



HRPP and IRB Policy Manual

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Section I: Human Research Protection Program

Western Michigan University Homer Stryker M.D. School of Medicine fosters a research environment that promotes the respect for the rights and welfare of individuals recruited for, or participating in, research conducted at, under the auspices of, or using the services or resources of the medical school. In the review and conduct of research, actions by the medical school are guided by the principles set forth in [*The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*](#): respect for persons, beneficence, and justice. The actions of the medical school also conform to all applicable federal, state, and local laws and regulations. In order to fulfill this mission, the medical school has established a Human Research Protection Program (HRPP). The medical school HRPP, in collaboration with its research community, is responsible for ensuring the ethical and equitable treatment of all human subjects in research conducted at, under the auspices of, or using the services or resources of the medical school. This includes research that is externally funded, funded from internal sources, or conducted without direct funding.

Mission

The mission of the HRPP is to:

- Safeguard and promote the health and welfare of human research subjects by ensuring that their rights, safety, and well-being are protected.
- Provide guidance and support to the research community in the conduct of research with human subjects.
- Assist the research community in ensuring compliance with relevant federal, state, and local laws and regulations.
- Provide timely and high-quality education, review, and monitoring of human research projects.
- Facilitate excellence in human subjects' research.

The HRPP implements procedures to:

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

Institutional Authority

The medical school HRPP operates under the authority of the medical school. The *Human Research Protection Program (HRPP) and Institutional Review Board (IRB) Policy Manual* serves as the governing policies and procedures for the conduct and review of all human research conducted at, under the auspices of, or using the services or resources of the medical school. HRPP policies and these operating procedures are made available to all medical school investigators and research staff on the medical school website.

- The medical school designates the dean of the medical school as the Institutional Official who has overall responsibility for the medical school HRPP. The duties of the Institutional Official include:
- Fostering, supporting, and maintaining an institutional culture that promotes and facilitates the ethical conduct of all research involving human subjects and the adherence to regulations and institutional policies.
- Ensuring that the Institutional Review Board (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.
- Oversight of the Institutional Review Board (IRB).
- Oversight of the conduct of research conducted by all medical school investigators.
- Ensuring the 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.
- Oversight of the development and implementation of an educational plan for IRB members, staff, and investigators.
- Ensuring compliance with institutional policies and all applicable regulations for the protection of human subjects.
- Serving as the signatory authority and ensuring compliance with the terms of the Federalwide Assurance to the Office of Human Research Protections (OHRP).
- Providing support to the HRPP by ensuring that the HRPP has sufficient staff and resources to fulfill its role and obligations.

In the performance of these duties, the Institutional Official has the authority to delegate such activities as may be necessary in order to fulfill these duties.

To conduct its responsibility effectively, the medical school maintains an IRB to review research protocols involving human subjects. The IRB is an autonomous administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the medical school. The IRB has the following authority:

- To approve, require modifications to secure approval, or disapprove all research activities overseen and conducted under the auspices of the medical school, regardless of location of the research activities.
- To 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 stated in the regulations be provided to subjects when, in the judgment of the IRB, the information would meaningfully add to the protection of the rights and welfare of subjects.
- To conduct continuing review of research at intervals appropriate to the degree of risk of the research, but not less than once per year.
- To suspend or terminate approval of research not being conducted in accordance with IRB requirements or that has been associated with unexpected serious harm to subjects.
- To observe, or have a third party observe, the consent process.
- To observe, or have a third party observe, the conduct of the research.
- To determine, with the assistant dean for Research Compliance, whether data or information gathered without IRB approval or in association with serious non-compliance may be published or used for research purposes. The IRB, the assistant dean for Research Compliance, and associate dean for Research must approve the publication or use of such data or information.

All IRB-approved research studies are subject to ongoing review, which must be conducted at least once annually by the IRB. If approval of a study by the IRB lapses, all research activity for the study must stop immediately unless it is determined to be in the best interest of subjects who are already enrolled to continue participating in the research. The investigator can petition the IRB to continue an individual subject's research intervention/interaction during a period of lapsed IRB approval if the investigator believes there is a safety concern or ethical issue such that it is in the best interests of the individual subject to do so.

The HRPP has jurisdiction over all human subject research conducted under the auspices of the medical school, regardless of funding source or performance site. Research under the auspices of the institution includes research:

- Using any medical school facilities, property, services, or resources.
- Conducted by, with, or under the direction of any employee or agent of the medical school, including faculty and students, in connection with their medical school responsibilities.
- Involving the use of non-public information that is held by the medical school to identify, contact, or study human subjects.

Any research involving human subjects must be conducted with IRB approval. No research may commence until all required institutional approvals are obtained, including IRB approval if needed. Exempt research is subject to IRB review for determination of exemption status. At the medical school, exemptions are reviewed and granted by the IRB chair and vice chair. For medical school research not involving

human subjects, review by the medical school IRB is not required. At the medical school, determinations of the need for IRB engagement are made by the IRB chair and vice chair.

At the discretion of the Institutional Official or designee, the medical school may enter into an agreement to rely upon an IRB other than the medical school IRB or to enter into a joint review arrangement.

The Institutional Official may review any human subjects research protocol and has the authority to disapprove or terminate any research protocol that has been approved by the IRB. However, no one at the medical school shall approve or implement human subjects research that has not been approved by the IRB, and no one at the medical school shall approve or implement human subjects research by ignoring or overriding a decision of the IRB to disapprove or terminate a research protocol.

All institutional and non-institutional performance sites for the medical school, domestic or foreign, are obligated by this policy to conform to ethical principles that are at least equivalent to those of the medical school, or more stringent as may be determined by the Department of Health and Human Services (DHHS) Secretary.

The Institutional Official and IRB shall adopt operating procedures to implement this policy, which are in the *Human Research Protection Program (HRPP) and Institutional Review Board (IRB) Policy Manual*. These procedures shall serve as the governing procedures for the conduct and review of all human subjects research conducted under the auspices of the medical school, under the oversight of the medical school IRB, or using any medical school facilities, property, services, or resources.

Definitions

- **Common Rule:** The Common Rule refers to the “Federal Policy for the Protection of Human Subjects” adopted by a number of federal agencies. Although the Common Rule is codified by each agency separately, the text is identical to DHHS regulations in [45 CFR 46 Subpart A](#). For the purposes of this document, references to the Common Rule cite the DHHS regulations.
- **Employee or Agent:** For the purposes of this document, *employees or agents* refers to individuals who: (1) act on behalf of the organization; (2) exercise institutional authority or responsibility; or (3) perform institutionally designated activities. Employees and agents can include staff, students, contractors, and volunteers, among others, regardless of whether the individual is receiving compensation.
- **Engagement:** Department of Health and Human Services (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 Office for Human Research Protection (OHRP) with a satisfactory assurance of compliance with the DHHS regulations, unless the research is exempt under [45 CFR 46.101\(b\)](#). “In general, an institution is considered

engaged in a particular non-exempt human subjects 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.” Additionally, institutions that receive an award through a grant, contract, or cooperative agreement directly from DHHS for the non-exempt human subjects research (ie, 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.

- **Human Subject:** A human subject as defined by the Common Rule is a living individual about whom an investigator conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens [[45 CFR 46.102\(f\)](#)].

The terms “subject” and “participant” are used interchangeably in this document and have the same definition.

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 research evaluating the safety or effectiveness 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 Subjects Research:** Human Subjects Research means any activity that meets the definition of “research” and involves “human subjects” as defined by the Common Rule, FDA regulations, or other applicable regulations.
- **Identifiable Information/Biospecimen:** Identifiable information/biospecimen means information/biospecimen that is individually identifiable (ie, the identity of the subject is or may readily be ascertained by the investigator or associated with the information/biospecimen).
- **Interaction:** An interaction means communication or interpersonal contact between investigator and subject.
- **Intervention:** An intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject’s environment that are performed for research purposes.
- **Private Information:** 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 which has been

provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).

- **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 or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

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 (ie, 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.” 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 Food and Drug Administration 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 Food and Drug Administration 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 Food and Drug Administration 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 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 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 FDA as part of an application for a research or marketing permit is considered to be 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:

- **Human drugs:** The primary intended use of the drug 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>
- **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>
- **Biological Products:** 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, and microorganism — and may be produced by biotechnology methods and other new 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>
- **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>

- **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>
- **Dietary Supplements:** A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains one or more “dietary ingredients.” The “dietary ingredients” in these products may include vitamins, minerals, herbs or other botanicals, amino acids, and other substances found in the human diet, such as enzymes. When a dietary supplement meets the definition of drug, it is regulated as such.
- **Medical Foods:** A medical food, as defined in section (b) of the Orphan Drug Act (21 U.S.C. 360ee (b) (3)), is a food which is formulated to be consumed or administered internally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.
- **Mobile Medical Apps:** Mobile apps are software programs that run on smartphones and other mobile communication devices. They can also be accessories that attach to a smartphone or other mobile communication devices, or a combination of accessories and software. Mobile medical apps are medical devices that are mobile apps, meet the definition of a medical device and are an accessory to a regulated medical device or transform a mobile platform into a regulated medical device.
- **Radioactive Drugs:** The term radioactive drug means any substance defined as a drug which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance but does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides. The term “radioactive drug” includes “radioactive biological product”.
- **Radiation-Emitting Electronic Products:** A radiation-emitting electronic product as any electrically-powered product that can emit any form of radiation on the electromagnetic devices, magnetic resonance

imaging (MRI) devices, laser toys, laser pointers, liquid crystal displays (LCDs), and light emitting diodes (LEDs).

- **Infant Formulas:** Infant formulas are liquid foods intended for infants and substitute for mother's milk.
- **Electronic Products:** The FDA regulates certain classes of electronic products including radiation-emitting electronic products such as microwaves and X-rays.

Ethical Principles

The medical school is committed to conducting research with the highest regard for the welfare of human subjects. With the exception of transnational research, where consideration of alternative ethical principles may apply see *Section 26, Transnational Research*, the medical school upholds and adheres to the principles of [*The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*](#) by The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 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 medical school Human Research Protection Program (HRPP), in collaboration with its research community, is responsible for ensuring the ethical and equitable treatment of all human subjects in research conducted at, under the auspices of, or using the services or resources of the medical school.

Regulatory Compliance

The HRPP is responsible for ensuring compliance with federal regulations, state law and institutional policies. Human subjects research conducted at, under the auspices of, or using the services or resources of the medical school is conducted in accordance with applicable regulations and requirements of, but not limited to, the Common Rule, FDA, Health Insurance Portability and Accountability Act (HIPAA), U.S. Department of Defense (DOD), U.S. Department of Education (DOE), U.S. Department of Justice (DOJ), and Family Educational Rights and Privacy Act (FERPA).

Research conducted, supported, or otherwise subject to regulation by any federal department or agency which adopts the Common Rule is reviewed and conducted in accordance with the Common Rule. Although the Common Rule is codified by each agency separately, the text is identical to DHHS regulations in 45 CFR 46 Subpart A. For the purposes of this document, references to the Common Rule will cite the DHHS regulations.

Research subject to FDA regulations is reviewed and conducted in accordance with applicable regulations including, but not limited to, 21 CFR 50, 21 CFR 56, 21 CFR 312 and 21 CFR 812.

Research involving the use of Protected Health Information is reviewed and conducted in accordance with the (HIPAA), 45 CFR Part [160](#), [162](#), and [164](#).

Research supported by the DOD is reviewed and conducted in compliance with [32 CFR 219](#), [10 USC 980](#), applicable parts of title [21 CFR \(50, 56, 312, 600, 812\)](#), [DOD Instruction 3216.02](#), [DOD Instruction 3210.07](#), and applicable additional requirements from respective DOD component(s). Researchers should consult the applicable DOD regulations, instructions, and directives when designing the research that may be supported by DOD. These rules include but are not limited to:

- Special education requirements for Navy-funded funded human subjects research.
- Appointment of research monitor for all research involving more than minimal risk to research participants.
- Special protections for U.S. military personnel participating in research.
- Disclosure and consent.
- Prohibition of research involving prisoners of war.

Review by the applicable DOD Human Research Protection Program and IRB may be required. The medical school will execute a DOD FWA or DOD Addendum to its FWA when required by the component of DOD that is involved. The IRB evaluates the research in accordance with these rules if applicable.

