's SR/NSR determination has significant consequences for the study sponsor, FDA, and prospective research subjects. SR device studies must be conducted in accordance with the full IDE requirements, and may not commence until 30 days following the sponsor's submission of an IDE application to FDA. Submission of the IDE application enables FDA to review information about the technical characteristics of the device, the results of any prior studies (laboratory, animal and human) involving the device, and the proposed study protocol and consent documents. Based upon the review of this information, FDA may impose restrictions on the study to ensure that risks to subjects are minimized and do not outweigh the anticipated benefits to the subjects and the importance of the knowledge to be gained. The study may not commence until FDA has approved the IDE application and the IRB has approved the study.

In contrast, NSR device studies do not require submission of an IDE application to FDA. Instead, the sponsor is required to conduct the study in accordance with the "abbreviated requirements" of the IDE regulations. Unless otherwise notified by FDA, an NSR study is considered to have an approved IDE if the sponsor fulfills the abbreviated requirements. The abbreviated requirements address, among other things, the requirements for IRB approval and informed consent, recordkeeping, labeling, promotion, and study monitoring. NSR studies may commence immediately following IRB approval.

Once the final SR/NSR decision has been rendered by the IRB (or FDA), the IRB must consider whether or not the study should be approved. In considering whether a study should

be approved, the IRB should use the same criteria it would use in considering approval of any research involving an FDA regulated product. FDA considers all SR studies to present more than minimal risk, and thus, full IRB review is necessary. In making its determination on approval, the IRB should consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures.

2. Significant and Nonsignificant Risk Medical Device Studies

The Investigational Device Exemption (IDE) regulations discriminate between two types of device studies; "significant risk" (SR) and "nonsignificant risk" (NSR). An SR device study is defined as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and

(1) is intended as an implant; or
(2) is used in supporting or sustaining human life; or
(3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or
(4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

An NSR device investigation is one that does not meet the definition for a significant risk study. NSR device studies, however, should not be confused with the concept of "minimal risk," a term utilized in the Institutional Review Board (IRB) regulations to identify certain studies that may be approved through an "expedited review" procedure. For both SR and NSR device studies, IRB approval prior to conducting clinical trials and continuing review by the IRB are required. In addition, informed consent must be obtained for either type of study.

3. Distinguishing Between SR and NSR Device Studies

The effect of the SR/NSR decision is very important to research sponsors and investigators. SR device studies are governed by the IDE regulations. NSR device studies have fewer regulatory controls than SR studies and are governed by the abbreviated requirements. The major differences are in the approval process and in the record keeping and reporting requirements. The SR/NSR decision is also important to FDA because the IRB serves, in a sense, as the Agency's surrogate with respect to review and approval of NSR studies. FDA is usually not apprised of the existence of approved NSR studies because sponsors and IRBs are not required to report NSR device study approvals to FDA. If an investigator or a sponsor proposes the initiation of a claimed NSR investigation to an IRB, and if the IRB agrees that the device study is NSR and approves the study, the investigation may begin at that institution immediately, without submission of an IDE application to FDA.

If an IRB believes that a device study is SR, the investigation may not begin until both the IRB and FDA approve the investigation. To help in the determination of the risk status of the device, IRBs should review information such as reports of prior investigations conducted with the device, the proposed investigational plan, a description of subject selection criteria, and monitoring procedures. The sponsor should provide the IRB with a risk assessment and the rationale used in making its risk determination.

4. SR/NSR Studies and the IRB: The NSR/SR Decision

The assessment of whether or not a device study presents a NSR is initially made by the

sponsor. If the sponsor considers that a study is NSR, the sponsor provides the reviewing IRB an explanation of its determination and any other information that may assist the IRB in evaluating the risk of the study. The sponsor should provide the IRB with a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of patient selection criteria and monitoring procedures, as well as any other information that the IRB deems necessary to make its decision. The sponsor should inform the IRB whether other IRBs have reviewed the proposed study and what determination was made. The sponsor must inform the IRB of the Agency's assessment of the device's risk if such an assessment has been made. The IRB may also consult with FDA for its opinion.

The IRB may agree or disagree with the sponsor's initial NSR assessment. If the IRB agrees with the sponsor's initial NSR assessment and approves the study, the study may begin without submission of an IDE application to FDA. If the IRB disagrees, the sponsor should notify FDA that an SR determination has been made. The study can be conducted as an SR investigation following FDA approval of an IDE application.

If the sponsor has an IDE number or the IRB requires an IDE, the investigator must submit to the IRB documentation of the assignment of an IDE number using the EIRB system. This documentation can be an e-mail from the FDA or sponsor, letter from the FDA or sponsor, or indication on the commercial sponsor protocol that gives the IDE number as assigned by the FDA. IRB staff will check for this documentation and return protocols with inadequate documentation of the IDE number.

5. Investigator-Initiated Research with Medical Devices

The following information is intended to provide sponsor-investigators with information to guide them through the FDA requirements for sponsor-investigators who hold an IDE. The federal regulations for IDEs are found under 21 CFR 812. Responsibilities of sponsors and investigators are also contained in the International Conference on Harmonisation (ICH) Guidance for Industry, E6 Good Clinical Practice. For more information, review the FDA's Center for Devices and Radiologic Health (CDRH) web site http://www.fda.gov/cdrh.

This is a synopsis of requirements specific to sponsor-investigators who hold IDEs. It is intended to be a guide, but does not include the complete text of the regulations. Hyperlinks are included throughout this document so that you may read the corresponding regulations. Sponsor-investigators must review and be familiar with the federal regulations before undertaking these responsibilities.

