Human Research Protection Program Policies and Procedures

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II. HUMAN RESEARCH PROTECTION PROGRAM

Presbyterian Healthcare Services fosters a research environment that promotes respect for the rights and welfare of individuals recruited for, or participating in, research conducted by or under the auspices of Presbyterian. The review and conduct of research actions by Presbyterian will be guided by the principles (i.e., respect for persons, beneficence, and justice) set forth in the *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (referred to as the *Belmont Report*). The actions of Presbyterian will also conform to all applicable federal, state, local laws, and tribal law passed by the official governing body of an American Indian or Alaska Native tribe and regulations, as well as Presbyterian organizational policy. In order to fulfill this policy, Presbyterian has established a human research protection program (HRPP) which (in partnership with its research community) is responsible for ensuring the ethical and equitable treatment of all human subjects in research conducted under its auspices. The research may be externally funded, funded from internal sources, or conducted without direct funding.

A. HRPO Mission

The mission of the Presbyterian HRPO is to advance the ethical treatment of research participants and ensure the responsible conduct of research by:

- Safeguarding the rights, privacy, and welfare of human participants in research projects conducted under the auspices of Presbyterian;
- Facilitating a culture of respect, integrity, responsibility, and trust; and
- Providing timely and high-quality education, review, and monitoring for human research projects.

The HRPO includes mechanisms to:

- Monitor, evaluate and continually improve the protection of human research participants;
- Dedicate resources enough to do so;
- Exercise oversight of research protection;
- Educate investigators and research staff about their ethical responsibility to protect research participants; and
- When appropriate, intervene in research and respond directly to concerns of research participants.

B. Organizational Authority

The Presbyterian HRPO operates under the institutional authority of two Presbyterian Healthcare Services policies: "Human Research Protections Program" (IRB.PHS-E.002 - adopted February 8, 2016), and "Human Research Protections and Institutional Review Board Policies and Standard Operating Procedures" (IRB.PHS-E.001 - adopted February 8, 2016). The latter describes the establishment of policies and procedures for the HRPO at Presbyterian as presented in this document. The Presbyterian institutional policies are available to all Presbyterian investigators via the internal Presbyterian Electronic Library (PEL). This document, the Presbyterian *Human Research Protections Program Policies and Standard Operating Procedures* manual, is also posted on the Presbyterian HRPP electronic submission platform, the IRB web-based management system, and on the PEL at http://docs.phs.org/idc/groups/public/@phs/@marketing/documents/phscontent/pel_002313 42.pdf.

C. Definitions

Clinical Trial. Clinical trial means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.

Common Rule. The Common Rule refers to the "Federal Policy for the Protection of Human Subjects" adopted by federal agencies. Although the Common Rule is codified by each agency separately, the text is identical to

Department of Health and Human Services (DHHS) regulations in 45 CFR 46 Subpart A. For the purposes of this document, references to the Common Rule will cite the DHHS regulations.

Department or Agency Head. Department or agency head means the head of any Federal department or agency, for example, the Secretary of HHS, and any other officer or employee of any Federal department or agency to whom the authority provided by these regulations to the department or agency head has been delegated.

Human Subject. A Human Subject as defined by the Common Rule is a living individual about whom an investigator (whether professional or student) conducting research: (i) Obtains information or bio-specimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or bio-specimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable bio-specimens.

- Intervention means both physical procedures by which information and/or biospecimens are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
- Interaction means communication or interpersonal contact between investigator and subject.
- Private information means 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 that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (for example, a medical record).
- Identifiable private information means private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.
- An identifiable biospecimen means a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

For research covered by FDA regulations, human subject means an individual who is or becomes a participant in a clinical investigation, either as a recipient of the test article or as a control. A subject may be in normal health or may have a medical condition or disease. In the case of a medical device, a human subject also includes any individual on whose specimen an investigational device is used or tested or used as a control.

Human Subject Research. Human Subject Research means any activity that meets the definition of "research" and involves "human subjects" as defined by either the Common Rule or FDA regulations. (Note: The terms "subject" and "participant" are used interchangeably in this document and have the same definition.)

Legally Authorized Representative (LAR). 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. If there is no applicable law addressing this issue, legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the non-research context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research.

Minimal Risk. 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.

Public Health Authority. An agency or authority of the United States, a state, a territory, a political subdivision of a state or territory, an Indian tribe, or a foreign government, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate.

Research. The Common Rule defines research as a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalized knowledge. Activities that meet this definition constitute research whether they are conducted or supported under a program that is considered

research for other purposes. For example, demonstration and service programs may include research activities. For purposes of the Common Rule, the following activities are deemed not to be research:

(1) Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, which focus directly on the specific individuals about whom the information is collected.

(2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during an event or crisis that threatens public health (including natural or man-made disasters)

(3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.

(4) Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

For the purposes of this policy, a "systematic investigation" is an activity that involves a prospective study plan that incorporates data collection, either quantitative or qualitative, and data analysis to answer a study question. Investigations designed to develop or contribute to generalizable knowledge are those designed to draw general conclusions (i.e., knowledge gained from a study may be applied to populations outside of the specific study population), inform policy, or generalize findings.

The FDA has defined "research" as being synonymous with the term "clinical investigation." A clinical investigation, as defined by FDA regulations, means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the FDA under these sections of the Federal Food, Drug, and Cosmetic Act, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations. [21 CFR 50.3(c), 21 CFR 56.102(c)]

Experiments that must meet the requirements for prior submission to the FDA under section 505(i) of the Federal Food, Drug, and Cosmetic Act means any use of a drug other than the use of an approved drug in the course of medical practice. [21 CFR 312.3(b)]

Experiments that must meet the requirements for prior submission to the FDA under section 520(g) of the Federal Food, Drug, and Cosmetic Act means any activity that evaluates the safety or effectiveness of a device. [21 CFR 812.2(a)]

Any activity in which results are being submitted to or held for inspection by the FDA as part of an application for a research or marketing permit is FDA-regulated research. [21 CFR 50.3(c), 21 CFR 56.102(c)]

Test Article. The FDA defines *"Test article"* as meaning 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 act or under sections 351 and 354- 360F of the Public Health Service Act [42 U.S.C. 262 and 263b-263n]. [21 CFR 50.3(j)]

Test articles covered under the FDA regulations include, but are not limited to:

(a) **Human Drugs** – The primary intended use of the product is achieved through chemical action or by being

metabolized by the body. A drug is defined as a substance recognized by an official pharmacopoeia or formulary; a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; a substance (other than food) intended to affect the structure or any function of the body; a substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device. Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process) *http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm*.

(b) **Medical Devices** - A device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them; intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes" *http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051512.htm* .

(c) **Biological Products** - include a wide range of products such as vaccines, blood, and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other innovative technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available *http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm.*

(d) **Food Additives** - A food additive is defined in Section 201(s) of the FD&C Act as any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristic of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use); if such substance is not Generally Recognized As Safe (GRAS) or sanctioned prior to 1958 or otherwise excluded from the definition of food *additives http://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm*.

(e) **Color Additives** - A color additive is any dye, pigment, or substance which when added or applied to a food, drug or cosmetic, or to the human body, is capable (alone or through reactions with other substances) of imparting color. Color additives for use in food, drugs, and cosmetics require premarket approval. Color additives for use in or on a medical device are subject to premarket approval if the color additive comes in direct contact with the body for a significant period of time. http://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm.

(f) **Foods** - Foods include dietary supplements that bear a nutrient content claim or a health claim.

(g) **Infant Formulas** – Infant formulas are liquid foods intended for infants which substitute for mother's milk.

(h) **Electronic Products** - The FDA regulates certain classes of electronic products including radiation-emitting electronic products such as microwaves and x-rays.

Written or In Writing. Written or In Writing means writing on a tangible medium (e.g., paper) or in electronic format.

D. Ethical Principles

Presbyterian is committed to conducting research with the highest regard for the welfare of human subjects. Presbyterian upholds and adheres to the principles of *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research* by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research (1979). These principles are:

- **Respect for Persons**, which involves obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations.
- **Beneficence**, which involves ensuring that possible benefits are maximized, and possible risks are minimized to all human subjects.
- **Justice**, which involves the equitable selection of subjects.

The Presbyterian HRPO, in partnership with its research community, is responsible for ensuring the ethical and equitable treatment of all human subjects in research conducted under its auspices.

E. Regulatory Compliance

The Presbyterian HRPO is responsible for ensuring compliance with federal regulations, state law, tribal law passed by the official governing body of an American Indian or Alaska Native tribe and Presbyterian organizational policies. The Presbyterian HRPP derives its regulatory authority from the following:

- Code of Federal Regulations (CFR) Title 45 Part 46 (45 CFR 46): "Protection of Human Subjects" (aka the "Common Rule");
- 21 CFR Part 56: "Institutional Review Boards;" and
- 21 CFR Part 50: "Protection of Human Subjects."

The actions of Presbyterian will also conform to all other applicable federal, state, local laws, and tribal law passed by the official governing body of an American Indian or Alaska Native tribe, and regulations such as Department of Defense (DoD), Department of Education (DoE), Family Educational Rights and Privacy Act (FERPA), and U.S. Department of Veterans Affairs (VA).

Research supported by the Department of Defense (DoD) is reviewed and conducted in compliance with part 219 of title 32 CFR, part 980 of title 10 USC, applicable parts of title 21 CFR (50, 56, 312, 600, 812), DoD Instruction 3216.02, DoD Directive 3210.07, and applicable additional requirements from respective DoD component(s).

Research involving the use of Protected Health Information (PHI) is reviewed and conducted in accordance with the Health Insurance Portability and Accountability Act (HIPAA), 45 CFR Part 160, 162, and 164.

Research involving the use of student educational records is reviewed and conducted in accordance with the Family Educational Rights and Privacy Act (FERPA), 34 CFR Part 99.

F. Federal Wide Assurance

The federal regulations require that federally funded human subject research only be conducted at facilities covered by a Federal Wide Assurance (FWA) approved by the U.S. Department of Health and Human Services' (DHHS) Office for Human Research Protections (OHRP). An FWA is an organization's assurance to the federal government that human subject research conducted at that site is in compliance with federal regulations pertaining to the protection of human subjects. The FWA designates the Institutional Review Board (IRB) that will review and oversee the research, specifies the ethical principles under which the research will be conducted, and names the individuals who will be responsible for the proper conduct of the research. Presbyterian has an OHRP-approved FWA (#00006178) and has designated one IRB (registration # IRB00001091) to review all human research projects.

G. Research Under the Auspices of the Organization

Research under the auspices of the organization includes research conducted at Presbyterian, conducted by or under the direction of any affiliated investigator (including students or residents) in connection with his, her, or their organizational responsibilities, conducted by or under the direction of any approved unaffiliated investigator proposing to use any Presbyterian property, facility, patient/employee population, or non-public information for research purposes.

Engagement. The DHHS regulations [45 CFR 46.103[a]] require that an institution "engaged" in human subject research conducted or supported by a federal department or agency provide the DHHS OHRP with a satisfactory assurance of compliance with the DHHS regulations, unless the research is exempt under 45 CFR 46.104. *"In general, an institution is considered engaged in a particular non-exempt human subject research project when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research."* In general, institutions that receive an award through a grant, contract, or cooperative agreement directly from DHHS for the non-exempt human subject's research (i.e., awardee institutions), are also considered engaged in research even where all activities involving human subjects are carried out by employees or agents of another institution. The HRPO/IRB Coordinator, with the assistance of the IRB Chair or Vice Chair and legal counsel as needed, will determine whether Presbyterian is engaged in a research study. Investigators and other institutions may not independently determine Presbyterian engagement.

When Presbyterian is engaged in research, the Institutional Official (IO) may agree to cede review to an external IRB through an "IRB Reliance Agreement." Studies for which review has been ceded to another external IRB are required to submit to the IRB a "Study Update Form:

Exempt/Ceded Review," which should include information about study status locally and study-wide, safety concerns that may affect participants, and significant protocol amendments that may impact risk level. Safety concerns will be forwarded to Presbyterian Compliance Office. Refer to Section XI for more information on Reliance Agreements.

For additional information on determining engagement please refer to Guidance on Engagement of Institutions in Human Subject Research, *http://www.hhs.gov/ohrp/policy/engage08.html.*

H. Written Policies and Procedures

This document (the "Human Research Protections Program Policies and Procedures") details the policies and regulations governing research with human subjects and the requirements for submitting research proposals for review by the IRB. This is not a static document. The policies and procedures are reviewed and revised regularly by the Presbyterian HRPO staff. In addition, the document's content will be periodically reviewed for technical accuracy by an independent consultant hired by Presbyterian to provide guidance on regulatory compliance issues, and all revisions will be approved by the IO or a designee. Presbyterian's "Human Research Protections Program Policies and Procedures" document will be available for download from the PEL, the HRPO public website, and from the Presbyterian HRPP electronic submission platform, the IRB web-based management system. Printed/electronic copies will be available upon request.

The HRPO/IRB Coordinator may keep the research community apprised of new information that may affect research activities, including laws, regulations, policies, procedures, and emerging ethical and scientific issues on the HRPO website and through email. Changes to the policies and procedures will be communicated to investigators, research staff, and IRB members via email.

I. Presbyterian Human Research Protections Program Structure

The Presbyterian HRPP consists of various individuals and committees such as the IO, the HRPO/IRB Coordinator(s), the IRB, Presbyterian legal counsel and Compliance Office, investigators, and research staff. The objective of this system is to assist the organization in meeting ethical principles and regulatory requirements for the protection of human subjects in research.

The following officials, administrative units, and individuals have primary responsibilities for human subject protections.

1. Institutional Official (IO)

The ultimate responsibility of the HRPP resides with the Institutional Official (IO) of the program. The IO is a Chief Officer and legally authorized to represent Presbyterian. The IO is the signatory of the FWA and assumes the obligations of the FWA.

The IO is responsible for ensuring that the HRPO and the IRB have the resources and support necessary to comply with all organizational policies, laws, and regulations that govern human subject research. Such resources include, but are not limited to:

- Staffing commensurate with the size and complexity of the research program;
- Appropriate office space, equipment, materials, and technology;
- Resources for the production, maintenance, and secure storage of HRPO and IRB records;
- Resources for auditing and other compliance activities and investigation of non- compliance;
- Access to legal counsel; and
- Support for educational opportunities related to human research protections for IRB members, relevant administrative staff, and all members of the research team.

The IO is also responsible for:

- Fostering, supporting, and maintaining an organizational culture that supports the ethical conduct of all research involving human subjects and the adherence to regulations and organizational policies; and
- Ensuring that the IRB functions independently by, among other mechanisms, being directly accessible to the IRB Chair(s) and members if they experience undue influence or if they have concerns about the function of the IRB.

The IO has the authority to suspend, terminate, or disapprove research or take other actions, such as sanctions or restrictions of research privileges or uses of research data, as necessary, to ensure the proper conduct of research, the protection of human subjects, the autonomy and authority of the IRB, compliance with regulatory and other requirements, or to protect the interests of Presbyterian. However, the IO may not approve research that has been disapproved (or not yet approved) by the IRB.

The IO must complete the OHRP "Human Subject Assurance Training" and any other appropriate training on human research protections (for example CITI). The HRPO will provide on-going continuing education for the IO concerning human research protections. The designated IO is made known to employees of the organization and is accessible by phone, email, in person or other methods of communication. The IRB Chair, HRPO Director, and HRPO/IRB Coordinator have access to the IO for any concerns or issues related to the HRPO.

In the performance of these duties, the IO has the authority to delegate such activities as may be necessary in order to effectively administer the program. However, the IO is ultimately responsible and is expected to be knowledgeable about all human subject protections responsibilities at the organization.

2. Director of the HRPO

The HRPO Director is selected by and reports to the IO and is responsible for the following:

- Providing oversight over the HRPO and the IRB;
- Providing oversight over the conduct of research conducted by all investigators;
- Ensuring that IRB members are appropriately knowledgeable to review research in accordance with ethical standards and applicable regulations;
- Ensuring that all investigators are appropriately knowledgeable to conduct research in accordance with ethical standards and applicable regulations;
- Providing oversight over the development and implementation of an educational plan for IRB members, staff, and investigators; and
- Advising the IO on key matters regarding research at Presbyterian.

The Director conducts and documents an annual review of HRPO and IRB function, requirements, and resources and adjusts as needed.

3. HRPO/IRB Coordinator

In addition to the leadership structure described above, the HRPO/IRB Coordinator reports to the Director of the HRPO. The coordinator must comply with all ethical standards and practices and is responsible for day-to-day operations of the HRPO, including the following:

- Developing, managing, and evaluating policies and procedures that ensure compliance with all state, tribal law passed by the official governing body of an American Indian or Alaska Native tribe and federal regulations governing research. This includes monitoring changes in regulations and policies that relate to human research protection and overseeing the administration of the IRB;
- Implementing the organization's HRPO policies and procedures;
- Submitting, implementing, and maintaining an approved FWA through the IO and the OHRP;
- Managing the finances of the IRB;
- Assisting investigators in their efforts to carry out Presbyterian's research mission;
- Developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program;
- Developing training requirements as required and as appropriate for investigators, IRB members. and research staff, and ensuring that training is completed on a timely basis;
- Serving as the primary contact at Presbyterian for the OHRP, the Food & Drug Administration (FDA), and other federal regulatory agencies; and
- Responding to questions regarding the protection of human subjects.

4. Institutional Review Board (IRB)

An Institutional Review Board (IRB) is a committee established to review and approve research involving human subjects. Presbyterian has established an on-site IRB to ensure the protection of human subjects in research conducted under the auspices of the organization. The IRB prospectively reviews and makes decisions concerning all non-exempt human research conducted at Presbyterian facilities, by any affiliated or unaffiliated investigators approved to conduct research, or under its auspices, unless another IRB has been designated to do so or it has been determined that Presbyterian is not engaged in the research. The IRB is responsible for the protection of rights and welfare of human research subjects at Presbyterian, through review and oversight of safe and ethical research. It discharges this duty by complying with the requirements of federal and state regulations, the FWA, and organizational policies (see Section V for a detailed discussion of the IRB).

The IRB functions independently of, but in coordination with, other organizational committees and

officials. The IRB, however, makes its independent determination whether to approve or disapprove a research plan based upon whether human subjects are adequately protected.

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of the organization. However, those officials may not approve human research that has not been approved or has been disapproved by the IRB. Study activities may not begin until notification of approval from the IRB has been received.

5. Presbyterian Legal Department

The HRPO may occasionally consult with the Presbyterian Legal Department (which includes Compliance and Risk Management) as necessary for interpretations and applications of regulations, state law, tribal law passed by the official governing body of an American Indian or Alaska Native tribe and the laws of any other jurisdiction where research is conducted as they apply to human subject research.

6. Presbyterian Departmental Heads and Organizational Unit Leaders

Presbyterian departmental heads and organizational unit leaders are responsible for reviewing all proposals before they are submitted to the IRB for review, and for ensuring that investigators have the resources (personnel, space, equipment, and time, etc.) required to conduct the research in a way that will protect the right and welfare of participants. The department head or organizational unit leader is required to sign a "Departmental Review and Coordination" form (1) indicating that the investigator is qualified and has the necessary resources to safely conduct the study, and (2) attesting to the scientific merit of this study, which means:

- The research uses procedures consistent with sound research design; and
- The research design is sound enough to reasonably expect the research to answer its proposed question.

7. The Investigator

The investigator is ultimately responsible for the protection of the human subjects who participate in research. The investigator is expected to abide by the highest ethical standards when developing a research plan that incorporates the principles of *The Belmont Report*. The investigator is expected to conduct research in accordance with the IRB-approved research plan and to oversee all aspects of the research by providing training and supervision of support staff, including oversight of the informed consent process. All subjects must give informed consent unless the requirement has specifically been waived by the IRB. Investigators must establish and maintain an open line of communication with research subjects under their responsibility. In addition to complying with all applicable policies and standards of regulatory bodies, investigators must comply with organizational and administrative requirements for conducting research. The investigator is responsible for ensuring that all research staff complete all organizational required training as well as training for their responsibilities in any given specific research study. When investigational drugs or devices are used, the investigator is responsible for providing a plan for their storage, security, dispensing, accounting, and disposal.

8. Affiliated Investigators

For a study to be eligible for review by the Presbyterian IRB, the principal investigator (PI) or a co-investigator must be affiliated with Presbyterian. An Affiliated Investigator is any individual who is qualified by experience, education, and training to conduct research at Presbyterian, and who falls into one of the following categories:

- A physician or advanced-practice clinician with clinical privileges at a Presbyterian facility;
- A private-practice physician on the Presbyterian medical staff who does not have clinical privileges;
- A paid employee of Presbyterian, including an employee currently enrolled as a student in an

academic program related to the study;
- An employee of a Presbyterian-contracted service (e.g., TriCore Labs, Radiology Associates of Albuquerque); or
- A resident who is participating in a program which has a clinical affiliation agreement with Presbyterian.

Affiliated investigators may function as the Principal Investigator (PI).

9. Unaffiliated Investigators

An Unaffiliated Investigator is any individual who

- Does not meet the above affiliation criteria (for example, a resident participating in a program which does not have a clinical affiliation agreement program with Presbyterian or a private-practice physician without clinical privileges); and
- Proposes to conduct research using any Presbyterian property, facility, patient/employee population, or non-public information.

Approval is required when a PI is not affiliated with Presbyterian or is not covered under the IRB of another institution. Any human research activities being proposed by an unaffiliated PI may be covered under the Presbyterian FWA only in accordance with a formal, written agreement stating a commitment to abide by Presbyterian's policies/procedures and IRB oversight. The Unaffiliated Investigator Agreement must be completed for this purpose and submitted to the IRB Chair. Presbyterian will maintain commitment agreements on file and provide copies to OHRP upon request. The IRB reserves the right to approve or deny requests for approval on a case-by-case basis.

10. Student Investigators

Student investigators must be paid Presbyterian employees in order to be the PI and to initiate a research project at Presbyterian. Student investigators must obtain educational institutional IRB approval/acknowledgement before submitting to the IRB. Students also must identify a Presbyterian study mentor who will provide guidance and oversight of the proposal development/submission process and the conduct of the research. Study mentors must formally approve and sign off on student/resident application and "Roles and Responsibilities form."

Students who are unaffiliated with Presbyterian must serve as a CO-I and are required to have a preceptor who is employed with Presbyterian and who will serve as the PI. Study mentors must formally approve and sign off on student/resident application and "Roles and Responsibilities form." To conduct research under the auspices of Presbyterian, a resident must be participating in a program which has a clinical affiliation agreement with Presbyterian.

J. Relationship Among Components

Presbyterian will ensure that a dialogue is maintained between the various compliance entities at Presbyterian, including Legal/Compliance, Finance, HRPO, and Administration. These entities will collaborate to monitor the effectiveness of existing compliance programs and identify areas for improvement.

1. Operational Approval

In order to evaluate and mitigate certain legal and compliance risks, as well as resource utilization and financial impact to the organization, operational approval is required for certain studies.

2. Departmental Review and Approval

The IRB requires that all protocols be approved by a Presbyterian department director prior to submission to the IRB. A department is defined as one of the clinical or organizational units at Presbyterian or its

affiliated entities/facilities. The department director must ensure the scientific merit, ethical issues, and the availability of departmental resources to carry out the research. Departmental approval allows the department director to be aware of departmental research activities and provides information for allocation of departmental resources.

All investigators submitting new protocols to the IRB must first submit the protocols to their department director for approval. The IRB will not review or approve any protocol that has not been approved by the relevant Presbyterian department director.

Investigators are required to complete a "Departmental Review and Coordination Form" for all new studies. In addition, a letter of support, collaboration, permission, or approval from the designated authority, may be submitted to the IRB along with an "Application for a New Study," depending on the circumstances. The IRB may request review or consultation with any of the above listed or other organizational committees or components even when such review or consultation is not technically required by policy.

Other committees and officials may not approve research involving human subjects to commence that has not been approved or has been disapproved by the IRB.

3. Departmental Coordination

In addition to obtaining review and approval from the departmental director, the Investigator must obtain and document using the "Departmental Review and Coordination" form the approval, support, and/or permission of other individuals and/or departments or entities that may be impacted by the research - as well as approval by other oversight committees. This may include, but is not limited to:

- Pathology/Laboratory
- Regional Hospitals
- Presbyterian Health Plan
- Pharmacy
- Radiology/Imaging
- Nuclear Medicine
- Nursing
- Operating/Procedural Suites
- Permission to enter hospital units
- Permission from external research locations (sites)
- Database access permissions (e.g., Medical/Educational Records)
- Appropriate departmental quality/safety committees (e.g., radiation safety committee)
- Compliance/Legal/Risk Management
- Medical Executive Committee
- Hospital Board
- Credentialing

K. Collaborative Research Projects

In the conduct of cooperative research projects, Presbyterian acknowledges that each organization is responsible for safeguarding the rights and welfare of human subjects and for complying with applicable federal regulations. "When a cooperative agreement exists, any institution located in the United States that is engaged in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States," Presbyterian will comply when applicable.

The reviewing IRB will be specified by the Federal department or agency supporting or conducting the research;

the “lead institution” may propose the reviewing IRB, but final federal approval will be required.

The following research is not subject to this provision: (i) Cooperative research for which more than single IRB review is required by law (Including tribal law passed by the official governing body of an American Indian or Alaska Native tribe); or (ii) Research for which any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the context.

Specifies circumstances when requirement for single IRB does not apply (reason of law or as determined by the federal department or agency conducting or supporting the research. A formal relationship must be established between Presbyterian and the other institution through an “IRB Reliance Agreement,” a “Memorandum of Understanding,” or other such written agreement. This relationship must be formalized before Presbyterian will accept any human research proposals from the other institution or rely on the review of the other institution.

It is the policy of Presbyterian to ensure that all facilities participating in a study involving human subjects receive adequate documentation about the study in order to protect the interests of study participants. Before a study can begin, it must be approved by the IRB of record for each participating facility and, where appropriate, the IRB of record for the coordinating facility.

For collaborative research, the investigator must identify all institutions participating in the research, the responsible IRB(s), and the procedures for dissemination of study information (IRB initial and continuing approvals, relevant reports of UAPs, study modifications, and interim reports) between all participating institutions.

When the Presbyterian IRB reviews research conducted in whole or in part at another institution, the characteristics of each institution’s local research context must be considered, either (1) through knowledge of its local research context by the IRB or (2) through subsequent review by appropriate designated institutional officials, such as the Chair and/or other IRB members.

If Presbyterian is the coordinating facility the investigator must document how the conduct of the research plan and the protection of human subjects will be communicated to and among the other participating facilities engaged in the research study. The investigator is responsible for serving as the liaison with regulatory and funding agencies, with other participating facilities, and for all aspects of internal review and oversight procedures. The investigator is responsible for ensuring that all participating facilities obtain review and approval from their IRB of record and adopt all research plan modifications in a timely fashion. The investigator is responsible for ensuring that the research study is reviewed and approved by any other appropriate committees at the coordinating facility and at the participating facilities prior to enrollment of participants.

The investigator must follow these procedures when Presbyterian is the coordinating facility:

- During the initial IRB submission of the multi-site study, the investigator indicates in writing on the application form or in an application letter that Presbyterian is the coordinating facility of a multi-site study.
- The investigator submits the following information in the IRB application materials:
  - ❖ Whether research activities at participating institutions are defined as engagement;
  - ❖ Name of each participating facility;
  - ❖ Confirmation that each participating facility has an FWA (including FWA number and expiration date);
  - ❖ Contact name and information for investigator/s at each participating facility;
  - ❖ Contact name and information for IRB of record at each participating facility;
  - ❖ Method for assuring all participating facilities have the most current version of the research plan;
  - ❖ Method for confirming that all modifications to the research plan are communicated to participating sites;
  - ❖ Method for communicating to participating facilities any serious adverse events and UAPs involving risks to subjects or others; and
  - ❖ Method of communicating regularly with participating sites about study events.
- The investigator submits approval letters from all IRBs of record for all participating sites.

- The investigator maintains documentation of all correspondence between participating sites and their IRB of record.

When Presbyterian is engaged in only part of a cooperative research project, the Presbyterian IRB only needs to approve the part(s) of the research in which the Presbyterian investigator is engaged. For example, if Presbyterian is operating the statistical center for a multicenter trial that receives identifiable private information from multiple other institutions, the Presbyterian IRB reviews and approves the research activities related to the receipt and processing of the identifiable private information by the statistical center. When Presbyterian is the prime awardee of a federal grant, Presbyterian will ensure that at least one IRB reviews the research in its entirety.

III. QUALITY ASSURANCE

Presbyterian performs quality assurance and improvement activities for the purposes of monitoring the safety of ongoing studies and measuring and improving human research protection effectiveness, quality, and compliance with Presbyterian policies and procedures and applicable federal, state, local laws and tribal law passed by the official governing body of an American Indian or Alaska Native tribe.

A. External Monitoring, Audit, and Inspection Reports

All reports from external monitors, auditors, or inspectors must be submitted by investigators to the IRB for review. The IRB Chair or designee will review such reports in order to monitor for issues that could impact the rights or welfare of human subjects and for issues indicative of possible serious or continuing non-compliance. If such issues are identified, the report will be forwarded to the convened IRB to determine what additional actions are necessary.

B. Investigator Compliance Reviews

The HRPO, with the assistance of a designated IRB member, is responsible for conducting any post-approval directed ("for cause") audits. In addition, periodic (not "for cause") compliance reviews of investigator research plans are conducted by the HRPO using an assessment tool.

Compliance reviews are conducted to assess investigator compliance with federal, state, and local law, tribal law passed by the official governing body of an American Indian or Alaska Native tribe and Presbyterian policies, to identify areas for improvement, and to provide recommendations based on existing policies and procedures. The results of compliance reviews will be reported to the HRPO Director, the IRB, and the investigator. Any noncompliance will be handled according to the procedures in Section XVII.

If it is identified that subjects in a research project have been exposed to unexpected serious harm, the reviewer will promptly report such findings to the HRPO Director and/or the IRB Chair for immediate action.

Compliance reviews may include:

- Requesting progress reports from investigators;
- Examining investigator-held research records;
- Contacting research subjects;
- Observing research sites where research involving human research subjects, and/or the informed consent process is being conducted;
- Reviewing advertisements and other recruiting materials;
- Reviewing projects to verify from sources other than the investigator that no unapproved changes have occurred since previous review;
- Assuring that the consent documents include the appropriate information and disclosures about conflicts of interest;

- Monitoring HIPAA authorizations; or
- Conducting other monitoring or auditing activities as deemed appropriate by the HRPO or IRB.

C. IRB Compliance Reviews and Quality Assessment/Improvement

The HRPO, with or without the assistance of an outside organization, will periodically review the activities of the IRB to assess compliance with regulatory requirements and to identify areas for improvement; this will include a review of IRB records at least every three years. Review activities may include:

- Review of the IRB minutes to determine that adequate documentation of the meeting discussion has occurred. This review will include assessing the documentation surrounding the discussion for protections of vulnerable populations as well as risk/benefit ratio and consent issues that are included in the criteria for approval;
- Review of the IRB minutes to ensure that quorum was met and maintained;
- Review of IRB documentation, including IRB minutes, to assess whether privacy provisions, according to HIPAA, have been adequately reviewed, discussed, and documented;
- Evaluating the continuing review discussions to ensure they are substantive and meaningful and that no lapse has occurred since the previous IRB review;
- Reviewing IRB files to ensure retention of appropriate documentation and consistent organization of the IRB file according to current policies and procedures;
- Reviewing the IRB database to ensure required fields are completed accurately;
- Verifying IRB approvals for collaborating institutions or external performance sites;
- Reviewing the appropriate metrics (for example, time from submission to first review) to evaluate the quality, efficiency, and effectiveness of the IRB review process;
- Reviewing the workload of HRPO/IRB staff to evaluate appropriate staffing level; and
- Other monitoring or auditing activities deemed appropriate.

The HRPO Director will review the results of IRB compliance reviews with the IRB Chair and/or the IO. If any deficiencies are noted in the review, a corrective action plan will be developed by the Director and Chair and approved by the IO. The Director will have responsibility for implementing the corrective action plan, the results of which will be evaluated by the IO.

The HRPO staff are responsible for continuously assessing program progress and tracking internal metrics that are informative in considering IRB and Investigator efficiency such as the amount of time from receipt of a submission through pre-review, assignment to the IRB, and final approval and the amount of time it takes investigators to develop and submit responses to pre-review and IRB requirements. Annually, the HRPO Director, in collaboration with HRPO staff, defines quality improvement goals for the year.

IV. RESEARCH EDUCATION AND TRAINING REQUIREMENTS

A. Purpose

HRPP's mission of facilitating excellence in research includes a commitment to ensure that all individuals conducting or facilitating research at Presbyterian receive research education and training in the protection of human research participants.

B. Applies to

All investigators and key personnel engaged in the conduct of human subject research and those who facilitate research under the auspice of Presbyterian Healthcare Services, including IRB Members and HRPP staff.

All Investigators, Key Personnel, IRB Members, and HRPP Team members are responsible for attaching their current CITI certificates to their electronic submission platform profile for IRB review and acknowledgement.

All required CITI training for investigators and key personnel must be completed prior to submission to the Presbyterian electronic submission platform and to the IRB of Record. Investigators and key personnel are responsible for maintaining accurate training records for all investigators and key personnel within their respective Service Lines.

1. **Investigators and Key Personnel Requirements:**

   The CITI Human Subject Protections (HSP) requirement must be satisfied by completing the appropriate course that most closely reflects the type of research conducted:

   - Biomedical Researchers – Comprehensive course focused on biomedical research and offers historic and current information on regulatory and ethical issues important to the conduct of research involving human subjects.
   - Social-Behavioral-Educational Researchers – Comprehensive course focused on social-behavioral research and offers historic and current information on regulatory and ethical issues important to the conduct of research involving human subjects
   - If the researcher will conduct both types of research, it is required that the Biomedical Researcher course be completed.

   The CITI Good Clinical Practice (GCP) course required for all investigators and key personnel involved in FDA-regulated studies, clinical trials funded by the National Institutes of Health (NIH), and research projects specified to comply with GCP standards.

   All CITI courses must be re-completed every 3 years.

   All who have completed equivalent CITI training elsewhere (includes external contractors/collaborators and new Presbyterian employed Investigators/key personnel) must affiliate their CITI accounts to Presbyterian Health Care Services, New Mexico. Such trainings must be current and comparable to be reviewed for consideration to meet HRPP CITI requirements.

2. **IRB Member Requirements**

   All IRB committee members, including alternates, are required to complete orientation sessions prior to serving on the Presbyterian IRB. Additionally, ongoing education sessions and training in the electronic application system will be offered by the HRPP team.

   All board members are required to complete the CITI IRB Member course which provide an overview of the regulatory and ethical considerations, IRB responsibilities, expectations, and the review process. In addition, the IRB members are reviewed to review the following:

   - Presbyterian Healthcare Services Human Research Protection Program (HRPP) Policies and Procedures
   - DHHS regulations (45 CFR 46)
   - FDA regulations (21 CFR 50 and 56)
   - Relevant Presbyterian IRB forms and templates

   All CITI IRB member course must be re-completed every 3 years.

3. **Human Research Protection Program (HRPP) Team Requirements**

   The HRPP team members, must complete the CITI Biomedical Researcher and CITI IRB Member course, which will provide an overview of regulatory and Institutional requirements associated with facilitating research at Presbyterian Healthcare Services.

   The CITI courses must be re-completed every 3 years.

V. INSTITUTIONAL REVIEW BOARD (IRB)

Presbyterian has established an IRB to ensure the protection of human subjects in research conducted under the auspices of the Presbyterian. All non-exempt human subject research must be reviewed and approved by the IRB or another designated IRB prior to the initiation of the research unless it has been determined that Presbyterian is not engaged in the research (see Section II.G). All requests for exempt determination will be reviewed and acknowledged by the IRB and limited IRB review will be performed if applicable. All research reviewed by the IRB will be reviewed either through Full Committee or the expedited review process.

A. IRB Authority

The IRB derives its authority from federal regulatory sources (45 CFR 46.107) and from Presbyterian policy (as cited in Section II. B above). Under the federal regulations, IRBs have the authority to:

- Approve, require modifications to secure approval, or disapprove all human subject research activities overseen and conducted under the auspices of the Presbyterian, including exempt research activities under 45 CFR 46.104 for which limited IRB review is a condition of exemption (under 45 CFR 46.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7), and (8));
- Require that informed consent be obtained and documented in accordance with regulatory requirements unless the criteria for the waiver or alteration of such requirements has been satisfied and approved by the IRB. The IRB may require that information, in addition to that specifically mentioned in the regulations, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects;
- Conduct continuing review of research at intervals appropriate to the degree of risk of the research, but not less than once per year; for studies that do not require continuing review a Study Update form must be submitted for acknowledgement. (Section VII.H)
- Suspend or terminate approval of research not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to participants;
- Observe, or have a third party observe, the consent process; and
- Observe, or have a third party observe, the conduct of the research.

The IRB functions independently. Attempts to coerce or otherwise unduly influence the actions of the IRB are forbidden by policy and are to be reported as described in Section V.F. Likewise, the IRB must remain free from the influence of financial and other organizational interests. No individual with responsibility for the business and financial interests of the organization may serve on the IRB.

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of the organization. However, those officials may NOT approve research if it has not been approved or has been disapproved by the IRB. Reviewing officials may strengthen requirements and/or conditions or add other modifications before approval or may require approval by an additional ancillary committee. Previously approved research proposals and/or consent forms must be re-approved by the IRB before initiating any changes or modifications that result from such additional reviews/approvals.

B. Composition of the IRB

The structure and composition of the Presbyterian IRB is appropriate to the amount and nature of the research that is reviewed. In order to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects, the IRB makes every effort to ensure member representation that has an understanding of the specialty areas that encompass most of the research performed at Presbyterian.

The IRB will include members who are knowledgeable about and experienced in working with vulnerable populations that typically participate in research and shall have appropriate scientific or scholarly expertise. A

member of the IRB may fill multiple membership position requirements for the IRB (e.g., a community member may also be a non-scientific member).

In accordance with federal regulations, the IRB must:

- Consist of at least five members;
- Be sufficiently qualified through the experience and expertise of its members, and possess the professional competence necessary to review research activities;
- Maintain professional diversity by ensuring that different professions are represented (the IRB shall not consist entirely of members of one profession);
- Ensure member diversity, including consideration of race, gender, and cultural backgrounds, and sensitivity to such issues as community attitudes,
- Be able to ascertain the acceptability of proposed research in terms of institutional commitments (including policies and resources) and regulations, applicable law, and standards of professional conduct and practice and include persons knowledgeable in these areas.
- Include at least one member whose primary concerns are in scientific areas and one member whose primary concerns are in nonscientific areas;
- Ensure that the membership does not consist entirely of men or entirely of women, including the organization's consideration of qualified persons of both sexes, so long as no selection is made to the IRB solely on the basis of gender;
- Include at least one member who is not otherwise affiliated with Presbyterian and who is a representative of the local community;
- Ensure that no members participate in initial or continuing review of any project in which that member has a conflicting interest, except to provide information requested by the IRB; and
- Ensure that if the IRB regularly reviews research that involves a vulnerable category of subjects (e.g., children, prisoners, pregnant women, or individuals with impaired decision-making capacity or economically or educationally disadvantage persons, consideration will be given to the inclusion of one or more individuals on the IRB, who are knowledgeable about and experienced in working with these subjects.
- An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

1. **Scientific Members**

   Scientific members must have expertise in the biomedical or behavioral sciences. Scientific members are expected to review assigned studies, as well as contribute to the evaluation of a research project on its scientific merits and standards of practice.

