Institutional Review Board Policies and Procedures Manual

SECTION 5: PRINCIPAL INVESTIGATOR RESPONSIBILITIES

5.1 PRINCIPAL INVESTIGATOR RESPONSIBILITIES

A. Introduction

A Principal Investigator (PI) is the individual who assumes full responsibility for a research project, including the supervision of any Sub-Investigator (Sub-I) and research personnel. The IRB only recognizes one Institutional PI per study. The PI must possess the expertise, time, and commitment to conduct and provide the necessary oversight for all aspects of the study, and must be willing to accept full responsibility for the study. The PI and other research personnel must provide evidence of their qualifications to the sponsor, IRB, or other regulatory authority upon request through up-to-date curriculum vitae or other relevant documentation. Other individuals engaged in the research may be designated as Sub-Is. A Sub-I is an investigator who will share responsibility for the scientific, technical, and administrative conduct and reporting of a project with the PI. An individual is considered research personnel if the individual is involved in one or more of the following research activities:

i. Individuals who are involved in study design

ii. Individuals who obtain consent from participating subjects;

iii. Individuals who intervene or interact for research purposes; or

iv. Individuals who obtain or have access to identifiable data or specimens for research purposes.

B. Investigator's Oversight of Research

The PI must be qualified by experience and training to conduct their proposed research. Additionally, the PI may have qualified research staff to assist them in carrying out their research. The PI and research staff must have the necessary backgrounds to conduct research in accordance with the approved protocol, all applicable regulatory requirements, Institutional policies, and relevant professional standards. The PI must familiarize themselves with the appropriate use of the investigational product when applicable, as described in the protocol, in the current investigator brochure, in the product information, and in other available information sources.

The PI must consider the qualifications, training, and experience of the research personnel before delegating responsibilities. All personnel engaged in research activity at the Institution should be listed on the study personnel in the electronic IRB system. All investigators and research staff must be familiar and act in compliance with Institutional and regulatory requirements governing the delegation of responsibilities for obtaining informed consent, dispensing and administering study drugs/devices, and performing other research-related procedures. The PI must also ensure that their research personnel are adequately trained on the IRB approved protocol as well as all applicable regulatory requirements and Institutional policies. The PI is ultimately responsible for the oversight and supervision of the research conduct.

C. Who May Serve as PI for Human Subjects Research Conducted at the Institution

Employees, physicians, and scientists of Lurie Children's or Northwestern University (NU) and its affiliates, including Northwestern Memorial Hospital (NMH), Northwestern Feinberg School of

Medicine (NFSM), Shirley Ryan Ability Lab, and Prentice Women's Hospital (PWH)*, may serve as principal investigators (PI) as long as they are able and willing to meet the requirements and responsibilities outlined in this policy (i.e., they can provide the necessary oversight of the study and study staff). In addition, residents and fellows of Lurie Children's may only serve as PI for studies conducted solely at Lurie Children's and its affiliates. *Any study conducted by a PI who is not on staff at Lurie Children's must have at least one Lurie Children's faculty member within the division/department where the research will be conducted, serve as a sub-investigator.

D. Ethical Standards

The PI must comply with all Institutional policies and has the primary responsibility for protecting the rights, safety, and welfare of human research subjects.

In order to fulfill the responsibility for protecting the rights and welfare of human research subjects, it is important for investigators to realize their ethical responsibilities towards research subjects.

i. Investigators are responsible for performing the research with sufficient resources to ensure appropriate care, oversight, and safety of the subjects.

ii. Investigators are responsible for understanding which activities constitute research and obtaining review and approval by the IRB prior to initiating the research.

iii. Investigators are bound to act within the parameters of their IRB approved protocols.

iv. Investigators have an obligation to respond in a timely manner to any concerns, complaints, or requests for information from research subjects.

v. Upon completion of the study, the investigator must ensure that subjects have continuity in their care, and so must provide pertinent information to help subjects transition from completing the study to receiving appropriate medical care when applicable.

vi. The PI must ensure that all members of the research team are current and certified in Human Subject Training as required by Institutional and NIH policies. The PI is responsible for maintaining documentation of this Human Subject Training.