NU Sponsor-investigators are required to follow all relevant federal regulations, NU policies, NU IRB requirements and guidance for Human Subjects research as provided on the OPRS website.

a) What is a Sponsor-Investigator?

When an Investigator holds an IDE for the product being tested in a particular research study, he/she must also assume the role of the Sponsor, and is called a "Sponsor-Investigator." The FDA defines a Sponsor-Investigator as "an individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used . . . . The obligations of a sponsor-investigator under this part include those of an investigator and a sponsor." [21

CFR 812.3]

b) What must the Sponsor-Investigator report to the FDA and/or IRB?

Sponsor-investigators have extensive reporting requirements under FDA regulations.

(1) Changes in the protocol.

Changes to the investigational plan or manufacturing process must be submitted to the FDA for approval if they significantly affect the validity of study data, risk-benefit ratio, scientific soundness of the study, or the rights, safety, or welfare of subjects. These changes should be submitted to the FDA as a supplement to the IDE protocol and must be approved by the FDA before being implemented.

Changes that do not meet the above criteria (e.g., adding follow-up visits, changing secondary endpoints, etc.) should be submitted to the FDA within 5 working days of implementation of the change. Minor changes to the purpose of the study, risk analysis, monitoring procedures, labeling, informed consent materials, and IRB information that do not affect the validity of study data, risk-benefit ratio, scientific soundness of the study, or the rights, safety, or welfare of subjects can be submitted with the annual report.

An investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a participant in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human participants, FDA and IRB in accordance with [21 CFR 812.35(a)]

(2) IDE safety/adverse device effects.

The sponsor-investigator must report all unanticipated adverse device effects to the FDA and the IRB within 10 working days of receiving the first notice of the event. Click here for a decision tree to help determine when to report adverse events relating to investigator-held IDEs.

(3) Withdrawal of IRB approval

The sponsor-investigator must inform the FDA, all reviewing IRBs, and participating investigators of withdrawal of approval of an investigation or any part of an investigation by any reviewing IRB. This notification must occur within 5 working days after receipt of the withdrawal of approval.

(4) Withdrawal of FDA approval

The sponsor-investigator must notify all reviewing IRBs and participating investigators of any withdrawal of FDA approval. This notification must occur within 5 working days

after receipt of the withdrawal of approval.

(5) Current investigator list

The sponsor-investigator must provide the FDA with a current list of investigators participating in the investigation. This list must be provided to the FDA every 6 months.

(6) Annual reports

The sponsor-investigator must submit a progress report to all reviewing IRBs at regular intervals, at least yearly. The first report must be within 60 days of the anniversary date that the IDE went into effect. For IDEs that have been determined to be significant risk, these reports must also be submitted to the FDA.

(7) Recall and device disposition

The sponsor-investigator must notify the FDA and all reviewing IRBs of any request that an investigator return, repair, or otherwise dispose of any units of a device. The notification must occur within 30 working days after the request is made.

(8) Discontinuation of an investigation

The sponsor-investigator must report the completion or termination of an investigation. These reports should be made by submitting a final report. For significant risk devices, the sponsor-investigator must notify the FDA within 30 working days and all reviewing IRBs within 6 months of the completion of the investigation. For non-significant risk devices, the sponsor must notify all reviewing IRBs within 6 months of completion of the study.

(9) Informed consent

The sponsor-investigator must report to the FDA any use of the IDE without informed consent. This report must be submitted within 5 working days of receipt of notice of this use.

(10) Significant risk device determinations

If an IRB determines that a device is significant risk, whereas the sponsor-investigator had proposed it to be a non-significant risk device, the sponsor-investigator must notify the FDA of this decision within 5 working days after learning of the IRB's determination.

In deciding whether or not a medical device is a significant risk, the IRB considers if the device:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a participant. [21 CFR 812.3(m)(l)].
- Is purported or represented to be for a use in supporting or sustaining human

life and presents a potential for serious risk to the health, safety, or welfare of a participant. [21 CFR 812.3(m)(2)].

- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a participant. [21 CFR 812.3(m)(3).]
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. [21 CFR 812.3(m)(4)].

(11) Financial disclosure reports

A clinical investigator shall disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements. The investigator shall promptly update any changes to financial disclosure information and report it to the FDA during the investigation and for 1 year following completion of the study.

c) What records must a sponsor-investigator maintain?

The sponsor-investigator is responsible for maintaining the following records during and for 2 years after completion **or termination** of the investigation or 2 years after the records are no longer needed to support a premarket approval application or a notice of completion of a product development protocol. 21 CFR 812.140d. The sponsor-investigator must make these available to FDA inspectors at their request.

1. Correspondence 21 CFR 812.140
The sponsor-investigator must maintain copies of all correspondence with other investigators, reviewing IRBs, monitors, and the FDA including required reports.

2. Financial interest 21 CFR 812.140
The sponsor-investigator must maintain records showing any financial interests of any of the clinical investigators involved in the study (see also 21 CFR 54).

3. Device records 21 CFR 812.140
A participating investigator shall maintain the following accurate, complete and current records relating to the investigator's participation in an investigation. The sponsor-investigator must maintain records relating to the shipment, receipt, use (including adverse effects), and disposition of the device.

Additionally, for *nonsignificant risk devices*, the investigator must maintain

- the name and intended use of the device (type and quantity of the device, the dates of its receipt, and the batch number or code mark).
- a brief explanation of why the device is not a significant risk.
- the name and address of each investigator and the names of all persons who received, used, or disposed of each device.
- why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of
- a statement of the extent to which Good Manufacturing Practice (GMP) regulations will be followed in manufacturing the device (see also 21 CFR 820).