2. **Nonscientific Members**

   Nonscientific members are not required to have expertise in any scientific area. Non-scientific members are expected to provide input on matters related to their individual knowledge, expertise, and experience, professional and otherwise.

3. **Non-Affiliated Community Members**

   Non-affiliated community members are expected to provide input regarding their individual knowledge about the local community and be willing to discuss issues and research from that perspective. Refer to the definition of affiliated above.

C. IRB Membership

The IRB is composed of a dedicated group of volunteers from Presbyterian Healthcare Services and the

community. Members of the IRB possess a breadth of knowledge that allows them to review a large range of research projects. The IRB serves an important role in protecting the rights of research subjects.

1. Roles and Responsibilities

In addition to regular and alternate members, the IRB has two elected offices: Chair and Vice Chair. Each IRB member and officer has specific responsibilities.

a) Chair of the IRB

The IRB Chair is elected to serve for a renewable two-year term. The IRB Chair should be a highly respected individual from within Presbyterian or the community. The Chair should be fully capable of facilitating the IRB, and the matters brought before it with fairness and impartiality. The IRB Chair must be perceived to be fair, impartial, and immune to pressure by administration, the investigators whose research plans are brought before the Chair, other committees, and professional and nonprofessional offices/sources.

The IRB Chair is responsible for the following:

- Reviewing all studies presented to the IRB and communicating with other reviewers as needed so that important IRB issues or concerns are resolved or identified prior to the convened IRB meeting;
- Convening the IRB meetings, and directing the proceedings and discussion;
- Conducting expedited reviews;
- Advising the HRPO Director and the HRPO/IRB coordinator about IRB member performance and competence; and
- Serving as signatory for correspondence generated by the IRB.

The IRB Chair is authorized to take immediate action to suspend a study or studies if information is presented regarding subject safety or for any other reason where such action would be deemed appropriate. Such action requires subsequent notice to and review by the convened IRB.

The IRB Chair may designate other experienced IRB members to perform duties such as expedited reviews and other IRB functions. The IRB Chair is a voting member of the IRB.

If the Chair is not acting in accordance with the IRB's mission, or following these policies and procedures, has an undue number of absences, or is not fulfilling the responsibilities of the Chair, he/she may be removed.

b) Vice Chair of the IRB

The Vice Chair serves as the Chair of the IRB in the absence of the Chair and has the same qualifications, authority, and duties as the Chair. The IRB Vice Chair is elected to serve for a renewable two-year term. The Vice-Chair is a voting member of the IRB.

If the Vice Chair is not acting in accordance with the IRB's mission, or following these policies and procedures, has an undue number of absences, or not fulfilling the responsibilities of the Vice Chair, he/she may be removed.

c) Appointment of Chair and Vice Chair

Candidates for the IRB Chair and Vice Chair positions are solicited. Members may nominate themselves or may be nominated by another member. Nominees for both the Chair and the Vice Chair position should be experienced IRB members (minimum of one year of service on an IRB) with appropriate knowledge and credentials to represent the IRB in an official capacity.

The HRPO staff will confirm that the individuals being nominated agree to serve and will develop a list

of nominees. The slate of nominees will then be presented to the Institutional Official by the HRPO Director. The Institutional Official shall appoint the IRB Chair and Vice Chair for three (3) year terms and will conduct an evaluation for continued service in these roles which may be renewed for additional terms by the Institutional Official.

Any change in the Chair or Vice Chair position, including resignation or removal, requires written notification.

d) IRB Members

The role of an IRB member is to ensure that human research activities comply with federal regulations, state, local laws, and tribal law passed by the official governing body of an American Indian or Alaska Native tribe, and organizational policies and procedures, by:

- Completing member education and training, both initial and on-going (Section IV);
- Maintaining the confidentiality of IRB deliberations and research review by the IRB;
- Conducting and documenting reviews of assigned research in a timely fashion;
- Attending IRB meetings as scheduled;
- Recusing self from final deliberations and vote when s/he has a conflict of interest; (Section XXV);
- Participating in subcommittees of the IRB if requested and available; and
- Conducting themselves in a professional and collegial manner.

(i) Conduct and Attendance

Members may be removed if they are not acting in accordance with the IRB's mission, are not following policies and procedures, or have an excessive number of unexcused absences.

Members should attend all meetings for which they are scheduled. If a member is unable to attend a scheduled meeting, he/she should inform the HRPO/IRB Coordinator. If an IRB member is to be absent for an extended period of time, he or she must notify the HRPO/IRB Coordinator in advance so that an appropriate alternate/replacement can be obtained. If the member has a designated alternate, the alternate can serve during the primary member's absence. Members with excessive absences will be notified once in writing that their membership status could be revoked. If absences continue after initial notification, members may be removed.

On an annual basis, members must complete a "Financial and Non-Financial Interests in Human Research Disclosure" form and a "Confidentiality Agreement."

e) Alternate Members

The appointment and function of alternate members is the same as that for regular IRB members. An alternate's expertise and perspective should be comparable to those of the regular member. The role of the alternate member is to serve as a voting member of the IRB, in part or in full, when the regular member is unavailable to attend a convened meeting, or the regular member has a conflict of interest regarding a protocol under review. The alternate member will receive and is expected to review the same materials that the primary members receive prior to the IRB meeting.

The IRB roster identifies the regular member(s) or class of members (e.g., physician scientist) for whom each alternate member may substitute. The alternate member will not be counted toward meeting quorum as a voting member unless the regular member is absent. The IRB minutes will document when an alternate member replaces a regular member.

Experienced alternate members may be designated by the Chair to conduct expedited reviews.

2. **Selection of Members**

   The HRPO accepts nominations and applications on a continuous basis from individuals interested in serving on the IRB. Applications are available from the HRPO. HRPO staff, along with the IRB Chair, review all completed applications with consideration for maintaining the diversity and specialty requirements as mandated by federal regulations. Recommended applications are then sent for formal institutional approval. Upon selection, new members will receive an appointment letter and will be required to complete the appropriate training and register with the Presbyterian HRPP electronic submission platform, after which they may attend IRB meetings as a voting member.

3. **Length of Terms of Service**

   Each member is appointed to a two-year renewable term. The effective date of term begins once all required documentation and training is complete. Members wishing to resign from the IRB before their two-year term expires must notify the HRPO in writing.

4. **Use of Expert Consultants**

   When necessary, the IRB Chair or the HRPO staff may solicit individuals from the organization or the research community with competence in special areas to assist in the review of issues or research plans which require appropriate scientific or scholarly expertise beyond or in addition to that available on the IRB. The HRPO will ensure that all relevant materials are provided to the outside reviewer prior to the convened meeting. Key information provided by consultants at meetings will be documented in the minutes and written statements from consultants will be kept in the IRB records.

   Outside consultants will be required to complete a “Financial and Non-Financial Interests in Human Research Disclosure” form and a “Confidentiality Agreement” form. Individuals who have a conflict of interest will not be invited to provide consultation.

   The consultant’s findings will be presented to the convened board for consideration either in person or in writing.

D. IRB Registration Updates

Changes in IRB registration will be reported to FDA and OHRP as follows:

- Within 90 days after changes regarding the contact person who provided the IRB registration information or the IRB Chair,
- If the IRB decides to review new types of FDA-regulated products (e.g., to review device studies if it only reviewed drug studies previously) or to discontinue reviewing clinical investigations regulated by FDA, it must report this within 30 days of the change.
- A Presbyterian decision to disband its registered IRB will be reported in writing within 30 days after permanent cessation of the IRB's review of DHHS-conducted or supported research.

E. Liability Coverage for IRB Members

The Presbyterian insurance coverage applies to employees and any other person authorized to act on behalf of Presbyterian for acts or omissions within the scope of their employment or authorized activity.

F. Reporting and Investigation of Allegations of Undue Influence

If an IRB Chair, member, or staff person feels that the IRB has been unduly influenced by any party, they shall make a confidential report to the HRPO Director or IO, depending on the circumstances. The IO will ensure that a thorough investigation is conducted and if the allegation is determined valid, that corrective action is taken to

prevent additional occurrences. In the event the allegation is regarding the IO, the matter will be referred to the Presbyterian Healthcare Services CEO for investigation and any necessary action.

Undue influence means attempting to interfere with a normal functioning and decision making of the IRB or to influence an IRB member of staff, or any other member of the research team outside of the establish processes or normal and accepted methods in order to obtain a particular result, decision, or action by the IRB or one of its members or staff.

VI. HUMAN SUBJECT RESEARCH DETERMINATION

The responsibility for initial determination of whether an activity constitutes human subject research rests with the investigator. Because they will be held responsible if the determination is not correct, investigators are urged to request a confirmation that an activity does not constitute human subject research from the HRPO. The request may be made by email or through a formal written communication. All requests must include enough description of the activity and the rationale for the investigator's initial determination.

The HRPO staff will determine whether an activity constitutes human subject research using the "Human Subject Research Determination Checklist." Determinations regarding less clear- cut activities will be referred to the IRB Chair, who may make the determination or refer the matter to the full IRB. Documentation of all determinations made through the HRPO will be recorded and maintained in the HRPO.

A. Exempt Studies

All human subject research must be reviewed and approved by the Presbyterian Healthcare Services IRB. Under federal regulation 45 CFR 46.101(b), certain categories of human subject research are exempt from IRB oversight. Human subject research that may fall into an Exempt category requires HRPP review for determination of exemption status.

Individuals involved in making the determination of an IRB exempt status of a proposed research project cannot be involved in the proposed research. Reviewers must not have any apparent conflict of interest.

Continuing review is generally not required for research determined to be exempt, however, IRB requires submission of a study closure report upon completion of the study. The report is acknowledged by the IRB Chair or designee.

1. Exempt Determinations and Limited IRB Review

Determinations regarding research requiring limited IRB review or a HIPAA determination (i.e., waivers or alterations of the requirement for HIPAA authorization), the review will be conducted by the IRB Chair or a Chair-designated member of the IRB and may be conducted using expedited review procedures. As with all other research subject to IRB review requirements, when conducting limited IRB review the IRB has the authority to approve, require modifications in (to secure approval), or disapprove all research activities. [§45 CFR46.109(a), 21 CFR 56.109(a)]

The IRB may determine that continuing review is required for a particular study, subject to limited IRB review, in which case it shall document the reasons for its determination in the IRB record and communicate the requirement to the investigator in the IRB determination letter.

Proposed modifications to the aspects of research subject to limited IRB review must be submitted to and approved by the IRB prior to implementation, except when necessary to eliminate apparent immediate hazards to the subject(s), in which case the change must be promptly reported to the IRB (i.e., within 24-72 hours). [§45CFR46.108(a)(3)(iii), 21 CFR 56.108(a)(4)]

VII. IRB REVIEW PROCESS

A. Definitions

Confidentiality. Methods used to ensure that information obtained by investigators about subjects is not improperly divulged.

Identifiable Information. Information where the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

Minimal Risk. Minimal risk means 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.

Minor Change. A minor change is one which, in the judgment of the IRB reviewer, makes no substantial alteration in (a) the acceptability of the risk-to-benefit analysis or increases the level of risks to subjects, (b) the research design or methods (adding procedures that are not eligible for expedited review (see Section 7.5.2) would be considered more than a minor change), (c) the number of subjects enrolled in the research (usually not greater than 10% of the total requested locally), (d) the qualifications of the research team, (e) the facilities available to support safe conduct of the research, and/or (f) any other factor which would warrant review of the proposed changes by the convened IRB.

Privacy. Having control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others. It is the state or condition of being free from unauthorized intrusion, being observed or disturbed by other people.

Private Information. Information that 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).

Quorum. A quorum of the IRB consists of a majority (more than half) of the voting membership, including at least one member whose primary concern is in a non-scientific area. When research involving an investigational new drug is on the agenda for review, a physician should be included in the quorum. At meetings of the IRB, a quorum must be established and maintained for the deliberation vote on all matters requiring a vote.

Sensitive Information. Data or information, on any storage media or in any form or format, which requires protection due to the risk of harm that could result from inadvertent or deliberate disclosure, unauthorized access, misuse, alteration, or loss or destruction of the information (e.g., could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation).

Suspension. A suspension of IRB approval is a directive of the IRB to temporarily stop some or all previously approved research activities. Suspended research studies remain open and requires continuing review.

Termination. A termination of IRB approval is a directive of the convened IRB to permanently stop all activities in a previously IRB-approved research study. Terminated research studies are closed and no longer require continuing review.

B. Submission Process and Required Materials

The IRB will review and ensure that research involving human subjects meets all required ethical and regulatory criteria for initial and continuing review and any modifications of approved research. The IRB may conduct their review using the following review methods:

- Expedited review
- Convened review

The following describe the procedures required for the review of research by the IRB. PIs must be registered in the Presbyterian HRPP electronic submission platform. All study materials, including completed applications, reports, consent forms, CITI certificates, and other documents must be submitted via the system. Emailed or hard copy materials will not be accepted. It is recommended that documents are submitted to the HRPO by the 10th day of the month to be considered for inclusion on the current IRB agenda. However, the workload of the HRPO may require that some submissions will be assigned to the next month's agenda. The IRB meets on a regular basis throughout the year (typically on the fourth Tuesday of the month).

A designated HRPO staff member or IRB representative is responsible for conducting a preliminary review of all submissions. The HRPO will notify the PI if the IRB needs additional information or clarification about the research project. The IRB also has the authority to request that a protocol undergo a different review level than submitted.

Depending on the type of submission, the following documents may be submitted:

- Cover letter;
- Study protocol;
- Investigator Brochure
- Initial study application/continuing review form/amendment form;
- Proposed informed consent/parental permission/assent form(s) or waiver of informed consent;
- HIPAA Authorization Addendum or request for waiver;
- Recruitment materials including advertisements, posters, and flyers intended to be seen or heard by potential subjects;
- Survey instruments/data collection tools/participant diaries, etc.;
- Data safety monitoring board (DSMB) reports;
- Adverse event/Safety reports;
- Financial conflict of interest form;
- Valid completion certificates for human subject protections training through the CITI Program for all study personnel;
- CVs/resumes for study personnel signed and dated within one year of study submission;
- Copies of professional licenses for investigators;
- Publications related to the study.

Note: Complete submission packet must be received within 90 days, or it may be withdrawn by the IRB office.

C. Pre-Review

The HRPO/IRB Coordinator will perform a pre-review of all submissions for determination of completeness and accuracy. Only complete submissions will be moved forward for IRB review. The investigator will be informed via the electronic submission platform of any clarification requests/modifications necessary to be reviewed by the IRB.

D. Primary and Secondary Reviewers

After it has been determined that the submission is complete, the HRPO/IRB Coordinator may assign submissions for review, paying close attention to the subject matter of the research, the potential reviewer's area/s of expertise, and representation for any vulnerable populations involved in the research. When the IRB is presented with a research study which may be outside of the knowledge base or representative capacity of the IRB members, an outside consultant will be sought (Section V).

Primary and secondary reviewers are responsible for:

- Having a thorough knowledge of all the details of the proposed research;

- Performing an in-depth review of the proposed research;
- Beginning the discussion of the proposed research at the convened meeting, by summarizing the proposed research (and leading the IRB through the regulatory criteria for approval;
- Making suggestions for changes to the proposed research, where applicable; and
- Completing all applicable IRB reviewer forms.

One or more secondary reviewers may be assigned in addition to the primary reviewer. A secondary reviewer may be assigned to review the full submission materials or may be asked to review specified sections of the submission (e.g., the consent/assent/permission forms). All IRB members receive and are expected to review all studies, not just those assigned as primary (or secondary) reviewer.

An absent reviewer can submit her/his written comments for presentation at the convened meeting. If an absent reviewer submits comments, those can indicate a recommendation regarding approval, but such recommendation will not be counted as a vote.

E. Expedited Procedures

DHHS and FDA regulations allow the IRB to review research on an expedited basis if the research constitutes a minor change in IRB already approved human subject research during which the approval is authorized; or the research is not more than minimal risk and falls within one of the Expedited Categories according to the 'Notice' in the *Federal Register* (45 CFR 26.110(b); 21 CFR 56.110(b)).

Under an expedited review procedure, the review may be carried out by the IRB Chair or by one or more designated IRB reviewers.

1. Appropriate Use of Expedited Review

In accordance with OHRP Guidance for Expedited Review, Expedited Review is appropriate for use by IRB when:

- Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the categories according to the 'Notice' in the Federal Register in accordance with 45 CFR 46.110 and 21 CFR 56.110. The activities listed are presumed to be of minimal risk unless justification of a more than minimal risk is provided by the reviewer.
- The expedited category determination applies regardless of the age of subjects, expect as noted in category two.
- 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 subject's financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no more than minimal risks.
- The research is not classified research involving human subjects.
- The expedited category determination pertains to both initial and continuing review.
- The expedited reviewer is knowledgeable of the Informed Consent requirements.

Human Subject Research projects that have received a determination from an IRB Expedited reviewer will be listed on the exempt/expedited report included with the next agenda and presented to the IRB for acknowledgement at the convened IRB meeting.

F. Convened IRB Meetings

Except when an expedited review procedure is used, the IRB will conduct initial and continuing reviews of all non-exempt research at convened meetings at which a quorum (see below) of the members is present.

1. IRB Meeting Schedule

The IRB meets on a regular basis throughout the year (typically on the fourth Tuesday of the month). The schedule for the IRB may vary due to holidays or lack of quorum. The schedule for IRB meetings is posted on the Presbyterian HRPP electronic submission platform. Special meetings may be called at any time by the Chair, HRPO/IRB Coordinator, or HRPO Director.

2. Quorum

A quorum of the IRB consists of a majority (more than half) of the voting membership, including at least one member who is unaffiliated and one member whose primary concern is in a non- scientific area. At meetings of the IRB, a quorum must be established and maintained for the deliberation and vote on all matters requiring a vote. The IRB Chair, with the assistance of the HRPO staff, will confirm that quorum is present before proceeding to agenda items, and will ensure that the meeting remains appropriately convened. If a quorum is not maintained, either by losing a majority of the members, losing all non-scientific members or another required member, the IRB cannot take further action or vote on regulatory determinations until quorum is restored.

It is generally expected that at least one unaffiliated member and at least one member who represents the general perspective of participants (one individual can serve in both capacities) will be present at all IRB meetings.

IRB members are considered present and participating at a duly convened IRB meeting when either physically present or participating through electronic means (e.g., teleconferencing or video conferencing) that permits them to listen to and speak during IRB deliberations and voting. Whether or not physically present, the IRB member must have received all pertinent materials prior to the meeting and must be able to participate actively and equally in all discussions.

3. Meeting Procedures

After calling the meeting to order, the IRB Chair will determine that a quorum is in place. The Chair will introduce any alternate members, who are present, as well as any guests, consultants, or investigators in attendance (if applicable). The Chair will also remind IRB members to recuse themselves from the discussion and votes by leaving the room when they have a conflict. The IRB will review and discuss the minutes from the prior meeting and determine if there are any revisions/corrections to be made. If there are no changes to be made, the minutes will be accepted as presented and considered final. If major revisions/corrections are necessary, the minutes will be amended and presented at the following IRB meeting.

The IRB reviews all submissions for initial and continuing review, as well as requests for modifications. The primary (and secondary) reviewer presents an overview of the research and assists the Chair in leading the IRB through the completion of the regulatory criteria for approval. For the research to be approved, it must receive the approval of a majority of those voting members present at the meeting.

A convened meeting may not be held without the attendance of the Chair, or Vice Chair or another member who is designated by the Chair to lead the meeting in his/her absence.

It is the responsibility of the HRPO/IRB Coordinator to record the proceedings of the session by taking minutes at each IRB meeting.

4. Guests

Investigators and research staff may be invited to the IRB meeting, at the discretion of the IRB, to make a brief presentation or to answer questions about proposed or ongoing research. The investigator/research staff may not be present for the deliberations or vote on the research.

The HRPO Director and staff regularly attend IRB meetings and may participate in the IRB discussion and deliberations but may not vote.

Other guests may be permitted to attend IRB meetings at the discretion of the IRB Chair and the HRPO/IRB Coordinator. Such guests will be asked to sign a confidentiality agreement, and do not participate in discussion unless requested by the IRB; under no circumstances may they vote.

G. Criteria for IRB Approval of Research

For the IRB to approve human subject research, either through expedited review or by the convened IRB, it must determine that the following requirements are satisfied. These criteria apply to all categories of IRB reviews including initial reviews, continuing reviews, and modifications of previously approved research.

- Risks to subjects are minimized: (i) by using procedures that are consistent with sound research design and that 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.
- 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. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.
- 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 the Federal Regulations [45 CFR 46.116].
- Informed consent will be appropriately documented or appropriately waived, in accordance with 45 CFR 46.116(f), 46.117(c), and/or 21 CFR 50.22, as applicable..
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- The Secretary of HHS will, after consultation with the Office of Management and Budget's privacy office and other Federal departments and agencies that have adopted this policy, issue guidance to assist IRBs in assessing what provisions are adequate to protect the privacy of subjects and to maintain the confidentiality of data.
- When some or all the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

While pregnant women are no longer described as vulnerable within the above criteria, the IRB shall continue to apply Subpart B "Additional Protections for Pregnant Women, Human Fetuses and Neonates" as described in the HRPP Policy and Standard Operating Procedures. The revised Common Rule does not eliminate or modify Subpart B.

1. **Risk / Benefit Analysis**

The goal of the assessment is to ensure that the risks to research subjects posed by participation in the research are justified by the anticipated benefits to the subjects or society. Toward that end, the IRB must (1) Judge whether the anticipated benefit, either of new knowledge or of improved health or other direct benefit for the research subjects, justifies asking any person to undertake the risks; and (2) Disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits.

The assessment of the risks and benefits of proposed research involves the following steps:

- Identify the risks associated with the research, as distinguished from the risks of activities, diagnostic tests, treatments, or therapies the subjects would receive even if not participating in research;
- Determine whether the risks will be minimized to the extent possible by evaluating the necessity of procedures that impart risk and whether the data could be gained by procedures that are already being performed for other purposes or by alternative procedures that impart less risk;
- Identify the anticipated benefits to be derived from the research, both direct benefits to subjects and possible benefits to society, science, and others; and
- Determine whether the risks are reasonable in relation to the benefits, if any, and assess the importance of the knowledge to be gained.

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 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 (e.g., the possible effects of the research on public policy) as among those research risks and benefits that fall within the purview of its responsibility.

2. **Scientific Review**

In order to assess the risks and benefits of the proposed research, the IRB must determine that

- The research uses procedures consistent with sound research design; and
- The research design is sound enough to reasonably expect the research to answer its proposed question.

In making this determination, the IRB may draw on its own knowledge and expertise, or the IRB may draw on the knowledge and expertise of others, such as reviews by a funding agency, or departmental review. When scientific review is conducted by an individual or entity external to the IRB, documentation that the above questions were considered must be provided to the IRB for review and consideration. Scientific review is documented and provided to the IRB via email correspondence.

3. **Equitable Selection of Subjects**

The IRB determines by reviewing the application, protocol/research plan, and other materials that the selection of subjects is equitable with respect to gender, age, class, etc. The IRB will not approve a study that does not provide adequately for the equitable selection of subjects or has not provided an appropriate scientific and ethical justification for excluding classes of persons who might benefit from the research. In making this determination, the IRB evaluates:

- The purposes of the research;
- The setting in which the research occurs;
- Scientific and ethical justification for including vulnerable populations such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons;

- The scientific and ethical justification for excluding classes of persons who might benefit from the research; and
- The inclusion/exclusion criteria and the procedures/materials intended for use for the identification and recruitment of potential subjects.

At the time of the continuing review the IRB will determine that the investigator has followed the subject selection criteria that were originally set forth at the time of the initial IRB review and approval.

4. Recruitment of Subjects

The investigator will provide the IRB with a plan for recruitment of all potential subjects. All recruiting materials will be submitted to the IRB, including (but not limited to) advertisements, flyers, scripts, information sheets, and brochures. The IRB should ensure that the recruitment plan and materials appropriately protect the rights and welfare of the prospective subjects (e.g., do not present undue influence).

The IRB must review and approve any and all advertisements prior to posting and/or distribution for studies that are conducted under the purview of Presbyterian. The IRB will review:

- The information contained in the advertisement;
- The mode/method of its communication;
- The final copy of printed advertisements; and
- The proposed script and final audio/video taped advertisements.

This information should be submitted to the IRB with the initial application or, if recruitment is proposed after study approval, as a modification request.

The IRB reviews the material to ensure that the material is accurate and is not coercive or unduly optimistic, creating undue influence on the subject to participate. This includes but is not limited to the following:

- Statements implying a certainty of favorable outcome or other benefits beyond what was outlined in the consent document and the research plan;
- Claims, either explicitly or implicitly, that the test article (drug, biologic or device) is safe or effective for the purposes under investigation; Claims, either explicitly or implicitly, that the test article was known to be equivalent or superior to any other drug, biologic or device;
- Using terms like “new treatment,” “new medication,” or “new drug” without explaining that the test article was investigational;
- Promising “free medical treatment” when the intent was only to say participants will not be charged for taking part in the investigation;
- Emphasis on payment or the amount to be paid, such as bold type or larger font on printed media;
- Offers for a coupon good for a discount on the purchase price of an investigational product once it has been approved for marketing; and
- The inclusion of exculpatory language.

Recruitment materials should be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included:

- The name and address of the investigator and/or research facility;
- The condition being studied and/or the purpose of the research;
- In summary form, the criteria that will be used to determine eligibility for the study;
- The time or other commitment required of the subjects;
- The location of the research and the person or office to contact for further information;

- A clear statement that this is research and not treatment; and
- A brief list of potential benefits (e.g., no-cost health exam).

Once approved by the IRB, an advertisement cannot be altered or manipulated in any way without prior IRB approval.

Directory listings of research such as ClinicalTrials.Gov are not considered advertisements and therefore do not require IRB review and approval if the listing is limited to the following basic trial information: title, purpose of the study, research plan summary, basic eligibility criteria, study site location(s), and how to contact the study site for further information.

The first contact prospective study subjects make is often with a person who follows a script to determine basic eligibility for the specific study. The IRB should ensure the procedures followed adequately protect the rights and welfare of the prospective subjects.

5. Payments to Research Subjects

Payment to research subjects may be an incentive for participation or a way to reimburse a subject for travel and other experiences incurred due to participation. However, payment for participation is not considered a research benefit. Regardless of the form of remuneration, investigators must take care to avoid unduly influencing subjects. The amount of compensation must be proportional to the time and inconveniences posed by participation in the study.

Investigators who wish to pay research subjects must submit to the IRB the amount and schedule of all payments. Investigators should indicate in their research project application the justification for such payment. Such justification should substantiate that proposed payments are reasonable and commensurate with the expected contributions of the subject and do not constitute (or appear to constitute) undue pressure on the potential subject to volunteer for the research study.

The IRB must review both the amount of payment and the proposed method and timing of disbursement to ensure that neither entails problems of coercion or undue influence.

Credit for payment should be prorated and not be contingent upon the participant completing the entire study. The IRB does not allow the entire payment to be contingent upon completion of the entire study. Any amount paid as bonus for completion of the entire study should not be so great that it could unduly induce subjects to remain in the study when they otherwise would have withdrawn.

- Payments to participants should be documented. If compensating a total value of $600 or greater to an individual participant, Presbyterian encourages a tracking log; this may include participants name and contact information. If compensation is $600 or more in a calendar year, participants will be asked to provide additional personal identifying (e.g., Social Security Number) information for tax reporting purposes. This information is stored confidentially and separate from research data. This may reduce the privacy protection that may be assured to participants as a result.

The consent form must describe the terms of payment including the amount and schedule of payments, and any conditions under which subjects would receive partial payment (e.g., if they withdraw from the study before their participation is completed) or no payment, According to the federal tax code, payment for purposes of research participation by cash, check, money order or gift card in the amount of $600 or more per year is taxable income. The consent form must inform subjects that:

- Participants name, contact information and other personal identifying information may be collected. This information is stored confidentially and separate from research data.

a) Non-Monetary Gifts and Incentives

Like financial incentives, non-monetary gifts or incentives can also present problems of undue

influence or coercion that impact a potential subject's ability to consider participation fully and freely in research.

If subjects will be provided with non-monetary gifts or tokens of appreciation, such as totes, books, toys, or other such materials, the approximate retail value must be described to the IRB and the IRB will be provided with a description, photo, or sample product to review.

The IRB will review all gifts and incentives being particularly sensitive to the influence of power or authority, whether perceived or actual, over free decision-making. Overt coercion (e.g., threatening loss of credit, or access to services or programs, to which the potential subjects are otherwise entitled) is never appropriate. Moreover, it must be clear that choosing to not participate will not adversely affect an individual's relationship with the organization or its staff or the provision of services in any way (e.g., loss of credits or access to programs).

Investigators should carefully structure incentives and methods of disbursement so that while the incentives may serve as a factor in an individual's decision to participate, that they have not served to unduly influence or coerce participation.

6. Informed Consent

The IRB will ensure that 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 and 21 CFR 50.20. In addition, the IRB will ensure that informed consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117 and 21 CFR 50.27. The IRB will ensure, as part of its review, that the information in the consent document and process is consistent with the research plan, and, when applicable, the HIPAA authorization. See Section XI below for detailed policies on informed consent.

7. Data and Safety Monitoring

For all research that is more than minimal risk (e.g., clinical trials), the investigator should submit a data and safety monitoring plan. The initial plan submitted to the IRB should describe the procedures for safety monitoring, reporting of UAPs involving risks to subjects or others, descriptions of interim safety reviews, and the procedures planned for transmitting the monitoring results to the IRB. This description should include information regarding an independent Data and Safety Monitoring Board (DSMB), if one exists, or an explanation why an independent data safety monitor is not necessary.

The IRB reviews the safety monitoring plan and determines if it makes adequate provision for monitoring the reactions of subjects and the collection of data to ensure the safety of subjects and address problems that may arise over the course of the study. If a plan was not submitted, the IRB determines whether a plan is required, and, depending on the circumstances, what the plan should include. The overall elements of the monitoring plan may vary depending on the potential risks, complexity, and nature of the research study.

The factors the IRB will consider in determining whether the safety monitoring plan is adequate for the research are as follows:

- Monitoring is commensurate with the nature, complexity, size, and risk involved;
- Monitoring is timely. Frequency should be commensurate with risk. Conclusions are reported to the IRB;
- For low-risk studies, continuous, close monitoring by the study investigator or an independent individual may be an adequate and appropriate format for monitoring, with prompt reporting of problems to the IRB, sponsor, and regulatory bodies as appropriate; and
- Data and Safety Monitoring plans should specify:

- ❖ The entity or person(s) who will perform the monitoring, and the independence or affiliation that the entity or person(s) has with the sponsor or investigator
- ❖ The safety information that will be collected and monitored, including serious adverse events and UAPs
- ❖ The frequency or periodicity of review of safety data
- ❖ The procedures for analysis and interpretation of the data
- ❖ The procedures for review of scientific literature and data from other sources that may inform the safety or conduct of the study
- ❖ The conditions that trigger a suspension or termination of the research, if applicable
- ❖ The procedures for reporting to the IRB, including a summary description of what information, or the types of information, which will be provided.

- For a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), the plan should describe the following:
  - ❖ The composition of the board or committee. Generally, a DSMB should be composed of experts in all scientific disciplines needed to interpret the data and ensure subject safety. Clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease/condition and treatment under study should be part of the monitoring group or be available if warranted.
  - ❖ Frequency and content of meeting reports.
  - ❖ The frequency and character of monitoring meetings (e.g., open or closed, public or private).
  - ❖ The Charter should be provided when one exists.

In general, it is desirable for a DSMB or DMC to be established by the study sponsor for research that is blinded, involves multiple sites, involves vulnerable subjects, or employs high- risk interventions. For some studies, the National Institutes of Health (NIH) require a DSMB. The IRB has the authority to require a DSMB or DMC as a condition for approval of research where it determines that such monitoring is needed. When DSMBs or DMCs are used, IRBs conducting continuing review of research may rely on a current statement, or the most recent report, from the DSMB or DMC which indicates that it has and will continue to review study-wide adverse events, study wide interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB.

8. Privacy and Confidentiality

The IRB will determine whether adequate procedures are in place to protect the privacy of subjects and to maintain the confidentiality of the data.

a) Privacy

The IRB must determine whether the activities in the research appropriately protect the privacy of potential and actual subjects. In order to make that determination, the IRB must obtain information regarding how the investigators plan to access subjects or subject's private, identifiable information and the subject's expectations of privacy in the situation. Investigators must have appropriate authorization to access the subjects or the subject's information.

In developing strategies for the protection of subject's privacy, consideration is given to:

- Methods used to identify and contact potential participants;
- Settings in which an individual will be interacting with an investigator;
- Appropriateness of all personnel present for research activities;
- Methods used to obtain information about participants, and the nature of the requested information including minimizing the information obtained to achieve the aims of the research; and

- Information that is obtained about individuals other than the "target subjects," (e.g., a subject provides information about a family member for a survey) and whether such individuals meet the regulatory definition of "human subject."

b) Confidentiality

The IRB must determine if appropriate protections are in place to minimize the likelihood that information about subjects will be inappropriately divulged. Safeguards designed to protect confidentiality should be commensurate with the potential of harm from unauthorized, inappropriate, or unintentional disclosure.

At the time of initial review, continuing review, and with any requests for modification, the IRB assesses whether there are adequate provisions to protect data confidentiality. The IRB does this through the evaluation of the methods used to obtain, record, share, and store information about individuals who may be recruited to participate in studies and about subjects. The investigator will provide the IRB with a plan regarding the procedures to be taken to protect the confidentiality (Section XXX).

In reviewing confidentiality protections, the IRB shall consider whether the data or other information accessed or gathered for research purposes is sensitive and the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research. It shall evaluate the effectiveness of proposed de- identification techniques, coding systems, encryption methods, methods of transmission, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections. In reviewing confidentiality protections, the IRB shall also consider regulations and organizational requirements and policies regarding the use of information and information security.

Research regulated by the FDA that involves the use of electronic data collection/storage systems must comply with the requirements of 21 CFR Part 11.

9. Vulnerable Populations

Certain individuals, by nature of their age or impaired decision-making capacity~~,~~ physical, economic, educational, or other situation, may be more vulnerable to coercion or undue influence than others. At the time of initial review, the IRB will consider the scientific and ethical reasons for including vulnerable subjects in research. The IRB may determine and require that, when appropriate, additional safeguards be put into place for vulnerable subjects, such as those without decision-making capacity.

For an extensive discussion about the IRB's review and approval process for individual populations of vulnerable subjects, please refer to Section XII.

10. Independent Verification That No Material Changes Have Occurred

The IRB recognizes that protecting the rights and welfare of subjects sometimes requires that the IRB use sources other than the investigator to independently verify that no material changes occurred during the IRB-designated approval period.

The IRB will determine the need for verification from outside sources on a case-by-case basis. The following factors will be considered when determining which studies require independent verification:

- The probability and magnitude of anticipated risks to subjects;
- The likely medical/psychological/social/legal/educational condition of the proposed subjects;
- The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed;
- Concern about possible material changes occurring without IRB approval have been raised based on

information provided in continuing review reports or from other sources;
- Investigators who have previously failed to comply with federal regulations and/or the requirements or determinations of the IRB;
- Research without a routine monitoring plan; or
- Any other factors the IRB deems verification from outside sources is relevant.

In making determinations about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period or may require such verification at the time of continuing review, review of modification requests and/or UAPs.

If any material changes have occurred without IRB review and approval, the IRB will decide the corrective action to be taken (Section XVII).

11. Consent Monitoring

In reviewing the adequacy of informed consent procedures for proposed research, the IRB may on occasion determine that special monitoring of the consent process by an impartial observer is required in order to reduce the possibility of coercion and undue influence, ensure that the approved consent process is being followed, or ensure that subjects are truly giving informed consent.

The IRB has the regulatory authority to observe the consent process at any time. Consent monitoring may be particularly warranted under the following circumstances:

- High risk studies;
- Studies that involve particularly complicated procedures or interventions;
- Studies involving highly vulnerable populations (e.g., ICU patients, children who are wards);
- Studies involving study staff with minimal experience in administering consent to potential study participants; or
- Other situations when the IRB is concerned that consent process may not be/is not being conducted appropriately (e.g., prior investigator non-compliance, etc.).

Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with an investigator or a research project.

If the IRB determines that consent monitoring is required, the IRB Chair and the HRPO/IRB Coordinator will develop a monitoring plan and submit it to the IRB for approval. The consent monitoring may be conducted by HRPO/IRB staff, IRB members or another party, either affiliated or not with Presbyterian. The investigator will be notified of the IRB's determination and the reasons for the determination. Arrangements will be made with the investigator for the monitoring of the consent process, typically for a specified number of subjects. When observing the consent process, the monitor will determine:

- Whether the informed consent process was appropriately conducted and documented;
- Whether the participant had enough time to consider study participation;
- Whether the consent process involved coercion or undue influence;
- Whether the information was accurate and conveyed in understandable language; and
- Whether the subject appeared to understand the information and gave their voluntary consent.

Following the monitoring, a report of the findings will be submitted to the IRB, which will determine the appropriate action to be taken.

12. Investigator Qualifications

The IRB reviews credentials, curriculum vitae, resumes, CITI training certificates, or other relevant materials to determine whether investigators and members of the research team are appropriately qualified to conduct the research. The IRB may rely upon other Presbyterian processes (e.g., credentialing)

to inform this determination. Curriculum vitae and resumes should be dated (updated within the last 12 months) and signed.

13. Investigator Conflicts of Interest (COI)

As part of its review process, the IRB will make a final determination as to whether any conflict of interest is adequately addressed and whether adequate protections exist for human subjects in the research. All study staff should complete and upload a Financial Conflict of Interest Form (available in the Presbyterian HRPP electronic submission platform) (Section XXIII).

14. Institutional Conflicts of Interest

As with individual conflict of interest, the IRB has final authority to determine whether the institutional conflict, the institutional financial interest, and the management plan, if any, allow the study to be approved.

15. Significant New Findings

During research, significant new knowledge or findings about the research, the test article, and/or the condition under study may develop. The investigator must report any significant new findings to the IRB and the IRB will review them regarding the impact on the subject's rights and welfare. Because the new knowledge or findings may affect the risks or benefits to subjects or subject's willingness to continue in the research, the IRB may require, during the ongoing review process, that the investigator contact the currently enrolled subjects to inform them of the new information. The IRB will communicate this requirement to the investigator. If the study is still enrolling subjects, the consent document should be updated. IRB may require that the currently enrolled subjects be re-consented or otherwise provided with the new information. The IRB may also require that former subjects be provided with the new information, e.g., if it impacts their rights or welfare.

16. State and Local Laws

The IRB considers and adheres to all applicable state, local laws and tribal law passed by the official governing body of an American Indian or Alaska Native tribe, in the jurisdictions where the research is taking place. The HRPO and IRB rely on Presbyterian legal counsel for the interpretation and application of New Mexico law and the laws of any other jurisdiction where research is conducted as they apply to human subject research. The IRB will ensure that consent forms are consistent with applicable state, local laws and tribal law passed by the official governing body of an American Indian or Alaska Native tribe.