Research conducted or supported by the DOE is subject to the Common Rule with regulations published at [34 CFR 97](#). In addition to the Common Rule, human subjects research involving education records conducted at institutions receiving DOE funding must comply with additional requirements, including [FERPA \(34 CFR 99\)](#) and the Protection of Pupil Rights Amendment ([PPRA](#)) ([34 CFR 98](#)). Investigators should consult these regulations and [resources provided by DOE](#) when developing their research protocol. The Registrar serves as the medical school's FERPA Officer. The IRB evaluates the research in accordance with these regulations if applicable.

Research conducted or supported by the DOJ is subject to the Common Rule, including Subpart C, with regulations published at [28 CFR 46](#). The DOJ has established additional requirements for research conducted with the federal Bureau of Prisons ([28 CFR 512](#)), and research involving the National Institute of Justice ([28 CFR 22](#)). Investigators should consult these regulations and [resources provided by NIJ](#) when developing their research protocol. The IRB evaluates the research in accordance with these regulations if applicable.

International Conference on Harmonization-Good Clinical Practices (ICH-GCP)

The medical school voluntarily applies the International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines (sometimes referred to as ICH-GCP or E6) to clinical trials when required by a sponsor or funding agency. The medical school applies the ICH-GCP guidelines only to the extent that they are compatible with FDA, DHHS, and other applicable regulations.

Federalwide Assurance (FWA)

The federal regulations require that federally conducted or supported human subject research only be conducted at facilities covered by a Federalwide Assurance (FWA) approved by the 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 ethical principles and federal regulations pertaining to the protection of human subjects.

The medical school has an OHRP-approved Federalwide Assurance (FWA00009755) and has designated an internal IRB (registered as IRB00010682) to review human research conducted under its auspices.

On January 19, 2017, the DHHS and fifteen other federal agencies issued revisions to the Common Rule. These changes go into effect on January 21, 2019 with the exception of a staged implementation on single IRB requirements. The medical school will implement these new rules for all research that is federally funded or supported or is subject to FDA regulations. For research that is not federally funded or supported and is not subject to FDA regulations the medical school ensures that human research subjects benefit from equivalent protections by applying the Common Rule standards with purposeful deviations that do not meaningfully diminish protections as noted within this manual.

In most cases, ongoing research will remain under the pre-2018 regulations (those issued in 1991.) The HRPP/IRB will maintain two sets of Standard Operating Procedures. Investigators are not required to make any changes to ongoing research. The IRB will issue guidance on how to request transition to the new rules, if desired, and the circumstances where transition might be beneficial. Investigators should be aware that transitioned studies might need additional IRB review and re-consenting of subjects. Final determination on whether to transition an individual study is made by the IRB.

Likewise, federal regulations require IRBs to register with DHHS if they will review human subjects research conducted or supported by DHHS or research subject to FDA regulations.

Research at the Medical School

Research at the medical school includes research meeting one or more of the following conditions:

- Conducted at, under the auspices of, or using the services or resources of the medical school.
- Conducted by or under the direction of any employee or agent of the medical school, including students, in connection with his/her medical school responsibilities.
- Conducted by or under the direction of any employee or agent, including students, of the medical school using any property or facility of the medical school.
- Involving the use of the medical school's non-public information to identify, contact, or study human subjects.

Even when the medical school IRB does not serve as the IRB of record, research conducted at, under the auspices of, or using the services or resources of the medical school is subject to quality review, monitoring, inclusion of local research context and all other requirements of the medical school HRPP.

FDA regulations are oriented to the responsibilities of IRBs, investigators, and sponsors as opposed to institutions. In general, FDA-regulated research conducted in medical school facilities or by medical school Principal or Sub-Investigators (as defined on the FDA 1572, or equivalent for medical device studies, or delegation of responsibilities log) requires review by an IRB designated by the medical school. Exceptions to this requirement may be granted on a case-by-case basis (eg, when the medical school's involvement in the research is limited to the provision of a common diagnostic procedure and associated reading or analysis).

External organizations and researchers that seek to conduct human subjects research that is under the auspices of the medical school must identify and designate a faculty member of the medical school to serve as the principal investigator, or other designation having the authority and responsibility of a principal investigator, for the scope of the research that is under the auspices of the medical school see *Section 1, Principal Investigators*. The principal investigator must consult with the medical school HRPP or IRB staff prior to initiating any research activities under the auspices of the medical school, and is responsible for following all medical school policies and procedures related to the research.

An IRB chair or vice chair, with the assistance of the HRPP director and/or IRB manager to determine whether the medical school is engaged in a particular research study. Investigators and other institutions may not independently determine whether the medical school is engaged in a particular research study.

When the medical school is engaged in research, the Institutional Official or designee may choose to enter into an agreement to cede review to an external IRB.

Additional information on determining engagement is available in [Guidance on Engagement on Institutions in Human Subjects Research](#) from the DHHS OHRP.

Written Policies and Procedures

Medical school policies and procedures for Human Research Protection detail the policies and regulations governing research with human subjects and the requirements for submitting research proposals for review by the medical school IRB. These policies and procedures are in this *Human Research Protection Program (HRPP) and Institutional Review Board (IRB) Policy Manual*. This is not a static document. The policies and procedures are reviewed at least annually and revised as needed. The medical school dean, as the Institutional Official, approves all revisions of policies and procedures.

The HRPP director ensures that the research community is apprised of new information that may affect the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues. Information is provided on the medical school website and distributed through electronic mailing lists. These policies and procedures are available on the medical school website and may be printed.

HRPP Structure

The HRPP encompasses individuals and committees with responsibilities for the protection of human subjects, and includes the Institutional Official, associate dean for Research, assistant dean for Research Compliance, HRPP director, HRPP/IRB staff, the IRB, Institutional Biosafety Committee, Research Committee, Sponsored Programs Administration director and staff, CCR administration and staff, Research Integrity Officer, Chief Compliance Officer, clinical research staff, legal counsel, investigators, and others. 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:

Institutional Official

The ultimate responsibility of the HRPP resides with the medical school dean as Institutional Official of the program. The Institutional Official is legally authorized to represent the medical school, is the signatory of the FWA, and assumes the obligations of the FWA. The Institutional Official is responsible for ensuring that the medical school HRPP and IRB have the resources and support necessary to comply with all institutional 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 HRPP and IRB records.

- Resources for reviewing and other compliance activities and investigation of non-compliance.
- Access to legal counsel when required.
- Supporting educational opportunities related to human research protections for HRPP/IRB staff, IRB members, and investigators and research staff.

The Institutional Official conducts and documents an annual review of HRPP and IRB function, requirements, and resources and makes adjustments as needed.

The Institutional Official is also responsible for:

- Ensuring compliance with medical school policies and all applicable regulations for the protection of human subjects.
- Fostering, supporting, and maintaining an institutional culture that supports the ethical conduct of all research involving human subjects and the adherence to regulations and institutional policies.
- Oversight of the medical school IRB.
- Ensuring that the medical school 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.
- Ensuring that medical school IRB members are appropriately knowledgeable to review research in accordance with ethical standards and applicable regulations.
- Oversight over the conduct of research conducted by all medical school investigators.
- Ensuring that all investigators are appropriately knowledgeable to conduct research in accordance with ethical standards and applicable regulations.
- Oversight of the development and implementation of an educational plan for IRB members, staff and investigators.

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 the medical school. However, the IO may not approve research that has been disapproved by the IRB.

The Institutional Official must complete OHRP Human Subject Assurance Training. The HRPP provides ongoing continuing education for the Institutional Official concerning human research protections.

The Institutional Official is made known to employees of the organization and is accessible by phone, email, in person, or other methods of communication. The IRB chair and HRPP director have access to the Institutional Official for any concerns or issues related to the HRPP.

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

HRPP Director

The HRPP director is selected by and reports to the assistant dean for Research Compliance, and is responsible for:

- Developing, managing, and evaluating policies and procedures that ensure compliance with all state, 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.
- Advising the associate dean for Research on key matters regarding research conducted at, under the auspices of, or using the services or resources of the medical school.
- Implementing HRPP policies and procedures.
- Submitting, implementing, and maintaining an approved FWA through the Institutional Official and DHHS OHRP.
- Obtaining a copy of the FWA for any organization for which the medical school IRB serves as the IRB of record.
- Assisting investigators in their efforts to carry out the medical school's research in accordance with regulations and accepted standards.
- Developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program.
- In conjunction with the medical school IRB, develop training requirements for investigators, subcommittee members and research study team members. The HRPP director will ensure that training is completed on a timely basis.
- Serving as the primary contact at the medical school for DHHS OHRP, FDA, and other federal regulatory agencies.
- Day-to-day responsibility for the operation of the HRPP and IRB, including supervision of HRPP/IRB staff.
- Responding to questions regarding the protection of human subjects.
- Working closely with the chair and vice chair of the IRB on the development of policy and procedures, as well as organizing and documenting the review process.

HRPP/IRB Staff

In addition to the leadership, support staff members for the HRPP and IRB include the IRB manager, and IRB specialists. The medical school HRPP/IRB staff must comply with all ethical standards and practices. The duties and responsibilities for all staff are found in their respective position descriptions, and their performance is formally evaluated at least annually and as needed. HRPP/IRB staff report to the HRPP director who is responsible for day-to-day operations.

Institutional Review Board (IRB)

The medical school supports one IRB with members that are appointed by the Institutional Official. The IRB prospectively reviews and makes decisions concerning all human research conducted at, under the auspices of, or using the services or resources of the medical school unless another IRB has been designated by the medical school to do so. The medical school IRB also provides IRB review and oversight for other local entities, the terms of which are described in IRB Services or Authorization Agreements executed prior to performing IRB review and oversight. The medical school IRB is responsible for the protection of rights and welfare of human subjects, 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 applicable institutional policies see *Section 4, Institutional Review Board*.

The IRB functions independently of, but in coordination with, other committees and officials with responsibilities related to human subject research. The IRB, however, makes its independent determination whether to approve or disapprove research based upon whether or not human subjects are adequately protected and regulatory requirements are satisfied.

Research that has been reviewed and approved by the IRB is subject to review and disapproval by officials of the medical school or organizations that rely upon the medical school IRB. However, those officials may not approve human research that has not been approved or has been disapproved by the IRB.

The medical school also uses the services of external IRBs. External IRBs are primarily relied upon for the review and oversight of industry-sponsored clinical trials. The medical school may enter into reliance agreements for other reasons, for example, when required as a term or condition of a grant.

Legal Counsel

The medical school HRPP relies on the medical school's designated legal counsel for the interpretations and applications of state law and the laws of any other jurisdiction where research is conducted as they apply to human subjects research. Counsel is available to provide guidance on other relevant topics as needed.

Department Chairs

For human subjects research conducted by medical school-employed investigators, the investigator's department chair, program chair or designee, reviews the proposal before it is submitted to the IRB for review. Approval of the department chair, program chair or designee, certifies that: (1) the investigators are appropriately qualified and possess the necessary credentials to safely conduct the research and perform the protocol-required procedures; (2) the investigators have access to adequate facilities, staff, and equipment to perform the research; and (3) emergency or specialized care will be available, should the need arise.

When the medical school IRB serves as the IRB of record for human subjects research conducted by investigators who are not employed by the medical school, an appropriate leader recognized by the medical school and from the organization that does employ the investigators provides these same certifications.

Principal Investigators

The Principal Investigator (PI) is ultimately responsible for the protection of the human subjects participating in research they conduct or oversee. The PI is expected to abide by the highest ethical standards when developing a research plan and to incorporate the

principles of the Belmont Report. The PI is expected to conduct research in accordance with the IRB approved research plan and to personally conduct or oversee all aspects of the research. In addition to complying with all applicable regulatory policies and standard, PIs must comply with institutional and administrative requirements for conducting research. The PI is responsible for ensuring that all investigators and research staff complete all institutional required trainings as well as training for their specific responsibilities in any given research study. When investigational drugs or devices are used, the PI is responsible for ensuring an appropriate plan for their storage, security, dispensing, accounting, and disposal.