4. Case Histories 21 CFR 812.140
The sponsor-investigator must maintain accurate case histories that record all observations and other data pertinent to the investigation on each subject exposed to the investigational device. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

5. Essential documents ICH E6 S8
The sponsor-investigator must maintain documents included in ICH E6 S8. These documents are considered essential to conducting a clinical trial and are subject to audit by regulatory authorities. Examples of essential documents are signed protocol and amendments, signed and dated informed consent documents, IRB approval notices, and signed, dated, and completed case report forms (CRFs), medical records including, for example, progress notes of the physician, the subject's hospital chart(s) and the nurses' notes.
Such records shall include:

- Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, and written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent.
- All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each participant upon entering and during the course of the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
- A record of the exposure of each participant to the investigational device, including the date and time of each use, and any other therapy.
- The protocol, with documents showing the dates of and the reasons for each deviation from the protocol.
- Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

For a complete list of essential documents, see ICH E6 S8
An investigator or sponsor may withdraw from the responsibility to maintain records for the period required in 21 CFR 812.140(d) and transfer custody of the records to any other person who will accept responsibility for them under 21 CFR 812.140, including the requirements of 21 CFR 812.145 [21 CFR 812.140(e)]. Notice of this transfer shall be given to the FDA not later than 10 working days after transfer occurs.

d) What are the sponsor-investigator's responsibilities as a sponsor?

The sponsor-investigator carries all responsibilities toward co-investigators that are normally assigned to the sponsor.

1. General responsibilities of sponsors 21 CFR 812.40
The sponsor-investigator is responsible for

- selecting qualified investigators and providing them with the information they need to conduct an investigation properly.
- ensuring proper monitoring of the investigation. For more information on monitoring guidelines, see Section 5.18 of the ICH Guidance.

- ensuring that IRB review and approval are obtained.
- submitting an IDE application to the FDA.
- ensuring that any reviewing IRB, FDA, and participating investigators are promptly informed of significant new information about an investigation.

2. Selecting and monitoring investigators 21 CFR 812.43 – 812.46
The sponsor-investigator is responsible for

- selecting qualified investigators and monitors.
- ensuring that the investigational device is shipped only to participating investigators.
- obtaining investigator agreements.
- obtaining statements from participating investigators attesting to their commitment to the proper conduct of the investigation.
- obtaining accurate financial disclosure statements from participating investigators.
- providing participating investigators with the investigational plan.
- informing co-investigators of new observations with regard to the investigational device and progress of the study.
- reviewing on-going investigations, including assuring compliance of all investigators with the protocol, reviewing and evaluating safety and efficacy data of the investigational device, and discontinuing studies that are deemed to pose an unreasonable and significant risk to subjects.

3. Adverse device effects and study termination 21 CFR 812.46

- The sponsor-investigator must immediately evaluate any unanticipated adverse device effect. If the sponsor-investigator determines that the device presents an unreasonable risk to subjects, the sponsor-investigator must terminate the study within 5 working days after making this determination, but not later than 15 working days after first receiving notice of the adverse effect.
- If the device is significant risk, the sponsor-investigator may not resume a terminated investigation without IRB and FDA approval.
- If the device is nonsignificant risk, the sponsor-investigator may not resume a terminated investigation without IRB approval.

4. Recordkeeping and record retention 21 CFR 812.140
The sponsor-investigator is responsible for maintaining study records, as described above.

5. Inspection of sponsor's records and reports 21 CFR 812.145
The sponsor-investigator must allow FDA employees access to all records and reports at their request. An investigator who has authority to grant access shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept). [21 CFR 812.145(a)].

An investigator shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation. [21 CFR 812.145(b)]. An investigator shall permit authorized FDA employees to inspect and copy records that identify participants, upon notice that FDA has reason to suspect that

adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading. [21 CFR 812.145(c)].

e) What are the sponsor-investigator's responsibilities as an investigator?

As an investigator, the sponsor-investigator has all the responsibilities of investigators in any clinical trial.

1. General responsibilities of investigators 21 CFR 812.100
An investigator may determine whether potential participants would be interested in participating in an investigation, but shall not request the written informed consent of any participant to participate, and shall not allow any participant to participate before obtaining IRB and FDA approval. [21 CFR 812.110]. The investigator is responsible for providing a letter or an e-mail from the FDA (as an attachment to the EIRB system) giving the IDE number, if applicable, as assigned by the FDA.

The sponsor-investigator is responsible for

- ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable **FDA** regulations.
- protecting the rights, safety, and welfare of subjects under the investigator's care
- ensuring the control of devices under investigation.

2. Compliance with protocol 21 CFR 812.110b
The sponsor-investigator must conduct the investigation in accordance with the signed agreement, the investigational plan, FDA regulations, and IRB conditions. [21 CFR 812.110]

3. Device use and disposition 21 CFR 812.110c
The sponsor-investigator must permit the use of an investigational device only with subjects under the investigator's supervision. Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs. [21 CFR 812.110]

4. Investigator recordkeeping and record retention 21 CFR 812.140a
The sponsor-investigator is responsible for maintaining study records, as described above.

5. Investigator reports 21 CFR 812.150
The sponsor-investigator must provide reports to the FDA as described above.

6. Inspection of investigator's records and reports 21 CFR 812.145
The sponsor-investigator must allow FDA employees access to all records and reports at their request.

N. Placebo-Controlled Trials

If an investigator proposes a clinical investigation in which a placebo is given for any length of time in lieu of an approved FDA indicated drug, the investigator must include risk management procedures in the research plan for the IRB for review. In order for the IRB to approve the use of placebo in a clinical investigation, the investigator must demonstrate that the subjects' safety is monitored frequently and that provisions are made for prompt medical rescue if indicated to protect the subject. Once an approval is granted, the investigator is bound to follow the risk management procedures as with any other provision of the approved protocol.