H. IRB Actions

1. Acknowledge

When a document or item is sent to the IRB that does not, according to applicable regulations or policy, require IRB approval.

2. Approve

The research, proposed modification to previously approved research, or another item is approved. The IRB has made all the determinations required for approval [i.e., approval criteria and any applicable special determinations (e.g., waivers, alterations, vulnerable population determinations, etc.)] and all criteria have been met according to 45 CFR 46.111. No further action is needed.

3. Approved with Conditions.

The research, proposed modification to the previously approved research, or other item is approved but conditions must be satisfied before the approval becomes effective. Study activities may not begin until

the conditions have been met.

The IRB may approve research with conditions if, given scope and nature of the conditions, the IRB is able, based on the assumption that the conditions are satisfied, to make all the determinations required for approval [i.e., approval criteria and any applicable special determinations (e.g., waivers, alterations, vulnerable population determinations, etc.)]. Any time the IRB cannot make one or more of the determinations required for approval, the IRB may not approve the study with conditions.

When the IRB approves research with conditions, the conditions will be documented in the IRB minutes for research reviewed at a convened meeting, and in the applicable reviewer's checklist for research reviewed under an expedited review procedure.

When the convened IRB approves research with conditions, the IRB may designate the HRPO/IRB coordinator [and/or other qualified individual(s)] to review responsive materials from the investigator and determine that the conditions have been satisfied. If the conditions have not been satisfied, or are only partially satisfied, the responsive materials must be referred to the convened IRB for review. When an expedited reviewer approves research with conditions, the original expedited reviewer [and/or other qualified individual(s)] will receive the response materials.

In some cases, the IRB may stipulate that certain component of the research, which the IRB has determined to meet the criteria for approval, may commence or continue while other components of the research that require modification or clarification cannot begin or continue until the outstanding issues are resolved and approved by the convened IRB. For example, the IRB could determine that a study may begin but that children cannot be enrolled until the investigator submits, and the IRB approves, a plan for assent.

After verification, the following will be documented in IRB records and written communication to the investigator:

- The date when verification was made that all IRB conditions have been satisfied (i.e., the "effective date");
- For initial approval, the date when approval becomes effective (i.e., the date on which the investigator's response has been accepted as satisfactory); and
- The date by which continuing review must occur.

The IRB will be informed of the outcome of the review of the investigator's response in the agenda of the next meeting.

4. Continuing Noncompliance

5. Defer – Information/Modification(s) Required

These actions are taken by the IRB when modifications are required (of the nature or amount that the full IRB cannot make or specify exact changes or parameters), or additional information or clarification is needed in order to determine that one or more criteria for approval are satisfied (e.g., the risks and benefits cannot be assessed with the information provided).

The basis for the determination is documented in the IRB minutes (for convened review) or**,** applicable reviewer's checklist (for expedited review) and is communicated to the investigator in writing. When the convened IRB determines that modifications or information are required, the responsive materials from the investigator will be provided to the convened IRB for review at a subsequent meeting. The original expedited reviewer will review the response materials whenever possible. If the original expedited reviewer is unavailable, the response will be reviewed by the IRB Chair or other qualified IRB member who has been designated to conduct expedited review. Study activities may not begin until modifications have been completed and approved by the expedited reviewer or convened IRB and a decision letter has been issued.

6. **Disapproved**

   The IRB may determine that the proposed research cannot be conducted at Presbyterian or by employees or agents of Presbyterian or otherwise under the auspices of Presbyterian. A "not approved" action can only be determined at the convened IRB meeting. An expedited reviewer cannot disapprove a study.

7. **Exempt Research**
8. **Non-Human Subject Research**
9. **Quality Improvement Project**
10. **Serious Adverse Event**
11. **Serious and Continuing Noncompliance**
12. **Serious Noncompliance**
13. **Suspension**
14. **Tabled**

    An application may be tabled for the following reasons:

    - Lack of meeting time to conduct thorough review of the item;
    - Loss of quorum;
    - Insufficient information to make a determination;
    - Other reasons as determined by the Chairperson; or
    - The application will be placed on a future IRB agenda.

    The investigator will not initiate any new research activities or implement proposed changes to previously approved research until the application has subsequently been reviewed by the IRB and they have received written notification of IRB approval.

I. Continuing Review

The IRB will conduct a continuing review of ongoing research at intervals that are appropriate to the level of risk for each research plan. FDA-regulated research will be reviewed at least once per year. The date by which continuing review must occur will be recorded in the IRB minutes or other IRB records and communicated in writing to the investigator.

Unless the IRB determines otherwise, continuing review of research is not required for research subject in the following circumstances:

- Research eligible for expedited review in accordance with §21 CFR 56.110; 45 CFR 46.110
- Research reviewed by the IRB in accordance with limited IRB review;
- Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
  - ❖ Data analysis, including analysis of identifiable private information or identifiable biospecimens, **or**
  - ❖ Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care

The IRB may determine that continuing review is required for any research protocol that falls within the above criteria. For example, the IRB may determine that continuing review is required when:

- Required by other applicable regulations (e.g., FDA);
- The research involves topics, procedures, or data that may be considered sensitive or controversial;
- The research involves particularly vulnerable subjects or circumstances that increase subject's vulnerability;

- An investigator has minimal experience in research or the research type, topic, or procedures; and/or
- An investigator has a history of noncompliance.

When the IRB determines that continuing review is required for such research, it will document the rationale in the IRB record and communicate the requirement to the investigator in the IRB determination letter. A Study Update Report is required for studies that are ceded or meet the requirement of limited IRB review. The Investigators must submit the following:

- Completed **"Study Update"** form;
- Most current CITI training certificates for each member of the research team (as applicable);
- Professional license (as applicable);
- COI documentation (as applicable);
- Any changes or reports that have not been previously submitted to the IRB; and
- Determination letters from the IRB of record

1. Approval Period

At the time of initial review and at continuing review, the IRB will make a determination regarding the frequency of review of the research study. All studies will be reviewed by the IRB at intervals appropriate to the degree of risk but no less than once per year. In some circumstances, such as when the research involves a high likelihood or severity of risks, when the research imparts significant risks without likelihood of direct benefit, or when the research population is especially vulnerable, a shorter review interval (e.g., semi-annually, quarterly, or after accrual of a specific number of participants) may be required (see below). For convened IRB review, the meeting minutes will reflect the IRB's determination regarding review frequency. For expedited review, the determination will be documented in the applicable reviewer's checklist

IRB approval is considered to have lapsed at midnight on the expiration date of the approval (i.e., the expiration date is the last day research can be conducted). For a new study reviewed by the IRB, the approval commences on the date that the IRB conducts its final review of the study; that is, the date that the convened IRB or expedited reviewer approves the research or the date ("effective date") that it is verified that the requirements of the IRB have been satisfied following an action of Approval with Conditions. The expiration date of the initial approval period, which is the date by which the first continuing review must occur, may be as one year minus one day after the effective date of initial IRB approval.

The HRPO has adopted a procedure for maintaining fixed anniversary dates for expiration of annual IRB approval. As a result, when the IRB performs continuing review and re-approves the research within 30 days before IRB approval expires, the IRB retains the anniversary of the expiration date of the initial IRB approval as the expiration date of each subsequent one-year approval period (for approvals less than one year, the same process is followed; however, changes occur in increments of less than a year). Thus, if the initial (or prior) IRB approval expires on 7/31/2017, the expiration date following re-approval would be 7/31/2018 providing the IRB re-approved the research between 7/1/2017 and 7/31/2017. If the IRB reviews and re- approves the protocol prior to 30 days before expiration, the new expiration date is calculated based on the date of the convened meeting where the IRB approves or modifies (without the need for further review at a convened meeting) the protocol or, for review by expedited procedures, the date when the IRB Chair (or designee) last reviews and either approves or modifies (without need for further review by the Chair or other IRB member) the protocol. When re-approval is not obtained by the expiration date (i.e., approval lapses), the expiration date when re-approval is finally obtained reverts to the anniversary date. Thus, if the expiration date is 7/31/2017 but the continuing review submission occurs after this date and re-approval is not obtained until 9/1/2017, the new expiration date is 7/31/2018.

The approval date and approval expiration date are clearly noted on IRB determination letters and must be strictly adhered to. Investigators should allow enough time for development and review of continuing review submissions.

IRB review of a proposed modification to research ordinarily does not alter the date by which continuing review must occur. This is because continuing review is review of the full research project, not simply a change to it.

The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of research must occur by midnight of the date when IRB approval expires. If the IRB performs continuing review within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing review must occur.

2. Continuing Review Process

The Presbyterian HRPP electronic submission platform system will automatically send out renewal notices to investigators 45 days and 30 days in advance of the expiration date or when the annual status report is due; however, it is the investigator's responsibility to ensure that the continuing review of ongoing research is approved prior to the expiration date. By federal regulation, no extension to that date can be granted.

Investigators must submit the following for continuing review:

- Cover letter;
- Completed **"Continuing Review Report"** form;
- Current protocol;
- Redacted copy(ies) of the most recently signed consents/assents if study is still enrolling;
- Most recent study-wide report (as applicable);
- Most recent data safety monitoring report (as applicable);
- Most recent study monitor report from the sponsor (as applicable);
- Recruitment tools or data collection instruments if any changes have occurred since initial approval (as applicable);
- Publications or presentations generated from this research (as applicable);
- Relevant literature (as applicable);
- Current conflict of interest disclosures for each member of the research team (as applicable); and
- Most current CITI training certificates for each member of the research team (as applicable).

3. Approval Considerations

In order to re-approve research at the time of continuing review, the IRB must determine that the regulatory criteria for approval continue to be satisfied. Because the research was previously found to satisfy the criteria for approval, the IRB focuses its considerations at the time of continuing review on whether any new information is available that would affect the IRB's prior determination that the criteria for approval are satisfied. The IRB pays particular attention to the following four aspects of the research:

- Risk assessment and monitoring;
- Adequacy of the informed consent process;
- Local investigator and organizational issues; and
- Research progress.

4. Convened Board Review (Continuing Review)

In conducting continuing review of research not eligible for expedited review, all IRB members are

provided with access to all required materials and are responsible for reviewing the project summary, the current consent document, the progress report, and, if applicable, the data and safety monitoring report, multi-center study progress reports, and any proposed modifications to the protocol/research plan, or consent. At the meeting, the Primary and Secondary Reviewers assist the Chair in leading the IRB through the completion of the regulatory criteria for approval in the applicable reviewer's checklist

Review of currently approved or newly proposed consent documents must occur during the scheduled continuing review of research by the IRB, but consent documents should be reviewed whenever new information becomes available that may require modification of information in the consent document.

If the research no longer requires continuing review under the Common Rule and the IRB determines that continuing review is required, the rationale shall be documented in the minutes.

5. Limited Review (Continuing Review)

In conducting review under expedited procedures, all IRB members are provided with access to all required materials. The Primary Reviewer completes the applicable reviewer's checklist to determine whether the research meets the criteria allowing continuing review using the expedited procedure and, if so, whether the research continues to meet the regulatory criteria for approval.

If research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, unless it is NOT FDA-regulated, and it has progressed to the point that it involves only one or both of the following:

- Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
- Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care; and in limited circumstances described by expedited review categories (8) and (9). It is also possible that research activities that previously qualified for expedited review have changed or will change, such that expedited IRB review would no longer be permitted for continuing review.

If the research no longer requires continuing review under the Common Rule and the IRB reviewer determines that continuing review is required, the reviewer shall document the rationale in the checklist.

6. IRB Actions after Continuing Review

As with initial review, at the time of continuing review/limited review the convened IRB or IRB member(s) conducting expedited review may take any of the following actions:

- Approval;
- Approved with Conditions; or
- Deferred/Modifications or Information Required.

Additionally, the convened IRB may vote to disapprove the study. If an IRB member conducting expedited review, or limited IRB review using expedited procedures, believes that the study should be disapproved, it will be referred to the convened board for review. If the IRB has significant concerns, the IRB may vote to suspend or terminate the research.

If a research study receives Approval with Conditions at the time of the continuing review/limited review, the IRB will specify whether any conditions need to be satisfied before an investigator can continue research activities related to those conditions or requirements that must be adhered to until the conditions of approval have been satisfied. For example, if at the time of continuing review/limited review, the IRB requires the investigator to change the research protocol to include a specific new procedure for screening prospective subjects, the IRB could approve the research with the following condition: research activities involving currently enrolled subjects may continue, but no new subjects may be enrolled until a designated IRB member reviews a revised protocol and verifies that the protocol includes the new

screening procedure. Additionally, the IRB may specify a time period, such as 1, 2, or 3 months, for the condition/s to be satisfied if the activity with conditions is not begun/restarted until approval is granted.

7. Lapses in Continuing Review

The regulations permit no grace period or approval extension after approval expiration. Research that continues after the approval period has expired is research conducted without IRB approval. If re-approval does not occur within the time set by the IRB, all research activities must stop, including recruitment (media advertisements must be withdrawn), enrollment, consent, interventions, interactions, and data collection. This will occur even if the investigator has provided the continuing information before the expiration date. Therefore, investigators must submit their continuing review materials enough in advance of expiration to allow enough time for IRB review before the expiration date.

The lapse of IRB approval due to a failure to complete continuing review and obtain re-approval prior to expiration of the prior approval does not ordinarily constitute a suspension or termination of IRB approval, for federal reporting purposes; however, the failure to meet continuing review obligations may be grounds for suspension or termination of the research. If the IRB notes a pattern of non-compliance with the requirements for continuing review (e.g., an investigator repeatedly or deliberately neglects to submit materials for continuing review in a timely fashion or the IRB itself is not meeting the continuing review dates), the IRB should determine the reasons for the non-compliance and take appropriate corrective actions. The IRB must report to FDA/OHRP any instance of serious or continuing non-compliance with FDA regulations or IRB requirements or determinations.

When the IRB approves research with conditions at the time of continuing review before the expiration date of the preceding IRB approval period, IRB approval does not lapse if the investigator needs additional time (beyond the date on which the preceding IRB approval would have expired) to satisfy some or all the IRB's conditions. However, the investigator and the IRB should make every effort to resolve any conditions and finalize approval in as timely a manner as possible.

The HRPO is responsible for notifying the investigator of the expiration of approval and that all research activities must stop.

However, the IRB recognizes that, while enrollment of new subjects cannot occur after the expiration of IRB approval, temporarily continuing participation of already enrolled subjects may be necessary or appropriate, for example, when the research interventions hold out the prospect of direct benefit to the subjects, or when withholding those interventions or safety monitoring procedures, would place subjects at increased risk. In these instances, the investigator should, at the earliest opportunity, contact the HRPO and submit a request to continue those research activities that are in the best interests of subjects. Such a request should specifically list the research activities that should continue, and provide justification, and indicate whether the request applies to all or only certain subjects. The IRB Chair or designee will review the request and provide a determination regarding what activities, if any, may continue during the lapse. Such a determination may include a time limit or other conditions or restrictions. If the IRB decides that already enrolled subjects should continue to receive the interventions that were being administered to subjects under the research project, data collection (especially safety information) should also continue for such subjects.

When there is insufficient time to obtain an IRB determination (e.g., the study regimen includes daily administration of an investigational agent), the investigator may make an initial determination, in consultation with the subject's treating physician, if appropriate. In such cases, the investigator must, as soon as possible, contact the HRPO and submit a request for confirmation that the IRB agrees with the determination. The IRB Chair or designee will review the request and provide a determination. In the event that the IRB does not agree with the investigator's determination, or only agrees in part (e.g., agrees that some but not all of the activities are in the best interests of subjects), the IRB will notify the

investigator who must then comply with the IRB's requirements or request a re-review of the determination by providing additional justification or information that the IRB may not have considered.

J. Modification of an Approved Protocol

Investigators may wish to modify or amend their approved applications. Investigators must seek IRB approval before making any changes, no matter how minor, in approved research - even though the changes are planned for the period for which IRB approval has already been given - unless the change is necessary to eliminate an immediate hazard to the subject (in which case the IRB must then be notified at once).

Modifications may be permanent (e.g., a protocol modification that makes changes to the protocol for all remaining subjects) or temporary (protocol exceptions) circumstances in which the specific procedures called for in a protocol are not in the best interests of a specific patient(s)/subject(s) (examples: patient/subject is allergic to one of the medications provided as supportive care; patient/subject is not eligible in a direct benefit study). Usually, an exception is a change that is planned and has prior agreement from the sponsor.

Investigators should consider whether the proposed changes to the research alter the original scope, purpose, or intent of the research. When the research itself is fundamentally changed, the IRB will typically require a new study application rather than allow such changes to be made through a modification to the existing research plan.

This requirement applies to all research approved by the IRB, including any aspects of exempt research subject to limited IRB review, and research for which continuing review is not required (Section VII).

1. Procedure for Requesting a Protocol Modification

Investigators must promptly report proposed changes in a research activity to the IRB and must conduct the research activity in accordance with the terms of the IRB approval until any proposed changes have been reviewed and approved by the IRB, except when necessary to eliminate apparent immediate hazards to the subject.

Investigators must submit documentation to inform the IRB about the proposed changes to the study, including, but not necessarily limited to the following:

- Completed “Modification Request with Exceptions” form;
- For protocol modifications, a revised protocol/research plan and/or study material (in tracked changes or with a detailed summary of changes and the locations of those changes);
- Revised consent/parental permission/assent documents (if applicable) or other documentation proposed to be provided to subjects when the proposed change(s) to the research might relate to their willingness to continue to participate in the study; and
- Any other relevant documentation provided by the sponsor or coordinating center.

HRPO staff will review the submission and make an initial determination whether the proposed changes may be approved through an expedited review process, if the changes are minor, or whether the modification warrants convened board review. The reviewer(s) using the expedited procedure has the ultimate responsibility to determine that the proposed changes may be approved through the expedited review procedure and, if not, must refer the research study for convened board review.

2. Convened Board Review of Modifications

When a proposed change in a research study is not minor, then the IRB must review and approve the proposed change at a convened meeting before the change can be implemented. The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB should be promptly informed of the change following its implementation and should review the change to determine that it is consistent with ensuring the subject’s continued welfare.

All IRB members are provided and review all documents provided by the investigator.

At the meeting, the primary reviewer presents an overview of the proposed modifications and assists the IRB Chair in leading the IRB through the completion of the regulatory criteria for approval. The IRB will also determine whether the research with the proposed modifications continues to meet the regulatory criteria for approval.

When the IRB reviews modifications to previously approved research, the IRB considers whether information about those modifications might relate to participants' willingness to continue to take part in the research and if so, whether to provide that information to future/current/past participants.

3. Expedited Review of Modifications

An IRB may use expedited review procedures to review minor changes in ongoing previously- approved research during the period for which approval is authorized. An expedited review may be carried out by the IRB Chair and/or experienced designee(s) among the IRB members.

The reviewer(s) completes the **"**applicable reviewer's checklist**"** checklist to determine whether the modifications meet the criteria allowing review using the expedited procedure, and if so, whether the research with the proposed modifications continues to meet the regulatory criteria for approval.

The reviewer will also consider whether information about those modifications might relate to future/current/past participants' willingness to continue to take part in the research and if so, whether to provide that information to participants.

4. Possible IRB Actions after Modification Review

As with initial review, at the time of continuing review, the convened IRB or IRB member(s) conducting expedited review may take any of the following actions:

- Approval;
- Approved with Conditions; or
- Deferred/Modifications or Information Required.

Additionally, the convened IRB may vote to disapprove the proposed changes. If an IRB member conducting expedited review or limited IRB review using expedited procedures believes that the proposed modifications should be disapproved, they will refer the proposed modification to the convened board for review. If the proposed changes raise significant concerns on the part of the IRB, the IRB may vote to suspend or terminate the research (Section VIII).

5. Protocol/Research Plan Exceptions

Protocol/research plan exceptions are circumstances in which the investigator wishes to deviate from eligibility criteria or one or more of the specific procedures called for in a research plan. Unlike modifications that apply to all subsequent subjects in the research, a protocol/research plan exception only applies to a specific subject or group of subjects.

Exceptions are planned, and the investigator gets approval from the sponsor and the IRB ahead of time. For sponsored research, prior approval from the sponsor is generally required. Depending on the nature of the exception, an expedited review is possible. In order to be approved under expedited review exceptions must not increase risk or decrease benefit, change the risk/benefit analysis, negatively affect the participant's rights, safety, welfare, or negatively affect the integrity of the resultant data. Review of exceptions that represent more than minor changes or risks levels greater than minimal must be done at a convened meeting of the IRB.

Procedures for exceptions are the same as for a protocol modification. The investigator must submit a

"Modification Request with Exceptions" form, along with any revised documentation to be presented to the subject(s) and documentation of sponsor approval, if applicable.

The only time a protocol/research plan exception would not require prior sponsor or IRB approval is when the exception is necessary to avoid an immediate hazard to the participant. In such cases, the exception must be submitted to the IRB as soon as possible.

K. Closure of Research Studies

The completion or early termination of the study is a change in activity and must be reported to the IRB. Although subjects will no longer be "at risk" under the study, a final report to the IRB allows it to close its files as well as providing information that may be used by the IRB in the evaluation and approval of related studies.

Studies may be closed when the involvement of human subjects ceases (interventions, interactions, observations, and the gathering, use, study, and analysis of identifiable private information, including specimens, are all complete). Studies may be closed when the only remaining research activity involves the analysis of unidentifiable individual level data, or aggregate data sets.

For multi-center research, the study may be closed once all research activities (as above) are complete at Presbyterian and any sites for which the IRB is the "IRB of record." If the investigator is serving as the lead investigator or Presbyterian is the coordinating center, please note that the study must remain open if the coordinating center is still receiving, studying, using, or analyzing identifiable private information from other sites (even if local interventions, interactions, observations, and data gathering is complete).

Investigators may submit study closures to the IRB on a "Study Closure Report" form. With closure submissions, the investigator must provide a summary of the research activity and any findings available at that time.

Investigators may maintain the data that they collected, including identifiable private data, if this is consistent with the IRB-approved research plan. However, investigators may not conduct any additional analysis of identified data without re-applying for IRB approval. Investigators must continue to protect the confidentiality of the data as described to the IRB and honor any other commitments that were agreed to as part of the approved research including, for example, future use of data or specimens, provision of research results to subjects, and provision of any outstanding payments or compensation.

The IRB will review study closure reports, typically by expedited review, and either approve the closure of the study or request additional information or confirmation of facts from the investigator.

L. Reporting IRB Actions

All IRB actions are communicated to the investigator, and/or designated contact person for the research study, in writing within ten (10) working days via a determination letter prepared by the HRPO staff and signed by the IRB Chair. For an approval, along with written notification of approval, a copy of the approved consent/assent/permission form/s (if applicable) containing the IRB stamp with the dates of the approval and expiration will be sent to the investigator. For approval with conditions, the notification will include a listing of the conditions that must be satisfied. For a deferral, the notification will include the modifications and/or clarifications required along with the basis for requiring those modifications. For a disapproval, termination, or suspension, the notification will include the basis for making that decision and give the investigator an opportunity to respond in person or in writing.

All letters to investigators must be filed electronically in the Presbyterian HRPP electronic submission platform. The IRB reports its findings and actions to the organization in the form of its minutes, which are distributed by HRPO staff to the HRPO Director, Compliance Office, Research and Sponsored Awards Office, and the IO.

M. Failure to Respond

Failure to submit a response to IRB requirements within 90 days of the IRB date of determination may result in administrative closure of the IRB file (for new study submissions). When research has IRB approval, and an investigator fails to respond to requirements related to a subsequent submission (e.g., a request for modification), the IRB Chair or HRPO staff will review the circumstances, including any potential impact on human subjects, and will contact the investigator to try to secure a response. If the investigator continues to be unresponsive, the failure of the investigator may be considered non-compliance and will be reviewed in accordance with the procedures in Section XVII. The investigator will receive notification, including an explanation. An extension beyond 90 days may be granted by the IRB if enough cause is provided by the investigator.

N. Appeal of IRB Decisions

When an IRB research study is disapproved or deferred, the IRB will notify the investigator in writing about the specific deficiencies and the modifications that are necessary for appropriate IRB approval. The IRB shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing within ten business days. Similarly, when research is suspended in part or in full, or terminated, the IRB will notify the investigator in writing of the suspension or termination and the reasons for its decision.

In cases where there is disagreement between the IRB and the investigator regarding the nature and extent of requested changes or the necessity of or basis for a suspension or termination, and these disagreements cannot be resolved, the investigator and/or the IRB may make an appeal to the IO for a resolution of the matter. The IO may organize a meeting to help facilitate discussion between the IRB and the investigator. While the IO may provide input and make recommendations to the investigator and IRB for expeditious resolution of the matter, final determinations for approval/disapproval remain under the purview of the IRB.

Because the IO is responsible for policies and procedures followed by the IRB, the IO may review IRB decisions to ensure that the decision-making process is appropriate. If the IO has concerns regarding the process that the IRB has followed in their determination, he/she may request that the IRB reconsider the decision. However, the IO cannot overrule an IRB decision.

1. **Research Previously Approved by another IRB**

   When an investigator transfers research to Presbyterian that was previously approved by another IRB, the investigator must submit the research for review under the procedures covered by this section. No research activity may take place under Presbyterian auspices without the appropriate review and approval.

   For research transfers where stopping research interventions might harm subjects, the investigator can request permission from the IRB to continue research interventions under the oversight of the prior organization's IRB until final Presbyterian approval is obtained.

VIII. STUDY SUSPENSTION, TERMINATION, AND INVESTIGATOR HOLD

A. Suspension / Termination

IRB approval may be suspended or terminated if research is not being conducted in accordance with IRB or regulatory requirements or has been associated with unexpected problems or serious harm to subjects.

In the event of an unanticipated problem, serious or continuing noncompliance, or a suspension or termination of approval, the IRB may require corrective or disciplinary action including, but not limited to, the following:

- A modification of the protocol or information disclosed in the informed consent document and process;
- information be provided to past participants;
- current participants be informed if the information may relate to their willingness to participate;
- re-consenting of currently enrolled participants;
- more frequent continuing review
- monitoring of the consent process or research project by a third party; and
- requiring additional education.

The IRB or IO may seek counsel from other institutional areas (e.g., legal counsel) in determining corrective action plans

The IRB will also review the underlying reason that caused the noncompliance or unanticipated problem to occur or for which a suspension or termination is imposed and may require that additional corrective action be taken to prevent subsequent occurrences. Corrective action may include, but is not limited to, the following:

- requiring additional education of the investigator;
- clarifying existing policies or implementing new policies;
- enhancing overall educational activities provided to investigators.

Suspension of IRB approval is a directive of the convened IRB or IRB Chair to temporarily stop some or all previously approved research activities. Suspensions made by the IRB Chair must be reported to a meeting of the convened IRB. Suspended research studies remain open and require continuing review. Investigators must continue to provide reports on adverse events and UAPs to both the IRB and sponsors just as if there had never been a suspension (i.e., all events that need to be reported during a study need to continue to be reported during the suspension period).

When approval of some or all research activities is suspended by the IRB, the IRB will consider notification of subjects and any actions necessary to ensure that the rights, safety, and welfare of subjects are appropriately protected.

The IRB shall notify the investigator in writing of suspensions and shall include a statement of the reasons for the IRB's actions and any requirements or conditions associated with the suspension (e.g., notification of subjects). The investigator shall be provided with an opportunity to respond in person or in writing. Suspensions of IRB approval must be reported promptly to the IO, sponsors (including federal department or agency heads), and federal oversight agencies according to applicable federal and organizational requirements.

Termination of IRB approval is a directive of the convened IRB to permanently stop all activities in a previously approved research study. Terminated research studies are closed and no longer require continuing review. Terminations of IRB approval of research studies must be made by the convened IRB. When study approval is terminated by the IRB, in addition to stopping all research activities, the IRB will consider notification of subjects and any actions necessary to ensure that the rights, safety, and welfare of subjects are appropriately protected.

The IRB shall notify the investigator in writing of a study termination and shall include a statement of the reasons for the IRB's actions and any requirements associated with the termination (e.g., notification of subjects). The investigator shall be provided with an opportunity to respond in person or in writing.

Terminations of IRB approval must be reported promptly to the IO, sponsors including federal department or agency heads, and federal oversight agencies according to applicable federal and organizational requirements (Section XVI).

Appeals can be made by a principal investigator on a decision to suspend or terminate a study. This appeal must be made in writing within ten working days following receipt of the written notice of suspension or termination (Section VII.M).

Reinstatement of project that has been suspended, the investigator must satisfactorily resolve any pending issues required by the IRB.

Suspensions and terminations involving exempt research and minor modifications of nonexempt research (e.g., expired training, personnel modifications, etc.) can be reinstated by the IRB Chair/ Co- Chair upon receipt and approval of the modification.

Suspensions and terminations of nonexempt approved research require review by the Convened IRB meeting and will be decided by a majority vote of the Convened IRB.

The possible actions that the IRB may take include, but are not limited to:

- Reinstate approval;
- Reinstate approval with stipulations or additional restrictions; or
- Continue suspension.

B. Investigator Hold

An investigator may request an investigator hold when the investigator wishes to stop temporarily or permanently some or all approved research activities. Such a hold is initiated by an investigator but must be immediately reported to the IRB so that the IRB can consider whether any additional actions are necessary to protect subjects. Administrative holds must not be used to avoid reporting deficiencies or circumstance that otherwise require reporting by federal agencies. Investigator holds are not equivalent to IRB suspensions or terminations and do not meet reporting requirements to OHRP, FDA and other federal agencies. During administrative hold, the research remains subject to continuing review and requirements for reporting non-compliance and unanticipated problems involving risks to subjects or others.

1. **Procedures**

   Investigators must notify the IRB in writing with the following information:

   - A statement that they are voluntarily placing a study on hold;
   - The reason(s) for the hold;
   - A description of the research activities that will be stopped;
   - Proposed actions to be taken to protect current participants; and
   - A description of actions that will be taken prior to IRB approval of proposed changes in order to eliminate apparent immediate risk of harm.

   Upon receipt of written notification from the investigator the HRPO/IRB Coordinator in consult with the IRB chair, reviews the form for completeness, contacts the investigator, if necessary, for additional information and makes a preliminary assessment of whether the request for administrative hold is appropriate.

   The IRB Chair and HRPO/IRB Coordinator, in consultation with the investigator, determines whether any additional procedures need to be followed to protect the rights and welfare of current participants.

   - Notification of subjects of the administrative hold through oral or written communications approved by the IRB.
   - Other measures to protect the rights and welfare of subjects and ensure the safe withdrawal of subjects (e.g., more frequent monitoring of research or consent process.

   The IRB Chair and HRPO/IRB Coordinator, in consultation with the investigators, determine how and when currently enrolled participants will be notified of the hold if applicable. If action is needed before the convened IRB meeting, the request is referred to the IRB Chair or designee. If not, it is added to the agenda of the next meeting. The action of the IRB chair or designee is reviewed by the convened IRB at

the next meeting.

The Investigator will receive a decision of the request in writing via the Presbyterian HRPP electronic submission platform. Determinations that may be made by the IRB (or IRB chair or designee) include:

- Approval of the administrative hold and action plan provided by the investigator;
- Approval of the administrative hold following acceptance by the investigator of additional IRB-mandated corrective actions;
- Request for further information;
- Disapproval of the administrative hold;
- Suspension or termination of part or all of the research

When PI is ready to resume research activities and the issues that led the PI to initiate the Administrative Hold have been resolved, the PI must notify the IRB, by submitting the "modification form" via Presbyterian HRPP electronic submission platform. The PI must await approval notification from the IRB before resuming research activities.

C. Protection of Currently Enrolled Participants

Before a study hold, termination, or suspension is put into effect, the Chair, HRPO Coordinator, or IRB considers whether any additional procedures need to be followed to protect the rights and welfare of current participants. Such procedures might include the following:

- Transferring participants to another investigator/site;
- Making arrangements for clinical care outside the research;
- Allowing continuation of some research activities under the supervision of an independent monitor;
- Requiring or permitting follow-up of participants for safety reasons;
- Requiring adverse events or outcomes to be reported to the IRB and the sponsor;
- Notification of current participants; or
- Notification of former participants.

IX. RELIANCE ON AN EXTERNAL IRB

This policy applies to all Presbyterian Health Services-affiliated facilities and entities including, but not limited to, all corporate departments, groups, and divisions (collectively "Presbyterian") engaged in human subject research. It applies to all members of the workforce including, but not limited to, physicians, team members, contractors, and volunteers.

Research projects ceded to the National Cancer Institute (NCI) – Central Institutional Review Board (CIRB) are only subject to Section IX.D of this Policy, unless otherwise explicitly noted to apply to NCI-CIRB research projects.

A. Purpose

All human subject research conducted under the auspice of Presbyterian Health Services must be reviewed and approved by a Presbyterian-approved IRB before research may begin. This includes human subject research conducted at an external institution.

B. Policy

In an effort to reduce duplicative study submissions and minimize the impact of multiple IRB reviews for the same protocol, the Presbyterian Human Research Protections Office (HRPO) allows external IRB reliance for research that is federally funded, research conducted under existing agreements, and for other research depending on risk

and merit.

The reviewing IRB must comply with federal regulations for IRB review and the relying institution shall ensure the conduct of the study meets requirements under the institution's Federalwide Assurance.

Both OHRP and the FDA permit an IRB the option to rely on review and study oversight of another IRB. When this is the intent, the two institutions enter into a Reliance Agreement also known as an IRB Authorization Agreement (IAA). This agreement is executed between the reviewing IRB (IRB of record) and one or more relying institutions.

1. **Reliance Requirements**

   Presbyterian Health Investigator-initiated research projects are not permitted to be ceded to an External IRB.

   Studies required to use a single IRB (sIRB) pursuant to funder policies or applicable law (e.g., NIH-funded multisite studies required to use a single IRB pursuant to the NIH Policy on the Use of Single IRB for Multisite Research or Common Rule changes effective in 2020) will be ceded to the designated external IRB in accordance with such requirements.

   The HRPO is responsible for determining if a reliance agreement is appropriate. If found to be appropriate, written agreements outlining specific responsibilities of each IRB/institution must be executed. This agreement, at a minimum, shall outline the responsibilities of parties, including the requirements for the IRB Chair and the HRPO to be notified of all actions of the external IRB.

   - Documentation of a Reliance Agreement between Presbyterian HRPO and an external IRB may be initiated by either IRB/institution.
   - Review by Presbyterian IRB legal is required prior to Institutional Official (IO) signature
   - All reliance agreements require Presbyterian IRB and Signatory Official of the external IRB signature

   Reliance agreements for external IRB review must include ALL applicable ancillary reviews (i.e., Radiation Safety Committee (RSC), Biosafety Committee, Hazardous Substances Committee (HSC)).

   Presbyterian HRPO and IRB remains responsible for overseeing compliance at the local level. Responsibilities may include, but are not limited to:

   - Privacy responsibilities;
   - Initial and ongoing research training and credentialing of all investigators and key personnel in accordance with Presbyterian requirements;
   - Conflicts of Interest (COI) responsibilities;
     - ❖ All COIs will be reviewed according to the HRPP Conflict of Interest policy. Any required COI management plan will be documented and are to be shared with the external IRB to be considered as part of its study approval.
   - Maintaining compliance with state, local, tribal law passed by the official governing body of an American Indian or Alaska Native tribe, or institutional requirements related to the protections of human subjects. When in conflict with the external IRB determinations, the most restrictive requirements apply;
   - Providing a mechanism to receive and address concerns from local study participants and other about the conduct of the research;
   - Assuring that study-specific incidents, experiences, or outcomes that appear to rise to the level of an unanticipated problem and/or serious or continuing noncompliance are reported to the external IRB; and
   - Reporting external IRB determinations of unanticipated problems and serious and/or continuing noncompliance to the OHRP and/or FDA as required by applicable law.

The external IRB must comply with the responsibilities set out in the Reliance Agreement between Presbyterian HRPO and the external IRB. Such responsibilities may include, but are not limited to:

- Conduct review of the ceded human subject research according to applicable law; and
- Review all Event Reports and notify Presbyterian Health Service IRB directly, within 48-hours of the following determinations:
  - ❖ Unanticipated Problems Involving Risk to Subjects or Others (UPIRSOs);
  - ❖ Suspension or termination of IRB approval; and
  - ❖ Serious and/or continuing noncompliance.
- The external IRB is responsible for reporting all UPIRSOs, Suspension, Termination, Serious and/or Continuing noncompliance determinations made by the external IRB to applicable federal agencies. Presbyterian HRPO shall be included on such communications;
- Notify Investigators and Presbyterian HRPO, in writing, of all determinations made of conducted reviews and make relevant IRB minutes available up request; and
- Specify a contact person and provide contact information for the external IRB.

2. Institutional Official (IO) Authority

The Institutional Official (IO) has the authority to suspend or terminate a study ceded to an external IRB at any time. The Presbyterian IRB shall notify the PI, external IRB, and applicable federal authorities of all suspensions and terminations in a timely manner.

C. Procedure

1. Initial Submission Process

If a research project meets the criteria for relying on an external IRB, as outlined above, the Investigator may submit to the Presbyterian Health Services IRB for pre-review within the electronic submission system, parallel to the execution of the Reliance Agreement.

- The Principal Investigator (PI) and Key personnel are responsible for presenting all applicable boilerplate language requirements, as set by the Presbyterian IRB prior to the sponsor prior to pre-review. Any funder/sponsor modifications of local boilerplate language requirements should be communicated to the Presbyterian IRB during pre-review.
- The Principal Investigator and Key Personnel are responsible for submitting a complete submission within the electronic submission system. The Presbyterian IRB holds the ability to request clarification/modification/more information to comprehensively review and apply state, local, and institutional policies for the research project.

The Presbyterian IRB will provide the PI with an *Authorization to Rely* letter upon completion of the pre-review. This letter will include:

- Authorization to rely on the External IRB per the Presbyterian IRB review; and
- Documentation of Presbyterian IRB responsibilities completed per the Reliance Agreement; and
- Information regarding any local organizational issues relevant to the research protocol or maintaining compliance with state, local, or institutional requirements related to the protection of human subjects. When in conflict with the external IRB, the most restrictive requirements apply.

The PI is required to submit the *Authorization to Rely* letter, and any COI management plan as applicable, to the external IRB. The PI is not permitted to submit any research project to an external IRB until:

- Operational Approval is obtained; and
- A Reliance Agreement is fully executed; and

- An *Authorization to Rely* letter is issued by the Presbyterian IRB.

Upon receipt of external IRB approval for Presbyterian engagement, the PI is responsible for submitting documentation of external IRB approval via the PHS electronic submission platform within 30-days.

- Any participant facing documents which received modification/revisions from the external IRB shall additionally be included for Presbyterian IRB acknowledgement.

2. Additional Submission Process

Principal Investigators (PI) are required to provide the following notifications to the Presbyterian IRB via the electronic submission platform for studies ceded to external IRBs prior to notifying the External IRB:

- Change in Principal Investigator; and
- Personnel modifications and any modifications that add or remove study procedures; and
- Change in Conflict of Interest for any Investigator and/or Key personnel; and
- Changes impacting Boilerplate Language and/or Privacy requirements.

PIs are required to provide the following notifications to the Presbyterian IRB via the electronic submission platform for studies ceded to external IRB in parallel to the external IRB:

- Possible Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOs); and
- Privacy breaches; and
- Possible noncompliance; and
- Research Participant complaints.