The IRB reviews investigator qualifications when review in research and may determine that an investigator may not serve as PI or may require the addition of other investigators to supplement the expertise available on the research team or to conduct or oversee certain aspects of the research.

At the medical school, only individuals with a faculty appointment at the rank of assistant, associate, or full professor are eligible to serve as the PI see *Section 19, Investigator Responsibilities*.

Individuals who are debarred, disqualified, or otherwise restricted from participation in research or as a recipient of grant funds for research by a federal, state, or other agency *may not* serve as PI.

Individuals with a history of compliance issues related to the conduct of research (eg, recipients of a FDA Warning Letter) will be considered on a case-by-case basis. Factors to consider include whether corrective actions have been accepted as adequate, whether information from an audit or quality review indicates that the issues have been resolved, and similar considerations.

Sponsored Programs Administration

Any sponsored research conducted at, under the auspices of, or using the services or resources of the medical school must be reviewed by SPA.

Sponsored Programs Administration staff review all research agreements with all sponsors including federal, foundation, and non-profit sponsors. This review ensures that all terms of the award (grant or contract) are in compliance with medical school policies. Sponsored Programs Administration reports to the assistant dean for Research Compliance.

Center for Clinical Research

The Center for Clinical Research at the medical school offers a wide variety of services supporting the proper conduct of research at the medical school and at its clinical and community collaborators. Services are customized to match investigator needs and may include, but are not limited to, the following:

- Feasibility assessments.

- Protocol development.
- Recruitment planning.
- Consent form development.
- Regulatory document management.
- IRB submission support.
- Research Navigator.
- Study coordinator services.
- Study visit management.
- Data entry and management.
- Specimen management including processing and shipping.
- Coordination with pharmacy, laboratory, radiology, and others.
- Liaison with sponsors, contract research organizations, and monitors.

Study-Specific Coordination

In addition to IRB approval, investigators conducting non-industry sponsored studies must obtain and document the approval, support, or permission of specific individuals, departments, and entities affected by the conduct of the research by indicating in the electronic system as follows:

- Sites where research activities will take place (eg, hospitals, outpatient clinics, physician practice offices, schools, community centers).
- Departments or units that will perform testing or provide services for the research (eg, pathology, pharmacy, radiology, nursing).
- Departments or units from which data will be requested (eg, medical records, registries, and databases, registrar).
- Studies that use medical school student, resident/fellow or faculty data (eg, surveys, opinions, academic information, etc.)
- Other medical school committees, as applicable (eg, Institutional Biosafety Committee).

The final signature required is the associate dean for Research for the medical school sites or the Authorized Institutional Official at the affiliated institutions. The final approval will be required prior to the Initial Study Application submission to the IRB can be processed. The application is reviewed by IRB staff to ensure that all necessary letters from collaborators are included. The IRB may request review or consultation with any individual department, committee, or entity even when such review or consultation is not specifically required by policy.

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

When applicable, a letter of support, collaboration, permission, or approval from the designated authority, should be included in the Initial Study Application to the IRB. The application will be reviewed in the IRB Office to ensure that all necessary letters are included. The IRB may request review by or consultation with any of the above listed or

other organizational committees or components even when such review or consultation is not required by policy.

If the research sites, or research personnel, are also under the jurisdiction of another IRB, documentation of the external IRB's approval or agreement to cede or waive review is required.

Section II: Quality Assurance and Improvement

The medical school 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 applicable federal, state, and local laws and institutional policies and procedures including the *WMed Legal Compliance Program Policy Manual*.

Audits and Inspections by Regulatory Agencies and Sponsors

The HRPP and all potentially affected services (eg, pharmacy) must be notified when investigators receive an audit or inspection announcement from a regulatory agency. The HRPP assists the investigator in preparing for such audits and, in the discretion of the assistant dean for Research Compliance, associate dean for Research, or designee, may attend entrance and exit interviews. All reports from regulatory audits must be submitted promptly to the HRPP, who provides the report to the IRB, assistant dean for Research Compliance, associate dean for Research, and appropriate ancillary services. When determined appropriate by the Institutional Official, associate dean for Research, or assistant dean for Research Compliance, HRPP/IRB staff will assist in preparing a response to the findings.

In the event the medical school IRB is audited by an external regulatory agency, the HRPP director immediately notifies the IRB chair, Institutional Official, associate dean for Research, assistant dean for Research Compliance, and all other appropriate persons within the institution. The IRB provides the regulatory agency with full access to all requested information, and is fully responsive to requests and required actions.

When the medical school is engaged in research reviewed by an external IRB, all reports from audits or inspections must be submitted to the HRPP/IRB for review. The HRPP may require corrective and preventative actions (CAPA), a follow up review, or other actions as needed to ensure the protection of human subjects and to support compliance.

Investigator Compliance Reviews

HRPP/IRB staff are responsible for conducting post-approval directed (“for cause”) and periodic (“not for cause”) compliance reviews of research conducted at, under the auspices of, or using the services or resources of the medical school. Additionally, the medical school IRB may appoint a subcommittee for the purpose of conducting a for-cause or not-for-cause compliance review of research under its jurisdiction. The subcommittee may be composed of IRB members, HRPP/IRB staff, and other individuals from inside and outside the medical school.

Compliance reviews are conducted to:

- Assess investigator compliance with federal, state, and local laws, and applicable policies.
- Provide recommendations based on existing policies and procedures.
- Identify areas for improvement.

The results of compliance reviews are reported to the HRPP director, investigator, and others as appropriate.

When the research is under the jurisdiction of the medical school IRB, the report or a summary, when appropriate, will be provided to the IRB by the HRPP director. Any non-compliance is managed according to the procedures in *Section 16, Non-compliance*. If it is identified that subjects in a research project may have been exposed to unexpected serious harm, the staff conducting the review will promptly report such findings to the HRPP director and the IRB chair for immediate action.

When the research is under the jurisdiction of an IRB other than the medical school IRB, the investigator is advised to report issues identified in the review to the IRB of record in accordance with their policies and procedures.

If issues are identified that indicate possible misconduct in research, the procedures in RES04 Misconduct in Research and Scholarly Activities are followed.

Compliance reviews may include:

- Requesting progress reports from investigators.
- Requesting investigator completion of a self-assessment.
- Examining investigator-held research records.
- Observing research sites where research involving human research subjects take place.
- Observing the informed consent process and documentation of such.
- 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 and commitment.
- Monitoring HIPAA authorizations.
- Monitoring investigator compliance with conflict management plans and disclosures.
- Conducting other monitoring or auditing activities as deemed appropriate by the HRPP or IRB.

IRB Compliance Reviews

The staff, with or without the assistance of an outside organization, will periodically review the activities of the medical school IRB to assess compliance with regulatory

requirements and to identify areas for improvement. This includes a review of IRB records at least annually. Review activities may include but are not limited to:

- Review of the IRB minutes to determine adequate documentation of the meeting discussion and IRB determinations has occurred, including, but not limited to, the “111” criteria, which are the basic criteria for approval under both OHRP and FDA regulations. Additional criteria may be indicated based on the specifics of a protocol (eg, subpart determinations, device determinations), level of risk, protections of vulnerable populations, waivers or alterations of consent, documentation of consent, HIPAA authorization, and the period of approval.
- Review of the IRB minutes to assure that quorum was met and maintained.
- Review of expedited review documentation to determine that adequate documentation of the review has occurred including, but not limited to, qualification for expedited review, the “111” criteria, level of risk, protections of vulnerable populations, waivers or alterations of consent, documentation of consent, HIPAA authorization, and the period of approval.
- Reviewing IRB correspondence to determine that investigators are provided with adequate documentation of IRB review and determinations.
- Reviewing IRB files to evaluate whether adequate documentation of exemptions, expedited review, and other outside of committee reviews has occurred.
- Reviewing consent forms to evaluate whether all required elements are included.
- Reviewing the IRB database to assure all required fields are completed accurately.
- Verifying IRB approval 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.
- Other monitoring or auditing activities deemed appropriate.

The results of compliance reviews are reported to the HRPP director, who reviews the results of IRB compliance reviews with the assistant dean for Research Compliance, and, when appropriate, associate dean for Research, IRB chair, Institutional Official and members of the IRB. If any significant deficiencies are noted in the review, a corrective action plan is developed by the HRPP director. The HRPP director has responsibility for implementing the corrective action plan, the results of which will be evaluated by the assistant dean for Research Compliance.

HRPP Quality Assessment and Improvement

At least annually, the HRPP director and assistant dean for Research Compliance meet and establish a quality assessment and improvement plan. The plan will, at a minimum, contain:

- The goals of the quality improvement plan with respect to achieving and maintaining compliance:
 - At least one objective to achieve or maintain compliance.
 - At least one measure of compliance.
 - The methods to assess compliance and make improvements when needed.
- The goals of the quality improvement plan with respect to achieving targeted levels of quality, efficiency, and effectiveness of the HRPP.
 - At least one objective of quality, efficiency, or effectiveness is defined.
 - At least one measure of quality, efficiency, or effectiveness is defined.
 - The methods to assess quality, efficiency, or effectiveness and make improvements are described.

HRPP/IRB staff are responsible for gathering the data necessary to evaluate the objectives described within the quality assessment and improvement plan and providing reports at pre-determined intervals to the HRPP director. If indicated, the HRPP director will refine the plan. At least annually, the HRPP director, assistant dean for Research Compliance, associate dean for Research review the results, determine whether the respective goals were achieved, and, if needed, develop corrective actions.

In addition to the above, the IRB staff are responsible for tracking internal data and metrics that are informative when considering efficiency, effectiveness, workload, and resources of the department. Metrics reports are available to the HRPP director and IRB Chair on an as needed basis.

Section III: Education & Training

Training and Continuing Education of the IRB Chair, IRB Members, & Staff

Recognizing that a vital component of a comprehensive human research protection program is an education program, the medical school is committed to providing training and continuing education for IRB members, HRPP/IRB staff, and investigators and their research staff, related to ethical concerns and regulatory and medical school requirements for the protection of human subjects.

Orientation

New IRB members, including alternate members, meet with the IRB chair, HRPP director, or a designated staff member for an informal orientation session. At the session, an overview of the federal regulations is reviewed and an orientation to IRB processes is provided. Also, the new member is provided with access to:

- The medical school *Human Research Protection Program (HRPP) and Institutional Review Board (IRB) Policy Manual*, which serves as the policies and procedures for the HRPP and IRB.
- [The Belmont Report](#).
- *Institutional Review Board Member Handbook* by Amdur and Bankert, or a comparable resource
- WMed IRB Member Reference Manual inclusive of but not limited to:
 - A resource list of federal regulations and guidance relevant to the IRB.
 - Medical school policies and procedures for the protection of human subjects.
 - Tools such as checklists used by IRB reviewers.

Initial Training and Education

New IRB members and HRPP/IRB staff must complete the modules of CITI courses that are required by the medical school: Protection of Human Research Subjects (biomedical or social behavioral track, as applicable), and Conflicts of Interest. Appointments of new members to the IRB do not become effective until the orientation and initial education requirements are completed.

Continuing Training and Education

To ensure that oversight of human research is ethically grounded and the decisions made by the IRB are consistent with current regulatory and policy requirements, training and education continues for IRB members throughout their service on the IRB. Beyond the initial training and education requirements, IRB members and HRPP/IRB staff must also satisfy continuing education requirements on an annual basis. The medical school offers continuing education via a variety of means including, but not limited to, the following:

- In-service education and training at IRB meetings.
- Education and training workshops.

- Distributing copies of appropriate publications.
- Distributing new information that might affect the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues to IRB members via email or during IRB meetings.
- Providing support for webinars and conferences.
- Access to the IRB resource library maintained by the HRPP.

IRB members and HRPP and IRB administrators and staff are also required to complete the modules of CITI courses that are required by the medical school every four years as part of the medical school continuing education requirements.

The activities for continuing education vary on a yearly basis depending on operating budget and areas of need, as determined by the HRPP director. The HRPP director in collaboration with the IRB chair determine which continuing education activities are mandatory for IRB members and staff in a given year, and establishes a mechanism to track whether each individual has satisfied the requirements. Members and staff who are unable to attend education sessions are provided with the materials provided in the session and, whenever possible, the opportunity to remediate the training that they missed. If a remediation session is not possible (eg, a webinar or conference), then an equivalent educational opportunity may be offered at the discretion of the HRPP director.