Use of placebos may be appropriate where the investigator demonstrates that:

- standard therapy is unavailable or is of unproved efficacy, or
- standard therapy possesses unacceptable side effects, or
- minimal harm may result from the use of placebo (e.g., ongoing disease has little adverse effect on the patient during the course of the trial and is reversible), or
- placebo itself may be an effective therapy, or
- the disease process is characterized by exacerbation and remission.

The risk management procedures should be in the written protocol, with the same level of detail as in the protocol itself. The following issues should be specified:

- the frequency of monitoring,
- whether monitoring is in person or by telephone,
- the criteria for managing a subject in the event of worsening, and
- how 24 hour-per-day, 7 day-per-week, medical care is made available in the event of questions, emergencies, worsening, or a desire to withdraw from the protocol.

In the informed consent documents, investigators must indicate the planned use of placebo and must adequately discuss the potential for harm from the use of placebos, as well as the importance of procedures for adequately monitoring subjects to ensure their safety.

O. Washout Issues in Drug Treatment Studies

When a subject is asked to stop taking some or all medications prior to beginning a drug treatment study, this is called a drug washout. Washouts may be ethically appropriate depending upon the disease to be studied and the nature of the proposed protocol. Washout studies require balancing the likelihood of harm, the effectiveness of monitoring, and the potential severity of the risk(s) to be avoided. When subjects are being washed out from a FDA approved and indicated drug, the individual investigator should clearly define the nature and degree of risk to the subjects and include risk management procedures in the research plan. To the extent that the investigator demonstrates that the subjects' safety is adequately monitored and provisions are made for immediate rescue if needed, the IRB will consider approval of the study. Once an approval is granted, the investigator is bound to follow the risk management procedures as with any other provision of the approved protocol. The risk management procedures should be in the written protocol, with the same level of detail as in the protocol itself. The following issues should be specified:

- careful definition as to when a subject would be withdrawn from the study,
- the frequency of monitoring,
- whether monitoring is in person or by telephone,
- the criteria for managing a subject in the event of worsening, and
- how 24 hour-per-day, 7 day-per-week, medical care is made available in the event of

questions, emergencies, worsening, or withdrawal from the protocol.

XI. Allegations of Noncompliance

The Principal Investigator bears the ultimate responsibility for the conduct of a research project. The investigator must comply with the requirements of the Northwestern University's Federalwide Assurance and with determinations of the IRB, as outlined in minutes and other correspondence. Information regarding allegations of noncompliance may come to the attention of the IRB through several pathways. These include information contained in application forms, IRB reporting forms, monitoring reports, or reports from collaborators, employees, subjects, or others not directly involved in the research. All members of the research community at Northwestern share responsibility for ensuring the ongoing compliance of our research conduct with the human subject protections outlined in this policy, in the relevant federal regulations and state laws, and in the specific requirements of the IRB.

When information comes to the attention of the IRB outside of a full-board meeting, the Chair of the appropriate IRB reviews the allegations of noncompliance. The Chair makes a determination as to whether the alleged practices appear to (1) cause injury or any other unanticipated problems involving risks to subjects or others, or (2) constitute serious or continuing noncompliance with federal human subject protection regulations, the requirements of this policy or specific IRB requirements for the research. If any of these are determined to be likely, the Chair may suspend the study procedures, or place a "partial clinical hold" on some aspect of the study (e.g., the enrollment of new subjects, or one arm of a study), taking into consideration the welfare of currently enrolled subjects, pending further investigation and review of the allegations. If the Chair determines that the potential noncompliance did not involve any risk to subjects or others, and did not constitute serious or continuing noncompliance, the Chair may resolve the issue directly with the Principal Investigator and research team.

When potential noncompliance is first identified during a full-board review, the full-board makes a determination as to whether the alleged practices appear to (1) cause injury or any other unanticipated problems involving risks to subjects or others, or (2) constitute serious or continuing noncompliance with federal human subject protection regulations, the requirements of this policy or specific IRB requirements for the research. In such cases, the full board may suspend the study procedures, or place a "partial clinical hold" to temporarily halt some aspect of the research procedures (e.g., the enrollment of new subjects), taking into consideration the welfare of currently enrolled subjects, and determine how further investigation will be conducted according to the procedures indicated below.

In cases that involve allegations of possible research misconduct, the OPRS will contact the NU Research Integrity Officer (RIO) for further action. This does not preclude the Chair or any member of the IRB from independently contacting the RIO about any allegation of scientific misconduct. Inquiries or investigations into research misconduct are independent of IRB review and required corrective actions that are designed to ensure the safeguarding of the rights and welfare of the subjects.

The following points outline procedures for investigating and resolving alleged noncompliance:

1. When made aware of an allegation of noncompliance, OPRS staff promptly notifies the Human Protections Administrator, who will work with one or more of the NU IRB Chairs to compile any required background file information. If the alleged noncompliance involves research conducted under another IRB's authority, the allegation is promptly reported to an NU IRB Chair, to appropriate institutional officials, and to the

appropriate IRB of record.

2. The Human Protections Administrator (HPA) and the NU IRB Chairs Committee make a determination as to whether to pursue the matter with the Principal Investigator via telephone call, e-mail, paper memo, or in person based on the nature and seriousness of the alleged noncompliance. The choice may also be made to send an IRB monitor to meet with research team members and review study materials as appropriate. The purpose of such contact is fact-finding, i.e. to determine if indeed there is noncompliance. Care is taken to maintain confidentiality when leaving messages for the Principal Investigator via voice mail or with support staff.

3. The HPA, IRB Chairs and other parties involved in the investigation document the outcome of any and all communications and discussions in writing, by either e-mail or paper memo with a copy to the IRB files. Such documentation should be factual and objective, and include timelines for resolution (e.g. meeting dates, response deadlines).