PIs are required to provide the following notifications to the Presbyterian IRB via the electronic submission platform for studies ceded to the external IRB post-external IRB approval:

- Continuing Review(s); and
- Amendment/Modification/Revision(s); and
  - ❖ All Amendment/Modification/Revision(s) can be submitted with the Continuing Review documentation except for those documented above.
- Determination by the external IRB of instances of serious and/or continuing noncompliance, UPIRSOs, research misconduct, suspension, and/or termination of research; and
  - ❖ Such determination(s) must be reported by the PI within 48-hours of receipt.
- Closure Report.

3. Research Quality Assurance

Studies that are overseen by an external IRB are subject to the same quality assurance reviews as any other research project conducted under the auspices of Presbyterian Health Services, in accordance with applicable institutional policies.

A quality assurance review may uncover reportable events that were not previously reported to the external IRB or Presbyterian IRB, in which case the reportable event (i.e., serious, and/or continuing noncompliance or UPIRSOs) will be referred to the Presbyterian IRB, and the PI will be responsible for reporting the event(s) and Presbyterian IRB determination(s) to the external IRB in accordance with its policies.

D. National Cancer Institute Central IRB (NCI-CIRB)

1. Policy

The Presbyterian HRPP will submit and maintain all institutional context considerations for the signatory

institution and all component and/or affiliate institutions within the Annual Signatory Institution Worksheet.

The Principal Investigator is responsible for submitting and maintaining their Annual Principal Investigator Worksheet in compliance with NCI-CIRB SOPs.

The Principal Investigator is responsible for submitting a Study-Specific Worksheet (SSW) with the local context consideration provided within the Annual Signatory Institution Worksheet and the Annual Principal Investigator Worksheet.

2. Procedure

Presbyterian HRPP shall retain all responsibilities indicated within the NCI-CIRB SOPs.

All individuals engaged in research projects reviewed by NCI-CIRB will be required to be added to the Presbyterian Health Services NCI-CIRB CTSU Roster. Such access will be granted by the Presbyterian HRPP.

- Research managers within respective departments are responsible for maintaining Presbyterian's NCI-CIRB CTSU Roster once access has been given.

Principal Investigator (PI) is required to provide the following notifications to the Presbyterian IRB via the electronic submission platform for studies ceded to NCI-CIRB prior to notifying the External IRB:

- Change in Principal Investigator; and
- Personnel modifications; and
- Change in Conflict of Interest for any Investigator and/or Key personnel; and
- Changes impacting Boilerplate Language and/or Privacy requirements; and
- Privacy breaches; and
- Possible noncompliance.

The PI is required to provide the following notifications to the Presbyterian IRB via the electronic submission platform for studies ceded to external IRB in parallel to the external IRB:

- Possible UPIRTSOs; and
- Research Participant complaints.

PIs are required to provide the following notifications to the Presbyterian IRB via the electronic submission platform for studies ceded to the external IRB post-external IRB approval:

- Initial Approval; and
- Continuing Review(s); and
- Amendment/Modification/Revision(s); and
  - ❖ All Amendment/Modification/Revision(s) can be submitted with the Continuing Review documentation except for those documented in Section VI.B.3.
- Determination by the external IRB of instances of serious and/or continuing noncompliance, UPIRSOs, research misconduct, suspension, and/or termination of research.
  - ❖ Such determination(s) must be reported by the PI within 48-hours of receipt.
- Closure Report.

X. DOCUMENTATION AND RECORDS

Presbyterian prepares and maintains adequate documentation of the IRB's activities. All records are accessible for inspection and copying by authorized representatives of the FDA, OHRP, sponsors, and other authorized entities at reasonable times and in a reasonable manner. The HRPO maintains attendance rosters and past meeting minutes

in the Presbyterian HRPO electronic submission platform and on the PHS shared drive.

A. HRPO / IRB Records

HRPO/IRB records include, but are not limited to the following:

- Written policies and operating procedures;
- IRB membership rosters;
- Training records documenting that investigators, IRB members, and HRPO/IRB staff have fulfilled Presbyterian's human subject training requirements;
- IRB correspondence including reports to regulatory agencies;
- IRB protocol files
- Convened IRB meeting minutes;
- Documentation of review by another institution's IRB when appropriate (e.g., Reliance Agreements, etc.);
    - ❖ For non-exempt research involving human subjects covered by the Common Rule (or exempt research for which limited IRB review takes place at an institution in which IRB oversight is conducted by an IRB that is not PHS, PHS and the organization operating the IRB shall document the PHS's reliance on the IRB for oversight of the research and the responsibilities that each entity will undertake to ensure compliance with the requirements of this policy (e.g., in a written agreement between PHS and the IRB, by implementation of an institution-wide policy directive providing the allocation of responsibilities between PHS and an IRB that is not affiliated with the institution, or as set forth in a research protocol);
- Documentation of cooperative review agreements (e.g., Memoranda of Understanding, etc.);
- Federal Wide Assurances;
- IRB Registrations; and
- Documentation of complaints and any related findings and/or resolution.
- Documentation of the rationale for an expedited reviewer's determination that research appearing on the expedited review list is more than minimal risk.
- Documentation of the rationale for conducting continuing review of research that otherwise would not require continuing review.

B. IRB Study Files

Accurate records are maintained of communications to and from the IRB and are kept on file. The IRB maintains a file in the Presbyterian HRPO electronic submission platform for each study that it receives for review. Study files include, but are not limited to, the following:

- Documentation of exemptions including exemptions related to emergency uses and exemptions with limited IRB review (documentation of verified exemptions consists of the reviewer's citation of a specific exemption category and written concurrence that the activity described in the investigator's request for satisfies the conditions of the cited exemption category as detailed in Section 7; when limited IRB review is required the documentation will include an IRB action for the aspects of the research subject to limited IRB review);
- Research plan and all other documents submitted as part of a new study application;
- Research plan and all other documents submitted as part of a request for continuing review or closure of research application;
- Documents submitted and reviewed after the study has been approved, including modification requests, protocol/research plan exception requests, proposed advertisements, data and safety monitoring reports, and reports of protocol/research plan violations, complaints, non-compliance, unanticipated adverse device events and UAPs;
- Copy of IRB-approved consent/assent/permission forms or waivers;
- DHHS-approved sample consent form document and research plan when they exist;

- IRB reviewer forms (when expedited review procedures are used);
- Documentation of scientific or scholarly review (if available);
- Documentation of type of IRB review. For exempt determinations and expedited review, this will include the category under which the review is allowed;
- For expedited review, documentation of any findings and determinations required by the regulations and study-specific findings supporting those determinations, including, but not limited to, waiver or alteration of consent, waiver of documentation of consent, research involving pregnant women, fetuses, and neonates, research involving prisoners, and research involving children (for research reviewed by the convened board these findings and determinations are also recorded in the minutes);
- For expedited review, documentation of the risk determination (for FDA-regulated research) or rationale for a reviewer's determination that research that falls within the expedited categories is greater than minimal risk, and the period of approval, when applicable (for research reviewed by the convened board these determinations are also recorded in the minutes);
- Documentation of all IRB review actions;
- Notification of expiration of IRB approval to the investigator and requirements related to the expiration;
- Notification of suspension or termination of research;
- Copies of IRB determination letters and forms that describe any requirements that the investigator must satisfy before beginning the study;
- IRB correspondence to and from research investigators;
- All other IRB correspondence related to the research;
- For studies evaluating the safety or effectiveness of medical devices, documentation of determination by IRB of significant risk/non- significant risk;
- Reports of UAPs involving risk to subjects or others; or
- Documentation of audits, investigations, reports of external site visits; and
- Any statements of significant new findings provided to subjects.
- The informed consent form must be posted on the Federal website after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subjects, as required by the protocol.

C. The IRB Minutes

Proceedings are written and available for review by the next regularly scheduled IRB meeting. Once accepted by the members, the minutes must not be altered by anyone, including a higher organizational authority. A copy of IRB-approved minutes for each IRB meeting will be distributed by HRPO staff to appropriate HRPP leadership and the IO.

Minutes of IRB meetings are considered confidential and must contain enough detail to show:

- Attendance (Note: The attendance list shall include those members present at the beginning of the meeting. The minutes will indicate, by name, those members who enter or leave the meeting. The vote on each action will reflect the numbers of members present for the vote on that item. Members who recuse themselves because of conflict of interest are listed by name and the reason documented.). including the following:
  - ❖ Names of members present at the start of the meeting;
  - ❖ Names of members or alternate members who are participating through videoconference or teleconference and documentation that those attending through videoconferencing or teleconferencing received all pertinent material prior to the meeting and were able to participate in all discussions actively and equally;
  - ❖ Names of alternates attending in lieu of specified (named) absent members (alternates may substitute for specific absent members only as designated on the official IRB membership roster);
  - ❖ Names of non-voting attendees present (staff, meeting recorder, consultants, investigators, guests (non-

voting);
  - ❖ Names of members not present; and
  - ❖ Names of alternates not present.
- The presence of a quorum throughout the meeting, including the presence of one member whose primary concern is in a non-scientific area.
- Business items discussed, and any education provided.
- Continuing education.
- Actions taken, including separate deliberations, actions, and votes for each research study undergoing review by the convened IRB.
- Vote counts on these actions (total number voting; number voting for; number voting against; number abstaining; number of those recused).
- Basis or justification for actions disapproving or requiring changes in research.
- Summary of controverted issues and their resolution.
- Approval period for initial and continuing reviews, when applicable, including identification of research that warrants review more often than annually and the basis for that determination.
- The rationale for requiring continuing review of research that otherwise would not require continuing review.
- Risk determination for initial and continuing reviews, and modifications when the modification alters the prior risk determination.
- Justification for deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document.
- Study-specific findings supporting that the research meets each of the required criteria when approving a consent procedure that does not include or that alters some or all the required elements of informed consent, or when waiving the requirement to obtain informed consent altogether.
- Study-specific findings supporting that that the research meets each of the required criteria when the requirements for documentation of consent are waived.
- Study-specific findings supporting that the research meets each of the criteria for approval for vulnerable populations under any applicable Subparts.
- Exempt, significant risk/non-significant risk device determinations and the basis for those determinations.
- Determinations of conflict of interest and acceptance or modification of conflict management plans.
- Identification of any research for which there is need for verification from sources other than the investigator that no material changes are made in the research.
- Review and determinations related to interim reports, e.g., UAPs or safety reports; modification requests; report of violation/deviations; serious or continuing non-compliance; suspensions/terminations, etc.
- A list of research approved under expedited review procedures, including limited IRB reviews conducted using expedited procedures, since the time of the last such report.
- An indication that, when an IRB member or alternate has a conflicting interest (Section XXV) with the research under review, the IRB member or alternate was not present during the final deliberations or voting.
- Key information provided by consultants will be documented in the minutes or in a report provided by the consultant.

D. IRB Membership List

A membership list of IRB members will be maintained; it will identify members sufficiently to describe each member's chief anticipated contributions to IRB deliberations. The list will contain the following information about members:

- Name, address/phone (home and work), email.
- Employer, department, and title.
- Professional degrees earned.

- Employment or other relationship between each member and PHS (i.e., affiliated, or non-affiliated). To be categorized as non-affiliated, neither the member nor an immediate family member of the member may be affiliated with PHS.
- Status as scientist or non-scientist. Members whose training, background, and occupation would incline them to view scientific activities from the standpoint of someone within a behavioral or biomedical research discipline are considered a scientist for the purposes of the roster, while members whose training, background, and occupation would incline them to view research activities from a standpoint outside of any biomedical or behavioral scientific discipline are considered a nonscientist.
- Indications of experience, such as board certifications, licenses, and areas of practice enough to describe each member's chief anticipated contributions to IRB deliberations.
- Representative capacities of each IRB member; including which IRB member(s) is a prisoner representative, and which IRB members are knowledgeable about or experienced in working with children, Pregnant women, adults with impaired decision-making capacity, and other vulnerable populations commonly involved in PHS research.
- Start and end IRB term dates.
- Role of the IRB (Chair, Vice-Chair, etc.) and dates of term in office.
- For alternate members, the primary member or class of members for whom the member could substitute.

The HRPO must keep the IRB membership list current. In addition to this master list, the PHS IRB maintains a membership roster for public dissemination that includes the minimum information required by the OHRP/FDA.

E. Documentation of Exemptions

Documentation of verified exemptions consists of the reviewer's citation of a specific exempt category and written concurrence that the activity described in the investigator's request satisfies the conditions of the cited exempt category. When an exemption includes limited IRB review, the documentation will include this fact and the IRB action taken on those aspects of the research subject to limited review in accordance with the procedures described for the review procedures used (expedited or convened board) elsewhere in this manual.

F. Documentation of Expedited Reviews

IRB records for initial and continuing review by the expedited procedure must include the reviewer's verification that the study qualifies for expedited review including the specific permissible category(ies) or status as exempt but requiring limited IRB review, documentation that the activity satisfies the criteria for approval, the period of approval (when applicable), and any determinations required by the regulations including study-specific findings justifying the following determinations:

- Approving a procedure which waives or alters the informed consent process;
- Approving a procedure which waives the requirement for documentation of consent;
- Approving research involving pregnant women, human fetuses, or neonates;
- Approving research involving prisoners;
- Approving research involving children.

G. Access to IRB Records

The IRB has policies and procedures to protect the confidentiality of research information:

- Electronic IRB records are stored in the Presbyterian HRPO electronic submission platform or on a PHS shared network drive which is accessible only to authorized users. Paper IRB records are kept in secure filing cabinets in the HRPO, and doors to the HRPO are closed and locked when the rooms are unattended.
- Ordinarily, access to all IRB records is limited to the HRPO Director, IRB Chair, IRB members, HRPO/IRB staff,

authorized organizational officials, and officials of federal and state regulatory agencies (e.g., OHRP and FDA). Research investigators are provided reasonable access to files related to their research. Appropriate accreditation bodies are provided access. All other access to IRB records is limited to those who have legitimate need for them, as determined by the IO and HRPO Director.

- Records are accessible for inspection and copying by authorized representatives of federal regulatory agencies during regular business hours.
- Records may not be removed from the HRPO; however, the HRPO/IRB staff will provide copies of records for authorized personnel if requested.
- All other access to IRB study files is prohibited.

H. Record Retention

To comply with the requirements of OHRP, FDA, HIPAA, and PHS, IRB records are maintained at the facility for at least seven years after completion of the research. After that time, those records will be shredded or otherwise destroyed. IRB records for research cancelled without participant enrollment will be retained at the facility for at least three years after closure.

IRB minutes are retained until all studies that were reviewed at that meeting have been completed for at least three years. After that time, those records will be shredded or otherwise destroyed.

XI. INFORMED CONSENT

No investigator conducting research under the auspices of PHS may involve a human being as a subject in research without obtaining the legally effective, written informed consent of the subject or the subject's legally authorized representative unless a waiver of consent has been approved by the IRB in accordance with applicable regulations. The IRB will evaluate both the consent process and the procedures for documenting informed consent to ensure that adequate informed consent is obtained from participants.

The IRB will evaluate both the consent process and the procedures for documenting informed consent to ensure that adequate informed consent is obtained from participants.

The following procedures describe the requirements for obtaining consent from participants in research conducted under the auspices of PHS.

A. Definitions

Family Member. For this section, family member means any one of the following adults and legally competent persons: spouses; parents; children (including adopted children); brothers, sisters, and spouses of siblings; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

Legal Guardian. A person appointed by a court of appropriate jurisdiction.

Legally Authorized Representative (LAR). A legally authorized representative is an individual or body authorized under applicable law to provide permission on behalf of a prospective subject for the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the non-research context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research ninety-three.

Planned Emergency Research. Research that involves subjects who, are in a life-threatening situation for which available therapies or diagnostics are unproven or unsatisfactory, and because of the subject's medical condition and the unavailability of legally authorized 109 representatives of the subjects, it is generally not possible to

obtain legally effective informed consent.

Reasonable Person. A hypothetical person in society who exercises average care, skill, and judgment in conduct and who serves as a comparative standard for determining liability.

B. General Requirements

The requirement to obtain the legally effective informed consent of individuals before involving them in research is one of the central protections provided for by the Federal regulations and PHS IRB. When informed consent is required, it must be sought prospectively, and properly documented.

The informed consent process involves three key features: (1) disclosing to the prospective human subject information needed to make an informed decision; (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether to participate in the research.

Informed consent is more than just a signature on a form. It is a process of information exchange to include reading, discussion, receiving answers to any questions, and signing the consent document. The informed consent process is the critical communication link between the prospective human subject and an investigator, beginning with the initial approach of an investigator and continuing through the completion of the research study. Investigators must have received the appropriate training and be knowledgeable about the study protocol in order that they may answer questions to help provide understanding to the study participant or potential study participant. Investigators must obtain consent prior to entering a subject into a study, gathering data about a subject, and/or conducting any procedures required by the research plan, unless consent is waived by the IRB.

These informed consent requirements are not intended to preempt any applicable federal, state, local laws (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe) that require additional information to be disclosed for informed consent to be legally effective.

C. Informed Consent Process

Informed consent must be obtained under the following circumstances:

- Informed consent may only be obtained from subjects who have the legal and mental capacity to give consent. For subjects without that capacity, permission must be obtained from a legal guardian or a legally authorized representative.
- The informed consent process provides the prospective subject (or legally authorized representative) with enough opportunity to read the consent document, when applicable.
- The informed consent process shall be sought under circumstances that provide the subject (or legally authorized representative) with enough opportunity to discuss and consider whether to participate.
- The informed consent process shall be sought under circumstances that minimize the possibility of coercion or undue influence.
- The informed consent information must be presented in language that is understandable to the subject (or legally authorized representative). To the extent possible, the language should be understandable by a person who is educated to eighth grade level and layman's terms shall be used in the description of the research.
- For subjects with limited English proficiency, informed consent must be obtained in a language that is understandable to the subject (or the subject's legally authorized representative). In accordance with this policy, the IRB requires that informed consent discussions include an interpreter when the prospective subject does not understand the language of the person who is obtaining consent.
- The informed consent process may not include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights or through which the investigator, the sponsor, PHS or its employees or agents are released from liability for negligence or appear to be so released.
- The investigator is responsible for ensuring that each prospective subject is adequately informed about all

aspects of the research and understands the information provided.

D. Determining a Potential Adult Subject's Ability to Consent to Research

For the purpose of this section, a subject has the capacity to consent to their own participation in a research activity if they demonstrate an appreciation:

- that the activity is research;
- of the risks and benefits of a study;
- of the study procedures and requirements;
- of the alternatives that are available if not participating; and
- that, by choosing not to participate, this decision will be accepted without penalty.

In reaching a decision about participation, it is essential for the potential subject to demonstrate an ability to use this information in a rational manner. Thus, in considering risks, benefits, and available alternatives, subjects must show they understand the aspects of these factors that are unique to them as individuals. The decision-making capacity of a potential research subject should be evaluated when there are reasons to believe that the subject may not be capable of making voluntary and informed decisions about research participation.

The investigator and research staff must have adequate procedures in place for assessing and ensuring subject's capacity, understanding, and informed consent or assent. The IRB will evaluate whether the proposed plan to assess capacity to consent is adequate including consideration of state and local law tribal law passed by the official governing body of an American Indian or Alaska Native tribe and PHS policy.

It is often possible for investigators and others to enable persons with some decisional impairments to make voluntary and informed decisions to consent, assent, or refuse participation in research. Potential measures include repetitive teaching, group sessions, audiovisual presentations, and oral or written recall tests. Other measures might include follow-up questions to assess subject understanding, videotaping, or audiotaping of consent interviews, second opinions, use of independent consent observers, allowing a waiting period before enrollment, or involvement of a trusted family member or friend in the disclosure and decision-making process.

Both investigators and IRB members must be aware that for some subjects, their decision- making capacity may fluctuate. For subjects with fluctuating decision-making capacity or those with decreasing capacity to provide consent, periodic reevaluation of capacity and re-consent or consent for continuing participation by a legally authorized representative may be necessary.

If research participants lose or become impaired in decision-making capacity after enrollment, and this is not anticipated in the research plan, the investigator is responsible for notifying the IRB. The investigator is responsible for developing a plan for the IRB's consideration which follows the guidelines outlined above for persons with fluctuating or diminishing capacity.

Whenever the participants have the capacity to give consent (as determined by qualified professionals), informed consent should be obtained and documented in accordance with applicable laws, regulations, and policies. When participants lack the capacity to give consent, investigators may obtain consent from the legally authorized representative of a subject as required by the IRB.

When assent is possible for some or all subjects, the investigator should provide the IRB with an assent plan that describes when and how assent will be obtained, provisions that will be taken to promote understanding and voluntariness, and how assent will be documented. Under no circumstances may subjects be forced or coerced to participate.

If the investigator plans to use audio or video recordings, computer video presentations, or written materials, to promote understanding, these materials must be provided to the IRB for review. If the investigator intends to use audio or video recordings to document assent, provisions to ensure the security of the recordings should be

described to the IRB. If the investigator will use an assent form to document assent, this must be submitted to the IRB for review.

E. Elements of Informed Consent

Federal regulations address the general requirements for informed consent (45 CFR 46.116 and 21 CFR 50.25). The following are the general requirements.

Before involving a human subject in research, an investigator shall obtain the legally effective informed consent of the subject or the subject's legally authorized representative (LAR).

An investigator shall seek informed consent only under circumstances that provide the prospective subject or the LAR enough opportunity to discuss and consider whether to participate and that minimize the possibility of coercion or undue influence.

The information that is given to the subject or the LAR shall be in language understandable to the subject or the LAR.

The prospective subject or the legally authorized representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.

Except for broad consent, all *non-exempt* research requiring informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension. 45 CFR 46.116(5)(i).

Generally, the beginning of an informed consent should include a concise explanation of the following:

- The fact that consent is being sought for research and that participation is voluntary;
- The purposes of the research, the expected duration of the prospective subject's participation, and the procedures to be followed in the research;
- The reasonably foreseeable risks or discomforts to the prospective subject;
- The benefits to the prospective subject or to others that may reasonably be expected from the research; and
- Appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the prospective subject.

However, based upon the facts of an individual protocol, the IRB may require that different (or additional) information be presented at the beginning of an informed consent to satisfy this requirement.

All *non-exempt* research requiring informed consent must present information in enough detail relating to the research and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate.

No informed consent may include any exculpatory language through which the subject or the LAR is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

The following are the basic elements requirements of information to potential subjects:

- 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 must be maintained;
- 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 subject's rights, and whom to contact in the event of a research-related injury to the subject; Note: A contact phone number for the PI
- 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;
- One of the following statements when research involves the collection of identifiable private information or identifiable biospecimens:
  - ❖ A statement that identifiers might be removed from the identifiable private information or identifiable biospecimen and then, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or LAR; OR
  - ❖ A statement that the participant's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used, or distributed for future research studies.
- For FDA-regulated studies, a statement that notes the possibility that the Food and Drug Administration may inspect the records;
- For "applicable" FDA-regulated clinical trials, the following statement must be included verbatim:
  - ❖ "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

F. Additional elements of informed consent to be applied, as appropriate:

- 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 involved in the study.
- A statement that the participant's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the participant will or will not share in this commercial profit.
- A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and
- For research involving biospecimens, whether the research will (if known) or might include whole genome

sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

- A witness signature line and date are mandatory for greater than minimal risk studies to document witnessing of a study participant's signature.

G. Elements of Broad Consent for the Storage, Maintenance, and Secondary Research Use of Identifiable Private Information (PII) or Identifiable Biospecimen

Broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens (collected for either research studies other than the proposed research or non-research purposes) is permitted as an alternative to the informed consent requirements. If the subject or the legally authorized representative is asked to provide broad consent, the following shall be provided to each subject or the subject's legally authorized representative:

To be valid, the broad consent process must provide the following basic elements requirements of information to potential subjects or the subject's LAR:

- 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 statement describing the extent, if any, to which confidentiality of records identifying the subject must be maintained;
- 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;
- For research involving biospecimens, a statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
- For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen);
- A general description of the types of research that may be conducted with the identifiable private information or identifiable biospecimens. This description must include enough information such that a reasonable person would expect that the broad consent would permit the types of research conducted;
- A description of the identifiable private information or identifiable biospecimens that might be used in research, whether sharing of identifiable private information or identifiable biospecimens might occur, and the types of institutions or researchers that might conduct research with the identifiable private information or identifiable biospecimens;
- A description of the period of time that the identifiable private information or identifiable biospecimens may be stored and maintained (which period of time could be indefinite), and a description of the period of time that the identifiable private information or identifiable biospecimens may be used for research purposes (which period of time could be indefinite);
- Unless the subject or legally authorized representative will be provided details about specific research studies, a statement that they will not be informed of the details of any specific research studies that might be conducted using the subject's identifiable private information or identifiable biospecimens, including the purposes of the research, and that they might have chosen not to consent to some of those specific research studies;
- Unless it is known that clinically relevant research results, including individual research results, will be disclosed to the subject in all circumstances, a statement that such results may not be disclosed to the subject; and

- An explanation of whom to contact for answers to questions about the subject's rights and about storage and use of the subject's identifiable private information or identifiable biospecimens, and whom to contact in the event of a research-related harm.

When investigators propose research involving the use of identifiable private information and/or identifiable biospecimens research for which broad consent was obtained, the investigators must include documentation of the IRB approval for the storage or maintenance of the information or specimens and a copy of the consent form and/or other materials. The PHS IRB will review the information provided with the aid of checklist to ensure that all requirements are satisfied. The outcome of the IRB's review will be communicated to the investigator in writing following the procedures described in the PHS HRPP SOP Manual.

Note: PHS is not currently adopting broad consent as of the date of this document.

H. Documentation of Informed Consent

Informed consent must be documented using a written consent form approved by the IRB (45 CFR 46.117 and/ or 21 CFR 50.22), unless otherwise waived.

Unless the requirement for documentation of consent is waived by the IRB, informed consent must be documented using written informed consent form (ICF) approved by the IRB and signed by the subject or the subject's LAR. A written copy must be given to the person signing the ICF.

- Informed consent is documented using a written consent form approved by the IRB and signed and dated (including in an electronic format) by the subject or the subject's legally authorized representative at the time of consent. For greater than minimal risk studies, the person obtaining consent will also sign the consent form, as well as the date consent was obtained.
- A written copy of the signed and dated consent form must be given to the person signing the form. The investigator should retain the signed original in the research records.
- The informed consent form may be either of the following:
  - ❖ A written consent document that embodies the basic and required additional elements of informed consent. The consent form may be read to the subject or the subject's legally authorized representative, but the subject or representative must be given adequate opportunity to read it before it is signed; or
  - ❖ A short form written informed consent document stating that the elements of informed consent required by 45 CFR 46.116 have been presented orally to the subject or the subject's legally authorized representative.

When short form informed consent is used:

- The oral presentation and the short form written document should be in a language understandable to the subject; Except for broad consent the (i) informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension. (ii) Informed consent must present information in sufficient detail relating to the research and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might participate."
- There must be a witness to the oral presentation; and
- The IRB must approve a written summary of what is to be said to the subject (the approved full consent document may serve as this summary); and
- The short form document is signed by the subject; and
- The witness must sign both the short form and a copy of the summary; and

- The person obtaining consent must sign a copy of the summary; and
- A copy of the summary must be given to the subject or representative, in addition to a copy of the short form.

When this procedure is used with subjects who do not speak, or read, English, or have limited proficiency in oral or written English, (i) the oral presentation and the short form written document should be in a language understandable to the subject; (ii) the IRB-approved English language informed consent document may serve as the summary; and (iii) the witness should be fluent in both English and the language of the subject. When the person obtaining consent is assisted by an interpreter, the interpreter may serve as the witness. The IRB must receive all foreign language versions of the short form document as a condition of approval. Expedited review of these versions is acceptable if the protocol/research plan, the full English language informed consent document, and the English version of the short form document have already been approved by the convened IRB.

I. Special Consent Circumstances

1. Enrollment of Persons with Limited English Language Proficiency

a) Expected Enrollment

In some studies, the investigator may be able to anticipate enrollment of persons who do not speak or read, or have limited proficiency in, oral or written English. When the target subject population includes such persons or the investigator and/or the IRB otherwise anticipates that consent will be conducted in a language other than English, the IRB requires a translated consent document, and other subject materials, to be prepared. In order to ensure that translated documents are accurate, the IRB may choose to require a certified translation, to have an independent back-translation or to have a review of the translated documents by an IRB member or other person who is fluent in that language. When non-English speaking subjects enroll, they and a witness sign the translated consent document. The subjects are given a copy of the signed translated consent document.

b) Unexpected Enrollment

If a person who does not speak or read, or has limited proficiency in, English presents for possible enrollment, an IRB-approved translated version of the written consent may not be available for use. Investigators should carefully consider the ethical and legal ramifications of enrolling subjects when a language barrier exists. If the subject does not clearly understand the information presented during the consent process or in subsequent discussions, his/her consent may not be informed, and therefore, not effective.

If an investigator decides to enroll a subject into a study for which there is not an extant IRB-approved consent document in the prospective subject's language, the investigator must receive IRB approval to follow the procedures for a “short form” written consent.

c) Use of Interpreters in the Consent Process

Unless the person obtaining consent is fluent in the prospective subject’s language, an interpreter will be necessary to facilitate the consent discussion. Preferably someone who is independent of the subject (i.e., not a family member) should assist in presenting information and obtaining consent. Whenever possible, interpreters should be provided copies of the translated consent, or short form and the IRB-approved consent script (typically the English-language version of the consent document) well before (24 to 48 hours if possible) the consent discussion with the subject. If the interpreter also serves as the witness, she/he may sign the translated consent, or short form consent document and script, as the witness and should note “Interpreter” under the signature line. The person obtaining consent must document that the “short form” process was used in the subject's research record, including the name of the interpreter.

2. Braille Consent

For blind subjects who read Braille, the IRB may approve a consent document prepared in Braille. In order to assure itself that a Braille consent document is accurate, the IRB may require a transcription into print text or review of the document by an IRB member or other person who reads Braille. If possible, the subject will sign the Braille consent; otherwise, oral consent will be obtained, witnessed, and documented as described under "Oral Consent" (Section XI.I.4).

3. Consenting in American Sign Language (ASL)

For deaf subjects who are fluent in ASL, the IRB may approve a consent process using ASL and the IRB-approved written consent form. When this process is approved, the individual authorized to consent prospective subjects must use a PHS-certified interpreter fluent in ASL to conduct the consent process and the documentation of the consent process must conform to the requirements set forth in (Section XI.H).

4. Oral Consent

When subjects are unable to read a written consent form (such as blind or illiterate subjects), the IRB may approve an oral consent process, provided the subject (1) retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained orally and (2) is able to indicate approval or disapproval to study entry.

For greater than minimal risk research, the consent form must be read to the subjects and the subjects must be given an opportunity to ask questions. An audio recording approved by the IRB may also be used. If capable of doing so, the subject signs, or marks an X to signify consent. If that is not possible, the subject will provide oral consent. The person obtaining consent and a witness will sign the written study consent form with a statement that documents that an oral process was used and, if necessary, that the subject gave oral consent. The consent process will also be documented in the subject's research record. Signed copies of the consent form are given to the subject and, whenever possible, these documents should be provided to the subject on audio or video recording.

J. Subject Withdrawal or Termination

For a variety of reasons, a subject enrolled in a research study may decide to withdraw from the research or an investigator or sponsor may decide to terminate a subject's participation in research regardless of whether the subject wishes to continue participating. Investigators must plan for the possibility that subjects will withdraw from research and include a discussion of what withdrawal will mean and how it will be handled in their research protocols/research plans and consent documents.

When seeking informed consent from subjects, the following information regarding data retention and use must be included:

- For FDA-regulated clinical trials, when a subject withdraws from a study, the data collected on the subject to the point of withdrawal remain part of the study database and may not be removed. The consent document cannot give the subject the option of having data removed.
- For research not subject to FDA regulations, the investigator should inform subjects whether the investigator intends to either (1) retain and analyze already collected data relating to the subject up to the time of subject withdrawal, or (2) honor a research subject's request that the investigator destroy the subject's data, or that the investigator exclude the subject's data from any analysis.

When a subject's withdrawal request is limited to discontinuation of the primary interventional component of a research study, research activities involving other types of participation for which the subject previously gave consent may continue. Investigators should ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection after their withdrawal from the interventional portion of

the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and procedures and continued follow-up in person, by phone, or via records review, of data and address the maintenance of privacy and confidentiality of the subject's information.

If a subject withdraws from the interventional portion of the study and agrees to continued follow-up as described in the previous paragraph, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original consent document). IRB approval of consent documents for these purposes would be required.

If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up, the investigator must not access or gather private information about the subject for purposes related to the study. However, an investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

K. Waiver or Alteration of Informed Consent

In order to approve a request from an investigator to waive or alter the requirement(s) for informed consent the IRB must determine and document that the below criteria are satisfied in accordance with 45 CFR 46.116(f)(3) and 21 CFR 50.22.

- The research involves no more than minimal risk to the subjects;
- The research activities could not practicably be carried out without the requested waiver or alteration;
- If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
- The waiver or alteration will not adversely affect the rights and welfare of the of the participants; and
- Whenever appropriate, participants or their legally authorized representative will be provided with additional pertinent information after participation.

Investigators may be asked to provide justification, or additional information or documentation, to support that the above criteria are satisfied. If an individual was asked to provide broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens and refused to consent, an IRB cannot waive consent for the storage, maintenance, or secondary research use of the identifiable private information or identifiable biospecimens.

1. Waiver of Alteration of Consent in Research Involving Public Benefit and Service Programs

In addition, an IRB may approve a consent procedure that does not include, or that alters, some or all the elements of informed consent; or waive the requirements to obtain informed consent, provided the IRB finds and documents that:

- The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
  - ❖ Public benefit or service programs;
  - ❖ Procedures for obtaining benefits or services under those programs;
  - ❖ Possible changes in or alternatives to those programs or procedures; or
  - ❖ Possible changes in methods or levels of payment for benefits or services under those programs; and
- The research could not practicable be carried out without the waiver or alteration.

If a broad consent procedure is used, an IRB may not waive or alter any of the elements. If an individual was asked to provide broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens and refused to consent, the IRB cannot waive

consent for the storage, maintenance, or secondary research use of the identifiable private information or identifiable biospecimens.

L. Waiver of Documentation of Informed Consent

The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds any of the following:

- The only record linking the subject and the research would be the informed consent document and the principal risk would be potential harm resulting from a breach of confidentiality.
  - ❖ Note 1: Subjects must be asked whether they want documentation linking them with the research, and their wishes must govern. (Example: domestic violence research where the primary risk is discovery by the abuser that the subject is talking to investigators.)
  - ❖ Note 2: In order to waive written documentation of consent where the only record linking the participant and the research would be the consent document, the IRB must determine that the research was not FDA-regulated. OR
- 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. Procedures such as non-sensitive surveys, questionnaires and interviews generally do not require written consent when conducted by non- investigators (e.g., marketing surveys, telemarketing). Note: The FDA does permit a waiver of documentation of consent if this condition is satisfied. This is most commonly applied in the context of minimal risk screening activities that are necessary to determine eligibility for enrollment in the full trial; OR
- If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained. This option does not apply to FDA-regulated research.

Unless the IRB has granted a full waiver of the requirement to obtain informed consent, investigators who seek and receive approval for a waiver of documentation of consent still must perform an adequate consent process.

In cases in which the documentation requirement is waived, the IRB requires the investigator to provide in the application materials a written summary of the information to be communicated to the subject, and the IRB will consider whether to require the investigator to provide subjects with a written statement regarding the research.

M. Waiver of Informed Consent for Planned Emergency Research

The conduct of planned research in life-threatening emergencies where the requirement to obtain prospective informed consent has been waived by the IRB is covered by 21 CFR §50.24 for FDA-regulated research and by the waiver articulated by DHHS at 61 FR 51531-33 for non- FDA-regulated research.

The FDA exception from informed consent requirements for emergency research under FDA regulations, 21 CFR 50.24, permits planned research in an emergency setting when human subjects who need emergency medical intervention, cannot provide legally effective informed consent themselves, and there is generally insufficient time and opportunity to locate and obtain consent from their legally authorized representatives (LARs).

The Secretary of Health and Human Services (DHHS) has implemented an Emergency Research Consent Waiver under 45 CFR 46.101(i) with provisions equivalent to those of the FDA apart from the requirements specified below. The DHHS waiver is not applicable to research involving prisoners, pregnant women, fetuses, or in vitro fertilization.

1. Procedures

According to 21 CFR 50.24, the IRB may approve the planned emergency research without requiring

informed consent of all research subjects prior to initiating the research intervention if the IRB finds and documents that the following conditions have been met:

- The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
- Obtaining informed consent is not feasible because
  - ❖ The subjects will not be able to give their informed consent due to of their medical condition;
  - ❖ The intervention under investigation must be administered before consent from the subject's legally authorized representatives is feasible; and
  - ❖ There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.
- Participation in the research holds out the prospect of direct benefit to the subjects because:
  - ❖ Subjects are facing a life-threatening situation that necessitates intervention;
  - ❖ Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
  - ❖ Risks associated with the research are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks, and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
- The research could not practicably be carried out without the waiver.
- The proposed research plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.
- The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 45 CFR 46.116 and 46.117 and 21 CFR 50.20, 50.25 and 50.27. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the research consistent with paragraph (7)(v) of this section.
- Additional protections of the rights and welfare of the subjects will be provided, including, at least:
  - ❖ Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the research will be conducted and from which the subjects will be drawn;
  - ❖ Public disclosure to the communities in which the research will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;
  - ❖ Public disclosure of enough information following completion of the research to apprise the community and investigators of the study, including the demographic characteristics of the research population, and its results;
  - ❖ Establishment of an independent data monitoring committee to exercise oversight of the research; and
  - ❖ If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within

the therapeutic window the subject's family member who is not a legally authorized representative and asking whether he or she objects to the subject's participation in the research. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

In addition, the IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the research, the details of the research and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the research and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into research with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the research is to be provided to the subject's legally authorized representative or family member, if feasible.

a) FDA-Regulated Planned Emergency Research

- A licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation must concur that the conditions described in Section XI.
- Studies involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies that such studies may include subjects who are unable to consent. The submission of those studies in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under 312.30 or 812.35.
- If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided in the regulations or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.
- The IRB determinations and documentation are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with 21 CFR 56.115(b).

b) Planned Emergency Research and Informed Consent

The IRB responsible for the review, approval, and continuing review of the research has approved both the research and a waiver of informed consent and has:

- Found and documented that the research is not subject to regulations codified by the FDA at 21 CFR Part 50, and
- Found and documented and reported to the OHRP that the conditions required

XII. VULNERABLE SUBJECTS / POPULATIONS

When some or all the participants in a research study conducted under the auspices of PHS are likely to be vulnerable to coercion or undue influence or have diminished decision-making capacity, the research must include additional safeguards to protect the rights and welfare of these participants. The IRB must ensure that all the regulatory requirements for the protection of vulnerable subjects are met and that appropriate additional protections for vulnerable subjects are in place.

The following procedures describe the requirements for involving vulnerable participants in research under the auspices of PHS.