When the research status of an intervention or data collection procedure is questionable, investigators should always consult ORIC for determination of whether activities meet the regulatory definition of human subject research.

E. Compliance with IRB Requirements

i. Initial Review of Research and Informed Consent

   a. All research involving human subjects conducted at the Institution must be reviewed and approved by the IRB, or certified for exemption, before any subjects can be enrolled or any of the research activity may begin.

   b. Investigators are responsible for obtaining and documenting informed consent in accordance with regulatory and Institutional requirements unless otherwise waived by the IRB. Investigators may delegate the authority to obtain informed consent to another authorized individual.

c. Investigators have an ethical responsibility, as part of the informed consent process, to ensure that subjects and families understand the nature of the research, requirements for participation, including that participation in the research is voluntary, the risks and benefits, and any alternatives.

d. Disclosures, such as any conflicts of interest, including financial disclosures, are to be included in the consent documents as appropriate.

e. Investigators are responsible for providing subjects with a copy of the IRB approved consent form at the time of consent, unless the requirement to obtain consent has been waived by the IRB.

f. It is the responsibility of the PI to submit an initial application via the electronic IRB system requesting approval for the involvement of human subjects in research. This submission must provide a complete description of the study design, including provisions for the protection of the rights and welfare of prospective subjects. This application must be submitted to the IRB, and must comply with all relevant federal, state, and Institutional policies and regulations. After the application is reviewed by the IRB, the PI must respond to any concerns that arose in the application comments on a timely basis and must comply with all conditions set by the IRB at the time of approval.

g. Letters of Support are required from departments/divisions that provide research support services or have personnel that are performing protocol procedures that are not within the department/division that has provided organizational sign-off. Written Letters of Support are to be obtained before study initiation. The PI must confirm the support services have been contacted, but the letter is not required to be uploaded into the electronic IRB system Initial Application. The following list are examples of required Letters of Support to be confirmed within the Initial Application in the electronic IRB system:

    1. A letter from the Research Laboratory and Department of Pathology for studies requiring the Research Laboratory to handle, process and ship samples to external entities, test any specimens, and/or will request and utilize samples from Pathology.

    2. A letter from Research Pharmacy if the research requires preparation, storage or dispensing of investigational medications or biological agents.

    3. A letter from the Medical Imaging Research Committee if the research will include imaging such as x-rays, MRI/CT scans, etc. for research purposes, and/or deviation from the Medical Imaging standard of care imaging protocol, and/or research imaging that is not being billed to patient insurance.

    4. A letter from the Clinical Research Unit (CRU) if the research will require the use of CRU space and/or CRU personnel to support study visits.

    5. A letter from the Cardiopulmonary Lab is required for research that involves cardiology or pulmonary testing for research purposes.

6. A letter from Infection Control and Prevention is required when studies 1) utilize equipment/instrumentation (provided or purchased) that will be used on more than one patient including items that requires sterilization/disinfection before first time use, and/or 2) that involves the administration of a microorganism or a product that contains one or more microorganisms (i.e., bacteria, fungi, or virus; even if attenuated/non-replicable) to a participant.
7. A letter from the Pediatric Intensive Care Unity (PICU) for research that will directly recruit from the PICU or utilize PICU services or staff for research purposes.
8. A letter from Ophthalmology is required when the research requires eye exams and ophthalmologic services for research purposes.
9. A letter from the Nursing Research Committee (NRC) when studies focus primarily on the nursing profession, nursing care, or includes nurses (APN's or RN's) as the study population and the Principal Investigator is an Advanced Practice Nurse (APN), Registered Nurse (RN) or Nursing Student.
10. A letter from the Lurie Cancer Center Scientific Review Committee Oncology for studies that have not been reviewed and approved by an NCI peer-review agency. In addition, NCI peer-reviewed studies need to be submitted for administrative review only and Oncology study revisions (amendments) must also be re-submitted.
11. A letter from the Radiation Oncology Department at Northwestern if the research involves radiation therapy.
12. If the study involves working with entities outside of the Institution (e.g., community organization, non-CPS schools, etc.), a Letter of Support from that entity must also be submitted.

ii. Renewal (Continuing Review) of Previously Approved Research

If the research is to continue beyond the expiration date of the initial IRB approval, the PI must complete a submission for Renewal of the project in the electronic IRB system. No research project may continue to recruit, enroll, treat subjects, or analyze data after the IRB approval expiration date. Continuance of research after expiration of IRB approval is a violation of federal regulations. Information on the current approval, including the expiration date, may be found in the electronic IRB system, on the study approval letter, and the footer of current approved consent.