IRB members who have not fulfilled their continuing education requirements are not assigned as primary or secondary reviewer until the requirements are fulfilled. Failure to complete training may result in the individual being removed or not renewed as an IRB member. Fulfillment of training requirements is included as part of the evaluation of the performance of IRB members/alternates.

Continuing Training and Education of Investigators and Research Staff

Investigators and research staff whose responsibilities include interaction with human subjects or their identifiable data must complete the modules of CITI courses that are required by the medical school: Protection of Human Research Subjects (biomedical or social behavioral track, as applicable), Health Information Privacy and Security; and Conflicts of Interest. Evidence of current training for each investigator and member of the research staff with the date of completion within four years of the application date must be included as part of every new research study application and application for continuing review. Training is verified by HRPP/IRB staff at the time of initial application and continuing review.

New research applications are not reviewed until human subjects training has been verified for the Principal Investigator and all research team members.

While applications for continuing review are accepted and reviewed if CITI training is not current, final study approval may be withheld or participation by a research staff member may be restricted until the Principal Investigator and all investigators and research staff have completed the training requirement.

Equivalent Training

External Investigators

If external investigators or research staff provide documentation verifying that they have successfully completed human subject research training that they believe equivalent to that required by the medical school, they may request that the medical school accept their training as equivalent to the required CITI courses. The HRPP director reviews the documentation and determines if it satisfies medical school requirements.

Refresher Training

Medical school investigators and research staff who attend a PRIM&R, OHRP, FDA, or other conferences where the primary focus is human subjects' protection, and provide documentation verifying attendance, may request that the medical school accept this training in lieu of completion of the refresher CITI course(s). The HRPP director reviews the documentation and determines if it satisfies medical school requirements.

Section IV: Institutional Review Board

The medical school has established an Institutional Review Board (IRB) to ensure the protection of human subjects in research conducted, research conducted at, under the auspices of, or using the services or resources of the medical school. All non-exempt human subject research conducted at, under the auspices of, or using the services or resources of the medical school must be reviewed and approved by the medical school IRB prior to the initiation of the research.

The medical school IRB may serve as the IRB of record for research conducted, in part or in full, by other organizations or investigators. A written agreement documenting the acceptance of the medical school IRB as the IRB of record and delineating the responsibilities of each organization or the medical school and the investigator must be executed prior to the medical school IRB accepting such research for review.

The Institutional Official or designee may also authorize use of external IRBs. The authorized external IRBs that serve as the IRB of record for the medical school have the same authority as the medical school IRB and as such all determinations and findings of the external IRBs are binding.

IRB Authority

The medical school IRB derives its authority from medical school policy, as cited in *Section 1, Institutional Authority*. Under the federal regulations, the WMed IRB has the authority:

- To approve, require modifications to secure approval, or disapprove all human subjects research conducted at, under the auspices of, or using the services or resources of the medical school or for which the medical school IRB serves as the IRB of record.
- To 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.
- To conduct continuing review of research at intervals appropriate to the degree of risk of the research, but not less than once per year.
- To suspend or terminate approval of research not being conducted in accordance with IRB requirements or that has been associated with unexpected serious harm to participants.
- To observe, or have a third party observe, the consent process.
- To observe, or have a third party observe, the conduct of the research.

By medical school policy, the IRB in conjunction with the assistant dean for Research Compliance and/or the associate dean for Research has the authority to determine,

whether data or information involving human subjects but gathered without IRB approval or in association with serious non-compliance may be published or used for research purposes. The IRB, the assistant dean for Research Compliance and the associate dean for Research must approve the communication or use of the data or information under these circumstances prior to use.

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 4, Reporting and Investigation of Allegations of Undue Influence*. Similarly, the IRB must remain free from the influence of financial and other institutional interests. No individual with primary 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 is also subject to review and approval by officials of the medical school or other organizations involved in the research. However, those officials may NOT approve research involving human subjects if it has not been approved or has been disapproved by the IRB. Reviewing officials may strengthen requirements and/or conditions, require modifications to the protocol/research plan, or require approval by an additional committee. Any changes required by reviewing officials or committees after research has been approved by the IRB must be submitted to the IRB and approved by the IRB before initiating the changes unless the change is necessary to eliminate an immediate hazard to human subjects.

Roles and Responsibilities

IRB Chair

The Institutional Official, in consultation with the assistant dean for Research Compliance, the associate dean for Research and HRPP director, appoints a chair and vice chair of the IRB to serve for three-year terms, which may be renewed for a maximum of two terms. Any change in appointment, including reappointment or removal, requires written notification.

The IRB chair should be a highly respected individual fully capable of ensuring that the matters brought before the IRB are managed with fairness and impartiality. The IRB must be perceived to be fair, impartial, and immune to influence and pressure by administration, the investigators whose research plans/protocols are brought before it, and other committees and professional and nonprofessional offices and entities.

The IRB chair is responsible for conducting IRB meetings, conducting expedited reviews, determining whether research qualifies for exempt status, determining whether proposals are research and whether research involves human subjects, and may serve 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 advises the Institutional Official and the HRPP director about IRB member performance and competence.

The performance of IRB chair is reviewed annually by the Institutional Official in consultation with the HRPP director, assistant dean for Research Compliance and associate dean for Research. Feedback from this review is provided to the chair. The Institutional Official may remove the chair if the chair is not acting in accordance with the IRB mission, not following medical school policies and procedures, has an undue number of absences, or not fulfilling the responsibilities of the chair, in the sole discretion of the Institutional Official.

IRB Vice Chair

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 performance of the IRB vice chair is reviewed on an annual basis by the Institutional Official in consultation with the HRPP director, assistant dean for Research Compliance, associate dean for Research, and IRB chair. Feedback from this review is provided to the IRB vice chair. The Institutional Official may remove the vice chair if the vice chair is not acting in accordance with the IRB mission, not following medical school policies and procedures, has an undue number of absences, or not fulfilling the responsibilities of the vice chair, in the sole discretion of the Institutional Official.

Full IRB Members

The role of a full IRB member is to ensure that human research activities comply with federal regulations, state and local laws, and medical school policies and procedures, by:

- Completing initial and ongoing education and training requirements see *Section 3, Training and Continuing Education of the IRB Chairs, IRB Members and Staff*.
- Maintaining the confidentiality of IRB deliberations and research reviewed by the IRB.
- Conducting and documenting reviews of assigned research in a timely fashion.
- Attending IRB meetings as scheduled. Members should attend all meetings for which they are scheduled. If a member is unable to attend a scheduled meeting, they should provide IRB staff with sufficient notice, whenever possible, for the staff to arrange for an alternate member to attend. If an IRB member is to be absent for an extended period of time, he or she must notify IRB staff at least 30

days in advance so that an appropriate alternate member can be scheduled to attend. If the member has a designated alternate, the alternate can serve during the primary member's absence.

- Recusing oneself from final deliberations and voting when the IRB member has a conflict of interest or commitment.
- Participating in subcommittees of the IRB if requested and available.
- Conducting themselves in a professional and collegial manner.

Experienced IRB members may be designated by the IRB chair to conduct expedited reviews.

The performance of IRB members is reviewed annually by the IRB chair and the HRPP director. Feedback from this review is provided to IRB members. The Institutional Official may remove an IRB member if an IRB member is not acting in accordance with the IRB mission, not following medical school policies and procedures, has an undue number of absences, or not fulfilling the responsibilities of an IRB member, in the sole discretion of the Institutional Official.

Alternate members

The appointment and function of alternate members is the same as that for full IRB members. An alternate member's expertise and perspective should be comparable to those of the primary member. The role of the alternate member is to serve as a voting member of the IRB when the full member is unavailable to attend a convened meeting. When an alternate member substitutes for a full member, the alternate member receives and reviews the same materials prior to the IRB meeting that the primary member received or would have received.

The IRB roster identifies the full member(s) and class of members (ie, physician scientist) for whom each alternate member may substitute. The alternate member is not to be counted toward meeting quorum as a voting member unless the full member is absent. The IRB minutes must document when an alternate member replaces a full member.

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

IRB Subcommittees

The IRB chair, in consultation with the HRPP director, assistant dean for Research Compliance, and associate dean for Research may designate one or more IRB members to a subcommittee of the IRB to perform duties and undertake IRB functions, and to make recommendations to the IRB (eg, to supplement the IRB initial review, continuing review, review of modifications, and/or review of reports of unanticipated problems or of serious or continuing non-compliance). The IRB chair, in consultation with the HRPP director, assistant dean for Research Compliance, and associate dean for Research may

appoint IRB members to serve on each IRB subcommittee that is created. The number and composition of the IRB subcommittee members shall depend on the scope of duties delegated by the IRB chair to each IRB subcommittee. No IRB subcommittee can approve research, which requires approval by the IRB at a convened IRB meeting.

IRB Composition

The IRB must promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects and possess the professional competence necessary to review the research that comes before it. The structure and composition of the medical school IRB is based upon regulatory requirements and the characteristics of the research it reviews. A member of the IRB may fill multiple membership position requirements (eg, nonscientific and unaffiliated).

- The IRB will have at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the organization.
- The IRB will be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.
- In addition to possessing the professional competence necessary to review specific research activities, the IRB will be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB will therefore include persons knowledgeable in these areas.
- If the IRB regularly reviews research that involves a vulnerable category of subjects (eg, children, prisoners, pregnant women, or handicapped or mentally disabled 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.
- Every nondiscriminatory effort will be made to ensure that the IRB 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. The IRB shall not consist entirely of members of one profession.
- The IRB includes at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.
- The IRB includes at least one member who is not otherwise affiliated with the organization and who is not part of the immediate family of a person who is affiliated with the organization.
- The IRB includes at least one member who represents the general perspective of participants.

- When reviewing nursing research from a facility with Magnet designation by the American Nurses Credentialing Center, the IRB will include at least one nurse representative.

One member may satisfy more than one membership category. The HRPP director and IRB staff may be appointed to serve as regular or alternate members of the IRB. Personnel from the medical school Sponsored Programs Administration, Accounting, and units with primary responsibilities for the business interests of the medical school may not serve as members of the IRB or be involved in the day-to-day operations of the IRB review process. Individuals from these units may provide information to the IRB and attend IRB meetings as invited guests.

On an annual basis, the HRPP director, assistant dean for Research Compliance, associate dean for Research, and IRB chair shall evaluate the membership and composition of the IRB, and recommend adjustments to the Institutional Official, if needed, to meet regulatory requirements and address institutional needs.

IRB Member Appointment

When a need is identified for a new, replacement, or alternate member for the IRB, the HRPP director, assistant dean for Research Compliance, associate dean for Research and IRB chair shall collaborate to identify qualified interested candidates and inform the Institutional Official. Department chairs and others may recommend individuals who may be interested and appropriate for IRB membership by contacting the HRPP director, assistant dean for Research Compliance, associate dean for Research, or IRB chair. The final decision in selecting a new, replacement or alternate member for the IRB is made by the Institutional Official.

Appointments are made for a renewable three-year term. Any change in appointment, including reappointment or removal before the end of a member's term, requires written notification. Members may resign by written notification to the HRPP director or IRB chair.

IRB Registration Updates

Changes that affect the medical school's federal IRB registration, including changes in IRB membership, must be reported to FDA and OHRP within the following time periods:

- Within 90 days of a change in the IRB membership roster.
- Within 90 days after changes of the IRB chair.
- Within 90 days after changes to the contact person who provided the IRB registration information.

- If an IRB is formed, before the IRB reviews research regulated by the FDA, before the IRB is designated under a FWA, and before the IRB reviews research conducted or supported by DHHS.
- If an IRB is disbanded, within 30 days after permanent cessation of IRB reviews.
- Within 30 days if an IRB decides to review additional types of FDA-regulated products (eg, to review device studies if it only reviewed drug studies previously) or to discontinue reviewing clinical investigations regulated by FDA.

Use of Consulting Reviewers

The HRPP director or IRB chair may solicit individuals with competence in special areas to assist in the review of issues or research plans/protocols, which require expertise beyond or in addition to that available on the IRB.