A. Definitions

Children. Persons who have 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. According to New Mexico State Law (NMSA 1978, Section 32A-1-4), minors are persons under the age of eighteen. The general rule is that a person may consent for his or her own medical care at the age of eighteen. Therefore, PHS IRB defines children as persons who are under 18 years of age. Certain statutes and case law, however, provide minors with "majority" status in some circumstances, giving them the right to consent to their own medical care. For example: emancipated minors New Mexico law enumerates certain categories of individuals who, although under the age of 18, have the right to make medical decisions on their own behalf, such as minors who are married, widowed or divorced, minors who are parents, etc.); mature minors New Mexico law recognizes that some minors may be sufficiently "mature" to give consent to medical treatment, even though they do not qualify as "emancipated"); or certain minors seeking care for drug addiction, sexually transmitted diseases, emotional disorders, or abortion or mental health treatment. Because New Mexico law does not specifically address consent of children with majority status to research, PHS IRB will review issues of consent related to enrollment of these children in research on a case-by-case basis.

Dead Fetus. A fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.

Delivery. A complete separation of the fetus from the woman by expulsion or extraction or any other means.

Fetus. The product of conception from implantation until delivery.

Guardian. An individual who is authorized under applicable state or local law and tribal law passed by the official governing body of an American Indian or Alaska Native tribe to consent on behalf of a child to general medical care.

Neonate. A newborn.

Nonviable Neonate. A neonate after delivery that, although living, is not viable.

Pregnancy. The period of time from implantation until delivery. An individual shall be assumed to be pregnant if they exhibit any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

Prisoner. Any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

Viable. As it pertains to the neonate, viable means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration.

B. Involvement of Vulnerable Populations

If the IRB reviews research that involves categories of participants vulnerable to coercion or undue influence, the review process should include one or more individuals who are knowledgeable about or experienced in working with these populations. Reviewers may be IRB members or consultants.

45 CFR 46 has additional subparts designed to provide extra protections for vulnerable populations which also have additional requirements for IRBs.

Subpart B - Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

Subpart C - Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Subpart D - Additional Protections for Children Involved as Subjects in Research

Non-exempt DHHS-conducted or supported research that involves any of these populations must comply with the requirements of the relevant subparts.

C. Responsibilities

The investigator is responsible for identifying the potential for enrolling vulnerable subjects in the research proposal, including the possible inclusion of subjects who are at risk for impaired decisional capacity, and who are being asked to participate in a research study with greater than minimal risk.

The IRB shall include representation, either as members or through the use of consultants, of individual(s) who are knowledgeable about or experienced working with the vulnerable populations involved in the research proposal under review.

The IRB reviews the investigator's justifications for including vulnerable populations in the research to assess appropriateness for inclusion in the research proposal.

The IRB must ensure that appropriate additional safeguards have been included in each study to protect the rights and welfare of vulnerable subjects at the time of initial review of the research proposal.

Information reviewed as part of the continuing review process should include the number of participants considered to be members of specific vulnerable populations.

D. Procedures

The following policies and procedures apply to all research involving subjects vulnerable to coercion or undue influence under the oversight of the PHS IRB regardless of funding. Subsequent sections address additional procedures and requirements that apply to specific populations.

1. **Initial Review of Research Proposal**

   The investigator identifies the potential to enroll vulnerable subjects in the proposed research at initial review and provides the justification for their inclusion in the study.

   The investigator describes safeguards to protect the subject's rights and welfare in the research proposal. IRB staff, in collaboration with the IRB Chair as needed, ensure that the IRB has the relevant expertise with the vulnerable population, and, if necessary, arrange for consultation. When the research involves no more that minimal risk and is eligible for expedited review, the designated reviewer may determine the need for additional expertise to ensure the protection of the vulnerable population(s);

   The IRB evaluates the proposed safeguards, including, if applicable, the proposed plan for obtaining consent from subjects or their legally authorized representatives and the plans for assent of children and adults unable to provide consent.

When applicable, the IRB considers any costs associated with participation in the proposed research and any plans for reimbursement of expenses or provision of compensation, and the potential impact of such on the vulnerable population(s);

The IRB evaluates the research to determine the need for additional protections and considers, if appropriate, the use of a data and safety monitoring board, consent monitor, or research subject advocate.

2. Modifications to Research

When an investigator proposes to add inclusion of a vulnerable population after research has already been approved by the IRB, the investigator must submit a modification request to the IRB identifying the population they would like to add, justification for inclusion of the population, and any modifications to the research plan to ensure protection of the subject's rights and welfare; and

The IRB staff and IRB will follow the procedures outlined for initial review above.

3. Continuing Review and Monitoring

At continuing review, the investigator should identify the number and categories of vulnerable subjects enrolled and any problems that arose relevant to their rights and welfare. When research does not include any interaction or intervention with subjects, and such information is not gathered, this should be noted on the continuing review report;

IRB staff, in collaboration with the IRB Chair as needed, ensure that the IRB has the relevant expertise with the vulnerable population, and, if necessary, arrange for consultation. When the research involves no more that minimal risk and is eligible for expedited review, the designated reviewer may determine the need for additional expertise to ensure the protection of the vulnerable population(s);

The IRB reviews the continuing review information, and any relevant information reported to the IRB during the period of approval and determines whether the inclusion of vulnerable populations and the plans to protect the rights and welfare of vulnerable subjects remains appropriate.

E. Research Involving Pregnant Women, Human Fetuses, and Neonates

According to the PHS FWA, Subpart B of 45 CFR 46 applies only to DHHS-funded research, the funding-source specific requirements are noted in the appropriate sections.

For DHHS-conducted or supported research, 45 CFR Subpart B applies to all non-exempt human subject research involving pregnant women, fetuses, and neonates.

Pregnant women or fetuses may be involved in research if all the following conditions are met:

- Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.
- 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 any other means.
- Any risk is the least possible for achieving the objectives of the research.
- If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a 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, then the consent of the

pregnant woman is obtained in accord with the provisions for informed consent.

- 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 in accord with the provisions for informed consent, 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.
- Each individual providing consent under paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
- For children (Section XII.A) who are pregnant, assent and permission are obtained in accord with the requirements of state law and the IRB.
- No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
- Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
- Individuals engaged in the research will have no part in determining the viability of a neonate.

1. Research Involving Neonates of Uncertain Viability or Nonviable Neonates

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

- Where scientifically appropriate, preclinical, and clinical studies have been conducted and provide data for assessing potential risks to neonates.
- Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
- Individuals engaged in the research will have no part in determining the viability of a neonate.
- The requirements of Neonates of Uncertain Viability or Nonviable Neonates (see below in this section) have been met as applicable.

2. Neonates of Uncertain Viability.

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

- The IRB determines that:
  - ❖ 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
  - ❖ 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
  - ❖ 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 in accord with the provisions of permission and assent, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

3. Nonviable Neonates.

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

- Vital functions of the neonate will not be artificially maintained;
- The research will not terminate the heartbeat or respiration of the neonate;
- There will be no added risk to the neonate resulting from the research;

- The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
- The legally effective informed consent of both parents of the neonate is obtained in accord with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission and assent do not apply.

However, if either parent is unable to consent because of unavailability or incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both parents of a nonviable neonate will not suffice to meet the requirements of this paragraph.

4. Viable Neonates

A neonate, after delivery, which has been determined to be viable may be included in research only to the extent permitted by and in accordance with the requirements for Research Involving Children (i.e., a viable neonate is a child for purposes of applying federal regulations and PHS policies).

5. Research Involving, After Delivery, the Placenta, the Dead Fetus, or Fetal Material

Research involving, after delivery (1) the placenta; (2) the dead fetus; (3) macerated fetal material; or (4) cells, tissue, or organs excised from a dead fetus, must be conducted only in accordance with any applicable federal, state, local laws, or tribal law passed by the official governing body of an American Indian or Alaska Native tribe and regulations regarding such activities.

If information associated with material described above in this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent sections of these policies and procedures are applicable.

6. Research Not Otherwise Approvable

DHHS-conducted or supported research that falls in this category (Research Not Otherwise Approvable) must be approved by the Secretary of Health and Human Services. If 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 the research is not approvable under the above provisions, then the research will be sent to OHRP for DHHS review.

F. Research Involving Prisoners

The requirements in this section are consistent with Subpart C of 45 CFR 46, which applies to DHHS-funded or supported research.

This policy applies to all biomedical and behavioral research conducted under the auspices of PHS involving prisoners as subjects. Even though the IRB may approve a research study involving prisoners as subjects according to this policy, investigators are still subject to the administrative regulations of the New Mexico Department of Corrections and any other applicable New Mexico state, local laws and tribal law passed by the official governing body of an American Indian or Alaska Native tribe. [45 CFR 46.301]

1. Minimal Risk in Studies Involving Prisoners

Minimal risk, in studies involving prisoners, means 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.

2. Composition of the IRB as Related to the Review of Studies Involving Prisoners

In addition to satisfying the general membership requirements detailed in other sections of these policies and procedures, when reviewing research involving prisoners, the IRB must also meet the following requirements:

- A majority of the IRB (exclusive of prisoner members) must have no association with the prison(s) involved, apart from their membership on the IRB;
- At least one regular or alternate member of the IRB must be a prisoner, or a prisoner
- representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB, only one IRB need satisfy this requirement; and
- The prisoner representative must be a voting member of the IRB. A comment may be added to the roster indicating that the prisoner representative will only count towards quorum when he or she is in attendance and reviewing studies covered by Subpart C.

3. Review of Research Involving Prisoners

a) Initial Review

- The prisoner representative must review research involving prisoners, focusing on the requirements in Subpart C.
- The prisoner representative must receive all review materials pertaining to the research (same as primary reviewer). The prisoner representative must be present at a convened meeting when the research involving prisoners is reviewed. If the prisoner representative is not present, research involving prisoners cannot be reviewed or approved. The prisoner representative may attend the meeting by phone, videoconference, or webinar, as long as the representative is able to participate in the meeting as if they were present in person at the meeting.

b) Modifications

- Minor modifications to research may be reviewed using the expedited procedure described below, using either of the two procedures described based on the type of modification.
- Modifications involving more than a minor change reviewed by the convened IRB must use the same procedures for initial review including the responsibility of the prisoner representative to review the modification and participate in the meeting (as described above).

c) Continuing Review

- Continuing review must use the same procedures for initial review including the responsibility of the prisoner representative to review the continuing review materials and participate in the meeting (as described above).

d) Expedited Review

- Research involving interaction with prisoners cannot be reviewed by the expedited review process.
- Research that does not involve interaction with prisoners (e.g., existing data, records review, etc.) may be reviewed by the expedited procedure, if a determination is made that the research involves no greater than minimal risk for the prison population being studied. Review by a prisoner representative is not required. The prisoner representative may review the research as a reviewer (if designated by the IRB Chair as an expedited reviewer) or consultant. Review of modifications and continuing review will follow these same procedures.

4. Incarceration of Enrolled Subjects

If a participant becomes a prisoner while enrolled in a research study that was not reviewed according to Subpart C, the investigator must promptly notify the IRB and the IRB shall:

- Confirm that the participant meets the definition of a prisoner.
- Consult with the investigator to determine if it is in the best interests of the participant to continue participation in the study, in part or in full, and if so, if there are specific study activities which are in the best interests of the subject and should continue until the IRB is able to review the research study under Subpart C.
- If the participant should continue, one of two options are available:
  - ❖ Keep the participant enrolled in the study and review the research under Subpart C. If some of the requirements of Subpart C cannot be met or are not applicable (e.g., procedures for the selection of subjects within the prison), but it is in the best interests of the participant to remain in the study, keep the participant enrolled and inform OHRP of the decision along with the justification.
  - ❖ Remove the participant from the study and keep the participant on the study intervention under an alternate mechanism such as compassionate use, off label use, etc.
- If a participant is incarcerated temporarily while enrolled in a study:
  - ❖ If the temporary incarceration has no effect on the study (i.e., there is no need for study activities to take place during the temporary incarceration), keep the participant enrolled.
  - ❖ If the temporary incarceration has an effect on the study, follow the above guidance.

5. Additional Duties of the IRB

In addition to all other responsibilities prescribed for IRB in other sections of this manual, the IRB will review research involving prisoners and approve such research only if it finds that:

- The research falls into one of the following permitted categories (45 CFR 46.306(a)(2)):
  - ❖ Study 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;
  - ❖ Study 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;
  - ❖ Research on conditions particularly affecting prisoners as a class (for example, research on diseases or social and psychological problems much more prevalent in prisons) provided that the study may proceed only after the DHHS Secretary has consulted with appropriate experts in penology, medicine, and ethics, and published notice in the Federal Register of his/her intent to approve the research;
  - ❖ Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols/research plans approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the DHHS Secretary has consulted with appropriate experts in penology, medicine, and ethics, and published notice in the Federal Register of his/her intent to approve the research
- 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;
- The risks involved in the research are commensurate with risks that would be accepted by non-

prisoner volunteers;

- 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 investigator provides to the IRB 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;
- The information is presented in language which is understandable to the subject population;
- Adequate assurance exists that parole boards will not consider 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
- Where the IRB finds there may be a need for follow-up examination or care of subjects after the end of their participation, adequate provision has been made for such examination or care, considering the varying lengths of individual prisoners' sentences, and for informing subjects of this fact.

6. Certification to DHHS

Under 45 CFR 46.305(c), the institution responsible for conducting research involving prisoners that is conducted or supported by DHHS shall certify to the Secretary (through OHRP) that the IRB has made the seven findings required under 45 CFR 46.305(a) and receive OHRP authorization prior to initiating any research involving prisoners. Certifications, and requests for DHHS Secretarial consultation, do not need to be submitted to OHRP for research not conducted or supported by DHHS, regardless of whether the institution has chosen to extend the applicability of its FWA and Subparts B, C, and D to all research.

For all DHHS conducted or supported research, PHS will send to OHRP a certification letter to this effect, which will also include the name and address of the institution and specifically identify the research study in question and any relevant DHHS grant application or protocol/research plan. DHHS conducted or supported research involving prisoners as subjects may not proceed until OHRP issues its authorization in writing to PHS on behalf of the Secretary under 45 CFR 46.306(a)(2).

Under its authority at 45 CFR 46.115(b), OHRP requires that the institution responsible for the conduct of the proposed research also submit to OHRP a copy of the research proposal so that OHRP can determine whether the proposed research involves one of the categories of research permissible under 45 CFR 46.306(a)(2), and if so, which one.

The term “research proposal” includes the IRB-approved protocol/research plan; any relevant DHHS grant application or proposal;

- Any IRB application forms required by the IRB; and
- Any other information requested or required by the IRB to be considered during initial IRB review.

OHRP also encourages the organization to include the following information in its prisoner research certification letter to facilitate processing:

- The OHRP Federal Wide Assurance (FWA) number;
- The IRB registration number for the designated IRB; and
- The date(s) of IRB meeting(s) in which the study was considered, including a brief chronology that encompasses
  - ❖ The date of initial IRB review; and
  - ❖ The date of Subpart C review, if not done at the time of initial IRB review.

7. Waiver for Epidemiology Research

The DHHS Secretarial waiver for certain epidemiological research conducted or supported by DHHS functions as a fifth category of permissible research (68 FR 36929). The criteria for this category are that

the research must have as its sole purpose (i) to describe the prevalence or incidence of a disease by identifying all cases, or (ii) to study potential risk factor associations for a disease. The organization still must review the research under subpart C and certify to OHRP that an appropriately constituted IRB has reviewed the proposal and made all other required findings under DHHS regulations at 45 CFR 46.305(a) and receive OHRP authorization prior to initiating any research involving prisoners. All the other requirements of subpart C apply to research in this category.

G. Research Involving Children

The requirements in this section are consistent with Subpart D of 45 CFR 46, which applies to DHHS-funded research and Subpart D of 21 CFR 50, which applies to FDA-regulated research involving children.

1. Allowable Categories

In addition to the IRB's normal duties, research involving children must be reviewed by the IRB to determine if it fits within and is permissible under one or more federally defined categories (OHRP/FDA). Each procedure or intervention that the child will undergo for the research must be taken into consideration, and, if the research includes more than one study group assignment (e.g., placebo vs. active, investigational agent vs. comparator) the category determination must be made for each group assignment. In other words, a component analysis must be conducted by the IRB. The categories are as follows:

- **[45 CFR 46.404/21 CFR 50.51] Research/Clinical Investigations not involving greater than minimal risk**. Research determined to not involve greater than minimal risk to child subjects may be approved by the IRB only if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.
- **[45 CFR 46.405/21 CFR 50.52] Research/Clinical Investigations involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.** Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may be approved by the IRB only if the IRB finds and documents that:
  - ❖ The risk is justified by the anticipated benefit to the subjects;
  - ❖ The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative options; and
  - ❖ Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.
- **[45 CFR 46.406/21 CFR 50.53] Research/Clinical Investigations involving greater than minimal risk and no prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition.** Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, may be approved by the IRB only if the IRB finds and documents 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 the assent of children and the permission of their parents or guardians.

- **[45 CFR 46.407/21 CFR 50.54] Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children.** When the IRB does not believe that the research meets the requirements of any of the above categories, and the IRB finds and documents that 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 IRB shall refer the research for further review as follows:
  - ❖ HHS conducted or supported research in this category will be referred for review by the Secretary of Health and Human Services. However, before doing so the IRB must determine that the proposed research also meets all the requirements of the Common Rule.
  - ❖ FDA-regulated research in this category will be referred for review by the Commissioner of Food and Drugs.

2. Parental Permission

The IRB must determine that adequate provisions have been made for soliciting the permission of each child's parent or guardian. Parents or guardians must be provided with the basic elements of consent and any additional elements the IRB deems necessary.

The IRB may find that the permission of one parent is sufficient for research to be conducted under category 1 (45 CFR 46.404, 21 CFR 50.51) and category 2 (45 CFR 46.405, 21 CFR 50.52) above. The IRB's determination of whether permission must be obtained from one or both parents will be documented in the reviewer's notes when a study receives expedited review, and in meeting minutes when reviewed by the convened committee.

Permission from both parents is required for research to be conducted under category 3 (45 CFR 46.406, 21 CFR 50.53) and category 4 (45 CFR 46.407, 21 CFR 50.54) above unless:

- One parent is deceased, unknown, incompetent, or not reasonably available; or
- When only one parent has legal responsibility for the care and custody of the child.

For research not covered by the FDA regulation, the IRB may waive the requirement for obtaining permission from a parent or legal guardian if:

- The research meets the provisions for waiver of consent (Section XI.K), or
- If the IRB determines that the research is designed to study conditions in children or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children) provided that an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and that the waiver is not inconsistent with Federal, State, tribal law passed by the official governing body of an American Indian or Alaska Native tribe or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol/research plan, the risk and anticipated benefit to the research subjects, and the child's age, maturity, status, and condition.

Parental permission may not be waived for research covered by the FDA regulations.

3. Assent from Children

The IRB is responsible for determining that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. This judgment may be made for all children to be involved in the study, or for each child, as the IRB deems appropriate.

If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds 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, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accordance with the applicable regulations. It is important to note that the FDA regulations do permit the IRB to waive the assent requirement if it finds and documents that:

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

Because "assent" means a child's affirmative agreement to participate in research, the child must actively show his or her willingness to participate in the research, rather than just complying with directions to participate and not resisting in any way.

The IRB should consider the nature of the proposed research activity and the ages, maturity, and psychological state of the children involved when reviewing the proposed assent procedure and the form and content of the information conveyed to the prospective subjects. For research activities involving adolescents whose capacity to understand resembles that of adults, the assent procedure should likewise include information like what would be provided for informed consent by adults or for parental permission. For children whose age and maturity level limits their ability to fully comprehend the nature of the research activity, but who are still capable of being consulted about participation in research, it may be appropriate to focus on conveying an accurate picture of what the actual experience of participation in research is likely to be (for example, what the experience will be, how long it will take, whether it might involve any pain or discomfort). The assent procedure should reflect a reasonable effort to enable the child to understand, to the degree they are capable, what their participation in research would involve.

Parents and children will not always agree on whether the child should participate in research. Where the IRB has indicated that the assent of the child is required for him or her to be enrolled in the study, dissent from the child overrides permission from a parent. Similarly, a child typically cannot decide to be in research over the objections of a parent. There are individual exceptions to these guidelines but in general, children should not be forced to be research subjects, even when permission has been given by their parents.

a) Documentation of Assent

When the IRB determines that assent is required, it also is responsible for determining whether and how assent must be documented. When the research targets very young children unable or with limited capacity to read or write, an oral presentation accompanied perhaps by some pictures with documentation of assent by the person obtaining assent in a research note is likely more appropriate than providing the child a form to sign. In this case, the investigator should provide the IRB with a proposed script and any materials that they intend to use in explaining the research.

When the research targets children who are likely able to read and write, investigators should propose a process and form that is age appropriate and study specific, considering the typical child's experience and level of understanding, and composing a document that treats the child respectfully and conveys the essential information about the study. The assent form should:

- Tell why the research is being conducted;
- Describe what will happen and for how long or how often;
- Say it is up to the child to participate and that it is okay to say no;

- Explain if it will hurt and if so for how long and how often;
- Say what the child's other choices are;
- Describe any good things that might happen;
- Say whether there is any compensation for participating; and
- Ask for questions.

Whenever possible, the document should be limited to one page. Illustrations might be helpful, and larger type and other age-appropriate improvements are encouraged when they have the potential to enhance comprehension. Studies involving older children or adolescents should include more information and may use more complex language.

b) Children Who are Wards

Children who are wards of the State or any other agency, institution, or entity can be included in research approved under 45 CFR 46.406/21 CFR 50.53 or 45 CFR 46.407/21 CFR 50.54, only if such 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 the research meets the condition(s) above, an advocate must be appointed for each child who is a ward (one individual may serve as advocate for more than one child), in addition to any other individual acting on behalf of the child as legal guardian or in loco parentis.

The advocate must be an individual who has 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 who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

H. Adults with Impaired Decision-Making Capacity

The requirements in this section apply to all research involving adults who cannot provide consent or with impaired decision-making capacity regardless of funding source. Research involving subjects without the ability to provide consent or with impaired decision- making capacity should only be conducted when the aims of the research cannot reasonably be achieved without their participation. Participation of such subjects in research cannot be justified solely on their availability or the convenience for the investigator.

When an investigator seeks to include such subjects in research, they must disclose this to the IRB and provide justification for why inclusion is necessary. If capacity to consent is questionable, or may fluctuate, investigators should include provisions for determining capacity to provide informed consent (Section XI), and, if appropriate to reevaluate capacity during participation. When capacity to consent may diminish, the procedures should include, when possible and appropriate, designation of a LAR, inclusion of the future LAR in the initial consent discussion and process, and memorialization of the participant's wishes regarding the research in writing. When the research includes subjects likely to regain capacity to consent, the investigator should include provisions to inform the subject regarding their participation and to seek consent for ongoing participation, if applicable.

When the IRB reviews research involving greater than minimal risk and the proposed subject population includes adults who cannot provide consent, may have impaired capacity to provide consent, or whose capacity can be expected to fluctuate over time, the IRB review process will include at least one member, or a consultant, who is experienced with or otherwise knowledgeable about the population.

In evaluating research, the IRB must be able to determine that the risks to subjects are reasonable not only in relation to any benefits, but also in relation to the importance of the knowledge that may reasonably be expected

to result. In considering the risks of research involving subjects unable to provide informed consent or with diminished capacity to do so, the IRB should consider whether any components of the research involve risks that are greater for participants with diminished capacity. For example, the population might experience increased sensitivity or discomfort to certain stimuli or may not be able to verbalize or otherwise demonstrate when they are experiencing discomfort or pain.

As appropriate, the IRB will consider the following in evaluating greater than minimal risk research involving adults unable to consent or with impaired decision-making capacity:

- Whether the aims of the research cannot reasonably be achieved without inclusion of the population
- Whether the research is likely to improve the understanding of the condition,
- disease, or issue affecting the subject population
- Whether any experimental procedure or interventions have undergone pre-clinical testing or human testing on other populations and whether the data from that testing supports its use in the proposed research
- Whether the procedures or interventions that the subject will undergo in the research place them at increased risk and if appropriate mechanisms are in place to minimize risks, when possible
- Whether the data and safety monitoring plan, including any stopping rules, is appropriate given the risks of the research and the vulnerability of the population
- Whether the procedures for withdrawing individual subjects from the research are appropriate
- Whether the recruitment procedures, consent process, and any plans for financial compensation support voluntariness and minimize the likelihood of undue influence or coercion
- Whether the subjects will be exposed to financial or other risks that they might not consider acceptable if they had the capacity to provide consent, and whether appropriate mechanisms have been put into place to minimize these risks
- Whether the procedures for determining capacity to provide consent, and for evaluating capacity on an ongoing basis, if applicable, are appropriate
- Whether the procedures for informing subjects who regain capacity about their involvement in the research, and for obtaining consent for on-going participation, if applicable, are appropriate
- Whether assent should be required when possible, and, if so, if the proposed procedures to obtain and document assent are appropriate
- Whether a research subject advocate or consent monitor should be required, for some or all subjects.

XIII. FDA-REGULATED RESEARCH

FDA regulations apply to research that involves an FDA-regulated test article in a clinical investigation involving human subjects as defined by the FDA regulations. For FDA-regulated research, the IRB must apply the FDA regulations at 21 CFR 50 and 21 CFR 56. If required by organizational policy or an FWA, 45 CFR 46 must also be applied.

Clinical trials with investigational drugs must be conducted according to FDA's IND regulations, 21 CFR Part 312, and other applicable FDA regulations. Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA's IDE regulations, 21 CFR Part 812, and other applicable FDA regulations.

The following procedures describe the review of FDA-regulated research conducted under the auspices of PHS.

A. Definitions

Biologic. Biological products include a wide range of products such as vaccines, blood, and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as

cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other technologies. In general, the term "drugs" includes therapeutic biological products.

Dietary Supplement. A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains a dietary ingredient. The dietary ingredients in these products can include vitamins, minerals, herbs and other botanicals, amino acids, other dietary substances intended to supplement the diet, and concentrates, metabolites, constituents, extracts, or combinations of the preceding types of ingredients. See section 201(ff) of the FD&C Act [21 U.S.C. 321(ff)].

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

Investigational Device. Investigational device means a device (including a transitional device) that is the object of an investigation. Investigation, as it pertains to devices, means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.

Investigational Drug. Investigational *or* experimental drugs are new drugs that have not yet been approved by the FDA or approved drugs that are being studied in a clinical investigation.

Investigational New Drug (IND). An investigational new drug application in accordance with 21 CFR Part 312.

Investigational Device Exemption (IDE). An investigational device exemption in accordance with 21 CFR 812.

In Vitro Diagnostic Product (IVD). In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. [21 CFR 809.3(a)]

Non-Significant Risk (NSR) Device. A non-significant risk device is an investigational device that does not meet the definition of a significant risk device.

Significant Risk (SR) Device. Significant risk device means an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- 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 subject; or
- 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 subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

B. FDA Exemptions

Under 21 CFR 46.104, the following clinical investigations are exempt from IRB review:

- Emergency use of a test article, provided that such emergency use is reported to the IRB within five working days. Any subsequent use of the test article at the institution is subject to IRB review [21 CFR §56.104(c)]

C. Procedures

The HRPO staff conducts a pre-review of the application and research materials provided by the Principal Investigator to (a) determine whether the FDA regulations apply, and, if yes, which FDA regulations apply, and (b)

determine whether the research requires review by a convened IRB, or is eligible for expedited review pursuant to Section VII.D.

The existence of, or apparent need for, an IND or IDE may disqualify the study for expedited review.

PHS does not follow ICH GCP Guidelines unless specifically required by the sponsor. It is the responsibility of the Principal Investigator to properly communicate these requirements within the PHS IRB electronic submission.

D. Investigator Responsibilities

The investigator holds additional responsibilities when conducting a clinical trial evaluating FDA-regulated drugs, devices, and other articles. These responsibilities include, but are not limited to, the following:

- The investigator is responsible for ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs (including biological products) or agreement for clinical investigations of medical devices, the investigational plan and other applicable regulations, and any requirements imposed by the IRB or FDA.
- The investigator is responsible for personally conducting or supervising the investigation. When certain study-related tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.
- The investigator must maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks (e.g., it can refer to an individual's CV on file and/or training conducted by the investigator/sponsor), and identify the dates of involvement in the study. An investigator should maintain separate lists for each study conducted by the investigator.
- The investigator is responsible for protecting the rights, safety, and welfare of subjects under their care during a clinical trial. This responsibility includes:
  - ❖ Informing subjects that the test articles is being used for investigational purposes and ensuring that the requirements relating to obtaining informed consent are met;
  - ❖ Providing reasonable medical care for study subjects for medical problems arising during participation in the trial that are, or could be, related to the study intervention;
  - ❖ Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable, or when specialized care is needed);
  - ❖ Adhering to the protocol/research plan so that study subjects are not exposed to unreasonable risks; and
  - ❖ As appropriate, informing the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and the subject agrees to the primary physician being informed.
- The investigator is responsible for reading and understanding the information in the investigator brochure or device risk information, including the potential risks and side effects of the drug or device.
- The investigator is responsible for maintaining adequate and accurate records in accordance with FDA regulations and to making those records available for inspection by the FDA. These records include correspondence with other investigators, the IRB, the sponsor, monitors, or the FDA; drug and device accountability records; case histories; consent forms; and documentation that consent was obtained prior to any participation in the study. Records must be maintained for a minimum of 2 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 approved for such. Other regulations, such as HIPAA, organizational policies, or contractual agreements with sponsors may necessitate retention for a longer period of time.

- The investigator is responsible for controlling drugs, biological products, and devices according to FDA regulations and the Controlled Substances Act, if applicable.
- The investigator proposing the clinical investigation will be required to provide a plan – to be evaluated by the IRB - that includes storage, security, and dispensing of the test article.
  - ❖ The investigator is responsible for investigational drug accountability that includes storage, security, dispensing, administration, return, disposition, and
  - ❖ records of accountability. Such details will be provided in the IRB submission and reviewed by the IRB and the Pharmacy Service for acceptability.
  - ❖ The investigator may delegate in writing, as part of the IRB submission, the responsibility detailed in 'a' above to the Pharmacy Service.
  - ❖ All devices received for a study must be stored in a locked environment under secure control with limited access. Proper instructions on the use of the device must be provided to the subjects. A log must be kept regarding the receipt, use, and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.
- The investigator shall furnish all reports required by the sponsor of the research including adverse events, progress reports, safety reports, final reports, and financial disclosure reports.
- The investigator will permit inspection of research records by the sponsor, sponsor representatives, HRPO and IRB representatives, the FDA, accrediting bodies, and any other agencies or individuals entitled to inspect such records under regulation, organizational policy, or contractual agreement.

E. Clinical Investigations of Drugs and Devices

1. IND/IDE Requirements

For studies evaluating the safety or effectiveness of medical devices or experiments using drugs, biologics, dietary supplements, and other compounds that may be considered a drug under FDA regulations, the investigator must indicate on the IRB application whether an IDE or IND is in place, and, if not, the basis for why an IDE or IND is not needed. Documentation must be provided by the sponsor or the sponsor-investigator. Documentation of the IND/IDE could be a:

- Industry sponsored study with IND/IDE number indicated on the protocol/research plan;
- Letter/communication from FDA;
- Letter/communication from industry sponsor; or
- Other document and/or communication verifying the IND/IDE.

For investigational devices, the study may be exempt from IDE requirements or, in the case of non-significant risk (NSR) device studies, follow abbreviated IDE requirements which do not require formal approval by the FDA. If a sponsor has identified a device within a study to be exempt from an IDE or NSR, then the investigator must include documentation with the submission providing the basis for the IDE exemption or NSR classification. If the FDA has determined that the device within a study is exempt from an IDE or NSR, documentation of that determination must be provided.

a) IND Exemptions

Under 21 CFR 312.2(b)(1), a clinical investigation involving a drug may be exempt from an IND application pending all of the following requirements are met:

- The clinical investigation includes a drug products that is lawfully marketed in the United States;
- The research is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug;
- The investigation not intended to support a significant change in the advertising for the product;

- The research does not involve a route of administration, dose, 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;
- The research is conducted in compliance with the requirements for IRB review as set forth in 21 CFR 56 and informed consent as set forth in 21 CFR 50;
- The research is conducted in compliance with the requirements of 21 CFR 312.7 (i.e., the research is not intended to promote or commercialize the drug product); and
- The research does not intend to invoke FDA regulations for planned emergency research [21 CFR 50.24].

b) IDE Exemptions

An IDE application is not required if the study meets one of the exemption categories in 21 CFR 812.2(c) that apply to human research. All criteria under each category must be true in order to meet the exemption category. IRB review and informed consent/authorization are still required in accordance with 21 CFR parts 56 and 50, respectively. For clinical investigations of devices, an IDE is not necessary if:

- Categories 1 & 2 - A clinical investigation with approved devices used in accordance with instructions for use / product labeling. The research involves a device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time. The research involves a device other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR 807 in determining substantial equivalence (a “501k” device);

- Category 3 – A clinical investigation that involves an in vitro diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
  - ❖ Is noninvasive;
  - ❖ does not require an invasive sampling procedure that presents significant risk;
  - ❖ Does not by design or intention introduce energy into a subject; and
  - ❖ Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure 21 CFR 812.2(c)(3);
- Category 4 – A clinical investigation with a marketed device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk;
- Categories 5 & 6 do not apply to human research - The research involves a device intended solely for veterinary use; the research involves a device shipped solely for research on or with laboratory animals and labeled in accordance with 21 CFR 812.5(c);
- Category 7 – A clinical investigation of a custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

c) Significant and Non-Significant Risk Device Studies

A device study is a Non-Significant Risk (NSR) Device study if it is not IDE exempt and does not meet the definition of a Significant Risk (SR) Device study.

Under 21 CFR 812.3(m), an SR device means an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare

of a subject;

- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- 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 subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

If applicable, the sponsor-investigator is responsible for providing the IRB with an explanation describing the basis for their initial determination of NSR and any other information that may help the IRB in evaluating the risk of the study (e.g., reports of prior investigations of the device).

If the FDA has already determined a study to be SR or NSR, documentation evidencing such should be provided to the IRB. The FDA's determination is final, and the IRB does not have to make the device risk determination. Otherwise, the IRB will review studies including devices in accordance with 21 CFR 812.2(m) to determine the device risk. The IRB may consult with the FDA or require the sponsor or investigator to obtain a determination from the FDA. The IRB will document the SR or NSR determination and the basis for it in the meeting minutes and provide the investigator with the determination in writing.

Non-significant risk device studies do not require submission of an IDE application to the FDA but must be conducted in accordance with the abbreviated requirements of IDE regulations (21 CFR 812.2(b)). Under the abbreviated requirements, the following categories of investigations are considered to have approved applications for IDE's, unless FDA has notified a sponsor under 812.20(a) that approval of an application is required:

- An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor (or sponsor-investigator):
  - ❖ Labels the device in accordance with 812.5;
  - ❖ Obtains IRB approval of the investigation after presenting the reviewing IRB with an explanation of why the device is not a significant risk device, and maintains such approval;
  - ❖ Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under Part 50 and documents it, unless documentation is waived by an IRB under 56.109(c).
  - ❖ Complies with the requirements of 812.46 with respect to monitoring investigations;
  - ❖ Maintains the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10);
  - ❖ Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), (7);
  - ❖ Complies with the prohibitions in 812.7 against promotion and other practices.

The Presbyterian IRB will not review a study including a SR device without an IDE approval order from the FDA.

XIV. HUMANITARIAN USE DEVICE (HUD)

A Humanitarian Use Device (HUD) is an approved (marketed) medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 8,000 individuals in the United States per year [21 CFR 814.3(n)]. Federal law requires that IRBs approve the use of a HUD at a facility. Once approved, the clinical use of the HUD may be considered as any other approved device, with the caution that effectiveness has not been shown in clinical trials.

A. Definitions

Humanitarian Device Exemption. A Humanitarian Device Exemption (HDE) is a "premarket approval application" submitted to FDA pursuant to Subpart A, 21 CFR Part 814 "seeking a humanitarian device exemption from the effectiveness requirements of sections 514 and 515 of the [FD&C Act] as authorized by section 520(m)(2) of the [FD&C Act]." HDE approval is based upon, among other criteria, a determination by FDA that the HUD will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from use of the device outweighs the risk of injury or illness from its use while considering the probable risks and benefits of currently available devices or alternative forms of treatment.

HDE Holder. An HDE Holder is a person who or entity that obtains to approval of an HDE from the FDA.

Humanitarian Use Device (HUD). A humanitarian use device is a device intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 8,000 individuals in the United States per year.

B. IRB Review Requirements

A Humanitarian Use Device (HUD) may only be used in a facility after an IRB has approved its use, except in certain emergencies. The HDE holder is responsible for ensuring that a HUD is provided only to facilities having an IRB constituted and acting in accordance with the FDA's regulations governing IRBs (21 CFR Part 56), including continuing review of use of the device.

When a HUD is used in a clinical investigation (i.e., research involving one or more subjects to determine the safety or effectiveness of the HUD), the full requirements for IRB review and informed consent apply (21 CFR 50 and 56) as well as other applicable regulations. It is essential to differentiate whether the HUD is being studied for the indication(s) in its approved labeling or for different indication(s). When the HUD is being studied for the indication(s) in its approved labeling, the IDE regulations at 21 CFR 812 do not apply. However, when the HUD is being studied for a different indication(s), 21 CFR 812 does apply, including the requirement for an FDA-approved IDE before starting the clinical investigation of a Significant Risk device.

C. Procedures

The relevant requirements and procedures for investigators and for IRB review described elsewhere in this manual apply to clinical investigations of HUDs. The material within this section applies to diagnostic or treatment uses of HUDs.

The health care provider seeking approval for diagnostic or treatment use of a HUD at PHS is responsible for obtaining IRB approval prior to use of the HUD at the facility and for complying with the applicable regulations, including those for medical device reporting, institutional policies, and the requirements of the IRB.

Health care providers seeking initial IRB approval for diagnostic or treatment use of a HUD for the indication(s) in the HUDs approved labeling should submit the following materials to the IRB:

- Application Form – HUD (non-research uses);
- A copy of the HDE approval letter from the FDA;
- A description of the device, such as a device brochure;
- The patient information packet for the HUD;
- The proposed clinical consent process;
- Other relevant materials (e.g., training certificates) as identified in the Application Form; and
- Conflict of interest disclosure from a physician requesting permission to use the HUD is not required for IRB review of a HUD and the HDE.

The IRB will review the proposal at a convened meeting ensuring that appropriate expertise is available either within the membership in attendance or via the use of consultants. The IRB will review the risks to patients that are described in the product labeling and other materials, the proposed procedures to ensure that risks are minimized, and will evaluate whether the risks are reasonable in relation to the potential benefits to patients at the facility. The IRB will evaluate the patient information packet and proposed consent process and will determine if the materials are adequate and appropriate for the patient population.

The IRB may specify limitations on the use of the device, require additional screening and follow up procedures, require interim reports to the IRB, require continuing review more often than annually, or set other conditions or requirements as appropriate to minimize risks to patients and ensure the safe use of the device in the facility.

Once use of the HUD is approved, the health care provider is responsible for submitting any proposed changes to the IRB-approved plan or patient materials and obtaining approval for those changes prior to implementation, unless the change is necessary to avoid or mediate an apparent immediate risk to a patient. Proposed changes may be submitted using the "Modification Request" form and should be accompanied by any revised materials or supporting documentation. The IRB may review these changes using expedited review procedures or refer the changes for review by the convened IRB.