4. The NU IRB Chairs Committee makes a decision based on the information gathered as to whether the allegation is credible.

5. If the NU Chairs believe the allegation is credible, they also are asked to determine whether the noncompliance meets the definition of UPIRSO or of serious or continuing noncompliance. In making this determination, the IRB Chairs Committee may defer the deliberation to a specific panel for discussion.

If the Chairs determine that the noncompliance is not serious or continuing, and does not involve unanticipated risk to subjects or others, the Chairs and the PI may work together to create an acceptable corrective action plan.

If the Chairs determine that the noncompliance is serious, continuing, or involves unanticipated risk to subjects or others, the Chairs may suspend or terminate IRB approval for the research activities, or place a "partial clinical hold" on some aspect(s) of the research (e.g., new enrollments to the protocol), taking into consideration the welfare of currently enrolled subjects, until an investigative report is reviewed by the full board along with a corrective action plan.

What is serious noncompliance? Serious noncompliance is noncompliance that results in unexpected risk of harm to subjects or others. This type of noncompliance may harm a person's physical, social, emotional, psychological well-being, social or legal welfare, or cause harm due to loss of the person's privacy or confidentiality.

What is continuing noncompliance? Any noncompliance that occurs repeatedly to the point of suggesting a pattern or an underlying problem. Continuing noncompliance may occur due to a lack of knowledge (unintentional) or due to deliberate choice to ignore regulations or determinations of the IRB (intentional).

Under this policy, the IRB Chairs Committee or a convened IRB may determine that the corrective action plan is adequate for the ongoing protection of research subjects when it has been determined that there was serious non-compliance. In cases of continuing non-compliance and allegations of non-compliance that are determined to be either not serious or not non-compliance, an IRB Chair may determine that the corrective action plan is

adequate or that none is needed respectively. After review of the reports and discussion, the IRB Chairs Committee shall vote to recommend specific actions. The possible actions that could be taken by the IRB include:

- Suspension or termination of IRB approval of protocols that are found to be noncompliant with institutional policies and procedures, state laws, and/or federal laws or regulations, taking into consideration the welfare of currently enrolled subjects,
- Placing a "partial clinical hold" on the research, requiring the cessation of some aspect of the research (e.g., a particularly risky arm of a study, or stopping additional enrollments) until the non-compliance issues have been resolved and an adequate corrective action plan implemented,
- Compliance audits,
- Letters of reprimand,
- Restrictions on serving as an investigator on human subjects protocols,
- Notification of currently enrolled subjects,
- Providing additional information to past subjects,
- Modification to research protocols,
- More frequent continuing review or monitoring,
- Monitoring of the consent process,
- Changes in consent process or documents,
- Requirement that currently enrolled subjects re-consent to participation,
- Request more information prior to making a final decision,
- Referral of the issue to other organizational entities such as NU legal counsel, risk management, or the research integrity officer, or
- Other actions as appropriate.

The goal of the IRB's review of allegations of non-compliance is corrective actions, on the part of the investigator and research team so as to ensure the adequate safeguarding of the rights and welfare of subjects.

If the IRB determines that the actions of the investigator or research staff are particularly egregious, the IRB may ask for a meeting with the HPA and the Institutional Official, who may initiate contact with University administrators in order to consider additional sanctions against the parties involved.

XII. Investigator Questions, Concerns and Suggestions

Staff in the OPRS are available to investigators and their research team members to answer questions about activities that are "not human subject research," exempt human subjects research, and the IRB review process. A staff listing along with their job titles and contact information may be found on the OPRS website. If the OPRS is unable to help with your issue, you may also contact the Office of the Vice President for Research.

XIII. Definitions for this Policy[1]

ACCRUAL TARGET: The number of required evaluable subjects, plus the number of anticipated inevaluable subjects, as described in the IRB-approved protocol and consent document.

ADVERSE EFFECT: An undesirable and unintended, although not necessarily unexpected, result of therapy or other intervention (*e.g.*, headache following spinal tap or intestinal bleeding associated with aspirin therapy).

ASSENT: Agreement by an individual not competent to give legally valid informed consent (*e.g.*, a child or cognitively impaired person) to participate in research.

ASSURANCE: A formal written, binding commitment that is submitted to a federal agency in which an institution promises to comply with applicable regulations governing research with human subjects and stipulates the procedures through which compliance will be achieved.

AUTONOMY: Personal capacity to consider alternatives, make choices, and act without undue influence or interference of others.

BELMONT REPORT: A statement of basic ethical principles governing research involving human subjects issued by the National Commission for the Protection of Human Subjects in 1978.

BENEFICENCE: An ethical principle discussed in the *Belmont Report* that entails an obligation to protect persons from harm. The principle of beneficence can be expressed in two general rules: (1) do not harm; and (2) protect from harm by maximizing possible benefits and minimizing possible risks of harm.

BENEFIT: A valued or desired outcome; an advantage.

CHILDREN: Persons who have not attained the legal age for consent to treatment or procedures involved in the research, as determined under the applicable law of the jurisdiction in which the research will be conducted. In Illinois, eighteen years of age is the age of majority, after which individuals ordinarily can give consent. In this policy "children" and "minors" are used interchangeably. Minors who have been adjudicated as "emancipated" by the courts may consent for themselves. [See also: Minors]

CLINICAL HOLD: See: PARTIAL CLINICAL HOLD

CLINICAL TRIAL: A controlled study involving human subjects, designed to evaluate prospectively the safety and effectiveness of new drugs or devices or of behavioral interventions.