Prospective consulting reviewers must complete the conflicts of interest and commitment reporting required by medical school policy GENo4, Conflicts of Interest and Commitment. The Research Integrity Officer reviews the conflicts of interest and commitment for prospective consulting reviewers to confirm that they do not have a conflict of interest or commitment prior to review. Individuals who have a conflict or whose spouse or immediate family members have a conflict with the research will not be invited or permitted to provide consulting review.

IRB staff ensure that all relevant study materials are provided to the consulting reviewer.

The consulting reviewer's findings are presented either in person or in writing to the convened board for consideration. If in attendance, consulting reviewers may not participate in the vote. For expedited reviews, the consulting reviewer provides documentation of their review for IRB chair, or designee, consideration. The consulting review must be available for discussion if needed.

Written statements from consulting reviewers are kept with IRB records. Key information provided orally by consulting reviewers at meetings must be documented in the minutes or recorded in review notes by the IRB chair, or designee, for expedited reviews.

Ad hoc or informal consultations requested by individual IRB members, rather than the convened board, are managed by the IRB member, or by IRB staff at the member's request, in a manner that protects the investigator's confidentiality and is in compliance with the medical school and IRB conflict of interest and commitment policy. Information from consultations is disseminated to other members prior to or during convened IRB reviews, or for expedited reviews, documented in the reviewer's notes.

Liability Coverage for IRB Members

Medical school professional liability insurance coverage applies to employees and any other person authorized to act on behalf of the medical school, for acts or omissions within the scope of their employment or authorized activity.

Reporting and Investigation of Allegations of Undue Influence

The medical school Hotline is 269.337.6505.

If the IRB chairs, and IRB members, or IRB staff feels that the IRB has been unduly influenced by any party, the individual may make a confidential report to the HRPP director, assistant dean for Research Compliance, associate dean for Research, Research Integrity Officer, or Institutional Official. The Institutional Official will ensure that a thorough investigation is conducted and, if the allegation is determined to be valid, that corrective action is taken to prevent additional occurrences. In the event that the allegation is regarding the Institutional Official, the matter will be referred and managed by the assistant dean for Research Compliance, Research Integrity Officer, and associate dean for Research for investigation and any necessary action.

Undue influence means attempting to interfere with the normal functioning and decision-making of the IRB, or to attempt to influence an IRB member or staff member or any other member of the research team, outside of the established 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.

Section V: Human Subject Research Determination

The responsibility for initial determination whether an activity constitutes human subject research rests with the investigator. The investigator should make this determination based on the definitions of “human subject, research, and clinical investigation” as provided by the Common Rule and FDA regulations, respectively. Because investigators are held responsible if the determination is not correct, investigators are urged to request confirmation that an activity does not constitute human subject research from the IRB.

Similarly, the responsibility for the initial determination of whether research involves “human subjects” rests with the investigator. Under the Common Rule, information is considered identifiable, and thus involving human subjects, when the identity of the subject is or may readily be ascertained by the investigator or associated with the information. It should be noted that this definition differs significantly from de-identified in accordance with HIPAA standards. FDA regulations do not incorporate the concept of “identifiability” in the evaluation of whether an activity is a clinical investigation (or research) subject to FDA regulations. For example, the use of de-identified human specimens to evaluate the safety or effectiveness of a diagnostic device is considered human subjects research subject to FDA regulations. Investigators are urged to submit for a determination whenever they are uncertain if a research study involves “human subjects” as defined by the Common Rule or FDA. Such requests should be submitted by sending a detailed narrative of the request via e-mail to the IRB office.

When research involves the use of coded private information or specimens, and the investigator makes an initial determination that the research does not include “human subjects,” the investigator must request confirmation following the procedures described below. The request may be made by email or in writing. All requests must include sufficient description of the activity and the rationale for the investigator’s initial determination.

The only exception to this policy is when the research is not subject to FDA regulations and the coded private information or specimens are to be obtained from an IRB-approved repository and the rules of that repository forbid the release of identifiable information, the key or code that would enable re-identification, or the release of sufficient information that investigators could readily ascertain the identity of subjects. Human Subjects Research Determinations must be submitted, and determined, prospectively (ie before the proposed activity or research begins). Conducting human subjects research without IRB approval or exemption is noncompliance. Determinations whether an activity constitutes human subject research are made according to the definitions in *Section 1, Human Subject Research Determination Checklist*. A determination letter will be issued to document the determination. Investigators conducting research under the auspices of the medical school *may not* rely upon determinations made by other organizations or through the use of electronic or other determination tools.

Documentation of all determinations made by the IRB are recorded and maintained in IRB records. Requests and responses to a determination are maintained in IRB records.

Section VI: Exempt Studies

All research using human subjects conducted at, under the auspices of, or using the services or resources of the medical school must be approved by the medical school. However, certain categories of human subject research are exempt from the requirement of continuing IRB oversight. Exempt research is subject to required IRB review for determination of exemption status. At the medical school, exemptions are reviewed and granted by the IRB chair or designee. The medical school may also choose to accept an exempt determination made by an external IRB and will consider such requests on a case-by-case basis.

Exemptions are determined or granted, rather than approved. Exempt studies are exempt from the requirements of the Common Rule (ie, IRB approval and full consent of research participants are not required). Exempt studies do require a determination or confirmation of exemption status by the medical school. Although exempt research is not covered by federal regulations, this research is not exempt from ethical considerations such as honoring the principles described in the Belmont Report. Other regulations, such as HIPAA, and medical school requirements, such as disclosure of conflicts of interest and commitment, apply. The IRB chair or designee who makes the determination of exemption also determines whether to require additional protections for human subjects in keeping with ethical principles (eg, requiring disclosure, consent, etc.).

Limitations on Exemptions

The following limitations on exemptions apply to research conducted or supported by DHHS:

- Research involving Children.
 - The exemption for research involving educational tests, survey or interview procedures, or observations of public behavior (#2) does NOT apply to research in children, except for research involving observations of public behavior when the investigator does not participate in the activities being observed.
 - The exemption for research involving behavioral interventions (#3) does NOT apply to children.
- Research involving Prisoners.
 - IRB review is required. Exemptions do NOT apply except for research aimed at involving a broader subject population that only incidentally includes prisoners.
- Research involving behavioral interventions (#3) with deceit:
 - The exemption does NOT apply unless the adult subject authorizes the deception through a prospective agreement to participate in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

Categories of Exempt Research

Within the limitations outlined in *Section 6, Limitations on Exemptions*, research activities that are not regulated by the FDA see *Section 6, FDA Exemptions* in which the only involvement of human subjects are determined to be in one or more of the following categories qualify for exempt status:

- **Category 1:** Research conducted in established or commonly accepted educational settings, involving normal educational practices that are not likely to adversely affect students' opportunity to learn required educational content or the assessment of educators who provide instruction, such as:
 - Research on regular and special education instructional strategies.
 - Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

- **Category 2:** Research that only includes interactions involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior (including visual or auditory recording), if at least one of the following criteria are met:
 - Information obtained is recorded in such a manner that the identity of the human subjects **cannot** readily be ascertained, directly or through identifiers linked to the subjects.
 - Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, educational advancement, or reputation.
 - There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

- **Category 3:** Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention/information collection and at least one of the following criteria is met:
 - The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects.
 - Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation.
 - There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant

adverse lasting impact on the subjects, and the investigator has no reasonable expectation that the subjects will find the interventions offensive or embarrassing.

- **Category 4:** Secondary research without consent involving the use of identifiable private information or identifiable biospecimens if at least one of the following criteria is met:
 - These sources are publicly available.
 - Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects.
 - Information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR 160 and 164, subparts A and E, for the purposes of "health care operation" or "research" or for "public health activities and purposes."
 - The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for non-research activities. If the research generates identifiable private information it may be subject to 208(b) of the E-Government Act of 2002 or subject to the Privacy Act of 1974, or the Paperwork Reduction Act of 1995.

- **Category 5:** Research and demonstration projects that are:
 - Conducted or supported by a federal department or agency, or otherwise subject to the approval of department or agency heads, and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs including 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.
 - The program under study must deliver a public benefit (eg, financial or medical benefits as provided under the Social Security Act) or service (eg, social, supportive, or nutrition services as provided under the Older Americans Act).
 - There must be no statutory requirement that the project be reviewed by an IRB.
 - The research must not involve significant physical invasions or intrusions upon the privacy of subjects.

Category 6: Taste and food quality evaluation and consumer acceptance studies:

- If wholesome foods without additives are consumed or food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection

Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Category 7: Collection of Data for Secondary Research with Consent – The medical school is not implementing this Exemption at this time.

Category 8: Use of Data for Secondary Research with Consent – The medical school is not implementing this Exemption at this time.

FDA Exemptions

The following categories of clinical investigations are exempt from the requirements for prior IRB review and approval:

- Emergency use of a test article, provided that such emergency use is reported to the IRB within five (5) business days. Any subsequent use of the test article is subject to IRB review. [[21 CFR 56.104\(c\)](#)] See *Section 13, FDA Exemptions* for detailed discussion of this exemption and the procedures for reporting an emergency use.
- Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [[21 CFR 56.104\(d\)](#)]

Procedures for Exemption Determination

To request an exemption determination, investigators must submit all of the following as applicable:

- Recruitment materials (eg, letter of invitation, recruitment script, flyer, etc.).
- Consent form, information sheet, etc.
- Request for a waiver of HIPAA authorization or HIPAA authorization as applicable.
- All surveys, questionnaires, instruments, and other related information.
- Letter of Support from non-affiliated performance site(s).
- Verification of current human research protection training for all investigators and research staff.
- Verification of COI completion.

The IRB chair or designee reviews request and determines whether the research qualifies for exempt status under the regulatory criteria outlined in *Section 6*.

If applicable, the reviewer also evaluates and takes any actions necessary under other regulations, such as HIPAA. The reviewer determines whether to require additional protections for subjects in keeping with the guidelines of the Belmont Report.

The exempt application and supporting documentation including the determination letter forwarded to the investigator are recorded and maintained in the same manner and for the same length of time as other IRB review documentation.

Exempt determinations do not have a termination date. Investigators must submit any proposed modifications to the research for a determination of whether or not the modified activity still qualifies for exemption. Investigators must report any proposed additions to study personnel so that CITI training can be verified and COI evaluated prior to their involvement with the research. The IRB may be notified when an exempt research project is complete so that the medical school can maintain an accurate database of active research.

Section VII: IRB Review Process

The medical school IRB reviews and ensures that research involving human subjects meets all required ethical and regulatory criteria for initial review, continuing review, and any modifications of approved research. The IRB may conduct their review using expedited review, or review by convened IRB.

The following describes the procedures required for the review of research by the medical school IRB. See *Section 9* for a description of medical school procedures for research reviewed by external IRBs.

Definitions

- **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:
 - The acceptability of the risk-to-benefit analysis (changes that increase the level of risks to subjects generally are considered major changes unless the overall risk of the study remains minimal or the increase in risks is so minor that it does not negatively impact overall risks-to-benefits).
 - The research design or methods. Adding procedures that are not eligible for expedited review would be considered more than a minor change, see *Section 7, Expedited Review Procedure*.
 - The number of local subjects to be enrolled in greater than minimal risk research (usually not greater than 10% of the total requested locally).
 - The qualifications of the investigators and research staff.
 - The facilities available to support safe conduct of the research.
 - Any other factor which would warrant review of the proposed changes by the convened IRB.
- **Suspension of IRB approval:** Suspension of IRB approval is a directive of the convened IRB to temporarily stop some or all research activities that have been previously approved by the IRB. Suspended research studies remain open and require continuing review by the IRB.
- **Termination of IRB approval** Termination of IRB approval is a directive of the convened IRB to permanently stop all activities that have been previously approved by the IRB. Terminated research studies are closed and no longer require continuing review by the IRB.

Expedited Review

An IRB may use the expedited review procedure to review studies meeting either or both of the following criteria:

- Some or all of the research appearing on the list of categories of research eligible for expedited review and found by the IRB reviewer(s) to involve no more than minimal risk.
- Minor changes in previously approved research during the period of one year or less for which approval is authorized. Review of minor changes does not alter the end-date of study approval.

The standard requirements for informed consent, or its waiver or alteration, apply regardless of the type of review—expedited or convened—used by the IRB.