The health care provider is responsible for submitting reports to the FDA, the IRB, and the manufacturer/HDE holder whenever a HUD may have caused or contributed to a death and must submit reports to the manufacturer (or to FDA and the IRB if the manufacturer is unknown) whenever a HUD may have caused or contributed to a serious injury (21 CFR 803.30 and 814.126(a)). Serious injury means an injury or illness that (1) is life-threatening, (2) results in permanent impairment of a bodily function or permanent damage to a body structure, or (3) necessitates medical or surgical intervention to preclude permanent impairment of a bodily function or permanent damage to a body structure (21 CFR 803.3). The specific requirements for this reporting are in the Medical Device Reporting (MDR) Regulation, at 21 CFR Part 803. The IRB will review these reports via either expedited or convened review, as appropriate, and will consider whether any changes are needed to the IRB-approved plan or patient materials.

The health care provider is responsible for submitting continuing review materials to the IRB sufficiently in advance of the expiration date to ensure IRB review and re-approval prior to expiration. Materials to be submitted include:

- The "Continuing Review Report – HUD" (non-research uses);
- Any safety reports or summaries provided by the HDE holder that had not previously been submitted;
- The current patient information packet, if applicable;
- The current consent, if applicable;
- Other materials as identified on the "Continuing Review Report – HUD" form; and
- Any other new relevant information or materials.

The IRB may conduct continuing review using expedited review procedures or review by the convened IRB.

D. Emergency Uses of HUDs

If an appropriately trained and licensed health care provider in an emergency situation determines that IRB approval for the use of the HUD at the facility cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be used without prior IRB approval. The health care provider must, within 5 days after the emergency use of the device, provide written notification of the use to the IRB including the identification of the patient involved, the date of the use, and the reason for the use.

If a HUD is approved for use in a facility, but an appropriately trained and licensed health care provider wants to use the HUD outside its approved indication(s) in an emergency or determines that there is no alternative device for a patient's condition, the physician should consult with the HDE holder and IRB in advance if possible, obtain informed consent if possible, and ensure that reasonable measures are taken to protect the well-being of the

patient such as a schedule and plan for follow up examinations and procedures to monitor the patient, taking into consideration the patient's specific needs and what is known about the risks and benefits of the device. The provider should submit a follow up report to the HDE holder and the IRB and must comply with medical device reporting requirements.

The IRB may require additional reports, patient protection measures, or other requirement, as appropriate given the specifics of the situation.

XV. EXPANDED ACCESS

A. Expanded Access to Investigational Drugs, Biologics, and Devices

Expanded access pathways, also referred to as "compassionate use," are designed to make investigational medical products available as early in the drug and device evaluation process as possible to patients without therapeutic options, because they have exhausted or are not a good candidate for approved therapies and cannot enter a clinical trial. Expanded access refers to access to investigational medical products outside of a clinical trial, where the intent is treatment, rather than research. Because the investigational products have not yet been approved by FDA as safe and effective, it is important to remember that the product may not be effective and there may be unexpected serious adverse effects and to take appropriate measures to ensure that this is understood by the patient or their representative and to monitor for safety.

B. Expanded Access to Investigational Drugs and Biologics

The FDA's expanded access rule for investigational drugs, including biologics classified as drugs, is intended to improve access to investigational drugs, and approved drugs with limited availability under a risk evaluation and mitigation strategy (REMS), for patients with serious or immediately life-threatening diseases or conditions who lack other therapeutic options and may benefit from the investigational diagnostic or therapy.

Under the FDA's expanded access rule, access to investigational drugs for treatment purposes will be available to:

- Individual patients, including in emergencies (21 CFR 312.310)
- Intermediate-size patient populations (21 CFR 312.315)
- Larger populations under a treatment protocol or treatment IND (21 CFR 312.320) Expanded Access submissions are categorized by FDA as either "Access Protocols", which involve a protocol amendment to an existing IND, or "Access INDs", which are managed separately from any existing INDs.

The FDA has also established a rule, "Charging for Investigational Drugs Under an Investigational New Drug Application," to:

- Provide general criteria for authorizing charging for an investigational drug [21 CFR 312.8(a)]
- Provide criteria for charging for an investigational drug in a clinical trial [21 CFR 312.8(b)]
- Set forth criteria for charging for an investigational drug under the expanded access for treatment use
- Clarify what costs can be recovered

Investigators, when seeking access to drugs under the expanded access provisions, should work closely with the sponsor or manufacturer, the FDA, and the PHS HRPO, to determine the appropriate access mechanism and ensure that proper regulatory procedures are followed.

Unless the conditions that permit an emergency use exemption are satisfied, prospective IRB review and approval are required for all expanded access uses, including clinical patient use. The IRB Chair, or designee, may approve the expanded access use through the expedited review process.

C. Expanded Access to Investigational and Unapproved Medical Devices

As with investigational drugs, unapproved medical devices may normally only be used in humans in an approved clinical trial under the supervision of a participating clinical investigator. However, there may be circumstances under which a health care provider may wish to use an unapproved device when a patient is facing life-threatening circumstances or suffering from a serious disease or condition for which no other alternative therapy or diagnostic exists or is a satisfactory option for the patient.

FDA has made the following mechanisms available for these circumstances:

- Emergency Use
- Planned Emergency Research
- Compassionate Use (or Single Patient/Small Group Access)
- Treatment Use
- Continued Access

Investigators, when seeking access to investigational or unapproved devices under one of the above provisions, should work closely with the sponsor or manufacturer, the FDA, and the PHS HRPO/IRB Coordinator, to ensure that proper regulatory procedures are followed.

Unless the conditions that permit an emergency, use exemption are satisfied, prospective IRB review and approval is required. The IRB Chair, or designee, may approve the expanded access use through the expedited review process. For more information: https://www.fda.gov/medical-devices/investigational-device-exemption-ide/expanded-access-medical-devices.

XVI. EMERGENCY USE

If an appropriately trained and licensed health care provider, in an emergency situation, determines that IRB approval for the use of an investigational drug/device at the facility cannot be obtained in time to prevent serious harm or death to a patient, the drug or device may be used without prior IRB approval. The health care provider must, within 5 days after the emergency use of the drug or device, provide written notification of the use to the IRB including the identification of the patient involved, the date of the use, and the reason for the use.

Note: DHHS regulations do not permit research activities to be started, even in an emergency, without prior IRB approval. When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject under 45 CFR Part 46. However, nothing in the DHHS regulations at 45 CFR Part 46 is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe.)

A. Emergency Exemption from Prospective IRB Approval

Under FDA regulations [21 CFR 56.104(c)], FDA exempts the emergency use of a test article from the requirement for prospective IRB approval, provided that such emergency use is reported to the IRB within five working days. Any subsequent use of the test article in the facility requires IRB review. However, FDA acknowledges that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had enough time to convene a meeting to review the issue.

FDA defines emergency use as the use of a test article in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not enough time to obtain IRB approval [21 CFR 56.102(d)]. If all conditions described in 21 CFR 56.102(d) exist, then the emergency exemption from prospective IRB approval found at 21 CFR 56.104(c) may be used.

Life-threatening, for the purposes of 21 CFR 56.102(d), includes both life-threatening and severely debilitating.

Unless the provisions for an emergency exception from the informed consent requirement are satisfied, informed consent must be obtained in accordance with 21 CFR 50 and documented in writing in accordance with 21 CFR 50.27.

The IRB must be notified within five working days when an emergency exemption is used. The IRB Chair or a designee will review the report to verify that circumstances of the emergency use conformed to FDA regulations. This must not be construed as an approval for the emergency use by the IRB, as an exemption from the requirement for prospective IRB approval has been invoked. When appropriate, in the event a manufacturer requires documentation from the IRB, the IRB will provide 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). Reports of emergency uses will be brought to the convened IRB for their information.

Investigators are reminded that they must comply with all other organizational policies and requirements applicable to the use of the investigational or unapproved article.

B. Emergency Exception from the Informed Consent Requirement

An exception under FDA regulations at 21 CFR 50.23(a-c) permits the emergency use of an investigational or unapproved test article without informed consent where the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions:

- The subject is confronted by a life-threatening situation necessitating the use of the test article;
- Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject;
- Time is not sufficient to obtain consent form the subject's legally authorized representative; and
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the life of the subject.

If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent physician determination in advance of using the test article, the determinations of the clinical investigator shall be made and, within five working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

The IRB must be notified within five working days when an emergency exception is used. The IRB Chair or a designee will review the report to verify that circumstances of the emergency exception conformed to FDA regulations.

XVII. REPORTABLE EVENTS

Regulations require an organization to have written procedures for ensuring prompt reporting to the IRB of proposed changes in research activity, and for ensuring that the investigators will conduct the research activity in accordance with the terms of the IRB approval until any proposed changes have been reviewed and approved by the IRB (except when necessary to eliminate apparent immediate hazards to the subject; and for the reporting of UAPs involving risk to subjects or others; and any instances of serious or continuing non-compliance to the IRB, organizational officials, and applicable federal agencies. In order to comply with this requirement, PHS has procedures to review issues that arise during the conduct of research.

The following section provides definitions and procedures regarding issues that arise during the conduct of

research that must be reported to the IRB.

A. Definitions

Adverse Event. For the purposes of these policies and procedures, an adverse event (AE) is any untoward or unfavorable occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether considered related to the subject's participation in the research. Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

Continuing Noncompliance. A repeated pattern or un- rectified instance of noncompliance by an individual investigator or research staff member either on a single protocol or multiple protocols that in the judgment of the convened IRB, suggests a likelihood that instances of non-compliance will continue unless the IRB or organization intervenes.

Protocol/Research Plan Deviations. A protocol/research plan deviation is defined as a variation from the IRB approved research plan that happens without prior review and approval of the IRB (e.g., study visit outside protocol/research plan window, blood work drawn outside protocol/research plan window, etc.). Depending on the details, protocol/research plan deviations may be determined to be non-compliance (serious, continuing, or otherwise).

Protocol/Research Plan Exceptions. Protocol/research plan exceptions are planned deviations from the protocol/research plan. Exceptions are anticipated and must occur with prior agreement from the sponsor, if applicable, and approval by the IRB. If an exception is implemented without IRB approval, it is a deviation, even when the sponsor has approved.

Related. There is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

Serious Non-compliance. Non-compliance that, in the judgment of the convened IRB, creates an increase in risks to subjects, adversely affects the rights, welfare or safety of subjects, or adversely affects the scientific integrity of the study. Willful violation of regulations and/or policies may also constitute serious non-compliance. Noncompliance may involve one or more of the following: (1) bringing harm to research participants; (2) exposing research participants to a significant risk of substantive harm; (3) compromising the privacy and confidentiality of research participants; (4) causing damage to scientific integrity of the research data that has been collected; (5) engaging in willful or knowing noncompliance; (6) impacting ethical principles adversely.

Unanticipated Adverse Device Effect. An Unanticipated Adverse Device Effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety, or welfare of subjects [21 CFR 812.3(s)].

Unanticipated Problems Involving Risk to Participants or Others. Unanticipated problems (UAPs) involving risks to subjects or others refer to any incident, experience, outcome, or new information that: (1) Is unexpected; (2) Is related or possibly related to participation in the research; and (3) Indicates that subjects or others are at a greater risk of harm (including physical, psychological, economic, legal or social harm) than was previously known or recognized.

Unexpected. The incident, experience or outcome is not expected (in terms of nature, severity, or frequency) given the research procedures that are described in the study- related documents, such as the IRB-approved research protocol/research plan and informed consent documents; and the characteristics of the subject

population being studied.

B. Procedures

1. Reporting

Adverse events in clinical trials must be reported to the sponsor in compliance with FDA regulations and sponsor requirements. Unless specifically required by the IRB (e.g., first in human clinical trials), the PHS IRB does not accept reports of adverse events and IND Safety Reports that do not meet the definition of a UAP involving risks to subjects or others.

If investigators are uncertain but believe that the event might qualify as a UAP, a report should be submitted.

Investigators must report the following events or issues to the IRB as soon as possible, but in no case later than five business days after the investigator first learns of the event.

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy.)
- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be a UAP. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). A summary and analyses supporting the determination should accompany the report.
- An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered a UAP involving risk to human subjects. A discussion of the divergence from the expected specificity or severity should accompany the report.
- A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). A discussion of the divergence from the expected rate should accompany the report.
- Changes made to the research without prior IRB approval to eliminate apparent immediate hazards to the subject(s).
- Adverse events involving direct harm to subjects enrolled by the investigator (i.e., local adverse events), which in the opinion of the investigator or sponsor, may represent a UAP involving risk to subjects or others.
- An unanticipated event related to the research that exposes subjects to potential risk but that does not involve direct harm to subjects (e.g., lost laptop).
- An unanticipated event related to the research that results in actual harm or exposes individuals other than the research participants (e.g., investigators, research assistants, students, the public, etc.) to potential risk.
- IND Safety Reports from sponsors that meet the criteria for a UAP involving risk to subjects.
- Data and Safety Monitoring Reports that indicate that risks are greater than previously known or that indicate that the study requires modification or should be suspended or terminated.

- New information that indicates an increase to the risks or decrease to potential benefits of the research. Examples include:
  - ❖ An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB.
  - ❖ A paper is published from another study that shows that the risks or potential benefits of the research may be different than initially presented to the IRB.
- New information that may impact the willingness of participants to continue in the research.
- A breach of confidentiality.
- Incarceration of a participant in a study not approved to enroll prisoners.
- Complaint of a subject when the complaint involves the health, safety, or rights of the subject or indicates unexpected risks, possible non-compliance, or cannot be resolved by the research team.
- Protocol/research plan deviations.
- Sponsor or lead investigator/coordinating center-imposed suspension or termination of some or all research activities.
- Unanticipated adverse device effects (UADEs). (Note: Regulations require that UADEs be reported to the sponsor and IRB as soon as possible but in no event later than ten working days after the investigator first learn of the event [21 CFR 812.150(a)(1)]).
- Any other adverse event or safety finding (e.g., based on animal or epidemiologic data) that indicates subjects or others might be at risk of serious, unanticipated harms that are reasonably related to the research. These would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects. An explanation of the conclusion should accompany the report.

2. Submission of Reports

Investigators or the study team must report potential problems or issues with the research to the HRPO in writing using the "Event Reporting" form which includes questions about the following:

- Detailed information about the event or issue, including relevant dates.
- Any corrective and preventative actions planned or already taken, to ensure that the issue or problem is corrected and will not occur again.
- An assessment of whether any subjects or others were placed at risk as a result of the event or suffered any harm (e.g., physical, social, financial, legal, or psychological) and any plan to address these consequences.
- If a report from a sponsor is the basis for the report of a possible UAP involving risks to subjects or others, or a sponsor has requested the submission to the IRB, the report should be accompanied by an analysis from the sponsor detailing (1) how the event or problem satisfies the definition of a UAP, (2) proposed study- wide corrective actions or modifications to the research along with a timeline for anticipated completion of the actions, and (3) whether or not the problem has been reported as a UAP to any relevant federal agencies.
- If a sponsor or lead investigator or coordinating center suspends or terminates some or all research activities, the report should be accompanied by information from the sponsor detailing (1) why the suspension or termination was enacted, (2) if it was due to a possible UAP (in which case the information in "d" above must be included), (3) any impact on subjects or actions to be taken to protect subjects, (4) any plan to inform subjects of the suspension or termination and other pertinent information, and (5) whether the suspension or termination has been reported to any relevant federal agencies.
- Any other relevant information.
- Any other information requested by the HRPO. Reports will be screened by the HRPO/IRB Coordinator and immediately forwarded to the IRB Chair or a designee if the coordinator believes that immediate

intervention may be required to protect participants or others from serious harm.

Upon receipt of a report from someone other than the investigator or study staff on behalf of the investigator, the investigator will be notified when appropriate.

3. IRB Procedures for Handling Reportable Events

Upon receipt of the "Event Reporting" form from an investigator, the HRPO/IRB staff checks the form for completeness. If any applicable sections of the form are incomplete or have been answered unsatisfactorily, the HRPO/IRB staff will contact the investigator or the designated contact person to obtain additional information. Corrections are documented in the IRB file, indicating the date, the person spoken with, and the HRPO/IRB staff making the correction.

The IRB Chair and/or other experienced member(s) designated by the IRB Chair receives and reviews the report. The IRB Chair (or designee) will make the initial determination as to whether the event is to be regarded as a UAP and/or non-compliance.

Based on the information received from the investigator, the IRB Chair or designee may suspend research to ensure protection of the rights and welfare of participants. Suspension directives made by the IRB Chair or designee must be reported to a meeting of the convened IRB and must follow notification procedures for IRB suspensions.

The IRB or the IRB Chair (or designee) has authority to require submission of more detailed contextual information by the investigator, the sponsor, the study coordinating center, or DSMB/DMC about any event occurring in a research study as a condition of the continuation of the IRB's approval of the research.

If the IRB Chair or designee determines that the problem does not possibly meet the definition of a UAP or serious or continuing non-compliance, the reviewer will consider whether any corrective or preventative actions are sufficient and whether modifications to the research plan, consent, or corrective action plan may be necessary, and refer the matter to the convened IRB for review if appropriate. The results of the review will be recorded in the study record and communicated to the investigator.

If the reviewer determines that the event may be a UAP, the report will be reviewed at a convened IRB meeting and must follow notification procedures for UPs.

C. UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS (UPIRTSO)

PHS complies with DHHS and FDA regulations which require organizations to have written policies on reporting unanticipated problems (UAPs) involving risks to subjects or others to the IRB, organizational officials and relevant federal agencies and departments.

The following procedures describe how UAPs are handled in research under the auspices of PHS. Unless specifically required by the IRB, the PHS IRB does not accept reports of adverse events that do not meet the definition of a UAP.

1. IRB Review

After a determination of a possible UAP involving risk to subjects or others, the report will be placed on the agenda for the next convened IRB meeting and a primary reviewer will be assigned. IRB members, including the primary reviewer, will be provided access submission documents.

After review of the study and event report, the full IRB will make findings and recommendations based on the following considerations:

- Whether the reported event is a UAP according to the definition in this policy;
- What action in response to the report is appropriate; and

- Whether suspension or termination of approval is warranted.

If the IRB finds that the event is not a UAP, according to the definition in the policy, the IRB may recommend any of the following actions:

- No action;
- Requiring modifications to the protocol/research plan;
- Revising the continuing review timetable;
- Modifying the consent process;
- Modifying the consent document;
- Providing additional information to current participants (e.g., whenever the information may relate to the subject's willingness to continue participation);
- Providing additional information to past subjects;
- Requiring additional training of the investigator and/or study staff; and
- Other actions as appropriate given the specific circumstances.

If the IRB finds that the event is a UAP, according to the definition in the policy, the IRB may recommend any of the following actions:

- Requiring modifications to the protocol/research plan;
- Revising the continuing review timetable;
- Modifying the consent process;
- Modifying the consent document;
- Providing additional information to current participants (e.g., whenever the information may relate to the subject's willingness to continue participation);
- Providing additional information to past participants;
- Requiring additional training of the investigator and/or study staff;
- Reconsidering approval;
- Requiring that current subject's re-consent to participation;
- Monitoring the research;
- Monitoring consent;
- Referral to other organizational entities (e.g., legal counsel, risk management, Institutional Official);
- Suspending the research approval;
- Terminating the research approval; and
- Other actions as appropriate given the specific circumstances.

If a report suggests that participant safety is at risk, the IRB may immediately suspend or terminate the research. Any suspension or termination of research by the IRB must be promptly reported to the IO and relevant federal regulatory agencies through the IO. This should be done in writing.

If, after reviewing a report, the IRB finds that the event is a UAP and that suspension or termination of approval is warranted, the IRB will:

- Notify the investigator in writing of its findings, with copies to the investigator's department head or organizational unit leader and other affected units; and
- Report its findings and recommendations to the IO for further reporting to the appropriate federal officials.

D. NON-COMPLIANCE

As part of its commitment to protecting the rights and welfare of human subjects in research, PHS reviews all reports and allegations of non-compliance and takes any necessary action to ensure the ethical conduct of

research.

All Investigators and other study personnel involved in human subject research are required to comply with all laws and regulations governing their research activities, as well as with requirements and determinations of the IRB. The following procedures describe how complaints and allegations of non-compliance are handled by the IRB.

1. **Reporting**

   Investigators and their study staff are required to report instances of possible non-compliance. The investigator is responsible for reporting any possible non-compliance by study personnel to the IRB. However, any individual or employee may report observed or apparent instances of non-compliance to the PHS IRB. In such cases, the reporting party is responsible for making these reports in good faith, maintaining confidentiality, and cooperating with any IRB and/or organizational review of these reports.

   If an individual, whether investigator, study staff or other, is uncertain whether there is cause to report non-compliance, he or she may contact the HRPO/IRB Coordinator or IRB Chair directly to discuss the situation informally.

   Reports of non-compliance must be submitted to the HRPO within ten working days of discovery of this non-compliance. The report must include a complete description of the non- compliance including any personnel involved. Complainants may choose to remain anonymous.

2. **Review of Allegations of Non-Compliance**

   All allegations of non-compliance will be reviewed by the IRB Chair or a designee, who will review the report or allegation and may request additional information or an audit of the research in question.

   When the Chair or designee determines that non-compliance did not occur because the incident was within the limits of an approved protocol/research plan for the research involved, the determination is reported in writing to the investigator and, if applicable, the reporting party. The determination letter will be copied to the IO in cases where the IO and any other parties had been notified of the allegation at the outset.

   If in the judgment of the IRB Chair or designee, the report or allegation does represent non-compliance, the non-compliance will be processed according to Section 16.4 (“Review of Findings of Non-Compliance”).

   If in the judgment of the IRB Chair or designee, any allegation, or findings of non-compliance warrants suspension of the research before completion of any review or investigation to ensure protection of the rights and welfare of participants, the IRB Chair may suspend the research as described in Section 8 with subsequent review by the IRB.

   The Chair or designee may determine that additional expertise or assistance is required to make these determinations and may request assistance from HRPO or IRB personnel or form an *ad hoc* committee to assist with the review and fact gathering process. When an *ad hoc* committee assists in the review process; the Chair or designee is responsible for ensuring that minutes of the meeting are generated and kept on file to support any determinations or findings made by the *ad hoc* committee.

3. **Review of Findings of Non-Compliance**

   a) Non-Compliance that is Not Serious nor Continuing

   When the Chair or designee determines that the non-compliance occurred, but the non- compliance does not meet the definition of serious or continuing non-compliance, the determination is reported in writing to the investigator and, if applicable, the reporting party. The Chair or designee will review any corrective and preventative actions taken or proposed by the investigator and determine if the actions are sufficient or if additional actions may be necessary. If additional actions may be warranted, the

matter will be referred to the convened IRB for review.

b) Serious and/or Continuing Non-Compliance

When the Chair or designee determines that non-compliance has occurred and that the non-compliance may meet the definition of serious or continuing non-compliance, the report of non-compliance is referred for review by the IRB at the next available convened meeting. However, the Chair or designee may use discretion and call an emergency IRB meeting should the circumstances warrant an urgent meeting.

All initial findings of potential serious or continuing non-compliance referred to the IRB will be reviewed at a convened meeting.

At this stage, the IRB may:

- Find that there is no issue of non-compliance;
- Find that there is non-compliance that is neither serious nor continuing and that an adequate corrective and/or preventive action plan is in place;
- Find that there is serious or continuing non-compliance and modify or require a corrective and/or preventive action plan; or
- Find that additional information is required to make a final determination. In this instance, the committee will request additional information, and indicate whether such information will be reviewed by the full committee or a subcommittee thereof; if the latter, a report will be written by the subcommittee for review by the full committee for final determination.

4. Final Review

The IRB will make a final determination as to whether the non-compliance is serious or continuing. Upon a finding of serious or continuing non-compliance, the IRB's possible actions could include, but are not limited to:

- Request a corrective and/or preventive action plan from the investigator;
- Verification that subject selection is appropriate;
- Observation of informed consent;
- Require an increase in data and safety monitoring of the research activity;
- Request a directed audit of areas of concern;
- Request a status report after each participant receives intervention;
- Modify the continuing review cycle;
- Require additional investigator and staff education;
- Notify current subjects (e.g., if the information about the non-compliance might affect their willingness to continue participation);
- Require modification of the protocol/research plan;
- Require modification of the information disclosed during the consent process;
- Require current subjects to re-consent to participation;
- Suspend the study (see below); or
- Terminate the study (see below).

In cases where the IRB determines that the event of non-compliance also meets the definition of a UAP involving risks to subjects or others, it will be managed according to Section 15.

The investigator is informed of the IRB determination and the basis for the determination in writing. If the IRB determines that the non-compliance was serious or continuing, the results of the final review will be reported as described below in Section 18.

E. COMPLAINTS

All complaints, written, or oral (including telephone complaints), and regardless of point of origin, are recorded in writing and forwarded to the IRB Chair or a designee.

The IRB Chair or a designee will promptly manage (or delegate to the HRPO Coordinator to handle) and, if necessary, investigate all complaints, concerns, and appeals. This includes complaints, concerns, and appeals from investigators, research participants, and others. Upon receipt of the complaint, the IRB Chair or a designee will make a preliminary assessment whether the complaint warrants immediate suspension of the research project.

If a suspension is warranted, the procedures in Section 8 will be followed. If the complaint meets the definition of non-compliance, it will be considered an allegation of non-compliance according to Section 16. If the complaint meets the definition of a UAP involving risk to subjects or others, it will be handled according to Section 15.

If the complaint is a query from a subject regarding study procedures, payments not received, etc., it will be forwarded to the investigator/study team for handling. The investigator/study team will be required to inform the IRB when the matter is closed (and the subject is satisfied with the answer).

Within three business days of receipt of the complaint, the HRPO/IRB Coordinator will generate a letter to acknowledge that the complaint has been received and is being investigated, if the person making the complaint provided contact information. Finding of the complaint will be provided by correspondence at the end of the investigation.

In cases where there is disagreement between the IRB and the complainant regarding the nature and extent of the findings and these disagreements cannot be resolved, the complainant and/or the IRB may make an appeal to the IO within ten business days for a resolution of the matter. The IO may organize a meeting to help facilitate discussion between the IRB and the complainant. While the IO may provide input and make recommendations to the complainant and IRB for expeditious resolution of the matter, final determinations for approval/disapproval remain under the purview of the IRB.

Because the IO is responsible for policies and procedures followed by the IRB, the IO may review IRB decisions to ensure that the decision-making process is appropriate. If the IO has concerns regarding the process that the IRB has followed in making a decision, he/she may request that the IRB reconsider the decision. However, the IO cannot overrule an IRB decision.

F. EXTERNAL REPORTING

Federal regulations require prompt reporting to appropriate organizational officials and, as applicable, the federal department or agency head or the FDA, of (i) any UAP involving risks to subjects or others; (ii) any serious or continuing non-compliance with this policy or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval. PHS IRB complies with this requirement as follows.

1. **Procedures**

   The HRPO/IRB Coordinator will initiate these procedures as soon as the IRB takes any of the following actions:

   - Determines that an event may be considered a UAP involving risks to participants or others;
   - Determines that non-compliance was serious or continuing; or
   - Suspends or terminates approval of research.

   The HRPO/IRB Coordinator or designee is responsible for preparing reports or letters which includes the following information:

   - The nature of the event (UAP involving risks to participants or others, serious or continuing non-

compliance, suspension, or termination of IRB approval of research);

- Name of the institution conducting the research;
- Title of the research project and/or grant proposal in which the problem occurred;
- Name of the investigator on the project;
- Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement);
- A detailed description of the problem including the findings of the organization and the reasons for the IRB's decision;
- Actions the institution is taking or plans to take to address the problem (e.g., revise the protocol/research plan, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.); and
- Plans, if any, to send a follow-up or final report by the earlier of:
  - ❖ A specific date.
  - ❖ When an investigation has been completed or a corrective action plan has been implemented.
- The IRB Chair and the IO review the letter and recommend modifications as needed.
- The IO is the signatory for all correspondence from the facility.
- The HRPO/IRB Coordinator or designee sends a copy of the report to:
  - ❖ The IRB by including the letter in the next agenda packet as an information item
  - ❖ The IO
  - ❖ The following federal agencies: (1) DHHS/OHRP; (2) FDA; (3) Department of Defense (DoD) as applicable.
  - ❖ Investigator
  - ❖ Sponsor, if the study is sponsored
  - ❖ The PHS Privacy Officer, if the event involved unauthorized use, loss, or disclosure of individually identifiable patient information from a covered entity
  - ❖ The PHS Cyber Security Officer, if the event involved violations of information security requirements of that organization
  - ❖ Compliance Officer
  - ❖ Others as deemed appropriate by the IO.

The HRPO/IRB Coordinator ensures that all steps of this policy are completed within sixty working days of the determination. For more serious actions, the HRPO Director will expedite reporting.

XVIII. RESPONSIBILITIES OF STUDY PERSONNEL

A. Types of Study Personnel

1. Principal Investigators (PI) and Co-Principal Investigators

Principal Investigators (PI) are responsible for the conduct of research. They may delegate tasks to appropriately trained and qualified members of their research team. However, investigators must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibilities.

At PHS, only affiliated investigators may function as the PI, including student PIs, on a research project involving human subjects. The PI has ultimate responsibility for the research activities.

Student investigators must be PHS staff members in order to initiate a research project at PHS. Student investigators must also identify a study mentor who will provide guidance and oversight of the proposal development/submission process and the conduct of the research. Study mentors must formally approve

and sign off on student applications.

PIs will ensure that research designed and conducted by students/residents has sound research design and is appropriately supervised.

Studies that require expertise or skills beyond those held by the PI must either be modified or have expertise and skills supplemented by the inclusion of one or more additional qualified co- investigators.

2. **Sub-Investigators**

   A sub-investigator is any individual other than the PI who is involved in the conduct of a research study. Such involvement could include:

   - Obtaining information about living individuals by intervening or interacting with them for research purposes;
   - Obtaining identifiable private information about living individuals for research purposes;
   - Obtaining the voluntary informed consent of individuals to be subjects in research; and
   - Studying, interpreting, or analyzing identifiable private information or data for research purposes.

3. **Key Personnel**

   Other study personnel may include Study Coordinator, Regulatory Coordinator, Ancillary Staff and Research Assistant.

B. Responsibilities

In order to satisfy the requirements of this policy, Principal Investigators who conduct research involving human subjects must:

- Develop and conduct research that is in accordance with the ethical principles in the Belmont Report;
- Develop a research plan that is scientifically sound and minimizes risk to the subjects;
- Incorporate into the research plan a plan to ensure the just, fair, and equitable recruitment and selection of subjects;
- When some or all the subjects are likely to be vulnerable to coercion or undue influence (e.g., children, prisoners, pregnant women individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons), include additional safeguards in the study to protect the rights and welfare of these subjects;
- Ensure that the research plan includes adequate provisions for the monitoring of subjects and data to ensure the safety of subjects;
- Ensure that there are adequate provisions to protect the privacy interests of subjects;
- Ensure that there are adequate provisions to protect data confidentiality and interests of subjects, including an information security plan that considers the collection, storage, maintenance, analysis, and transmission of data and other identifiable information;
- Have sufficient resources necessary to protect human subjects, including:
  - ❖ Access to a population that would allow recruitment of the required number of subjects.
  - ❖ Sufficient time to conduct and complete the research.
  - ❖ Adequate numbers of qualified staff.
  - ❖ Adequate facilities.
  - ❖ Necessary equipment.
  - ❖ A plan to ensure proper supervision of the research including a plan for periods of absence or decreased availability.
  - ❖ Availability of medical, psychological, or other support that subjects might require during or as a consequence of their participation in the research.

- Ensure that all procedures in a study are performed with the appropriate level of supervision and only by individuals who are licensed or otherwise qualified to perform such under the laws of New Mexico and the policies of PHS;
- Ensure that all study personnel are educated in the regulatory requirements regarding the conduct of research and the ethical principles upon which they are based;
- Ensure that all persons assisting with the research are adequately trained and informed about the protocol/research plan and their specific duties and functions.
- Promptly report any changes in, addition to, or departure of investigators or research staff to the IRB for evaluation and approval (note that investigators and staff may not begin work on the research until IRB-approved);
- Protect the rights, safety, and welfare of participants;
- Ensure that when private health information is used, legally effective HIPAA Authorization is obtained for each subject unless the IRB has approved a waiver of the requirement;
- Ensure that the language in the consent form is consistent with that in the protocol/research plan and, when applicable, in the HIPAA authorization;
- Obtain and document informed consent and ensure that no human subject is involved in the research prior to obtaining consent or consent/permission from their legally representative, unless a waiver of the requirement has been approved by the IRB;
- Have a procedure to receive questions, complaints, or requests for additional information from subjects and respond appropriately;
- Ensure that all information provided to the IRB is accurate and complete so that the IRB may fulfill its responsibilities to review the research and make the required determinations;
- Ensure that all research involving human subjects receives IRB review and approval in writing or a determination of exemption before research begins;
- Ensure that all research involving human subjects is reviewed by other experts and organizational components and committees as applicable to the research;
- Comply with all IRB decisions, conditions, and requirements;
- Ensure that studies receive timely continuing IRB review and approval;
- Report UAPs, deviations, complaints, non-compliance, suspensions, terminations, and any other reportable events to the IRB;
- Notify the IRB if information becomes available that suggests a change to the potential risks or benefits of the research
- Obtain IRB review and approval before changes are made to the research unless a change is necessary to eliminate apparent immediate hazards to the subject(s);
- Seek HRPO or IRB assistance when in doubt about whether proposed research requires IRB review;
- Retain records for the time period and in the manner required by applicable regulations, contractual agreements, and organizational policies.
- Additional investigator responsibilities, including specific responsibilities for investigators engaged in FDA-regulated research are described elsewhere in this document.

C. Investigator Records

Under these policies investigators must maintain, at a minimum but not limited to, the following research records. In addition, investigators must also comply with all record-keeping sponsor requirements.

1. Study Records

- Individual subject records
- Recruitment materials

- Documentation of consent process (who, what, when and how)
- Signed consent and HIPAA authorization forms
- UAPs and "Event Reporting Forms"
- Subject complaint reports
- Results of all procedures conducted on the subject, including final visit (if no final visit, reason: e.g., removal from study, withdrawal from study, death).

2. Regulatory Records

- Most recent IRB-approved protocol/research plan
- Previous versions of protocol/research plan
- All correspondence (i.e., approvals, reporting forms and responses, etc.) to and from the IRB
- All correspondence with the sponsor and others regarding the study
- "Continuing Review Report" forms
- "Modification Request with Exceptions" forms
- Investigational product accountability records, when applicable

3. Record Retention

Investigator records must be retained in accordance with regulatory, organizational and sponsor or grantor requirements, but no less than seven years following the completion of the research. All records must be maintained securely with limited access. Disposal of investigator records must be done in such a manner that no identifying information can be linked to research data.

4. Subject Recruitment Materials

The FDA and DHHS consider advertising (subject recruitment) to be the first component in the informed consent process. Therefore, the PHS IRB must review and approve recruitment methods and content of the materials to ensure adequate subject protection. The IRB must review the information contained in all advertisements and the mode of their communication. Advertisements cannot be displayed or used until the IRB has approved the final copy of printed ads and the final version of audio/video tape-recorded advertisements.

Federal regulations require that the institutional human research protection program and investigators protect potential and current research subjects from coercion or undue influence, and this requirement underpins PHS IRB advertising guidelines. Federal regulations also require investigators to use fair and equitable recruitment practices. The IRB has established the following requirements for advertisements seeking subjects to participate in research studies at PHS.

All advertisements shall be written in simple language (eighth grade reading level). Please use the Flesch-Kincaid test or other readability tool to analyze the grade level of your materials before submitting to the PHS IRB.

Ads should be submitted electronically by the investigator through the Presbyterian HRPO electronic submission platform as part of new protocol submissions and amendments. An ad must be re-submitted to the PHS IRB for approval, via an amendment, when any revisions are made to the IRB-approved version of the ad. All ads must have PHS IRB approval before being exhibited.

5. Distribution of Ads Within PHS, Clinics, and Hospitals

After IRB approval, research ads can be posted via approved venues (PHS.org, print publications, etc.). Research posters, flyers and brochures can be placed in designated areas within clinics and clinical departments at PHS with department management approval. Posters and flyers are prohibited on walls, lobbies, restrooms, stairwells, hallways, elevators, and other general public areas.

6. Internet Postings

OHRP guidance on internet website advertising, issued September 20, 2005, may be found at: http://www.hhs.gov/ohrp/policy/clinicaltrials.html. FDA guidance on advertisements and recruiting study subjects may be found at: http://www.fda.gov/oc/ohrt/irbs/toc4.html#recruiting (FDA Information Sheets, Guidance for IRBs, and Clinical Investigators, 1998 Update). This Guidance also addresses the question of internet postings and IRB review:

> *'IRB review and approval of listings of clinical trials on the internet would provide no additional safeguard and is not required when the system format limits the information provided to basic trial information, such as: the title; purpose of the study; protocol summary; basic eligibility criteria; study site location(s); and how to contact the site for further information. Examples of clinical trial listing services that do not require prospective IRB approval include the National Cancer Institute's cancer clinical trial listing (PDQ) and the government-sponsored AIDS Clinical Trials Information Service (ACTIS). However, when the opportunity to add additional descriptive information is not precluded by the data base system, IRB review and approval may assure that the additional information does not promise or imply a certainty of cure or other benefit beyond what is contained in the protocol and the informed consent document.'*

In keeping with DHHS and FDA Guidance, the PHS IRB has determined that IRB review/approval for brief internet postings is not necessary provided that the information is limited to:

- Study title;
- Purpose of the study;
- Protocol summary;
- Basic eligibility criteria;
- Study site location(s); and
- How to contact the study site for further information.

When information posted on a clinical trial website goes beyond directory listings with the basic descriptive information given above, such information is considered part of the informed consent process and therefore requires IRB review and approval. Information exceeding such basic listing information includes descriptions of clinical trial risks and potential benefits, or solicitation of identifiable information from potential research subjects.

OHRP guidance states that IRBs, in their review of all advertising/recruitment materials, should pay particular attention to risk and potential benefit information to ensure it is presented in a balanced and fair manner. The information presented should not mislead, for example, by promising benefits or implying a benefit beyond that potentially provided by the research.

The PHS IRB, when reviewing clinical trial websites, also will assess the types of incentives, if any, that are being offered to prospective subjects. Monetary and non-monetary incentives (e.g., access to services or programs) can create undue influence on a potential subject's decision about research participation. The PHS IRB will ensure that the clinical trial website makes clear that participation in a trial is voluntary, and that incentives for participation are not so great that they compromise a prospective subject's assessment of the risks or affect the voluntariness of his or her choices.

Some clinical trial websites ask viewers to answer questions regarding eligibility for a specific clinical trial. If identifiable private information is collected via the clinical trial website, the IRB will review plans for protecting the confidentiality of that information. The IRB will assess whether the website clearly explains how identifiable private information might be used.

Informed consent must be obtained for the collection of any identifiable private information about the

respondent unless the IRB has determined that the informed consent requirement can be waived. Respondent authorization must also be obtained if protected health information is collected unless the IRB has determined that the authorization requirement can be waived.

Additional examples of clinical trial listing services that do not require prospective IRB approval include amfAR clinical trial directory listings and the National Institutes of Health (NIH) ClinicalTrials.gov website, providing that the clinical trial information posted is of the limited nature described above.

D. Investigator Concerns

Investigators who have concerns or suggestions regarding PHS's HRPO or IRB should convey them to the IRB Chair, HRPO Director, or the IO or other responsible parties, when appropriate. The IRB Chair, HRPO Director, or the IO will consider the issue, and when deemed necessary, seek additional information, and convene the parties involved to form a response for the investigator or make necessary procedural or policy modifications, as warranted. In addition, the Chair of the IRB or the HRPO/IRB Coordinator will be available to address investigators' questions, concerns, and suggestions.