CLOSED TO ACCRUAL: In contrast to a temporary suspension, the closure of a study to accrual typically is a permanent status change which occurs when the Investigator has either reached the

[1] Many of the definitions in this policy are taken directly from the online version of the OHRP IRB Guidebook.

target enrollment, or has decided for other reasons to end further accessions.

COMPASSIONATE USE: See Emergency Use

COMPENSATION: Payment or medical care provided to subjects injured in research; does not refer to payment (remuneration) for participation in research.

COMPETENCE: A legal term, used to denote capacity to act on one's own behalf; the ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a "reasoned" choice.

COMPLETED: When all research data have been analyzed, and all subjects have been either enrolled on a long-term follow-up study or have been taken off of a study, the Investigator may petition the IRB for completion of the study, usually in the context of a continuing review report. Only the IRB can complete the study, and once the study is completed, no further analysis of the data or any other research activity may be performed, including the recording of long-term follow-up data (without a new approval from the IRB).

CONFIDENTIALITY: Pertains to the treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others without permission in ways that are inconsistent with the understanding of the original disclosure.

CONTINUING NON-COMPLIANCE: For the purpose of this policy, continuing non-compliance refers to repeated acts of non-compliance in the conduct of human subjects research so that there appears to be a pattern indicative of a lack of understanding or attention to the safeguarding of the rights and welfare of human subjects in research. Continuing non-compliance is characterized by the frequency rather than the magnitude of the non-compliance, and may include non-compliance with applicable federal regulations pertaining to human subject protections, with the NU HSPP policy, Illinois state law relating to the research, or the specific determinations of the IRB. [See also "Non-Compliance" and "Continuing Non-Compliance"]

CONTROL (SUBJECTS) OR CONTROLS: Subject(s) used for comparison who are not given a treatment under study or who do not have a given condition, background, or risk factor that is the object of study. Control conditions may be concurrent (occurring more or less simultaneously with the condition under study) or historical (preceding the condition under study). When the present condition of subjects is compared with their own condition on a prior regimen or treatment, the study is considered historically controlled.

DATA AND SAFETY MONITORING BOARD: A committee of scientists, physicians, statisticians, and others that analyzes data during the course of a clinical trial to monitor for adverse effects and other trends (such as an indication that one treatment is significantly better than another, particularly when one arm of the trial involves a placebo control) that would warrant modification or termination of the trial or notification of subjects about new information that might affect their willingness to continue in the trial.

DECLARATION OF HELSINKI: A code of ethics for clinical research approved by the World Medical Association in 1964 and widely adopted by medical associations in various countries. It was revised in 1975 and 1989.

DHHS: A federal agency: U.S. Department of Health and Human Services; formerly the Department of Health, Education and Welfare (DHEW).

DRUG: Any chemical compound that may be used on or administered to humans as an aid in the diagnosis, treatment, cure, mitigation, or prevention of disease or other abnormal conditions.

EMANCIPATED MINOR: A legal status conferred by the courts upon persons who have not yet attained the age of legal competency as defined by Illinois law. Minors who are emancipated by the courts may consent for themselves to participate in research.

EMERGENCY USE: There are situations when a patient may have an indication for the use of an unapproved medical device or drug, but does not meet the criteria for enrollment onto an IRB-approved study. The Clinician must abide by the FDA and local IRB provisions for emergency use, including reporting the use to the IRB prospectively if possible, but at least within 5 days of the emergency use. Patients treated according to emergency use provisions are by definition not research subjects and their data may not be analyzed as part of a study.

ENROLLMENT: A subject is considered to be enrolled on a research study when a written informed consent document is signed.

EXPEDITED REVIEW: Review of proposed research by the RIB chair or a designated voting member of group of voting members rather than by the entire IRB. Federal rules permit expedited review for certain kinds of research involving no more than minimal risk and for minor changes in approved research.

EXPERIMENTAL: Term often used to denote a therapy (drug, device, procedure) that is unproven or not yet scientifically validated with respect to safety and efficacy. A procedure may be considered "experimental" without necessarily being part of a formal study (research) to evaluate its usefulness.

EXPERIMENTAL STUDY: A true experimental study is one in which subjects are randomly assigned to groups that experience carefully controlled interventions manipulated by the experimenter according to a strict logic allowing causal inference about the effects of the interventions under investigation.

FDA: Food and Drug Administration; an agency of the federal government established by Congress in 1912 and presently part of the Department of Health and Human Services.

FETUS: The product of conception from the time of implantation until delivery. If the delivered or expelled fetus is viable, it is designated an infant. The term "fetus" generally refers to later phases of development; the term "embryo" is usually used for earlier phases of development.

FULL BOARD REVIEW: Review of proposed research at a convened meeting at which a majority of the

membership of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. For the research to be approved, it must receive the approval of a majority of those members present at the meeting.

GRANT: Financial support provided for research study designed and proposed by the principal investigator(s). The granting agency exercises no direct control over the conduct of approved research supported by a grant.

GUARDIAN: An individual who is authorized under applicable state or local law to give permission on behalf of a child to general medical care.

HUMAN SUBJECTS: Human subjects are defined as: living individual(s) about whom an investigator conducting research obtains: (1) data through intervention or interaction with the individual; or (2) identifiable private information.

INFORMED CONSENT: A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic, or preventive procedure. In giving informed consent, subjects may not waive or appear to waive any of their legal rights, or release or appear to release the investigator, the sponsor, the institution or agents thereof from liability for negligence.

INSTITUTIONAL REVIEW BOARD: A diverse Committee(s) appointed by the Associate Vice President for Research, and meeting the memberships requirements of federal regulation and this policy which is established and maintained to provide ethical oversight of human subject research conducted by NU faculty, staff and students.