Categories of Research Eligible for Expedited Review

The medical school IRB applies the categories of research eligible for expedited review, which were published in the Federal Register notice 63 FR 60364-60367, November 9, 1998.

The categories of research listed in this section should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure if the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

The categories in this list apply regardless of the age of subjects, except as noted in category 2.

The expedited review procedure may not be used if identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, *unless* reasonable and appropriate protections are implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal risk.

The expedited review procedure may not be used for classified research involving human subjects.

Research Categories one (1) through seven (7) may be used for both initial and continuing IRB review:

- (1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
 - (a) Research on drugs for which an investigational new drug application () is not required. Research on marketed drugs is not eligible for expedited review if the research significantly increases the risks or decreases the acceptability of the risks associated with the use of the product.

- (b) Research on medical devices for which (i) an investigational device exemption application () is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
- (2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture meeting one or both of the following conditions:
 - (a) Collection from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 mL in an 8-week period, and collection may not occur more frequently than 2 times per week; or
 - (b) Collection from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 mL or 3 mL per kg in an 8-week period and collection may not occur more frequently than 2 times per week. Children are defined as "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.
- (3) Prospective collection of biological specimens for research purposes by noninvasive means. Examples include:
 - (a) Hair and nail clippings in a nondisfiguring manner.
 - (b) Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction.
 - (c) Permanent teeth if routine patient care indicates a need for extraction.
 - (d) Excreta and external secretions, including sweat.
 - (e) Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue.
 - (f) Placenta removed at delivery.
 - (g) Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor.
 - (h) Supragingival and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.
 - (i) Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings.
 - (j) Sputum collected after saline mist nebulization.
 - (k) Vaginal swabs that do not go beyond the cervical os; rectal swabs that do not go beyond the rectum; and nasal swabs that do not go beyond the nares.
- (4) Collection of data through noninvasive procedures, not involving general anesthesia or sedation, routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be approved for marketing. Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review,

including studies of approved medical devices for new indications. Examples include:

- (a) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy.
 - (b) Weighing or testing sensory acuity.
 - (c) Magnetic resonance imaging.
 - (d) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography.
 - (e) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.
- (5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and (b)(2) and b(3). This listing refers only to research that is not exempt.)
- (6) Collection of data from voice, video, digital, or image recordings made for research purposes.
- (7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior); or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and (b)(2) and (b)(3). This listing refers only to research that is not exempt.

Categories 8 and 9 apply only to continuing review.

- (8) Continuing review of research previously approved by the convened IRB meeting one or more of the following conditions:
- (a) Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects. "Long-term follow-up" includes research interactions that involve no more than minimal risk to subjects (eg, quality of life surveys); and collection of follow-up data from procedures or interventions that would have been done as part of routine clinical practice to monitor a subject for disease progression or recurrence, regardless of whether the procedures or interventions are described in the research study, but not interventions that would not have been performed for clinical purposes, even if the research interventions involve no more than minimal risk.
 - (b) Where no subjects have ever been enrolled, and no additional risks have been identified, which means that neither the investigator nor the IRB has

identified any additional risks from any institution engaged in the research project or from any other relevant source since the IRB's most recent prior review.

- (c) Where the remaining research activities are limited to data analysis. Simply maintaining individually identifiable private information without using, studying, or analyzing such information is not human subject research and thus does not require continuing review.

For a multicenter research project, an expedited review procedure may be used by the IRB for a particular institution whenever the conditions of category (8)(a), (b), or (c) are satisfied for that institution.

- (g) Continuing review of research previously approved by the IRB at a convened meeting that meets all of the following conditions:
 - (a) The research is not conducted under an investigational new drug application (IND) or an investigational device exemption (IDE).
 - (b) Expedited review categories (2) through (8) do not apply to the research.
 - (c) The IRB has determined and documented at a convened meeting that the research, or the remaining research activity involving human subjects, involves no greater than minimal risk to the subjects.
 - (d) No additional risks of the research have been identified. "No additional risks have been identified" means that neither the investigator nor the IRB has identified any additional risks from any institution engaged in the research project or from any other relevant source since the IRB's most recent prior review.

Expedited Review Procedure

Under an expedited review procedure, the review may be carried out by the IRB chair or by one or more reviewers designated by the IRB chair from among members of the IRB. On at least an annual basis, the IRB chair designates IRB members who are eligible to conduct expedited reviews. The designees must be members or alternate members of the IRB who are experienced, meaning having served on an IRB for at least one year or deemed qualified at the discretion of the chair.

HRPP/IRB staff select expedited reviewers from the list of designated reviewers. Selected reviewers must have the qualifications, experience, and knowledge in types of research to be reviewed unless specific expertise is not needed to conduct the review (eg, minor administrative changes), as well as be knowledgeable of the requirements to approve research under expedited review. IRB members with a conflict of interest or commitment with the research see *Section 20, Definitions* may not be selected to perform the expedited review.

When reviewing research under an expedited review procedure, the IRB chair, or designated IRB member, receives and reviews all documentation that would normally be submitted for convened board review. This requirement applies to all categories of submissions including initial reviews, continuing reviews, and modifications. The reviewer determines and documents the regulatory criteria allowing use of the expedited review procedure by using the *Initial Study Review Form*.

If the research meets the criteria allowing review using the expedited procedure, the reviewer conducting initial or continuing review completes the appropriate review form checklist (*Initial Study Review Checklist* or *Continuing Review Checklist*) to determine whether the research meets the regulatory criteria for expedited review and approval. The same criteria of approval apply to reviews conducted via expedited review as to those conducted by the convened board. If the research does not meet the criteria for expedited review, then the reviewer indicates that the research requires convened board review and the research study is placed on the next available agenda for an IRB meeting.

In reviewing the research, the reviewers must follow the review procedures described in *Section 7, Expedited Review and Criteria for IRB Approval of Research* and may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure by the convened IRB see *Section 7, Convened IRB Meetings*.

Reviewers indicate approval, required modifications, or requirement for convened board review on the *Initial Study Review Checklist*. The HRPP/IRB staff informs the investigator of the review outcome in writing or by email.

In the event that expedited review is performed by more than one IRB member and the expedited reviewers disagree, the IRB chair may make a final determination or refer the study to the convened IRB for review.

Informing the IRB

All members of the IRB shall be apprised of all expedited review approvals by means of a list in the agenda for the next scheduled IRB meeting. Any IRB member may request to review any study by contacting the HRPP/IRB staff.

Convened IRB Meetings

Except when an expedited review procedure is used, the IRB conducts initial reviews and continuing reviews of all non-exempt research at convened meetings at which a quorum, see *Section 7, Quorum* of the members is present.

IRB Meeting Schedule

The IRB meets on a regular basis throughout the year, usually once per month. The schedule for the IRB may vary because of holidays, workload, or lack of quorum for scheduled meetings. The schedule for IRB meetings is posted on the IRB website. Special meetings may be called at any time by the IRB chair or HRPP director.

Preliminary Review

HRPP/IRB staff perform a preliminary review of all submissions for determination of completeness and accuracy. Only complete submissions are placed on the IRB agenda for review. The Principal Investigator is informed either by e-mail, phone, or in person of missing materials and the necessary date of receipt for receipt of materials to permit inclusion on the IRB agenda. The Principal Investigator may request consultation with HRPP/IRB staff at any step in the review process.

Primary and Secondary Reviewers

After it has been determined that the submission is complete, HRPP/IRB staff, with the assistance of the IRB chair as needed, assigns submissions for review paying close attention to the subject matter of the research, potential reviewer's areas of expertise and, representation of any vulnerable populations involved in the research. One "primary reviewer" is assigned to each submission and conducts an in-depth review of all submission materials. A single reviewer may be assigned several submissions or other items for review. When the IRB is presented with a research study that is deemed by the IRB to be outside of the knowledge base or representative capacity of the IRB members, an outside consultant is sought see *Section 4, Liability Coverage for IRB Members*. Research studies for which appropriate expertise cannot be obtained for a given IRB meeting are deferred to another IRB meeting when appropriate expertise is available.

Primary reviewers are responsible for:

- Having a thorough knowledge of all of 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 see *Section 7, Criteria for IRB Approval of Research*.
- Making suggestions for changes to the proposed research, where applicable.
- 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 components of the submission (eg, the consent/assent/permission forms).

All IRB members receive and are expected to review all studies, not just those assigned to them as primary or secondary reviewer.

When it can be anticipated that the primary reviewer may be absent from the meeting, a new primary reviewer may be assigned provided that they have sufficient time to review the materials in advance of the meeting. Alternatively, an absent reviewer may submit their written comments for presentation at the convened meeting. If an absent reviewer submits comments, the comments may indicate a recommendation regarding approval or non-approval, but such recommendation shall not be counted as a vote.

Materials received by the IRB

All required materials must be submitted to the IRB 15 business days prior to the convened meeting for inclusion on the IRB meeting agenda. The meeting agenda is prepared by HRPP/IRB staff in consultation as needed with the IRB chair. All IRB members must receive the IRB agenda, prior meeting minutes, applicable business items, continuing education materials, and research submission materials no less than 7 business days before the scheduled IRB meeting to allow sufficient time for the review process. On occasion, when a review is time sensitive, the IRB office may make an exception to this rule provided that there is still sufficient time for all members to review the submission materials.

Each IRB member receives and is expected to review, at minimum, the following:

- A Protocol Summary or the complete protocol/research plan.
- The study application.
- Proposed consent/parental permission/assent form(s), if applicable.
- Recruitment materials including advertisements intended to be seen or heard by potential subjects, if applicable.

The primary and secondary reviewers receive and review, in addition to the above: (1) the complete protocol/research plan; (2) the grant application when the organization is the prime awardee of a HHS grant; (3) the investigator's brochure, when one exists, and/or other risk information; (4) questionnaires, diaries, and other materials intended for use with or completion by subjects; and (5) any other relevant research materials. For DHHS-supported multicenter clinical trials, this should include a copy of the DHHS-approved sample informed consent document(s), when one exists, and the complete DHHS-approved protocol/research plan, when one exists.

The materials provided to the primary reviewer are available to all IRB members.

If an IRB member requires additional information to complete the review, they may contact the investigator directly or may contact HRPP/IRB staff to make the request of the investigator.

Primary reviewers use the *Initial Study Review Checklist* as a guide to completing their review.

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 drug is on the agenda for review, a physician should be included in the quorum. When nursing research from a facility with Magnet designation by the American Nurses Credentialing Center is on the agenda for review, a nurse should be included in the quorum. 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 HRPP/IRB staff, confirms that quorum is present before calling the meeting to order. The IRB chair, with the assistance of HRPP/IRB staff, is responsible to ensure that the IRB meeting remains appropriately convened. If a quorum is not maintained, either by losing a majority of the members, or losing all non-scientific members or another required member, the IRB cannot take further actions or vote on regulatory determinations until quorum is restored. If quorum cannot be restored, study(ies) are placed on the next month's agenda.

It is generally expected that at least one unaffiliated member and at least one member who represents the general perspective of participants is present at all IRB meetings. A single individual may serve in both capacities simultaneously. The IRB may, on occasion, meet without this representation; however, this should be the exception and not routine.

If the IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or persons with impaired decision-making capacity, one or more individuals (eg, IRB members, alternate members, or consultants) who are knowledgeable about and experienced with those subjects should be present during the review of the research.

IRB members are considered present and participating at a duly convened IRB meeting when either physically present or participating through means such as teleconferencing and videoconferencing 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.

Opinions of absent members that are transmitted by mail, telephone, facsimile, or e-mail may be considered by the attending IRB members but may not be counted as votes or to satisfy the quorum for convened meetings.

Members who are recused from voting on a specific study because of conflicting interests may not be counted toward the quorum.

Meeting Procedures

The IRB chair calls the IRB meetings to order once it has been determined that a quorum is in place. The IRB chair reminds IRB members to recuse themselves from discussion and votes by leaving the room when they have a conflict of interest or commitment. The IRB reviews and discusses the minutes from the prior meeting and determines whether there are any revisions or corrections to be made. If there are no changes to be made, the minutes are accepted as presented and considered final. If substantive revisions or corrections are necessary, the minutes are amended and presented at the following IRB meeting. Minor revisions and corrections may be verified by the IRB chair or vice chair after the meeting to meet the intent of the revisions or corrections that were discussed at the meeting.