The PI is responsible for the following:

- Reporting the progress of the approved research in sufficient detail as required by the IRB and no less than once per year so that the IRB can conduct a meaningful and substantive review.
- Preparation and submission of the Renewal in the electronic IRB system and supporting documents per IRB requirements.

- Although it is ultimately the PI's responsibility to track their approval and expiration dates, and submit the Renewal in a timely manner, as a courtesy, the electronic IRB system sends reminder notices to PIs of upcoming expiration dates.

Note: While not mandated by OHRP, the Institution still requires annual continuing review of all non-exempt human subjects research. This annual review will allow the Institution to track ongoing research while offering added protection to our research participants who are mostly children, a vulnerable population.

iii. Modifications (Amendments) to Previously Approved Research

The PI is responsible for the following:

a. Preparation and submission of the Modification in the electronic IRB system and supporting documents describing any proposed changes to a previously approved research activity.

b. The PI must not implement such changes without IRB review and approval unless they foresee an **immediate hazard** to subjects:

1. If changes to an IRB approved protocol are required to eliminate apparent immediate hazards to the subject, such changes may be initiated without prior IRB approval; however, the PI must report this occurrence as a deviation from the approved protocol to the IRB, study sponsor, and FDA (for FDA-regulated, PI-sponsored studies).

2. Such deviations must be reported to the IRB as per IRB requirements.

3. If the deviation identifies a need for a permanent change, (e.g., permanent reduction in dose, etc.), the PI is required to submit a protocol Modification.

iv. Study Closure

PIs are required to close/inactivate the study with the IRB once all study activities have been completed to terminate the IRB approval by submitting a Closure application via the electronic IRB system.

The IRB has the authority to suspend or terminate research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. If the IRB terminates or suspends approval of a sponsored clinical trial, the PI must promptly (within 48 hours) notify the sponsor. Upon completion of a clinical trial, the PI/sponsor must submit any reports required to the Institution and any applicable regulatory authority. If the sponsor terminates or suspends approval of a clinical trial, the PI must promptly (within 48 hours) notify the IRB.

v. Reporting Requirements

In addition to reporting changes to the research (Modifications) and the progress of the research at the time of Renewal, the PI is required to report to the IRB, per IRB policy the following:

a. Any unanticipated problem or internal serious adverse event that meets the criteria of 1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures and (b) the characteristics of the subject population being studied; 2) related or possibly related to participation 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;

b. Deviations from the approved protocol and protocol violations that increased risk of harm to subjects or have the potential to recur;

c. New information that may adversely affect the safety of the subjects or the conduct of the research;

d. Copies of external monitoring reports, Data, Safety and Monitoring Board/Committee, (DSMB/C), reports, correspondence, and FDA documentation, such as annual reviews, as applicable;

e. Any noncompliance with regulations of Institutional policies and procedures;

f. Any research-related complaint by a research subject or another person;

g. Incarceration of a research subject;

h. Death of a research subject thought to be either related to the research or possibly related to the research; and

i. Any suspension or temporary cessation of study enrollment by the PI or study sponsor.

vi. Protocol Documentation

a. For clinical trials of investigational drugs/devices, the PI is to maintain research documents as specified in the ICH GCP Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirements.

b. For each study, PIs are responsible for maintaining a current and organized protocol file/binder containing, at minimum, the following documents:

1. IRB approved protocol and/or research plan, IRB application, IRB approval letter; and if the Institution is the lead site for a multi-center protocol, the current IRB approvals from each site;

2. Approved informed consent/assent forms;

3. Approved recruitment materials and other study materials such as surveys, questionnaires, data collection tools, etc.;