INVESTIGATIONAL NEW DRUG OR DEVICE: A drug or device permitted by FDA to be tested in humans but not yet determined to be safe and effective for a particular use in the general population and not yet licensed for marketing.

INVESTIGATOR: In clinical trials, an individual who actually conducts an investigation. Any interventions (*e.g.,* drugs) involved in the study are administered to subjects under the immediate direction of the investigator.

LEGALLY AUTHORIZED REPRESENTATIVE: A person authorized either by statute or by court appointment to make decisions on behalf of another person. In human subjects' research, an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

MEDICAL DEVICE: A diagnostic or therapeutic article that does not achieve any of its principal intended purpose through chemical action within or on the body. Such devices include diagnostic test kits, crutches, electrodes, pacemakers, arterial grafts, intraocular lenses, and orthopedic pins or other orthopedic equipment.

MINIMAL RISK: A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily

encountered in daily life or during the performance of routine physical or psychological examinations or tests. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination. The definition of minimal risk for research involving prisoners differs somewhat from that given for non-institutionalized adults.

MINORS: [See: Children]

MONITORING: The collection and analysis of data as the project progresses to assure the appropriateness of the research, its design and subject protections.

NIH: National Institutes of Health: a federal agency within the Public Health Service, DHHS, comprising 21 institutes and centers. It is responsible for carrying out and supporting biomedical and behavioral research.

NON-COMPLIANCE: For the purpose of this policy, non-compliance refers to acts of commission or omission which result in the conduct of human subjects research that is inconsistent with the requirements established in the federal regulations relating to human subject protections, with Illinois state law, the Northwestern University HSPP policy, or the specific requirements of the NU IRB or another IRB with the authority and responsibility for overseeing the research. This includes conduct of activities that are inconsistent with an IRB-approved research protocol or informed consent document or process. [See also "Serious Non-Compliance" and "Continuing Non-Compliance"]

OFFICE FOR PROTECTION FROM RESEARCH RISKS (OPRR): The office within the Department of Health and Human Services, responsible for implementing DHSS regulations (45 CFR Part 46) governing research involving human subjects.

PARTIAL CLINICAL HOLD: When reviewing allegation of serious or continuing non-compliance, or unanticipated problems involving risks to subjects or others, the IRB may suspend or terminate IRB approval, or may place a "partial clinical hold" on the research—temporarily halting some aspect of the study, but not suspending the entire research study. The study retains its "approved" status while additional information is gathered or corrective actions are planned. As examples, the partial hold may include temporarily stopping the enrollment of new subjects, or not enrolling subjects for one of the conditions in the study. When placing a study on "clinical hold," the IRB is not suspending its approval. Relevant institutional officials will be promptly notified, but notification will not be sent to federal oversight agencies.

PHASE I, II, III, IV DRUG TRIALS: Different stages of testing drugs in humans, from first application in humans (Phase I) through limited and broad clinical tests (Phase III), to postmarketing studies (Phase IV).

Phase I Drug Trial Phase 1 trials include the initial introduction of an investigational new drug

into humans. These studies are typically conducted with healthy volunteers; sometimes, where the drug in intended for use in patients with a particular disease, however, such patients may participate as subjects. Phase I trials are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses (to establish a safe dose range), and, if possible, to gain early evidence of effectiveness; they are typically closely monitored. The ultimate goal of Phase I trials is to obtain sufficient information about the drug's pharmacokinetic and pharmacological effects to permit the design of well-controlled, sufficiently valid Phase II studies. Other examples of Phase I studies include studies of drug metabolism, structure-activity relationships, and mechanisms of actions in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects involved in Phase 1 investigations is generally in the range of 20-80.

Phase II Drug Trial Phase II trials include controlled clinical studies conducted to evaluate the drug's effectiveness for a particular indication in patients with the disease or condition under study, and to determine the common short-term side effects and risks associated with the drug. These studies are typically well-controlled, closely monitored, and conducted with a relatively small number of patients, usually involving no more than several hundred subjects.

Phase III Drug Trial Phase III trials involve the administration of a new drug to a larger number of patients in different clinical settings to determine its safety, efficacy, and appropriate dosage. They are performed after preliminary evidence of effectiveness has been obtained, and are intended to gather necessary additional information about effectiveness and safety for evaluating the overall benefit-risk relationship of the drug, and to provide an adequate basis for labeling. In Phase III studies, the drug is used the way it would be administered when marketed. When these studies are completed and the sponsor believes that the drug is safe and effective under specific conditions, the sponsor applies to the FDA for approval to market the drug. Phase III trials usually involve several hundred to several thousand patient-subjects.

Phase IV Drug Trial Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain postmarketing (Phase IV) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in Phase II studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.

PLACEBO: A chemically inert substance given in the guise of medicine for its psychologically suggestive effect; used in controlled clinical trials to determine whether improvement and side

effects may reflect imagination or anticipation rather than actual power of a drug.

PRINCIPAL INVESTIGATOR: The scientist or scholar with primary responsibility for the design and conduct of a research project.

PROTOCOL: The formal design or plan of an experiment or research activity; specifically, the plan submitted to an IRB for review and to an agency for research support. The protocol includes a description of the research design or methodology to be employed, the eligibility requirements for prospective subjects and controls, the treatment regimen(s), and the proposed methods of analysis that will be performed on the collected data.

PROTOCOL DEVIATION: An intended or unintended modification of the procedures employed in the conduct of a research study that differs from the procedures in the IRB-approved protocol or consent document/process (excluding situations of emergency use). If the unapproved modification does not appear to have exposed research subjects to any unintended risks, and the modification does not adversely impact the statistical analysis of the primary or secondary objectives, then it is called a deviation. Protocol deviations must be reported to the IRB in a timely manner and the IRB will review them under its responsibility for the ongoing oversight over the conduct of human subjects' research.