XIX. SPONSORED RESEARCH

It is PHS policy that any sponsored research conducted under the auspices of PHS is conducted in accordance with federal guidelines and ethical standards. The following describe the procedures required to ensure that all sponsored research meets this requirement.

A. Definitions

Sponsor. Sponsor means the company, institution, individual donor, or organization responsible for the initiation, management, or financing of a research study.

Sponsored Research. Sponsored research means research funded by external entities (public, industry, or private) through a grant or contract that involves a specified statement of work (e.g., the research proposal), including clinical trials involving investigational drugs, devices, or biologics.

B. Responsibility

Sponsor grants, contracts, and other written agreements will be reviewed for the following by the PHS Research and Sponsored Awards Office, the PHS Legal Department, and PHS contract department with consultation with the IRB, as necessary:

- All sponsor contracts have a written agreement with the Sponsor that addresses medical care for research participants with a research-related injury, when appropriate.
- In studies where Sponsors conduct research site monitoring visits or conduct monitoring activities remotely, the sponsor contracts have a written agreement with the Sponsor that the Sponsor promptly reports to the PHS findings that could affect the safety of participants or influence the conduct of the study.
- When the Sponsor has the responsibility to conduct data and safety monitoring, the sponsor contracts have a written agreement with the Sponsor that addresses provisions for monitoring the data to ensure the safety of participants and for providing data and safety monitoring reports to PHS.
- Sponsor contracts have a written agreement with the Sponsor about plans for disseminating findings from the research and the roles that investigators and Sponsors will play in the publication or disclosure of results.
- When participant safety could be directly affected by study results after the study has ended, the sponsor contracts have a written agreement with the Sponsor that the investigator or PHS will be notified of the results in order to consider informing participants.

- Payment in exchange for referrals of prospective participants from investigators (physicians) ("finder's fees") is not permitted. Similarly, payments designed to accelerate recruitment that are tied to the rate or timing of enrollment ("bonus payments") are also not permitted.

XX. CONFLICT OF INTEREST IN RESEARCH

This policy applies to all persons within Presbyterian who perform research, including, but not limited to medical and non-medical staff and other members of Presbyterian, regardless of title, who are responsible for the design, conduct, or reporting of research at Presbyterian (hereinafter "Covered Individual.")

A. Purpose

This Policy is intended to provide reasonable expectation that the design, conduct, reporting, and publication of research will not be influenced/biased by conflicts of interest (COI). Presbyterian Healthcare Services' goal is to promote the identification, reporting, and, if required, elimination or management of such conflicts in the context of research.

In addition to research specific policies, all HRPO employees are required to understand and adhere to all Presbyterian Healthcare Services policies regarding conflict of interest and external activities.

B. Policy

1. Significant Financial Interest

Any actual or potential financial interest consisting of one or more of the following known interests of the covered individual or the covered individual's immediate family member that reasonably appears to be related to the covered individual's institutional responsibilities:

- Any remuneration received from a business, or other external entity, in the twelve-month period immediately prior to the disclosure or expected from a business, or other external entity, in the twelve-month period immediately following the disclosure. For purposes of this policy, remuneration includes salary and any payment for services not otherwise identified as salary (e.g., consulting fees, honoraria, paid authorship) that is not described in a clinical trial agreement or grant.
- Any equity interest in a business. For the purpose of this policy, equity interest includes any stock, stock option, or other ownership interest regardless of value, as determined through reference to public prices or other reasonable measures of fair market value; or
- Any intellectual property rights (e.g., patents, copyrights), royalties from such rights, and agreements to share in royalties related to such rights.

Other 'support' as defined by the NIH may be considered a significant financial interest and may be deemed a financial conflict of interest (FCOI) when not reported to the applicable funding agency at the time of grant submission, grant awarded, prior to any expenditures, and throughout the life of the grant as required by the funding agency.

The term significant financial interest does not include:

(i) Income from investment vehicles, such as mutual funds and retirement accounts, as long as the covered individual or immediate family member does not directly control the investment decision made in these vehicles;
(ii) Incomes from seminars, lectures, and teaching engagements sponsored by a federal, state, or local government agency, an institution of higher education, an academic teaching hospital, a medical center, or a research institution of higher education in the United States; or
(iii) Income from service on advisory committees or review panels for federal, state, or local government

agency, an institution of higher education, an academic teaching hospital, a medical center, or a research institute that is affiliated with an institution of higher education in the United States.

The activities and relationships described in (ii) and (iii) must always be disclosed if they are performed for organizations or governments located outside of the United States.

C. Procedure

1. Disclosures

a) Initial Disclosure

Covered Individuals have principal responsibility for avoiding Financial Conflicts of Interest. Covered Individuals are required to make full, written disclosure of their and their immediate family members' significant financial interest and other requested information to the Presbyterian IRB. Covered individuals must make disclosures prior to submission of each Public Health Services funded grant application, and prior to submission of any non-Public Health Services funded grant application if required by the external funding entity. In addition, covered individuals must make disclosures prior to engaging in a new research protocol if a disclosure was not made as part of a grant application submission. Disclosures should provide sufficient detail to permit an accurate and objective evaluation and must be submitted through PHS IRB electronic submission platform.

b) Updated Disclosure

Disclosures must be updated annually by covered individuals, except for investigators of internally funded exempt human subject research. Such updated disclosures shall include significant financial interests not previously disclosed and updates to previously disclosed significant financial interests.

Additionally, covered individuals are required to report new significant financial interests within 30 days of discovering or acquiring the interest. An update is required when the value of the previously reported interest reaches a dollar value that would affect the outcome of a financial conflict of interest review, e.g., an increase in value from below $5,000 to above that amount, or actual or expected increases above the $25,000 threshold for FCOI and related non-regulated research, or $10,000 for regulated research. Also, an increase in time and effort greater than 20% or approaching 20% of a covered individual's salary, must be promptly reported. Updates should be submitted according to the same procedure as initial disclosures, described above.

2. Review of Disclosures

Upon receipt of a disclosure of a significant financial interest greater than or equal to $5,000.00, the PHS IRB will determine (a) whether the significant financial interest is related to the research, and if so related, (b) whether the significant financial interest is a financial conflict of interest. A covered individual's significant financial interest is related to the research when the HRPO reasonably determined that the significant financial interest could be affected by the research or is in an entity whose financial interest could be affected by the research.

Initial review and determination of related significant financial interest is delegated to the Presbyterian HRPO. A financial interest could directly and significantly affect the design, conduct, and/or reporting of the research.

A significant financial interest related to human subject research will be referred to the PHS IRB for review and determination of risk to subjects and if applicable, an appropriate management plan. The IRB has the final authority to decide whether the interest and its management, if any, allows the research to be approved. The IRB will communicate the decision to the HRPO and the Principal Investigator. The IRB may not override a decision by the HRPO to disapprove the research.

3. Management of Actual or Apparent Conflicts of Interest

If a financial conflict of interest (FCOI) is identified prior to the expenditure of award funds or engaging in any research, the HRPO will develop a proposed management plan specifying the actions that will be taken to manage, reduce or eliminate the FCOI. The HRPO will provide the proposed management plan to the covered individual for input, and then the HRPO will develop and submit a final management plan to the PHS IRB for approval. If the covered individual is not the Principal Investigator, the HRPO may consult with the Principal Investigator on the management plan.

Examples of conditions or restrictions that might be imposed to manage a FCOI include, but are not limited to:

- Public disclosure of the Financial Conflict of Interest (e.g., when presenting or publishing the research);
- For research projects involving human subjects, disclosure of Financial Conflicts of Interest directly to participants;
- Appointment of an independent monitor capable of taking measures to protect the design, conduct, and reporting of the research against bias resulting from the Financial Conflict of Interest;
- Modification of the research plan;
- Change of personnel or personnel responsibilities, or disqualification of personnel from participation in all or a portion of the research;
- Reduction or elimination of the Financial Conflict of Interest (e.g., sale of an equity interest);
- Severance of the relationships that create actual or potential Financial Conflict of Interest; or
- Notification of other individuals involved in the research.

Determination of the existence of a FCOI and the means adopted by the HRPO and approved by the PHS IRB for eliminating or managing the conflict will be communicated in writing to the affected covered individual and other appropriate personnel.

The HRPO may monitor the covered individual's compliance with any management plan implemented pursuant to this section on an ongoing basis until completion of the research project.

4. Reports to Outside Sponsors

Prior to grant submission, and prior to expenditure of funds, the principal Investigator is responsible for verifying that applicable personnel have submitted a conflict of interest (COI) disclosure as required by the Sponsor. The Principal Investigator is responsible for communicating and required COI management plan set by the PHS HRPO and IRB.

5. Record Retention

Records relating to all covered individuals' disclosures of significant financial interests related to the research and Presbyterian's review of, and response to, such disclosures will be maintained for at least three years from the termination or completion of the research or for such longer periods as prescribed in any grant or contract, or applicable regulations. Upon authorized request of a sponsoring agency, disclosure documents and related records pertaining to the specific sponsored project will be made available to appropriate officials.

6. Sanctions

All persons subject to this policy are expected to comply fully and promptly with applicable requirements. Failure to make required disclosures or making incomplete, erroneous, or misleading disclosures, failure to comply with the prescribed management plan(s), and other violations of this policy constitutes noncompliance and will be reported to the PHS HRPO, IRB, and Institutional Official.

Possible sanctions to be imposed on the individual may include but are not limited to (a) formal admonition, (b) ineligibility to engage in research within PHS, or (c) dismissal.

D. Additional Provisions Applicable to the U.S. Public Health Service (PHS) Sponsored Research

Research funded or proposed for funding by the U.S. Public Health Services (PHS), including to the National Institutes of Health (NIH), is subject to certain requirements imposed by PHS regulations, as amended from time to time (https://www.govinfo.gov/content/pkg/FR-2011-08-25/pdf/2011-21633.pdf). Such research is also subject to the policy presented prior to this section, in addition to this section. The extent of any conflict between a provision of the policy and a provision of this section, the provisions of this section shall govern.

1. Disclosure Obligations

In addition to the obligation to disclose significant financial interests as set forth in this policy, covered individuals who are listed as the PI, Project Director, or other Key Personnel, engaged in PHS funded research must disclose the occurrence of any reimbursed or sponsored travel, for themselves and their immediate family, related to their institutional responsibilities, regardless of the relationship to PHS funding, unless the travel is reimbursed or sponsored by Presbyterian, a federal, state, or local government agency, an institution of higher education, an academic teaching hospital, a medical center, or a research institute that is affiliated with an institution of higher education. The disclosure must include, at a minimum, the purpose of the trip, the identity of the sponsor/organization, the destination, and the duration. Sponsored travel means travel that is paid on behalf of the covered individual and not reimbursed to the covered individual (so that the exact monetary amount may not be readily determined).

2. Review of Conflicts of Interest

If during the course of an ongoing PHS-funded project (i) a significant financial interest is disclosed by a new covered individual, (ii) an existing covered individual discloses a significant financial interest not previously reported, or (iii) it comes to the attention of Presbyterian officials that a significant financial interest related to the PHS-funded research was not disclosed in a timely manner by a covered individual, the significant financial interest shall be reviewed pursuant to this policy within 60 days and a decision shall be made as to whether the significant financial interest constitutes a FCOI. If the Presbyterian HRPO determines that a FCOI exists, the HRPO shall implement, on at least an interim basis, a management plan, as set forth in this policy, that shall specify the actions that have been, or will be taken, to manage the FCOI.

3. Retrospective Review

Whenever a financial conflict of interest involving a PHS-funded research is not identified in a timely manner, including failure by the covered individual to disclose a significant financial interest that is determined by the Presbyterian HRPO to constitute a FCOI, failure by the HRPO to review or by Presbyterian to manage such FCOI, or failure by the covered individual to comply with the management plan, the Presbyterian HRPO or its designee shall, within 120-days of his/her/their determination of noncompliance, complete a retrospective review of the covered individual's activity and the PHS-funded research to determine whether any PHS-funded research, or portion thereof, conducted during the time period of noncompliance was biased in design, conduct, or reporting of such research.

The Presbyterian HRPO or its designee shall document the retrospective review. Such documentation shall include the following elements:

- Project/Contract number and title;

- Principal investigator;
- Name of the covered individual with the FCOI;
- Name of the entity in which the covered individual has a significant financial interest that give rise to the FCOI;
- Reason for the retrospective review;
- Detailed methodology used for the retrospective review;
- Findings of the review; and
- Conclusions/determination of the review.

4. Conflict of Interest Reports to the U.S. Public Health Services

Prior to Presbyterian's expenditure of any funds under a PHS-funded research project, Presbyterian will provide the PHS Awarding Component with a financial conflict of interest report ('report') regarding any significant financial interest, including significant financial interest of subrecipient investigators, related to the PHS-funded research that Presbyterian finds to be a financial conflict of interest (FCOI) and, to the extent required by regulation, will ensure that Presbyterian has implemented a management plan as set for in this policy. In addition, during the course of a PHS-funded research project, Presbyterian will provide the PHS Awarding Component with a report within 60-days of identifying any significant financial interest that Presbyterian identifies as conflicting which was not included in its initial report.

The report will contain all elements as required by regulation, which may include:

- Project/Contract number;
- Principal investigator;
- Name of the covered individual with the FCOI;
- Name of the entity in which the covered individual has a significant financial interest that gives rise to the FCOI;
- Nature of the financial interest;
- Value of the financial interest, within dollar ranges, or if the value cannot be readily determined through reference to public prices or other reasonable measures, a statement to that effect; and
- A description of the key elements of the management plan, including:
    - The role and principal duties of the conflicted covered individual in the research project
    - Conditions of the management plan
    - How the management plan is designed to safeguard objectivity in the research project
    - Confirmation of the covered individual's agreement to the management plan
    - How the management plan will be monitored to ensure the covered individual's compliance; and
    - Other information as needed.

If a retrospective review is performed as provided in Section XV.D.3, previously submitted reports affected by the review will be updated to specify the actions taken to manage the FCOI going forward. If the retrospective review finds that the PHS-funded research was biased, Presbyterian will promptly notify the PHS Awarding Component and submit a mitigation report which shall include:

- The key elements documented in the retrospective review;
- A description of the impact of the bias on the research project; and
- Presbyterian's plan of action or actions taken to eliminate or mitigate the effect of the bias.

Presbyterian will submit updated reports annually to PHS, addressing the status of previously identified FCOI and any changes to management plans, including whether the FCOI is still being managed or, if it no longer exists, an explanation as to why it no longer exists. Reports will be submitted for the duration of the PHS-funded project period.

5. **Sub awardees and Collaborators**

   If Presbyterian conducts PHS-funded research through a subrecipient (e.g., subgrantees, contractors, or collaborators), Presbyterian will include in its written agreement with the subrecipient a statement as to whether this policy or that of the subrecipient applies to the subrecipient's investigators.

   If the subrecipient's COI policy applies to the subrecipient investigators, the subrecipient shall certify as part of the agreement that its policy complies with the PHS regulations. If the subrecipient cannot make such a certification, this policy, including Section XV.D, will apply to subrecipient investigators.

   If the subrecipient's COI policy applies, Presbyterian will include in the subrecipients agreement time periods for the subrecipient to report all identified FCOI to Presbyterian. Such time periods must provide Presbyterian with sufficient time to review the reports and make timely reports to PHS, as necessary.

6. **Public Disclosure of Information**

   Presbyterian shall make this policy available via a publicly accessible website. In addition, Presbyterian shall provide a written response to a requestor within five business days of the receipt of the Presbyterian HRPO of a request for information concerning a significant financial interest held by a covered individual if Presbyterian has determined that the significant financial interest constitutes a FCOI in PHS-funded research.

   If the Department of Health and Human Services (DHHS) determines that a PHS-funded project of clinical research whose purpose is to evaluate the safety or effectiveness of a drug, medical device, or treatment has been designed, conducted, or reported by a covered individual with a FCOI that was not managed or reported by Presbyterian as required by this policy, Presbyterian will require that the covered individual disclose the FCOI in each public presentation of the results and to request an addendum to previous published presentations.

7. **Notification of the U.S. Public Health Services**

   Presbyterian will promptly notify the PHS Awarding Component if failure of a covered individual to comply with this policy or management plan provided for hereunder as biased the design, or conduct, or reporting of PHS-funded research.

XXI. INSTITUTIONAL CONFLICT OF INTEREST IN RESEARCH

Presbyterian and its institutional decision makers will follow established federal and state laws, regulations, and principles that govern disclosure, reporting, and management of potential and actual institutional conflicts of interest.

A. Definitions

Compelling Circumstances. The facts that convince the Presbyterian HRPO and the IRB that research should be allowed to be conducted at or under the auspices of Presbyterian despite the presence of an institutional conflict of interest in research. Whether the circumstances are deemed compelling will depend in each case upon the nature of the science, the nature of the overlapping interests, how closely the interest is related to the research, the degree to which the interest may be affected by the research, the degree of risk that the research poses to human subjects and the integrity of the research, and the degree to which the institutional conflict of interest in research can be effectively managed. In the case of non-clinical research, the Presbyterian HRPP/IRB should carefully consider the possible risk(s) that the institutional financial interest poses to the scientific judgment and research integrity involved in the research.

Covered Official. An Institutional decision maker in the following roles: (1) Presbyterian Healthcare Services

President and/or CEO; (2) Executive Vice Presidents; (3) Chief Commercialization Officer; (4) Presbyterian Institutional Official; (5) Senior Vice Presidents; (6) Department Chairs; (7) Executive Directors of Departments.

Disclosed Entities. The entities identified by covered officials with whom they have a potential institutional conflict of interest in research.

Institutional Conflict of Interest in Research (ICOI). (1) Any Presbyterian significant financial interest that reasonably poses a risk of significant and direct influence on decisions involving Presbyterian Healthcare Services' primary interest or mission; and/or (2) Any financial interest of institutional decision makers or service by an institutional decision maker as an officer, director, managing member, manager, or as a fiduciary of any for profit legal entity or competitor of Presbyterian Healthcare Services that reasonably poses a risk of significant and direct influence on decision involving Presbyterian's primary interest or mission.

Presbyterian. Abbreviation of the Presbyterian Healthcare Services encompassing all of its subsidiaries, affiliates, and joint venture systems operated by Presbyterian Healthcare Services.

Research. A systematic investigation designed to develop or contribute to generalizable knowledge. The scope of research as used in this Policy covers both current and anticipated research performed with human subjects (as defined in 45 CFR 46 & 21 CFR 56) regardless of the source of funding.

B. Purpose

It is the purpose of this policy to assure that institutional conflicts of interest (COI) are identified, disclosed, and managed or eliminated in order to protect the integrity of clinical research operations at Presbyterian and to assure its patients, research subjects, and the public that any institutional conflict of interest that may arise will not compromise the objective conduct and reporting of scientific and clinical endeavors.

Presbyterian holds the presumption that research will not be performed at or under the auspice of Presbyterian where an institutional interest exists that could be reasonable perceived as influencing the research and/or related activities. If compelling circumstances exist, the conflict may be allowed, but only pursuant to a transparent evaluation process and recommended management plan developed by the Presbyterian HRPP and approved by an independent decision-making group comprised of the Chief Legal Officer, the Chief Medical Officer, and the system Business Practices Officer of Presbyterian. In the event that any of such persons have the conflict then the Chief Executive Officer of Presbyterian will be included in the approval process. If the CEO has the conflict, then this matter will be referred to the Board of Directors of Presbyterian Healthcare Services for resolution.

C. Policy

1. Significant Financial and Fiduciary Interests

The following significant financial and fiduciary interest of Presbyterian warrant formal review of potential institutional conflicts of interest in research:

a) Gifts

Substantial gifts, exceeding $250,000.00, received by Presbyterian from current or potential sponsors of research or a company that owns or controls products being studied or tested in research.

b) Non-Publicly Traded Equity

An equity interest, or entitlement to equity of any value, including options or warrants, in a non-publicly traded company that is either the sponsor of research or is the manufacturer of a product to be studies or tested in research.

c) Publicly Traded Equity

An ownership interest, or entitlement to equity, including options or warrants, exceeding $250,000.00 in value (when valued in reference to current public prices, or where applicable, using accepted valuation methods) in a publicly traded company that either sponsors research or is the manufacturer of a product to be studies or tested in research.

d) Royalties

Significant milestone payments and/or other monies from the sales of an investigation product that is the subject of the research. There may be additional situations that would warrant a formal review of potential institutional conflicts of interest in research.

2. Relationships of Covered Officials

The following relationships of covered officials with the type of entities described below are potential institutional conflicts of interest in research. Prior to Presbyterian, any covered official, or any other employee at Presbyterian conducting any research on behalf of or with a disclosed entity, a formal review of the potential conflicts of interest in research must be completed.

a) Appointment to Service - Fiduciary

Service in either a personal or representative capacity in a fiduciary role for a company that either sponsors research or is the manufacturer of a product to be studied or tested in research.

b) Appointment to Service – Scientific Advisory Board

Service on a scientific advisory board of a commercial sponsor of human subject research.

c) Consulting

Consulting fees for the sake of this policy may include consulting fees, remuneration, honoraria, gifts, or other emoluments, or 'in kind' compensation.

Compensation exceeding or expected to exceed $10,000.00 per annum from a company that either sponsors or is the manufacturer of a product to be studies or tested in research.

d) Non-Publicly Traded Equity

An equity interest, or entitlement to equity of any value, including options or warrants, in a non-publicly traded company that is either the sponsor of research or is the manufacturer of a product to be studies or tested in research.

e) Publicly Traded Equity

An ownership interest, or entitlement to equity, including options or warrants, exceeding $250,000.00 in value (when valued in reference to current public prices, or where applicable, using accepted valuation methods) in a publicly traded company that either sponsors research or is the manufacturer of a product to be studies or tested in research.

There may be other relationships of covered officials that would warrant a formal review of potential institutional conflicts of interest in research.

D. Procedure

Formal review and recommended management plans of the conduct of research at Presbyterian of under the auspices of Presbyterian with a disclosed entity will be conducted and provided by the HRPP. This review and recommendation by the Presbyterian HRPP will be provided to an independent decision-making group comprised

of the Chief Legal Officer, the System Business Practices Officer, and the Chief Medical Officer who will accept, reject, or modify the recommendation and management plan. In the event that the covered official is a member of such group then the CEO of Presbyterian will replace such person. In the event that the covered official is the CEO of Presbyterian, then the Board of Directors of Presbyterian shall fill the role of the independent group.

Management plans will be developed to appropriately manage, which may include reducing or eliminating, the conflicts. An Executive Vice President (EVP) from the independent decision-making group will sign-off and approve the recommended or modified management plan(s) and communicate final decisions to the HRPP and the Entity Business Practice Officer.

Research cannot proceed until the complete formal review process has been conducted, this includes HRPP/IRB recommendation and management plan, EVP signoff, and acceptance and implementation of any requested management plan.

XXII. IRB MEMBER CONFLICT OF INTEREST

IRB members, staff, and consultants who are responsible for the review and approval of research protocols should be sensitive to the potential impacts of financial and/or non-financial relationships with research sponsors on the research and on the participation and protection of research participants. Such relationships, or interests, may affect either the professional objectivity in the review of the research, the ethics of the individual, or the actions of the Presbyterian IRB. They may also reflect negatively on the IRB, which is required by Presbyterian to ensure that interests that may compromise the protection of human research participants are managed, reduced, or eliminated. Thus, the review and approval of research by an IRB member or staff, who has, or appears to have, a conflicting interest may undermine the public trust in the IRB and in Presbyterian Healthcare Services.

No IRB member or alternate may participate in the review of any research project in which the member has a COI, except to provide information as requested. It is the responsibility of each IRB member to disclose any COI related to a study submitted for review and recuse him/herself from the deliberations and vote by leaving the room.

For example, all members and alternate members of the IRB complete a "**Financial and Non- Financial Interests in Human Research Disclosure"** form when first appointed and annually thereafter or sooner when their circumstances change. The form must be completed annually by (1) all Presbyterian IRB members; (2) Presbyterian HRPO/IRB staff who are not IRB members and who review human research protocols or have input into IRB review of protocols; and (3) consultants to the IRB. All disclosures made pursuant to this form should be for interests related to ongoing research, as well as research that could reasonably be expected to come before the Presbyterian IRB within the next year. If at any time the information reported on the form should change, resulting in a need for further disclosure, then the individual should provide an amendment to the form and submit it to the Presbyterian IRB for review. The fact that a conflict exists, but not the details of a member conflict, will be known to IRB staff in order to help ensure conformance with IRB procedures.

The forms are submitted to the HRPO/IRB Coordinator, who determines if a COI exists. To protect the privacy of members, the specific details of the conflict will not be given to staff or other members; however, the type of research where a COI exists will be provided (e.g., all studies from X sponsor; studies using X device/drug; studies involving X investigator). The HRPO/IRB Coordinator, in turn, ensures that IRB members and alternates are not assigned to conduct reviews of studies for which the member has a conflict and to ensure appropriate recusal during convened meetings. HRPO/IRB Coordinator may consult with the HRPO Director to clarify whether a specific study involves a member COI.

IRB members, alternates, or consultants <u>may</u> be considered to have a conflicting interest requiring recusal when they, or an immediate member of their family, have any of the following:

- Involvement in the design, conduct, and reporting of the research;

- Significant financial interests (refer to the **"Financial and Non-Financial Interests in Human Research Disclosure"** form for descriptions of significant financial interests) related to the research being reviewed; or
- Any other situation where an IRB member believes that another interest conflicts with his or her ability to deliberate objectively on a study.

The IRB Chair will ask IRB members at the beginning of each convened meeting if any members have a COI regarding any of the items to be reviewed and reminds members that they must recuse themselves by leaving the room during the discussion and vote of the specific research study. If a conflicted member is participating by conference call, videoconference or web meeting, the member's participation (connection) is terminated, or the member may be placed in a segregated electronic "waiting room" for discussion and voting.

IRB members with a conflicting interest are excluded from being counted towards quorum. Recusals of members with COIs are recorded in the minutes.

XXIII. HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA) IN RESEARCH

The *Health Insurance Portability and Accountability Act of 1996* (HIPAA) required the creation of a Privacy Rule for identifiable health information. While the primary impact of the Privacy Rule is on the routine provision of and billing for health care, the Rule also affects the conduct and oversight of research.

The Privacy Rule defines individually identifiable health information transmitted or maintained by a covered entity in any form (electronic, written, or oral) as "protected health information" (PHI) and establishes the conditions under which investigators may access and use this information in the conduct of research.

Except as otherwise permitted, the Privacy Rule requires that a research subject "authorize" the use or disclosure of his/her PHI to be used in research. This authorization is distinct from the subject's consent to participate in research, which is required under the Common Rule and FDA regulations.

Under the Privacy Rule, a HIPAA Authorization may be combined with the consent document for research. When the consent document is combined with an Authorization as it is at Presbyterian Healthcare Services, 45 CFR parts 46 and 21 and CFR part 56 require IRB review of the combined document.

At Presbyterian, for exempt projects and other categories of research not subject to IRB review, the Presbyterian IRB is designated to act upon requests for waivers and alterations of the Authorization requirement for research purposes.

A. Definitions

Access. Access is the mechanism of obtaining or using information electronically, on paper, or other medium for the purpose of performing an official function.

Accounting of Disclosures. Information that describes a covered entity's disclosures of PHI other than for treatment, payment, and health care operations; disclosures made with Authorization; and certain other limited disclosures. For those categories of disclosures that need to be in the accounting, the accounting must include disclosures that have occurred during the 6 years (or a shorter time period at the request of the individual) prior to the date of the request for an accounting. However, PHI disclosures made before the compliance date for a covered entity are not part of the accounting requirement.

Authorization. An individual's written permission to allow a covered entity to use or disclose specified PHI for a particular purpose. Except as otherwise permitted by the Privacy Rule, a covered entity may not use or disclose PHI for research purposes without a valid Authorization.

Covered Entity. A health plan, a health care clearinghouse, or a health care provider who transmits health

information in electronic form in connection with a transaction for which DHHS has adopted a standard.

Data Use Agreement. An agreement into which the covered entity enters with the intended recipient of a limited data set that establishes the ways in which the information in the limited data set may be used and how it will be protected.

Designated Record Set. A group of records maintained by or for a covered entity that includes: (1) medical and billing records about individuals maintained by or for a covered health care provider; (2) enrollment, payment, claims adjudication, and case or medical management record systems maintained by or for a health plan; or (3) used, in whole or in part, by or for the covered entity to make decisions about individuals. A record is any item, collection, or grouping of information that includes PHI and is maintained, collected, used, or disseminated by or for a covered entity.

Disclosure. The release, transfer, access to, or divulging of information in any other manner outside the entity holding the information.

Health Information. Health Information means any information, whether oral or recorded in any form or medium, that (1) is created or received by a health care provider, health plan, public health authority, employer, life insurer, school or university, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual.

Individually Identifiable Health Information. Information that is a subset of health information, including demographic information collected from an individual, and (1) is created or received by a health care provider, health plan, employer, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; (a) the provision of health care to an individual; and (a) that identifies the individual; or (b) with respect to which there is a reasonable basis to believe the information can be used to identify the individual.

Limited Data Set. Refers to PHI that excludes sixteen categories of direct identifiers and may be used or disclosed, for purposes of research, public health, or health care operations, without obtaining either an individual's Authorization or a waiver or an alteration of Authorization for its use and disclosure, with a data use agreement.

Minimum Necessary. The standard that uses the least information reasonably necessary to accomplish the intended purpose of the use, disclosure, or request. Unless an exception applies, this standard applies to a covered entity when using or disclosing PHI or when requesting PHI from another covered entity. A covered entity that is using or disclosing PHI for research without Authorization must make reasonable efforts to limit PHI to the minimum necessary. A covered entity may rely, if reasonable under the circumstances, on documentation of IRB or Privacy Board approval or other appropriate representations and documentation under section 164.512(i) as establishing that the request for protected health information for the research meets the minimum necessary requirements.

Privacy Board. A board that is established to review and approve requests for waivers or alterations of Authorization in connection with a use or disclosure of PHI as an alternative to obtaining such waivers or alterations from an IRB. A Privacy Board consists of members with varying backgrounds and appropriate professional competencies as necessary to review the effect of the research plan on an individual's privacy rights and related interests. The board must include at least one member who is not affiliated with the covered entity, is not affiliated with any entity conducting or sponsoring the research and is not related to any person who is affiliated with any such entities. A Privacy Board cannot have any member participating in a review of any project in which the member has a conflict of interest.

Protected Health Information. PHI is individually identifiable health information transmitted by electronic media, maintained in electronic media, or transmitted or maintained in any other form or medium. PHI excludes individually identifiable health information in education records covered by the Family Educational Rights and

Privacy Act, as amended, 20 U.S.C. 1232g, records described at 20 U.S.C. 1232g(a)(4)(B)(iv), and employment records held by a covered entity in its role as employer.

Research. A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. This includes the development of research repositories and databases for research.

Use. With respect to individually identifiable health information, the sharing, employment, application, utilization, examination, or analysis of such information within the entity or health care component (for hybrid entities) that maintains such information.

Waiver or Alteration of Authorization. The documentation that the covered entity obtains from an investigator or an IRB or a Privacy Board that states that the IRB or Privacy Board has waived or altered the Privacy Rule's requirement that an individual must authorize a covered entity to use or disclose the individual's PHI for research purposes.

Workforce. Employees, volunteers, student/resident, and other persons whose conduct, in the performance of work for a covered entity, is under the direct control of the covered entity, whether they are paid by the covered entity.

B. The IRB's Role under the Privacy Rule

Under the Privacy Rule, IRBs gained authority to consider and act upon requests for a partial or complete waiver or alteration of the Privacy Rule's Authorization requirement for uses and disclosures of PHI for research. Although DHHS and FDA Protection of Human Subject Regulations include protections to help ensure the privacy of subjects and the confidentiality of information, the Privacy Rule supplements these protections by requiring covered entities to implement specific measures to safeguard the privacy of PHI. If certain conditions are met, an IRB may grant a waiver or an alteration of the Authorization requirement for research uses or disclosures of PHI.

Presbyterian Healthcare Services has designated the IRB to fulfill the functions of a Privacy Board for human subject research.

The Privacy Rule does not change the composition of an IRB. The Privacy Rule permits a covered entity to accept documentation of waiver or alteration approval from any qualified IRB or Privacy Board -- not only the IRB overseeing the organization's research.

When acting upon a request to waive or alter the Authorization requirement, an IRB must follow the procedural requirements of the DHHS Protection of Human Subject regulations and, if applicable, FDA regulations, including using either the normal review procedures (review by the convened IRB) or the expedited review procedures.

When a request for a waiver or an alteration of the Authorization requirement is considered by the convened IRB, a majority of the IRB members must be present at the meeting, including at least one member whose primary concerns are in nonscientific areas. For an approval of a waiver or an alteration of the Privacy Rule's Authorization requirement to be effective, it must be approved by a majority of the IRB members present at the convened meeting. If a member of the IRB has a conflicting interest with respect to the PHI use and disclosure for which a waiver or an alteration approval is being sought, that member may not participate in the review. DHHS and FDA have established categories of research that may be reviewed by an IRB through an expedited review procedure. Expedited review of a request for a waiver or an alteration of the Authorization requirement is permitted where the research activity is on the DHHS or FDA list of approved categories and involves no more than minimal risks. In addition, 45 CFR 46.110 and 21 CFR 56supported by any permit an IRB to use an expedited review procedure to review minor changes in previously approved research. A modification to a previously approved research plan, which only involves the addition of an Authorization for the use or disclosure of PHI to the IRB-approved informed consent, may be reviewed by the IRB through an expedited review procedure, because this type of modification

may be determined as no more than a minor change to research. If expedited review procedures are appropriate for acting on the request, the review may be carried out by the IRB Chair or by one or more experienced reviewers designated by the Chair from among the IRB members. A member with a conflicting interest may not participate in an expedited review. If an IRB uses expedited review procedures, it must adopt methods for keeping all its members advised of requests for waivers or alterations of the Authorization requirement as well as those requests that have been granted under an expedited review procedure. IRB documentation of approval of a waiver or alteration of the authorization requirement includes:

- The identity of the approving IRB;
- The date on which the waiver or alteration was approved;
- A statement that the IRB has determined that all the specified criteria for a waiver or an alteration were met;
- A brief description of the PHI for which use, or access has been determined by the IRB to be necessary in connection with the specific research activity;
- A statement that the waiver or alteration was reviewed and approved under either normal or expedited review procedures; and
- The required signature of the IRB Chair or the Chair's designee.

Presbyterian Healthcare Services will not release PHI to investigators without individual authorization or proper documentation of an IRB or Privacy Board approval of a waiver or alteration of the requirement. In order to ensure that appropriate approvals are in place and that uses of patient information for research are in accordance with Presbyterian standards, Presbyterian does not accept waivers or alterations approved by a non-Presbyterian Privacy Board or IRB without review and approval of the requested disclosure by the Presbyterian IRB.

C. Authorization

Except as otherwise permitted, the Privacy Rule requires that a research subject “authorize” the use or disclosure of his/her PHI to be used in research. This authorization is distinct from the subject’s consent to participate in research, which is required under the Common Rule and FDA regulations. Just as a valid consent under Common Rule and FDA regulations must meet certain requirements, a valid authorization must contain certain statements and core elements [45 CFR 164.508(c)]. At Presbyterian, authorization language is to be incorporated into the consent document. Template consent documents, which include HIPAA authorization language, are available from the HRPO.

Once executed, a signed copy must be provided to the individual providing authorization. Signed authorizations must be retained by the covered entity for seven years from the date of creation or the date it was last in effect, whichever is later.

A research subject has the right to revoke their authorization at any time. Investigators are not required to retrieve information that was disclosed under the authorization before learning of the revocation. Additionally, investigators may continue to use, and disclosure PHI already obtained for the research under an authorization to the extent necessary to protect the integrity of the research.

When an authorization is obtained for research purposes, the Privacy Rule requires that it pertain only to a specific research study, not to nonspecific research or to future, unspecified projects. The Privacy Rule considers the creation and maintenance of a research repository or database as one specific research activity, the subsequent use or disclosure by a covered entity of information from the database for a specific research study requires separate authorization unless a waiver of the requirement is granted.

When an Authorization permits disclosure of PHI to a person or organization that is not a covered entity (such as a sponsor or funding source), the Privacy Rule does not continue to protect the PHI disclosed to such entity. However, other federal and state law and tribal law passed by the official governing body of an American Indian or Alaska Native tribe s and agreements between the covered entity and recipient such as a Business Associate

Agreement (BAA) or Confidentiality Agreement may establish continuing protections for the disclosed information. Under the DHHS Protection of Human Subject regulations or the FDA Protection of Human Subject regulations, an IRB may impose further restrictions on the use or disclosure of research information to protect subjects.

Authorization Core Elements:

- A description of the PHI to be used or disclosed, identifying the information in a specific and meaningful manner.
- The names or other specific identification of the person or persons (or class of persons) authorized to make the requested use or disclosure.
- The names or other specific identification of the person or persons (or class of persons) to whom the covered entity may make the requested use or disclosure.
- A description of each purpose of the requested use or disclosure.
- Authorization expiration date or expiration event that relates to the individual or to the purpose of the use or disclosure ("end of the research study" or "(#) years past the study closure date" are permissible for research, including for the creation and maintenance of a research database or repository).
- Signature of the individual and date. If the individual's legally authorized representative signs the Authorization, a description of the representative's authority to act for the individual must also be provided.

Authorization Required Statements:

- A statement of the individual's right to revoke his/her Authorization and how to do so, and, if applicable, the exceptions to the right to revoke his/her Authorization or reference to the corresponding section of the covered entity's notice of privacy practices.
- Whether treatment, payment, enrollment, or eligibility of benefits can be conditioned on Authorization, including research-related treatment and consequences of refusing to sign the Authorization, if applicable.
- A statement of the potential risk that PHI will be re-disclosed by the recipient. This may be a general statement that the Privacy Rule may no longer protect health information disclosed to the recipient.

D. Waiver or Alteration of the Authorization Requirement

Obtaining signed authorization to access and use of PHI for research is not always feasible. The Privacy Rule contains criteria for waiver or alterations of authorization. If a covered entity has used or disclosed PHI for research pursuant to a waiver or alteration of authorization, documentation of the approval of the waiver or authorization must be retained for seven years from the date of its creation or the date it was last in effect, whichever is later.

For research uses and disclosures of PHI, an IRB or Privacy Board may approve a waiver or an alteration of the authorization requirement in whole or in part. A complete waiver occurs when the IRB or Privacy Board determines that no authorization will be required for a covered entity to use and disclose PHI for a particular research project. A partial waiver of authorization occurs when the IRB determines that a covered entity does not need authorization for all PHI uses and disclosures for research purposes, such as accessing PHI for research recruitment purposes. The IRB may also approve a request that removes some PHI, but not all, or alters the requirements for an authorization (an alteration).

For an IRB to waive or alter authorization, the Privacy Rule (45 CFR 164.512(i)(2)(ii)) requires the IRB to determine the following:

- The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
  - ❖ An adequate plan to protect health information identifiers from improper use and disclosure.
  - ❖ An adequate plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a healthcare or research justification for retaining them or a legal requirement to do so).