4. IRB correspondence and letters, including emails as applicable;

5. Sponsor correspondence as applicable; and

6. Investigator Brochures, FDA forms and letters if applicable

c. PIs are responsible for the safe and secure storage of the research data, both electronic and paper, and protecting the confidentiality and privacy of the data as per IRB, Institutional, regulatory, and sponsor requirements.

d. In accordance with DHHS and FDA regulations, the IRB requires that all research records be maintained for at least three years after the study is closed. 45 CFR 46.115(b) and 21 CFR 56.115(b)

e. FDA regulations pertaining specifically to investigational drug research state that PIs are required to maintain records "for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or if no application is to be filed or if the application is not to be approved for such indication, until two years after the investigation is discontinued and FDA is notified." 21 CFR 312.62(c)

f. FDA regulations pertaining specifically to investigational device research state that PIs are required to maintain records "for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol" 21 CFR 812.140(d)

g. When research records are ready to be destroyed at a time deemed appropriate for the study, the manner in which these records are destroyed must adhere to Institutional policies for the destruction of medical records.

vii. Participant/Investigator Care and Concerns

a. The researcher informs the subject's primary physician about the subject's participation in the clinical trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

b. During and following a subject's participation in a clinical trial, the researcher ensures that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the clinical trial.

c. The researcher follows the clinical trial's randomization procedures, if any, and ensures that the code is broken only in accordance with the protocol. If the clinical trial is blinded, the researcher promptly documents and explains to the Sponsor any premature unblinding.

d. A qualified physician or dentist, when appropriate, who is a PI or a co-investigator for a research study, is responsible for all research-related medical or dental decisions.

e. Researchers inform subjects when medical care is needed for other illnesses of which the researchers become aware.

f. PIs are responsible for immediately addressing any concern, question, or complaint raised by a research subject before, during, or after the research has ended.

g. Although a subject is not obliged to give their reasons for withdrawing prematurely from research, the researcher makes a reasonable effort to ascertain the reason, while fully respecting the subject's rights.

h. PIs are responsible for addressing any concern or question raised by any member of the research team and this includes:

1. Routinely communicate and meet with the research team to review the progress of the research and discuss any concerns, whether they are general regarding the research activities or specific to a subject.
2. Inform each member of the team of their responsibility, as per the Institution's Code of Conduct, to voice any concerns without fear of repercussions. PIs may not punish an individual who brings a concern to their attention.
3. No concern may be dismissed. The PI must take concerns seriously and is obligated to investigate each concern.
4. PIs are responsible for **promptly** reporting to ORIC any concerns that result in findings related to subject safety, compliance, informed consent/assent violations, or the integrity of the data.

viii. Protocol Exceptions and Deviations

A *protocol deviation* is any aberration, whether accidental, unintentional, or intentional, from the IRB-approved protocol/research plan. Major protocol deviations, sometimes referred to as *protocol violations*, are those that cause harm to subjects or others, place them at increased risk of harm, impact the scientific integrity of the research, compromise the human subject protection program, have the potential to recur or represent possible serious or continuing non-compliance. Such major protocol deviations require reporting to the IRB via an Incident Report in the electronic IRB system.

Any intentional or planned protocol deviations require approval by both the sponsor and the IRB prior to implementation (e.g., enrolling a participant who does not meet study eligibility criteria, modifying safety monitoring procedures or timing, etc.). Sometimes these intentional protocol deviations are a one-time event, and other times they lead to the implementation of a permanent change to the protocol or other research documents. Investigators must submit planned protocol deviations to the IRB for review via a Modification in the electronic IRB system.

ix. Informed Consent and Assent

a. The requirement to obtain the legally effective informed consent/assent of individuals before involving them in research is one of the central protections provided for under the HHS regulations at 45 CFR Part 46.
b. Informed consent and assent refer to the voluntary choice of an individual to participate in a research study based on an accurate and complete understanding of, among other factors that may influence the individual's decision, research purposes, procedures, risks, benefits, and alternatives.
c. Unless specifically waived by the IRB, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of that subject (or of that subject's legally authorized representative) or, for minors, permission from the parent(s)/guardian.