PROTOCOL EXEMPTION: There are situations when an eligibility criterion, or some other aspect of the research protocol needs to be modified in order to enroll a particular research subject on a clinical investigation. In the circumstances of a medical emergency, with the likelihood of impending permanent morbidity or mortality, the Investigator-Clinician should employ as many prospective human subject protections as practicable, including informing the IRB Chair, obtaining written informed consent from the patient/parents, and the concurrence of an independent physician (which should be documented in the medical record). Patients who do not meet the eligibility criteria according to the IRB-approved protocol may receive the test article with the permission of the Sponsor (and FDA), but the Investigator should receive the written, prospective approval of the IRB if the research is federally funded or if the investigator intends to collect and use their data as part of the research.

PROTOCOL VIOLATION: An intended or unintended modification of the procedures employed in the conduct of a research study that differs from the procedures in the IRB-approved protocol (excluding situations involving emergency use). If the unapproved modification appears to have exposed research subjects to unintended risks, or the modification adversely impacts the statistical analysis of the primary or secondary objectives, then it is called a protocol violation. Protocol violations must be reported to the IRB Chair or Administrator as soon as reasonably possible and the IRB will review them under its responsibility for the ongoing oversight over the conduct of human subjects' research.

RESEARCH: A systematic investigation (i.e., the gathering and analysis of information) designed to

develop or contribute to generalizable knowledge.

RISK: The probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary from minimal to significant. Federal regulations define only "minimal risk."

SERIOUS NON-COMPLIANCE: For the purpose of this policy, serious non-compliance refers to non-compliance with specific requirements of the IRB, or of the NU HSPP policy, applicable state laws, and relevant federal regulations pertaining to the protection of human subjects in research when that conduct compromises the safeguarding of the rights and welfare of subjects or compromises the integrity or interpretability of the data gathered from them. Serious non-compliance results in unexpected risks of harm to subjects. [See also "Non-Compliance" and "Continuing Non-Compliance"]

SPONSOR (OF A DRUG TRIAL): A person or entity that initiates a clinical investigation of a drug – usually the drug manufacturer or research institution that developed the drug. The sponsor does not actually conduct the investigation, but rather distributes the new drug to investigators and physicians for clinical trials. The drug is administered to subjects under the immediate direction of an investigator who is not also a sponsor. A clinical investigator may, however, serve as a sponsor-investigator. The sponsor assumes responsibility for investigating the new drug, including responsibility for compliance with applicable laws and regulations. The sponsor, for example, is responsible for obtaining FDA approval to conduct a trial and for reporting the results of the trial to the FDA.

SPONSOR-INVESTIGATOR: An individual who both initiates and actually conducts, alone or with others, a clinical investigation. Corporations, agencies, or other institutions do not qualify as sponsor-investigators.

TARGET ACCRUAL: See accrual target.

VOLUNTARY: Free of coercion, duress, or undue inducement. Used in the research context to refer to a subject's decision to participate (or to continue to participate) in a research activity.

ACKNOWLEDGEMENT

1. The outline for this policy, and many sections of the text were copied from or adapted with permission from the University of Iowa's HSPP policy posted on the web, accessed from http://research.uiowa.edu/hso/?get=inv_guide_toc on 02/08/2007.
2. Additional language within this policy was copied or adapted from regulations and guidance documents posted on the websites for OHRP and/or FDA.

Investigational Devices

Please specify what Devices will be used in this project:

1.0 Humanitarian Use Device:

	Name
[View]	Humanitarian Use Device

2.0 FDA Cleared, Approved Use:

	Name
[View]	FDA Cleared, Approved Use Device

3.0 FDA Cleared, Unapproved Use:

	Name
[View]	FDA Cleared, Unapproved Use Device

4.0 Non-FDA Cleared:

	Name
[View]	Non-FDA-Cleared Device

Humanitarian Use Device

Device Name:

Please upload the Device Brochure for this Device:

name	description
There are no items to display	

Provide the Humanitarian Device Exemption # (HDE):

Is the IDE held by the sponsor?

radio **Yes** radio **No** **Clear**

If yes, attach the Humanitarian Device Exemption (HDE) documentation as provided by the sponsor.
If No, please provide a copy of the IDE application or documentation that one is not required.

name	description
There are no items to display	

FDA Cleared, Approved Use

Device Name:

Please upload the Device Brochure for this Device:

name	description
There are no items to display	

FDA Cleared Unapproved Use

Device Name:

Please upload the Device Brochure (IDE application and subsequent FDA correspondence for investigator-sponsored IDE) for this Device:

name	description
There are no items to display	

Select the option below which reflect the status of this device:

☐ **Exempt from FDA IDE requirements. Upload justification for this choice below**

☐ **Non-significant risk. Upload justification for this choice below**

☐ **Significant risk**

Provide the IDE number:

Is the IDE held by the sponsor?

☑ Yes ☐ No Clear

If No, please provide a copy of the IDE application or documentation that one is not required:

name	description
There are no items to display	

Non-FDA-Approved Device

Device Name:

Please upload the Device Brochure (IDE application and subsequent FDA correspondence for investigator-sponsored IDE) for this Device:

name	description
There are no items to display	

Select the option below which reflect the status of this device:

☐ **Exempt from FDA IDE requirements. Upload justification for this choice below**

☐ **Non-significant risk. Upload justification for this choice below**

☐ **Significant risk**

Provide the IDE number:

Is the IDE held by the sponsor?

◉ Yes ○ No Clear

If No, please provide a copy of the IDE application or documentation that one is not required:

name	description
There are no items to display	