The IRB reviews all submissions for initial review and continuing review, as well as requests for modifications. The primary reviewer presents an overview of the research and assists the IRB chair in leading the IRB through the evaluation of the regulatory criteria for approval. When applicable, relevant documents are projected on the screen for IRB consideration. In order for the research to be approved, it must receive the approval of a majority of those voting members present at the meeting.

HRPP/IRB staff are responsible for recording minutes at each IRB meeting.

Guests

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

The HRPP director and HRPP/IRB staff regularly attend IRB meetings and may participate in the IRB discussion and deliberations, but may not vote unless they are attending as members or as alternates in place of members.

Other guests may be permitted to attend IRB meetings at the discretion of the IRB chair and the HRPP director. Guests may be asked to sign a confidentiality agreement and may not participate in discussion unless requested by the IRB chair or vice chair, and under no circumstances may they vote on any action of the IRB.

Criteria for IRB Approval of Research

In order for the IRB to approve human subjects research, either through expedited review or by convened IRB, the IRB 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 which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- 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 consider the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of

research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

- Informed consent 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, 21 CFR 50].
- Informed consent will be appropriately documented, in accordance with, and to the extent required by the Federal Regulations [45 CFR 46.117, 21 CFR 50.27].
- When appropriate, the protocol/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.
- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Risk/Benefit Assessment

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:

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

The IRB should not consider any compensation that subjects may receive to be a benefit of the research.

When research subjects are assigned to different arms or otherwise undergo differing interventions, procedures, or exposures, the evaluation of risk and benefit should be made for each subject group (ie, “component analysis”). This is especially important when a subset of subjects will have no possibility of direct benefit but will be exposed to greater than minimal risks.

Scientific or Scholarly 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 yield the expected knowledge.

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 an external reviewer, funding agency, departmental review, or research committee. When scientific or scholarly review is conducted by an individual or entity external to the IRB, documentation of the scientific review should be included in the submission to the IRB.

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, and other characteristics. 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, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
- The scientific and ethical justification for excluding classes of persons who might benefit from the research.
- The inclusion/exclusion criteria, and the procedures and materials intended for use for the identification and recruitment of potential subjects.

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

Recruitment of Subjects

The investigator provides the IRB with a plan for recruitment of all potential subjects and selection of subjects. All recruiting materials must be submitted to the IRB, including advertisements, flyers, scripts, information sheets, and brochures. The IRB ensures that the recruitment plan and materials appropriately protect the rights and welfare of the prospective subjects and do not present undue influence. See *Section 7, Advertisements and Recruitment Materials* for a discussion of IRB review of advertisements and *Section 7, Payments for Research Subjects* for a discussion of IRB review of payments.

Informed Consent

The IRB must ensure that informed consent is 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 ensures that informed consent is appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117 and 21 CFR 50.27. The IRB ensures, as part of its review, that the information in the consent document and process is consistent with the protocol/research plan, and, if applicable, the HIPAA authorization. See *Section 11, Obtaining Informed Consent from Research Subjects* for detailed policies on informed consent.

Data and Safety Monitoring

For all research that is greater than minimal risk, the investigator should submit a data and safety monitoring plan. The initial plan submitted to the IRB should describe what data will be collected and monitored for safety, how and to whom the data will be reported, descriptions of interim reviews, if any, and the actions that may be taken as a result of the monitoring.

The IRB reviews the safety monitoring plan and determines if it makes adequate provision to monitor 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 or not 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 considers the following in determining whether the safety monitoring plan is adequate for the research:

- Monitoring is commensurate with the nature, complexity, size and risk involved.
- Monitoring is timely. Frequency of monitoring should be commensurate with risk.

- Conclusions are reported to investigators, sponsors, regulatory authorities, and the IRB, as applicable.
- For lower 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 authorities as appropriate.
- For greater than minimal risk studies that do not include a plan for monitoring by a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), and that are blinded, multi-site, involve vulnerable populations, or involve high-risk interventions or procedures, the IRB carefully evaluates the proposed DSM plan and may require establishment of a DSMB, DMC, or other methods to enhance the monitoring and management of safety.
- 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 unanticipated problems
 - 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 (ie, stopping rules), if applicable
 - The procedures for reporting to the IRB and others, including a summary description of what information, or the types of information, will be provided, when, and to whom
- For a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), the plan should also describe:
 - The composition of the board or committee. Generally, a DSMB or DMC 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.
 - The frequency and character of monitoring meetings (eg, open or closed, public or private)
 - The DSMB or DMC charter should be provided, if available.

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. A DSMB is required for some studies sponsored by the National Institutes of Health (NIH). The IRB has the authority also to require a DSMB or DMC as a condition for approval of research if the IRB determines that such monitoring is necessary and appropriate. When a DSMB or DMC is used, the IRB conducting the continuing review of research may rely on a current statement, or the most recent report, from the DSMB or DMC that 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.

Privacy and Confidentiality

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

Definitions

- **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.
- **Confidentiality:** Methods used to ensure that information obtained by investigators about subjects is not improperly divulged.
- **Private information:** Information that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).
- **Sensitive Information:** Information, on any storage media or in any form or format, which requires protection because of the risk of harm that could result from inadvertent or deliberate disclosure, unauthorized access, misuse, alteration, or loss or destruction of the information; information that could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation.
- **Identifiable information:** Information where the identity of the subject is, or may readily be, ascertained by the investigator or associated with the information.

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 subjects' private, identifiable information and the subjects' expectations of privacy in the situation. Investigators must have appropriate authorization to access the subjects or the subjects' information.

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

- Methods used to identify and contact potential participants.

- Settings where recruitment and research activities will occur.
- Appropriateness of all personnel present for research activities.
- Methods used to obtain information about participants and the nature of the requested information, including whether the data is the minimum necessary to achieve the aims of the research.
- Information that is obtained about individuals other than the “target subjects,” (eg, a subject provides information about a family member for a survey) and whether such individuals meet the regulatory definition of “human subject.”

Confidentiality

The IRB must determine if appropriate protections are in place to minimize the likelihood that information about subjects may 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 that may affect confidentiality, 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 Principal Investigator provides the IRB with a plan regarding the procedures to be taken to protect the confidentiality of research data and sensitive information. Additionally, the investigator provides information regarding information security procedures and plans to address the protection of paper documents, other physical media (eg, audio or videotapes), and electronic data and information including the use, maintenance, storage, and transmission of information. The IRB reviews all information received from the investigator and determine whether or not the confidentiality of research data is sufficiently protected. In some cases, the IRB may also require that a Certificate of Confidentiality be obtained to additionally protect research data, see *Section 26, Certificates of Confidentiality*.

In reviewing confidentiality protections, the IRB shall consider whether or not 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 institutional 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.

Vulnerable Populations

Certain individuals, by nature of their age or mental, physical, economic, educational, or other situation, may be more vulnerable to coercion or undue influence than others. When research that includes vulnerable populations is proposed, the IRB must consider the scientific and ethical reasons for including vulnerable subjects in the research. The IRB may determine and require that, when appropriate, additional safeguards be put into place for vulnerable subjects.

Section 12, Vulnerable Subjects in Research provides additional information about the IRB review and approval process for specific populations of vulnerable subjects.

Additional Considerations

Determination of Risk

At the time of initial and continuing review, the IRB makes a determination regarding the risks associated with the protocol/research plan. Risks associated with the research are generally classified as either “minimal risk” or “greater than minimal risk” with additional classifications as required by the various subparts or FDA regulations. When modifications are proposed, the IRB evaluates whether the modification changes the risk determination. Risk determinations may vary over the life of a protocol/research plan depending on the procedures and risks that subjects are exposed to as the research progresses. The level of risk associated with the research influences eligibility for expedited review. The IRB meeting minutes must reflect the convened IRB determination regarding risk levels. Expedited reviewers must document the determination of risk level on the *Expedited Review Checklist*.

Period of Approval

At the time of initial review and at continuing review, the IRB makes a determination regarding the period of approval. All studies are reviewed by the IRB at intervals appropriate to the degree of risk but no less than once per year (12 months). In some circumstances, a shorter review interval (eg, semi-annually, quarterly, or after accrual of a specific number of participants) may be required. The IRB meeting minutes must reflect the convened IRB determination regarding review frequency. Expedited reviewers must document the determination of risk level on the *Expedited Review Checklist*.

IRB approval is considered to have lapsed at midnight on the expiration date of the approval. The expiration date is the last day research may 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 “Conditions Required for Approval.” The expiration date of the initial approval period, which is the date by which the first continuing review must occur, may be as late as one year after the effective date of initial IRB approval.

The use of the effective date of IRB approval to determine the latest permissible date for continuing review only applies to the first continuing review. For all subsequent continuing reviews of a research study subject to convened board review, the date the convened IRB or the date that the expedited reviewer conducts continuing review and approves the study (with or without conditions) determines the latest permissible date of the next continuing review.

The approval date and approval expiration date are clearly noted on IRB determination letters and must be strictly adhered to. Investigators should allow sufficient 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 review of the proposed change.

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.

Review More Often Than Annually

The IRB considers the following factors in determining those studies that require review more frequently than on an annual basis:

- The probability and magnitude of anticipated risks to subjects.
- The likely medical/psychological/social/legal/educational condition of the proposed subjects.
- The overall qualifications of the Principal Investigator, other investigators, and research staff.
- The specific experience of the Principal Investigator, other investigators, and research staff in conducting similar research.
- The nature and frequency of adverse events observed in similar research.
- The novelty of the research making unanticipated adverse events/unanticipated problems more likely.
- For clinical trials, the phase of the research, and whether the research is first-in-humans.
- The involvement of especially vulnerable populations likely to be subject to undue influence or coercion (eg, the terminally ill).
- A history of serious or continuing non-compliance on the part of the Principal Investigator, other investigators, and research staff.
- Any other factors that the IRB deems relevant.

In specifying an approval period of less than one year, the IRB may define the period with either a time interval or a maximum number of subjects that may be either studied or enrolled. If a maximum number of subjects studied or enrolled is used to define the approval period, it is understood that the approval period in no case can exceed one year and that the number of subjects studied or enrolled determines the approval period only when that number of subjects is studied or enrolled in less than one year. If an approval period of less than one year is specified by the IRB, the reason for more frequent review should be documented in the IRB minutes and also the *Expedited Review Checklist*.

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 submission of monitoring, audit, and inspection reports serves as one source of independent verification. Beyond this, the IRB determines the need for verification from outside sources on a case-by-case basis. The following factors may 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.
- 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 a single point in time. The IRB may request that HRPP staff perform the independent verification, may form a subcommittee for this purpose, or may rely on a consultant reviewer or other source to perform the review.

If any material changes have occurred without IRB review and approval, the IRB evaluates the issue in accordance with the procedures described in *Section 16, Non-compliance*.

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 (eg, consent monitor) 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.

Such monitoring may be particularly warranted for:

- High-risk studies.
- Studies that involve particularly complicated procedures or interventions.
- Studies involving vulnerable populations (eg, persons with impaired decision-making capacity, children who are wards).
- Studies involving research staff with minimal experience in administering consent to potential study participants.
- Other situations when the IRB has concerns that consent process may not be/is not being conducted appropriately (eg, prior investigator non-compliance).

If the IRB determines that consent monitoring is required, the IRB develops a monitoring plan. The consent monitoring may be conducted by HRPP/IRB staff, IRB members, or another individual designated by the IRB, either affiliated or not with the medical school. Arrangements are made with the Principal Investigator for the monitoring of the consent process, typically for a specified number of subjects. When observing the consent process, the monitor evaluates:

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

Following the monitoring, a report of the findings is submitted to the IRB, which determines the appropriate action to be taken, if any.

Investigator Qualifications

The IRB may review credentials, curricula vitae, resumes, and other relevant materials to determine whether investigators and research staff are appropriately qualified to conduct the research. The IRB may rely upon other processes and entities (eg, a statement from a hospital, facility, or department chair that the investigators have the necessary expertise and credentials) to inform this determination.