d. Informed consent must be documented in writing unless the signature is specifically waived by the IRB. This includes documentation of the consent process, as applicable.

e. A PI may request, and the IRB Chair may grant, a waiver of assent under specific circumstances and on a case-by-case basis.

f. For clinical trials conducted or supported by a Federal department or agency approved on or after January 21, 2019, investigators that are the awardee, or designated responsibility for a multi-site trial, must publicly post the trial consent forms on a publicly available Federal website that will be established as a repository for such informed consent forms. The informed consent form must be posted after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.

x. Responsibilities for PIs leaving the Institution

When planning to leave the Institution, a PI of an active study must arrange the timely transfer of study responsibilities to a new PI within the Institution. PIs are to work with division and departmental chairs to ensure the careful transfer of responsibilities and care of participants, when applicable. The new PI must be willing to assume all PI responsibilities as outlined above. A Modification must be submitted via the electronic IRB system and the new PI must submit a New Principal Investigator Certification letter with the Modification to sign off on this transfer of responsibility.

If a study meets the criteria for inactivation, then a closure application is to be submitted in the electronic IRB system.

These activities are to be completed before the PI leaves the Institution.

F. Privacy and Confidentiality of Data

PIs are required to maintain and protect the privacy and confidentiality of all personally identifiable information collected about subjects during the course of their participation in research, in accordance with all applicable Federal and State laws. In the initial application and in all subsequent submissions, PIs should outline for the IRB the provisions for protection of subject privacy and confidentiality and should indicate for subjects in the consent form the mechanisms in place to safeguard their identity.

Privacy refers to a person's desire to control the access of others to themselves. The research proposal should outline strategies to protect privacy including how the investigator will access information from or about subjects.

Confidentiality refers to the researcher's agreement with the subject about how the subject's identifiable private information will be handled, managed, and disseminated. The research proposal must include the IRB standard HIPAA language and must outline strategies to maintain confidentiality of identifiable data, including controls on storage, handling, sharing of data, and plans for the destruction of identifiers. When appropriate, Certificates of Confidentiality could be used to maintain the confidentiality of identifiable data.

In designing procedures for the protection of confidentiality, PIs should keep in mind that subjects can be directly identified most obviously through the use of their names, but also through the use of unique identification numbers/codes (See Table 1: List of HIPAA

Identifiers). Whenever a PI proposes to collect data that may be traced to an individual subject, the IRB requires that the PI use the following methods to minimize the possibility of a breach of confidentiality:

i. Store research data in a locked cabinet in a secure location or in a password-protected computer file that is stored on an encrypted server, and limit access to personnel who have been delegated responsibility for managing the data;

ii. Limit the amount of personal information that is recorded in the research record to that which is essential for the conduct of the research;

iii. Do not include subject's initials in the study ID number for research unless it is necessary to facilitate the clinical care of patient subjects (this principle is especially important for research involving sensitive issues);

iv. Where research records are identified with codes that are linked to subjects' names, destroy this link as soon as possible without compromising patient safety or the goals of the research;

v. Plan for the disposal of all identifying information after the completion of the research;

vi. Apply for a Certificate of Confidentiality when personally identifiable, sensitive information is collected.

Table 1: 18 HIPAA Identifiers

1. Names
2. All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP Code, and their equivalent geographical codes, except for the initial three digits of a ZIP Code if, according to the current publicly available data from the Bureau of the Census:
    a. The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people.
    b. The initial three digits of a ZIP Code for all such geographic units containing 20,000 or fewer people are changed to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age,
4. Telephone numbers
5. Facsimile numbers
6. Electronic mail addresses
7. Social security numbers
8. Medical record numbers
9. Health plan beneficiary numbers
10. Account numbers
11. Certificate/license numbers.
12. Vehicle identifiers and serial numbers, including license plate numbers
13. Device identifiers and serial numbers
14. Web universal resource locators (URLs)
15. Internet protocol (IP) address numbers
16. Biometric identifiers, including fingerprints and voiceprints
17. Full-face photographic images and any comparable images
18. Any other unique identifying number, characteristic, or code,

except that such ages and elements may be aggregated into a single category of age 90 or older.		unless otherwise permitted by the Privacy Rule for re-identification.