- ❖ Adequate written assurances that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.
- The research could not practicably be conducted without the waiver or alteration.
- The research could not practicably be conducted without access to and use of the PHI.

The Privacy Rule allows institutions to rely on a waiver or an alteration of Authorization obtained from a single Privacy Board (e.g., the Presbyterian IRB) to be used to obtain or release PHI in connection with a multi-site project. However, DHHS also recognizes that "covered entities may elect to require duplicate Privacy Board reviews before disclosing [PHI] to requesting researchers" (67 *Federal Register* 53232, August 14, 2002). At Presbyterian, PHI may not be disclosed for the purposes of research pursuant to a waiver provided by a non-Presbyterian Privacy Board without the approval of the Presbyterian IRB.

E. Activities Preparatory to Research

Under the preparatory-to-research provision of the Privacy Rule, a covered entity may permit an investigator who works for that covered entity to use PHI for purposes preparatory to research such as assessing the feasibility of conducting a research project, developing a grant application, or identifying potential subjects. A covered entity may also permit, as a disclosure of PHI, a researcher who is not a workforce member of that covered entity to review PHI (within that covered entity) for purposes preparatory to research.

The covered entity must obtain from an investigator representation that (1) the use or disclosure is requested solely to review PHI as necessary to prepare a research plan or for similar purposes preparatory to research, (2) the PHI will not be removed from the covered entity in the course of review, and (3) the PHI for which use or access is requested is necessary for the research.

At Presbyterian, this is accomplished by the investigator submitting both an Operational Approval Determination form (for projects in development) and submit the Waiver of Documentation of Consent and/or Waiver or Alteration of Consent form to the IRB.

F. Research Using Decedent's Information

The HRPO obtains from the investigator: (a) Representation that the use or disclosure sought is solely for research on the protected health information of decedents; (b) documentation, at the request of the covered entity, of the death of such individuals; and (c) representation that the protected health information for which use, or disclosure is sought is necessary for the research purposes.

G. Future Uses: Databases and Repositories

The Privacy Rule recognizes the creation of a research database or a specimen repository to be a research activity if the data/specimens to be stored contain PHI. There are two separate activities that the covered entity must consider: (1) the use or disclosure of PHI for creating a research database or repository and (2) the subsequent use or disclosure of PHI in the database for a particular research plan.

Individual authorization for the storage of PHI for future research must be sought unless the IRB has determined that the criteria for a waiver of the authorization requirement are satisfied. See Section 23.4 of this policy manual for a discussion of waivers of authorization.

At Presbyterian, consent for research and authorization for use and/or disclosure of PHI are combined in one document. As with any research activity, the combined consent/authorization for future research must describe the arch uses in enough detail to allow the potential subject to make an informed decision. The investigator and IRB should be cognizant of uses of information/specimens that the target community may consider particularly

sensitive, such as genetics, mental health, studies of origin, and use of tissues that may have cultural significance.

The consent/authorization for future research can be a stand-alone document or may be incorporated into another consent/authorization if the information/specimens will originate from another research activity, such as a clinical trial, unless the research involves the use or disclosure of psychotherapy notes. Authorizations for the use or disclosure of psychotherapy notes can only be combined with another authorization for a use or disclosure of psychotherapy notes.

If the consent/authorization for future research is combined with another research consent/authorization, the consent/authorization must clearly differentiate between the research activities and allow the individual to opt-in to the future research. Opt-outs for future research are not permitted under the Privacy Rule because an opt-out process does not provide individuals with a clear ability to authorize the use of their information/specimens for future research and may be viewed as coercive.

H. Corollary and Sub studies

As with any other research, subject participation in corollary or sub-studies not essential to the primary aims of the research should be on a voluntary basis. This is particularly important when the primary research offers a potential benefit, such as treatment, which might compel the potential subject to agree to something that they otherwise would not.

HIPAA reinforces this ethical principle by explicitly stating that authorization for "unconditioned" activities, for which there is no associated treatment, benefit or other effect on the individual subject associated with participation, cannot be required. The published preamble to HIPAA Omnibus clarifies the basis for this position, and the requirement that authorization for unconditioned activities involve a clear opt-in mechanism, stating:

> "This limitation on certain compound authorizations was intended to help ensure that individuals understand that they may decline the activity described in the unconditioned authorization yet still receive treatment or other benefits or services by agreeing to the conditioned authorization." and "an opt out option does not provide individuals with a clear ability to authorize the optional research activity and may be viewed as coercive by individuals."

As with authorization for future research, it is acceptable to combine in a single document the authorization for a conditioned activity, such as a clinical trial, with authorization for an unconditioned activity such as a corollary or sub-study that does not directly benefit or effect the individual participant, provided that:

- The authorization clearly differentiates between the conditioned and unconditioned research activities;
- The authorization clearly allows the individual the option to opt into the unconditioned research activities; and
- Enough information is provided for the individual to be able to make an informed choice about both the conditioned and unconditioned activities.

Separate authorization must be obtained for each research activity that involves the use and disclosure of psychotherapy notes. For example, authorization for the use and disclosure of psychotherapy notes for a clinical trial cannot be combined with an authorization for the use and disclosure of those psychotherapy notes for a corollary research activity.

I. De-identification of PHI under the Privacy Rule

Covered entities may use or disclose health information that is de-identified without restriction under the Privacy Rule. The "Safe Harbor" method permits a covered entity to de-identify data by removing all eighteen data elements that could be used to identify the individual or the individual's relatives, employers, or household members. The covered entity also must have no actual knowledge that the remaining information could be used

alone or in combination with other information to identify individuals. Under this method, the identifiers that must be removed are the following:

- Names
- 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:
  - ❖ The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people
  - ❖ The initial three digits of a ZIP Code for all such geographic units containing 20,000 or fewer people are changed to 000.
- 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 eighty-nine and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older
- Telephone numbers
- Facsimile numbers
- Electronic mail addresses
- Social security numbers
- Medical record numbers
- Health plan beneficiary numbers
- Account numbers
- Certificate/license numbers
- Vehicle identifiers and serial numbers, including license plate numbers
- Device identifiers and serial numbers
- Web universal resource locators (URLs)
- Internet Protocol (IP) address numbers
- Biometric identifiers, including fingerprints and voiceprints
- Full-face photographic images and any comparable images
- Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification.

Alternatively, a qualified statistician may certify that the risk is exceedingly small that health information could be used, alone or in combination with other available information, to identify individuals. The qualified statistician must document the methods and results of the analysis that justify such a determination. This analysis must be retained by the covered entity for 6 years from the date of its creation or when it was last acted on, whichever is later.

The Privacy Rule permits a covered entity to assign to, and retain with, the de-identified health information, a code, or other means of record re-identification if that code is not derived from or related to the information about the individual and is not otherwise capable of being translated to identify the individual. The covered entity may not use or disclose the code or other means of record identification for any other purpose and may not disclose its method of re-identifying the information.

NOTE: Data that is considered de-identified under HIPAA may still be considered human subject data under the Common Rule, particularly when working with a small data set that can be further divided into smaller subsets. Additionally, while coded information may be de- identified under HIPAA, if the investigator holds or could access both the code and the data, the information is considered identifiable private information under the Common Rule.

J. Limited Data Sets and Data Use Agreements

Limited data sets are data sets stripped of certain direct identifiers. Limited data sets may be used or disclosed only for public health, research, or health care operations purposes. Because limited data sets may contain identifiable information, they are still PHI and as such are not considered de-identified under the Privacy Rule. Unlike de-identified data, protected health information in limited data sets may include addresses other than street name or street address or post office boxes, all elements of dates (such as admission and discharge dates) and unique codes or identifiers not listed as direct identifiers. The following direct identifiers must be removed for PHI to qualify as a limited data set:

- Names;
- postal address information, other than town or city, state, and ZIP code;
- telephone numbers;
- fax numbers;
- email addresses;
- social security numbers;
- medical record numbers;
- health plan beneficiary numbers;
- account numbers;
- certificate or license numbers;
- vehicle identifiers and license plate numbers;
- device identifiers and serial numbers;
- URLs;
- IP addresses;
- biometric identifiers; and
- full-face photographs and any comparable images.

Before disclosing a limited data set, a covered entity must enter into a data use agreement (DUA) with the recipient, even when the recipient is a member of its workforce. The data use agreement establishes the parameters around the proposed uses and disclosures of the data, who is permitted to have access to the data, and stipulates that no other use will be made of the data, no attempt will be made to identify or contact individuals whose data are included in the limited data set, that appropriate safeguards are in place to protect the data from unauthorized use and that the recipient will report any uses or disclosures of the PHI that they become aware of that not in keeping with the terms of the DUA. DUAs for the purposes of research are available through the HRPO. DUAs should be submitted to the IRB along with the other project materials so that Presbyterian Healthcare Services has a record of the agreement.

K. Research Subject Access to PHI

With few exceptions, the Privacy Rule guarantees individuals' access to their medical records and other types of health information. One exception is during a clinical trial, when the subject's right of access can be suspended while the research is in progress. The subject must have been notified of and agreed to the temporary denial of access when providing consent and authorization. Any such notice must also inform the individual that the right to access will be restored upon conclusion of the clinical trial. Language accommodating this exclusion is included in the applicable Presbyterian research consent/authorization templates.

L. Accounting of Disclosures

The Privacy Rule generally grants individuals the right to a written "Accounting of Disclosures" of their PHI made by a covered entity without the individual's authorization in the six years prior to their request for an Accounting. A

covered entity must therefore keep records of such PHI disclosures for 6 years.

It is important to understand the difference between a use and a disclosure of PHI. In general, the use of PHI means communicating that information within the covered entity. A disclosure of PHI means communicating that information to a person or entity outside the covered entity. The Privacy Rule restricts both uses and disclosures of PHI, but it requires an accounting only for certain PHI disclosures.

Generally, an Accounting of Disclosures is required for:

- Routinely Permitted Disclosures (e.g., under public health authority, to regulatory agencies, to persons with FDA-related responsibilities) with limited exceptions (e.g., law enforcement, national security, etc.)
- Disclosures made pursuant to:
  - ❖ Waiver of Authorization
  - ❖ Research on Decedents' Information
  - ❖ Reviews Preparatory to Research

An accounting is not needed when the PHI disclosure is made:

- For treatment, payment, or health care operations.
- Under an Authorization for the disclosure.
- To an individual about themselves.
- As part of a limited data set under a data use agreement.

The Privacy Rule allows three methods for accounting for research-related disclosures that are made without the individual's Authorization or other than a limited data set: (1) A standard approach, (2) a multiple-disclosures approach, and (3) an alternative for disclosures involving fifty or more individuals. Whatever approach is selected, the accounting is made in writing and provided to the requesting individual. Accounting reports to individuals may include results from more than one accounting method.

See Presbyterian Healthcare Services policy COM.PHS-E.228 for a detailed discussion on Accounting for Disclosures.

XXIV. INFORMATION SECURITY

Presbyterian Healthcare Services has established standards and safeguards to protect patient's information and to ensure compliance with federal and state information security regulations. It is the responsibility of investigators to familiarize themselves with and comply with these standards. The use of personal laptops, desktops, portable/USB drives, and other non-Presbyterian devices for storage of research data is prohibited. In the instances when a non-Presbyterian computer or device must be used for the purposes of storing, even temporarily, or transmitting PHI or PII (Personally Identifiable Information) for research, the safeguards of the device must be verified by Information Security and a User Agreement completed. Additionally, any potential or known breach of a device or of research data must be immediately reported to both the IRB and the Presbyterian Healthcare Services Compliance Office so that appropriate steps can be taken to assess the situation, protect the information, and comply with regulations. Lost or stolen Presbyterian devices must also be reported to Information Security.

Provisions for data security must be described in applications to the IRB and updated, as necessary. When information containing direct identifiers such as Social Security numbers or PHI including data considered sensitive is to be transferred outside of the institution, the provisions for data security may be subject to further review and approval by the Information Security officer.

See the Presbyterian Healthcare Services policies on patient privacy and information security for further information.

XXV. SPECIAL TOPICS

A. Community Based Research

Community based research (CBR) is research that is conducted as an equal partnership between academic investigators and members of a community. In CBR projects, the community participates fully in all aspects of the research process. Community is often self-defined, but general categories of community include geographic community, a community of individuals with a common problem or issue, or a community of individuals with a common interest or goal.

Where research is being conducted in communities, investigators are encouraged to involve members of the community in the research process, including the design and implementation of research and the dissemination of results when appropriate.

The most significant community involvement is in a subset of CBR called Community Based Participatory Research (CBPR) where there is an equal partnership between the academic investigators and members of a community, with the latter actively participating in all phases of the research process including the design and implementation of research and the dissemination of results when appropriate.

B. Transnational Research

The IRB will review all transnational research involving human participants to ensure adequate provisions are in place to protect the rights and welfare of the participants. Approval of research is permitted if "the procedures prescribed by the foreign institution afford protections that are at least equivalent to those provided in 45 CFR 46."

All policies and procedures that are applied to research conducted domestically should be applied to research conducted in other countries, as appropriate.

For transnational research, the Presbyterian IRB seeks enough knowledge of the local research context by requesting approval for the project from local IRBs or ethics committees (which may or may not be OHRP-registered) and/or local letters of support. The source of this information will depend on the nature of the study, on the country and on the resources available to the investigator. Where there is a local IRB/IEC, Presbyterian IRB must receive and review the foreign institution or site's IRB/IEC review and approval of each study prior to beginning the research at the foreign institution or site.

In some circumstances where research may be performed internationally and/or in settings where there are no IRBs, the Presbyterian IRB may, prior to approval of the research, require additional verification and information from people outside the particular research project who are familiar with the customs, practices, or standards of care where the research will be taking place, such as local IRBs or ethics committees, other Presbyterian investigators with knowledge of the region, or a consultant who is an expert on the region. These individuals may either provide a written review of a research plan or attend an IRB meeting to provide the Presbyterian IRB with recommendations based on his or her expertise.

For Federally funded research, approval of research for foreign institutions or sites "engaged" in research is only permitted if the foreign institution or site holds an Assurance with OHRP and local IRB review and approval is obtained.

Approval of research for foreign institutions or sites "not engaged" in research is only permitted if one or more of the following circumstances exist:

- When the foreign institution or site has an established IRB/IEC, the investigator must obtain approval to conduct the research at the "not engaged" site from the site's IRB/IEC or provide documentation that the site's IRB/IEC has determined that approval is not necessary for the investigator to conduct the proposed research at the site.

- When the foreign institution or site does not have an established IRB/IEC, a letter of cooperation must be obtained demonstrating that the appropriate institutional or oversight officials permit the research to be conducted at the performance site.
- IRB approval to conduct research at the foreign institution or site is contingent upon receiving documentation of the performance site's IRB/IEC determination, or letter of cooperation, as applicable.

1. IRB Responsibilities

In addition to standard IRB review, the IRB will consider the following in the review of transnational research:

- The investigator and research staff are qualified to conduct research in that country including knowledge of relevant laws, regulations, guidance, and customs.
- The consent process and consent documents are appropriate for the languages of the subjects and communication with the subject population. Arrangements are considered to communicate with the subjects throughout the study (e.g., to answer questions).
- The IRB considers how modifications to the research will be handled. The IRB and investigators should consider as many contingencies (e.g., survey questions) as possible when research is reviewed and approved.
- The IRB considers how complaints, non-compliance, protocol/research plan deviations and UAPs involving risks to participants or other are handled.
- The IRB considers how post-approval monitoring will be conducted.
- The IRB considers if the investigator has obtained the appropriate host country permissions to conduct research (e.g., institutional, governmental, or ministerial, IRB, local or tribal). When appropriate, the IRB communicates and coordinates with the local institutions or ethics committees.
- The IRB considers mechanisms for communicating with the investigators and research staff when they are conducting the research in other countries.

2. Investigator Responsibilities

It is the responsibility of Presbyterian investigator and the foreign institution or site to assure that the resources and facilities are appropriate for the nature of the research.

- It is the responsibility of Presbyterian investigator and the foreign institution or site to confirm the qualifications of the investigators and research staff for conducting research in that country(ies).
- Investigators obtain all appropriate host country permissions to conduct research (e.g., institutional, governmental, or ministerial, IRB, local or tribal).
- It is the responsibility of Presbyterian investigator and the foreign institution or site to ensure that the consent process and consent document are appropriate for the languages of the subjects and communication with the subject population. Arrangements are considered to communicate with the subjects throughout the study (e.g., to answer questions). It is the responsibility of Presbyterian investigator and the foreign institution or site to ensure that the following activities will occur.
- Initial review, continuing review, and review of modification
- Post-approval monitoring
- Handling of complaints, non-compliance and UAPs involving risk to subjects or others.
- The IRB will not rely on a local ethics committee that does not have policies and procedures for the activities listed above.
- Investigators will consider how complaints, non-compliance, protocol/research plan deviations and UAPs involving risks to participants or other are communicated to the IRB.
- It is the responsibility of Presbyterian investigator and the foreign institution or site to notify the IRB promptly if a change in research activities alters the performance site's engagement in the research

(e.g., performance site "not engaged" begins to obtain consent of research participants, etc.).

- Investigators cooperate with the IRB regarding how and when post-approval monitoring will be conducted.
- Investigators consider mechanisms for communicating with the IRB when they are conducting the research in other countries.

3. Consent Documents

The informed consent documents must be in a language understandable to the proposed participants. Therefore, the IRB will review the document and a back translation of the exact content contained in the foreign language informed consent document which must be provided by the investigator, with the credentials of the translator detailed in the IRB application or **"Modification Request with Exceptions"** form. Verification of the back translation should be placed in the IRB file.

4. Monitoring of Approved Transnational Research

The IRB is responsible for the ongoing review of international research conducted under its jurisdiction through the continuing review process in accordance with all applicable federal regulations. When the IRB and a local ethics committee will both be involved in the review of research, there is a plan for coordination and communication with the local IRB/IECs.

The IRB will require documentation of regular correspondence between the Presbyterian investigator and the foreign institution or site and may require verification from sources other than the Presbyterian investigator that there have been no substantial changes in the research since its last review.

C. Research Repositories and Research Involving Coded Private Information or Biological Specimens

1. Biological Specimens

All activities involving the collection of human biological specimens for research purposes, as well as the research use of specimens collected for clinical care, must be conducted under the terms of an IRB-approved research protocol. The collection and use of human biological specimens (either identifiable or de-identified) must comply with all applicable laws and regulations for research involving human biological specimens or superseding requirements.

2. Regulatory Oversight

Under HHS regulations, a human subject is a living individual about whom an investigator (whether professional or student) conducting research:

- Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
- Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

Whether research involving biological specimens meets the definition of human subject research is based on (a) how the specimens were obtained, and (b) whether the specimens include identifiable private information. If the specimens are obtained specifically for research purposes, then they have been collected through intervention (includes both physical procedures by which data information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes) or interaction (includes communication or interpersonal contact between investigator and subject) with the individual and, thus, the research meets the definition of human subject research. If the specimens were not collected for research purposes but as

part of routine clinical care or other non-research purpose, then the research only meets the definition of human subject's research if the specimens include identifiable private information (see below for policies on coded specimens).

FDA regulations do not apply to biological specimens unless they are gathered as part of a clinical investigation involving human subjects or being used to test a medical device (see Section 13 for more detail on FDA regulations). HIPAA does not cover biological specimens but does cover protected health information (PHI) linked to the specimens (see Section 23 for more detail on HIPAA).

If the research meets the definition of human subject research, then all the requirements of this document apply.

3. IRB Review

Research involving only biological specimens may be exempt under Exemption Category #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." .

Non-exempt research only involving biological specimens may be eligible for expedited review if it is minimal risk and falls within one of the following categories:

- Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture [with restrictions]
- Prospective collection of biological specimens for research purposes by noninvasive means.
- Research involving materials that have been collected, or will be collected solely for non-research purposes

All non-exempt research involving biological specimens that are not eligible for expedited review must be reviewed at a convened IRB meeting. For all non-exempt research involving biological specimens, informed consent and documentation of consent is required unless waived by the IRB.

4. Coded Human Data or Biological Specimens

For purposes of this policy, ***coded*** means that: (1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

Guidance: ***Obtaining*** identifiable private information or identifiable specimens for research purposes constitutes human subject research. ***Obtaining*** identifiable private information or identifiable specimens includes, but is not limited to:

- Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that have been provided to the investigator from any source; and
- Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that were already in the possession of the investigator.

In general, private information or specimens are individually identifiable when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. Private information or specimens are not considered to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

In some cases, an investigator who obtains coded private information or specimens about living individuals under one of the conditions cited in 2(a)-(c) above may (1) unexpectedly learn the identity of one or more

living individuals, or (2) for previously unforeseen reasons now believe that it is important to identify the individual(s). If, as a result, the investigator knows, or may be able to readily ascertain, the identity of the individuals to whom the previously obtained private information or specimens pertain, then the research activity now would involve human subjects. Unless this human subject research is determined to be exempt (see Section 6), IRB review of the research would be required. Informed consent of the subjects also would be required unless the IRB approved a waiver of informed consent (see Section 11.9).

5. Who Should Determine Whether Coded Private Information or Specimens Constitutes Human Subject Research

The investigator in consultation with the HRPO Coordinator or IRB Chair will determine if the research involving coded information or specimens requires IRB review following the procedures for Human Subject Research Determinations described in Section 5.

D. Data or Biological Sample Repositories

A repository is a collection of data or biological specimens whose organizers:

- Receive data or specimens from multiple sources
- Maintain the data or specimens over time
- Control access to and use of data or specimens by multiple individuals and/or for multiple purposes, which may evolve over time

These policies and procedures apply to both data and biological sample repositories. For simplicity, both will be referred to as samples in this document.

There are two types of repositories:

- Non-research repositories created and maintained for purposes that are unrelated to research. Such purposes may include diagnosis, treatment, billing, marketing, quality control, and public health surveillance.
- Research repositories created and maintained specifically for research purposes.
- Such purposes may include databases to identify prospective subjects, patient outcome information to evaluate treatment effectiveness, and tissues samples for future research. Non-research repositories that are altered to facilitate research (e.g., through the addition of data fields not necessary for the core purpose of the repository) are considered research repositories.

1. Non-Research Repositories

Even though repositories were not created for research purposes, they may contain information that is of great interest to researchers. The creation (or operation) of non-research databases or repositories does not involve human subject research and does not require IRB oversight. However, IRB oversight is required for use in research of identifiable private information or identifiable human specimens from non-research databases and repositories (including data/tissue banks and registries).

- When research involves identifiable private information or identifiable human specimens each research use must receive prospective IRB review and approval and continuing IRB oversight
- Researchers should submit an application for IRB review and receive IRB approval before initiating the research.
- Where available, the application should include any available information about the circumstances under which the information or specimens were originally collected.
- Investigators who believe their research may be exempt from the human subject regulations should include a request for exemption with the IRB application.
- The IRB may require researchers to obtain the informed consent of subjects for research involving information or specimens contained in non-research databases or repositories. The IRB can waive the

requirement for informed consent if the research meets the criteria in the regulation

2. Research Repositories

Research repositories involve three components:

- the collectors of samples;
- the storage and data management center; and
- the recipient investigators.

E. Sample Collection

If the samples were collected for research purposes or are associated with information that can identify the donor, then informed consent must be obtained from the donor unless appropriately waived by the IRB.

Informed Consent information should include:

- A clear description of the operation of the database;
- The specific types of research to be conducted;
- The conditions under which data will be released to recipient-investigators;
- Procedures for protecting the privacy of subjects and maintaining the confidentiality of data;
- A statement regarding future withdrawal of the data from the study (i.e., state whether subjects may, in the future, request that their data be destroyed or that all personal identifiers be removed from data); and
- Other information, such as the length of time that data will be stored, subject access to information learned from the research, and secondary uses of the samples should be considered as appropriate.

Repositories should have data submission policies to ensure that the data was collected in an ethical manner, such as informed consent and IRB approval.

1. Sample Storage and Management

Repositories should have written policies on:

- Data and tissue submission requirements (1) Informed consent; (2) IRB review
- Physical and procedural mechanisms for the secure receipt, storage, and transmission of information and specimens
- Policies on release of information and specimens: (1) Coding; (2) Release of identifier; (3) Certificates of Confidentiality

2. Recipient Investigators

Recipient-investigators should have a written agreement with the repository. The agreement should specify under what conditions the data is being released to the recipient-investigator(s). The terms under which the data is released determine whether the research requires IRB oversight.

3. IRB Oversight

Operation of a research repository and its data management center under the auspices of Presbyterian is subject to oversight by the Presbyterian IRB. Proposals to establish a repository must be submitted to the IRB using the “Establishment of a Repository” form, specifying the conditions under which data and specimens may be accepted and shared, and ensuring adequate provisions to protect the privacy of subjects and maintain the confidentiality of data. The IRB also reviews and approves a sample collection protocol and informed consent document for distribution to sample collectors and their local IRBs.

F. Presbyterian Healthcare Services Employees as Subjects

When Presbyterian employees are being recruited as potential subjects, investigators must ensure that there are additional safeguards for these subjects. The voluntary nature of their participation must be primary and without undue influence on their decision. Investigators must emphasize to subjects that their employment will not be affected by their participation decision. To minimize coercion, investigators should avoid, whenever possible, the use of their employees in procedures which are neither therapeutic nor diagnostic.

G. Student and Resident-Initiated Research

Student investigators must be paid Presbyterian employees in order to be a PI who initiate a research project at Presbyterian. Student investigators must also identify a study mentor who will provide guidance and oversight of the proposal development/submission process and the conduct of the research. Study mentors must formally approve and sign off on student application and "Roles and Responsibilities form" To conduct research under the auspices of Presbyterian Healthcare Services, a resident must be participating in a program which has a clinical affiliation agreement with Presbyterian.

Students who are unaffiliated with Presbyterian must service as a CO-I and are required to have a mentor/precentor who is employed with Presbyterian and who will serve as the PI. Study mentors must formally approve and sign off on student/resident application and "Roles and Responsibilities form." To conduct research under the auspices of Presbyterian Healthcare Services, a resident must be participating in a program which has a clinical affiliation agreement with Presbyterian.

1. **Human Subject Research and Course Projects**

   Learning how to conduct ethical human subject research is an important part of a student's educational experience. Research activities that are designed as part of a course requirement for purposes of learning experience only and are not "designed to develop or contribute to generalizable knowledge" may not require IRB review and approval if all the following conditions are true:

   - Results of the research are viewed only by the course instructor for teaching purposes and discussed within the classroom for teaching and learning purposes.
   - Results of the research are not made public through presentation (outside of the classroom) and are not published in paper or electronic format (e.g., cannot be made available on the internet, cannot be published in a journal, etc.).
   - Research procedures are no more than minimal risk.
   - Vulnerable populations are not targeted (e.g., children under age 18, prisoners, persons who are cognitively impaired, etc.).
   - Data collected are recorded in such a manner that the subjects are not identifiable (images in video recordings and photographs and voices on audio recording are identifiable).
   - When appropriate, an informed consent process is in place.

2. **Responsibility of the Study Mentor and/or the Course Instructor**

   The Presbyterian study mentor is responsible for communicating to the student the ethics of human subject research, for ensuring the protection of human subjects (including a process is in place for obtaining voluntary informed consent from research subjects when appropriate), and for monitoring the student's progress.

   When designing a project, students should be instructed on the ethical conduct of research and on the preparation of the IRB application when such is required. Instructors and students should:

   - Understand the elements of informed consent;

- Develop appropriate consent documents;
- Plan appropriate strategies for recruiting subjects;
- Identify and minimize potential risks to subjects;
- Assess the risk-benefit ratio for the project;
- Establish and maintain strict guidelines for protecting privacy and confidentiality; and
- Allow enough time for IRB review (if necessary) and completion of the project.

In deciding whether a class research project requires IRB review, the study mentor is encouraged to contact the IRB office for assistance.

H. Genetic Studies

Genetic research studies may create special risks to human subjects and their relatives. These involve medical, psychosocial, legal, and economic risks, such as the possible loss of privacy, insurability, and employability, change in immigration status and limits on education options, and may create a social stigma. Knowledge of one's genetic make-up may also affect one's knowledge of the disease risk status of family members.

In studies involving genetic testing, several questions need to be addressed, including:

- Will test results be given?
- Will disease risk be quantified, including the limits on certainty of the testing?
- Will a change in a family relationship be disclosed, such as mistaken paternity?
- Does the subject or family member have the option not to know the results? How will this decision be recorded?
- Could other clinically relevant information be uncovered by the study? How will disclosure of this added information occur?
- Do any practical limitations exist on the subject's right to withdraw from the research, withdraw data, and/or withdraw DNA?
- Is the subject permitted to participate in the study while refusing to have genetic testing (such as in a treatment study with a genetic testing component)?

For DNA banking studies, several questions need to be addressed, including:

- Will DNA be stored or shared? If shared, will the subject's identity be known by the new recipient investigator?
- Will the subject be contacted in the future by the investigator to obtain updated clinical information?
- How can the subject opt out of any distribution or subsequent use of their genetic material?

I. Research Supported by the Department of Defense (DoD)

Research supported by the Department of Defense (DoD) is reviewed and conducted in compliance with part 219 of title 32 CFR, part 980 of title 10 USC, applicable parts of title 21 CFR (50, 56, 312, 600, 812), DoD Instruction 3216.02, DoD Directive 3210.07, and applicable additional requirements from respective DoD component(s).

XXVI. CASE REPORT

In general, an anecdotal report on one or two patients seen in one’s own practice and a comparison of these patients to existing reports in the literature is not research and does not require IRB approval. However, a review of three or more cases (i.e., case series); or going beyond one’s own practice to seek out and report cases seen by other clinicians creates the appearance of a systematic investigation with the intent to contribute to generalizable knowledge and therefore is considered research and would require IRB approval.

A. Definitions

Single Case Report. The external reporting (e.g., publication, poster, or oral presentation) of an interesting clinical situation or medical condition of a single patient. Case reports normally contain detailed information about an individual patient and may include demographic information and information on diagnosis, treatment, response to treatment, follow-up after treatment, as well as a discussion of existing relevant literature. The patient information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience.

Case Series. The external reporting (e.g., publication, poster, or oral presentation) of an interesting clinical situation or medical condition in a series of patients (i.e., more than two patients). Case series usually contain detailed information about each patient and may include demographic information and information on diagnosis, treatment, response to treatment, follow-up after treatment, as well as a discussion of existing relevant literature. The information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience.

XXVII. CERTIFICATE OF CONFIDENTIALITY (COC)

Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, tribal law passed by the official governing body of an American Indian or Alaska Native tribe or local level. A CoC does not protect against voluntary disclosures by the investigator, but those disclosures must be specified in the informed consent form. An investigator may not use the CoC to withhold data if the participant consents in writing to the disclosure.

CoCs are obtained as follows:

- CoCs are issued automatically when research is conducted or supported by NIH and falls within the scope of the NIH policy.
- Research that is not funded by NIH (non-NIH research) may still have the protections afforded by CoCs through successful application to the NIH, FDA, or other authorized Federal agencies or departments.

Additional information about CoCs and the application process for non-NIH research is available on the NIH CoC Website.

A. Definitions

Identifiable, sensitive information means information that is about an individual and that is gathered or used during the course of biomedical, behavioral, clinical, or another research and (1) Through which an individual is identified; or (2) 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.

1. Protections and Requirements

When a CoC is issued, whether automatically or under an approved application, the person(s) engaged in the research must not disclose or provide the name of a subject or any information, document, or biospecimen that contains identifiable, sensitive information about the subject and that was compiled for the purposes of the research:

- In any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, unless the disclosure is made with the consent of the individual to whom the information, document, or

biospecimen pertains; or

- To any other person not connected with the research, unless:
  - ❖ Required by federal, state, or local laws, but excluding proceedings as described above;
  - ❖ Necessary for the medical treatment of the subject to whom the information, document, or biospecimen pertains and made with the consent of the subject;
  - ❖ Made with the consent of the individual to whom the information, document, or biospecimens pertains; or
  - ❖ Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

2. Additional Protections

Identifiable, sensitive information protected under a CoC, and all copies thereof, are immune from the legal process, and shall not, without the consent of the of the individual to whom the information pertains, be admissible as evidence or used in any action, suit, or other judicial, legislative, or administrative proceeding. Identifiable, sensitive information that has been collected under a CoC, and all copies thereof, are protected for perpetuity. Nothing in the rule (42 U.S.C. 241(d)) may be construed to limit the access of a subject to information about himself or herself collected during the research.

When consent is obtained, the consent should inform subjects that a CoC is in place and describe the protections and limitations. The NIH Policy on CoCs applies to *"all biomedical, behavioral, clinical, or other research funded wholly or in part by the NIH, whether supported through grants, cooperative agreements, contracts, other transaction awards, or conducted by the NIH Intramural Research Program, that collects or uses identifiable, sensitive information"* that was commenced or ongoing on or after December 13, 2016.

CoCs are automatically granted, and the requirements of such must be complied with, whenever a NIH-funded activity falls within the scope of the policy. Investigators and institutions are responsible for determining when a NIH-funded activity falls within the scope of the policy.

NIH policy expands upon 42 U.S.C. 241(d) by explaining that NIH considers research in which identifiable, sensitive information is collected or used, to include:

- Human subject research as defined in 45 CFR 46, including research determined to be exempt (except for exempt research when the information obtained is recorded in such a manner that human subjects cannot be identified or the identity of the human 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 an exceedingly 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 human subjects can be identified or the identity of the human 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, as defined in subsection 301(d) of the Public Health Service Act.

3. NIH CoC Policy Determination

At Presbyterian Healthcare Service, Research and Sponsored Award (RSA) staff in the Finance department

will, in consultation with the investigator(s) (or Program or Project Director, if applicable), determine if the NIH policy applies to any NIH-funded activity. The questions outlined in the NIH policy will be used to guide the analysis. When it has been determined that the NIH policy does not apply, investigators (or Program or Project Directors, if applicable) are responsible for consulting with RSA whenever they are proposing changes to the NIH-funded activity that may impact or change the analysis.

The NIH policy includes additional responsibilities and requirements for internal controls and for ensuring that recipients of identifiable, sensitive information protected by a CoC understand that they are also subject to the requirements of subsection 301(d) of the Public Health Service Act.

4. Application Procedures for non-NIH Research

Any person engaged in human subject's research that collects or uses identifiable, sensitive information may apply for a CoC. For most research, CoCs are obtained from NIH, an investigator may apply for a CoC through the NIH Institute or Center funding research in a scientific area similar to the project.

If the research is conducting a sensitive research project that is covered by the Agency for Healthcare Research and Quality (AHRQ) confidentiality statute (42 U.S.C. section 299c-3(c)) or the Department of Justice (DoJ) confidentiality statute (42 U.S.C. section 3789g), then a CoC may not be needed.

If there is an Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE), the sponsor can request a CoC from the FDA. CoCs may also be issued by other Federal agencies and departments, such as CDC, SAMSHA, or HRSA. For more information, see the NIH CoC Website.

Investigators are responsible for clearly representing in the IRB submission that a CoC is in place, or that an application for CoC has been submitted. When the CoC application is in process or pending, the IRB may condition final approval upon its receipt. For studies that are already underway, investigators must submit a Modification Request to the IRB, along with updated consent language (if applicable), when a CoC is applied for, or when automatically issued under the NIH policy.

When reviewing research under a CoC, the Presbyterian IRB will evaluate whether the research plan is consistent with the obligations to protect information and specimens under a CoC and whether the consent language, if applicable, discloses the CoC and appropriately describes the associated protections and limitations. Sample consent language is available on the NIH CoC Website and in the template consent forms available on the Presbyterian HRPP electronic submission platform.

When non-NIH research is not under a CoC, the IRB may require an investigator to apply for a CoC if the research includes identifiable, sensitive information and the IRB determines that a CoC is necessary to minimize risks and adequately protect the subject's privacy and the confidentiality of subject's information or specimens.

B. Mandatory Reporting

While any person may make a report if they have reasonable cause to believe that a child or elder was abused or neglected, New Mexico law mandates that certain persons who suspect child or elder abuse or neglect report this to the New Mexico Adult Protective Services. Presbyterian Healthcare Services policy requires the solicitation of informed consent from all adult research subjects and, where appropriate, assents from children involved as research subjects, in addition to the permission of their parents. In situations where conditions of abuse or neglect might be revealed, mandated reporters should make themselves known as such to parents of children under age 18, to subjects who are children, and to subjects who are potential victims of abuse or neglect.

Investigators should consult applicable state and local sources to determine if potential subjects should be advised of mandatory reporting requirements during the informed consent process.

XXVIII. COVID-19 ADDENDUM, OCTOBER 13, 2020

The Presbyterian HRPP SOP COVID-19 Addendum aligns with the October 8, 2020, Office for Human Research Protections (OHRP) guidance on exceptions to the Single IRB Review Requirements for Certain HHS-Conducted or -Supported Cooperative Research Activities Subject to the 2018 Requirements During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency.

C. Background

Section 46.114 of the 2018 Requirements requires that any institution located in the United States that is engaged in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States (45 CFR § 46.114(b)(1)). Cooperative research projects are those projects covered by the 2018 Requirements that involve more than one institution (45 CFR § 46.114(a)). The compliance date for this requirement was January 20, 2020.

The 2018 Requirements provide that the Federal department or agency conducting or supporting cooperative research may except the research from the single IRB mandate. To do so, the Federal department or agency must both determine and document that using a single IRB is not appropriate for the particular context (45 CFR 46.114(b)(2)(ii)).

Due to the public health emergency posed by COVID-19, the Office for Human Research Protections (OHRP) is exercising its discretion, as specifically permitted by 45 CFR § 46.114(b)(2), to issue this exception to apply in the conditions outlined herein, on the basis that using a single IRB is not appropriate for this research context. We believe that this determination of exception is a statement of agency policy that is not subject to the notice and comment requirements of the Administrative Procedure Act (APA) (5 U.S.C. § 553(b)(A)). For the same reasons explained above, OHRP additionally finds that, even if this determination of exception were subject to the public participation provisions of the APA, prior notice and comment is impracticable and contrary to the public interest, and there is good cause to issue this determination of exception without prior public comment and without a delayed effective date (5 U.S.C. §53(b)(B) & (d)(3)). This exception is applicable as of October 8, 2020.

D. Determination of Exception

To ensure that institutions conducting cooperative research can take advantage of the most appropriate IRB review structure, OHRP has determined that, for studies that are conducted or supported by HHS and subject to the 2018 Requirements, and for purposes of 45 CFR 46.114(b) (2)(ii), an exception to the requirement to use a single IRB is appropriate for the following category:

Cooperative research:

- that is ongoing or initially reviewed by the IRB during the Coronavirus Disease 2019 (COVID-19) public health emergency, as declared by the Secretary of Health and Human Services,
- where reliance on a single IRB would not be practical; and
- for which the HHS division supporting or conducting the research approves of the use of this exception.

This exception applies for the duration of the research.

OHRP has made this exception determination due to concerns regarding the application of the single IRB requirement to cooperative research subject to the 2018 Requirements when this research is initially reviewed or ongoing during the COVID-19 public health emergency. The COVID-19 public health emergency has created unprecedented burdens and disruption to the research enterprise, while at the same time requiring urgent research responses that necessitate flexible approaches to oversight in order to provide vital information and to allow other research to continue where possible. This exception represents an effort to prioritize the health and safety of both research subjects and investigators and provides flexibility to institutions in seeking IRB review due

to the unique challenges created by the COVID-19 outbreak.

Presbyterian IRB will comply as applicable.