G. Certificates of Confidentiality

Effective October 01, 2017 Certificates of Confidentiality will be issued automatically for any NIH-funded project using identifiable, sensitive information that was on-going on/after December 13, 2016. The term "identifiable, sensitive information" means information about an individual that is gathered or used during the course of biomedical, behavioral, clinical, or other research, where the following may occur:

- An individual is identified; or
- For which there is at least a very small risk, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual.

NIH considers research in which identifiable, sensitive information is collected or used, to include:

- Human subjects research as defined in 45 CFR 46, including exempt research unless the research that is determined to be exempt if the information obtained is recorded in such a manner that subjects cannot be identified or the identity of the subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
- Research involving the collection or use of biospecimens that are identifiable to an individual or for which there is at least a very small risk that some combination of the biospecimen, a request for the biospecimen, and other available data sources could be used to deduce the identity of an individual;
- Research that involves the generation of individual level, human genomic data from biospecimens, or the use of such data, regardless of whether the data is recorded in such a manner that subjects can be identified or the identity of the subjects can readily be ascertained; or
- Any other research that involves information about an individual for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual.

A Certificate of Confidentiality prohibits the disclosure of, or provision in an Federal, State, or local civil, criminal, administrative, legislative, or other proceedings, the name of research subjects or any identifiable research information, documentation, or biospecimen about the individual subject, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains. It also prohibits disclosure to any other person not connected with the research. Disclosure is only permitted when required by Federal, State or local laws, necessary for the medical treatment of the individual (with written consent from the individual), if consent has been obtained for the disclosure, or for the purposes of other scientific research that is in compliance with applicable regulations governing the

protection of human subjects research. If identifiable, sensitive information is disclosed to any investigator or institution not funded by the NIH, they are also subject to the terms of the Certificate.

For studies in which informed consent is sought, investigators are to inform research subjects of the protections and the limits to protections provided by a Certificate.

This Certificate will be issued as a term of the award. If the research is not federally funded, the NIH may continue issue a Certificate to an investigator or institution engaged in such research, upon application.

Institutional policy upholds the protections offered by a Certificate, unless mandated to disclose by law (i.e., when there is suspected abuse/neglect, or in order to report cases of certain infectious diseases).

H. Responsibilities of Sponsor- Investigators

Investigators who function as sponsors of clinical drug or device trials should understand the additional administrative and reporting requirements by the FDA, and should consult with the FDA and ORIC and review Section 8 of this policy manual to ensure that they have fulfilled all of their responsibilities. The FDA has also issued guidance documents that discuss the duties and responsibilities of study investigators.

I. Additional Responsibilities for the Institution when Coordinating a Multi-Center Trial

When a PI coordinates a multi-site trial, they accept responsibility to oversee the conduct of the trial at each participating site and serve as a central reporting entity that will be responsible for preparing timely summary reports of adverse events or unanticipated problems, protocol Modifications, and interim results for distribution among the participating sites.

As part of the study protocol, investigators of coordinating centers must provide a detailed description of how each of the responsibilities listed below will be managed to ensure timely communications with all participating sites:

i. Each participating site must maintain current IRB approval.

ii. The center's coordinating plan should include a justification for the sample size and its relation to the availability of the patient pool, and the likelihood that the target sample size will be achieved;

iii. The coordinating plan should address the appropriateness of the general statistical approach and specific analytic techniques and plans for handling dropouts, missed visits, and losses to follow-up. The plan should also indicate the plan for conducting interim analysis and describe how this analysis, if any, will be shared with the participating sites.

iv. The coordinating plan should outline the procedures for technical monitoring of the study centers for adherence to protocol and for data and safety monitoring and indicate how data and safety monitoring will occur. The plan should also indicate what measures are in place to receive from and distribute to all participating investigators reports of unanticipated problems related to the research, new information affecting

risks to subjects, and other relevant information related to the conduct of the ongoing research.

v. The coordinating plan should describe how randomization procedures and patient assignments will be coordinated. The plan should indicate how data will be transmitted to the coordinating center.

The appropriateness of the coordinating center's oversight plan is subject to the approval of the IRB.