Investigator Conflicts of Interest

The IRB research application asks specific questions regarding the investigator and research staff compliance with disclosure requirements and whether or not any conflict management plans are in place. As part of the review process, the IRB makes a final determination as to whether any conflict of interest or commitment is adequately addressed and protects the human subjects in the research. *Section 21 Participation Outreach*, provides additional discussion of conflicts of interest and commitment.

Institutional Conflicts of Interest

As with individual conflict of interest, the IRB has final authority to determine whether institutional conflicts, financial interests, and the management plan, if any, allow the study to be approved. *Section 20, Management of Conflicts of Interest and Commitment*, provides additional discussion of institutional conflicts of interest.

Significant New Findings

During the course of research, significant new knowledge or findings about the research, the test article, and/or the condition under study may develop. The Principal Investigator must report any significant new findings to the IRB. The IRB reviews the findings with regard to the impact on the subjects' rights and welfare. Because the new knowledge and findings may affect the risks or benefits to subjects or subjects' willingness to continue in the research, the IRB may require, during the ongoing review process, that the Principal Investigator or research staff contact the currently enrolled subjects to inform them of the new information. The IRB communicates this requirement to the Principal Investigator. If the study is still enrolling subjects, the consent document should be updated. The 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, such as when it affects their rights or welfare.

Advertisements and Recruitment Materials

The IRB must review and approve any and all advertisements prior to posting or distribution for studies. The IRB reviews:

- The information contained in the advertisement.
- The mode/method of its communication.
- The final copy of printed advertisements.
- 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 assure that the material is accurate and is not coercive or unduly optimistic, creating undue influence to the subject to participate. This includes but is not limited to:

- Statements implying a certainty of favorable outcome or other benefits beyond what was outlined in the consent document and the protocol/research plan.
- Claims, either explicitly or implicitly, that the test article (drug, biologic, or device) or procedure is safe or effective for the purposes under investigation.
- Claims, either explicitly or implicitly, that the test article or procedure is known to be equivalent or superior to any other drug, biologic, device or procedure.
- Using terms like “new treatment,” “new medication,” or “new drug” without explaining that the test article or procedure is investigational.
- Promising “free medical treatment” when the intent is only to say participants will not be charged specifically for participating in the research.
- 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.
- 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 Principal Investigator and/or research facility.
- The condition being studied and/or the purpose of the research.
- In summary form, the criteria that are used to determine eligibility of subjects 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.
- A brief list of potential benefits (eg, 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](https://clinicaltrials.gov) are not considered advertisements and therefore do not require IRB review and approval if the listing is limited to the following basic study information: title, purpose of the study, protocol/research plan summary, basic eligibility criteria, study site location(s), and how to contact the study site for further information.

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 assure that neither raises concerns 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 permit the entire payment to be contingent upon completion of the entire study. Any amount paid as incentive 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.

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 (eg, if they withdraw from the study before their participation is completed) or no payment.

If applicable, the consent must disclose when identifying information (eg, name, address, Social Security Number) may be provided to a component within an organization such as Accounts Payable to issue checks, cash, or gift certificates to subjects, and also that an IRS Form 1099 may be issued if payments to an individual exceed \$600 in a calendar year.

Non-Monetary Gifts and Incentives

Similar to financial incentives, non-monetary gifts or incentives can also present problems of undue influence or coercion that impact a potential subject's ability to fully and freely consider participation in research.

If subjects are 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 must be provided with a description, photo, or sample product to review.

The IRB reviews all gifts and incentives being particularly sensitive to the influence of power or authority, whether perceived or actual, over free decision-making. Overt coercion (eg, 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 not to participate will not adversely affect an individual's relationship with the organization or its staff or the provision of services in any way (eg loss of credits or access to programs).

State and Local Laws

The HRPP and IRB considers and adheres to all applicable state and local laws in the jurisdictions where the research is taking place. The HRPP and IRB rely on medical school counsel for the interpretation and application of Michigan law and the laws of any other jurisdiction where research is conducted as they apply to human subjects research. The IRB ensures that consent forms are consistent with applicable state and local laws.

Possible IRB Actions

Approval

In conducting its review of research, the IRB may take any of the following actions. With the exception of disapproval, the actions listed below may be used for either expedited or convened board review. Disapproval can only be decided at a convened IRB meeting. An expedited reviewer cannot disapprove a study.

The research, proposed modification to previously approved research, or other item is approved. The IRB has made all of the determinations required for approval, meeting approval criteria and any applicable special determinations such as required waivers, alterations, or accommodations for vulnerable population determinations. No further action is needed.

Conditions Required for Approval

The research, proposed modification to the previously approved research, or other item is approved but conditions must be satisfied before the approval becomes effective.

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 of the determinations required for approval, meeting approval criteria and any applicable special determinations such as required waivers, alterations, or accommodations for vulnerable population determinations. Any time the IRB cannot make one or more of the determinations required for approval, the IRB may not approve the study with conditions.

The IRB may require the following as conditions of approval of research:

- Confirmation of specific assumptions or understanding on the part of the IRB regarding how the research will be conducted (eg, confirmation that research excludes children).
- Submission of additional documentation (eg, certificate of training).
- Precise language changes to the study, consent, or other study documents.
- Substantive changes to the study, consent, or other study documents along with clearly stated parameters that the changes must satisfy.

When the IRB approves research with conditions, the conditions must be documented in the IRB minutes for research reviewed at a convened meeting or in the *Initial Study Review Checklist* for research reviewed under an expedited review procedure.

When the convened IRB approves research with conditions, the IRB may designate the IRB chair 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. If the conditions have been satisfied and the expedited reviewer approves research with conditions, the original expedited reviewer and/or other qualified individual(s) are provided the responsive materials. HRPP/IRB staff can be designated by the convened IRB or expedited reviewer to review non-substantive conditions when they are appropriately qualified to do so.

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

- The date when the IRB determined that the criteria for approval were satisfied (ie, the "approval date").
- The date when verification was made that all IRB conditions have been satisfied (ie, the "effective date").
- For initial approval and continuing reviews, the date by which continuing review must occur.

The IRB is informed of the outcome of the review of the investigator's response as part of the agenda of the next meeting.

Partial Approval

The IRB may stipulate that certain components 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. The IRB may also stipulate that an approval is limited to certain components of the research (eg, phase 1 of a proposed research project) or populations (eg, approved for adults but not children).

Deferred

This action is 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 (eg, the risks and benefits cannot be assessed with the information provided).

The deferral and the basis for the deferral is documented in the IRB minutes (for convened review) or *Expedited Review Checklist* (for expedited review) and is communicated to the investigator in writing.

When the convened IRB defers approval, the responsive materials from the investigator are provided to the convened IRB for review at a subsequent meeting. When an expedited reviewer defers approval, the original expedited reviewer reviews the response materials whenever possible. In the event that the original expedited reviewer is unavailable, the response is reviewed by the IRB chair or other qualified IRB member who has been designated to conduct expedited reviews.

Disapproved

The IRB may determine that the proposed research cannot be conducted at the site or sites included in the IRB submission. Disapproval can only be decided at the convened IRB meeting. An expedited reviewer cannot disapprove a study.

Approval in Principle

As per federal regulations [45 CFR 46.118], there are circumstances in which a sponsoring agency may require certification of IRB approval as a condition of submitting for or releasing funds but before definitive plans for the involvement of human subjects have been developed (eg, certain training grants or grants in which the procedures involving human subjects are dependent on the completion of animal studies or instrument development). In these circumstances, the IRB may grant “approval in principle” without having reviewed the as yet undeveloped procedures or materials. The IRB chair or designee reviews the available information (ie, the grant or proposal and any supplemental information provided by the investigator) and, if appropriate, provides certification of IRB approval in principle. If the proposal is funded, the investigator must submit the materials required for initial submissions for review and approval before beginning any human subject activities, including recruitment or collection of pilot data.

In addition to the above actions, the IRB may acknowledge reports and other items that don’t involve prospective changes to already approved research. For example, the IRB may acknowledge the report of a protocol deviation but approve, require modifications in, or disapprove any associated corrective action plan. Further, the IRB may approve an item but include comments noting certain requirements. Approval must also be obtained from another IRB with jurisdiction and that the letter documenting that approval must be submitted to the medical school IRB before human research activities involving the collaborating organization or personnel may commence.

Continuing Review

The IRB conducts a continuing review of ongoing research at intervals that are appropriate to the level of risk for each protocol/research plan. Unless the IRB determines otherwise during the initial review, continuing review is not required for research that is non-exempt and minimal risk (expedited research). The IRB Member

must provide a justification on why the non-exempt, minimal research qualifies for continuing review. Research requiring review by a convened IRB conducts a continuing review not less than once per year. The date by which continuing review must occur is recorded in the IRB minutes or other IRB records and communicated in writing to the Principal Investigator. Continuing review must occur as long as the research remains active. The following circumstances also do not require continuing review: (i) Research reviewed in accordance with the limited IRB review as required in exemption category 2 or category 3; (ii) Research that has progressed to the point it involves only data analysis, including analysis of identifiable private information or identifiable biospecimens; (iii) Research that is accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

Continuing Review Process

As a courtesy to investigators, HRPP/IRB staff send out renewal notices to investigators three months, two months, and again one month in advance of the expiration date. 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:

- The initial study application form updated with any changes approved by the IRB since the initial or last continuing review.
- The current protocol/research plan.
- The current consent document.
- The current Investigator's Brochure (if applicable).
- The most recent report from the DSMB or DMC (if applicable).
- The most recent multi-center progress report (if applicable).
- Any previously un-submitted publications or presentations resulting from the research.
- The *Continuing Review Request Form* (progress report).

IRB members have access to the full study file. Archived records can be requested by contacting HRPP/IRB staff.

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 four aspects of the research:

- Risk assessment and monitoring.
- Adequacy of the informed consent process.
- Local investigator and institutional issues.

- Research progress.

Convened Board Review

In conducting continuing review of research not eligible for expedited review, all IRB members are provided with access to all of the materials listed in *Section 7, Approval Considerations* and are responsible for reviewing the project summary, the current consent document, the progress report, and, if applicable, the data and safety monitoring report and multi-center study progress reports. The primary reviewer is responsible for conducting an in depth review of all materials. At the meeting, the primary reviewer provides a summary of the research and the progress report and assists the IRB Chair in leading the IRB through the evaluation of the regulatory criteria for approval.

Expedited Review

In conducting continuing review under expedited procedures, the reviewers receive all of the previously noted materials. The reviewer(s) complete the *Continuing Review 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.

Generally, 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, except in limited circumstances described by expedited review categories (8) and (9) of *Expedited Review Categories in Section 7*. 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.

Possible IRB Actions after Continuing 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. See *Section 7, Possible IRB Actions* for a detailed description of IRB actions.

- Approval.
- Conditions Required for Approval.
- Deferred.
- Partial Approval.

Additionally, the convened IRB may vote to disapprove the study. If an IRB member conducting expedited review believes that the study should be disapproved, it is referred to the convened board for review. If the IRB has significant concerns, the IRB may vote to suspend or terminate the research. See *Section 8, Study Suspension, Termination, and Investigator Hold* for a detailed discussion of suspensions and terminations.

If a research study receives “Conditions Required for Approval” at the time of the continuing review, the IRB specifies whether any conditions need to be satisfied before

an investigator can continue particular 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, 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 as long as the restricted activity is not begun or restarted until approval is granted.

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 occurs 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 sufficient 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 (eg, 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 of 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.

HRPP/IRB staff are responsible for notifying the investigator of the expiration of approval and that all research activities must cease.

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 HRPP/IRB staff 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 reviews the request and provides 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 subjects already enrolled in the study 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 (eg, the study regimen includes daily administration of an investigational agent), the investigator may make an initial determination, in consultation with the subjects' treating physician, if appropriate. In such cases, the investigator must, as soon as possible, contact HRPP/IRB staff and submit a request for confirmation that the IRB agrees with the determination. The IRB chair or designee reviews the request and provides a determination. In the event that the IRB does not agree with the investigator's determination, or agrees only in part (eg, agrees that some but not all of the activities are in the best interests of subjects), the IRB notifies the Principal Investigator who must then comply with the IRB requirements or request a re-review of the determination by providing additional justification or information that the IRB may not have considered.

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* unless the change is necessary to eliminate apparent immediate hazards to the subject, in which case the IRB must then be notified at once.

Modifications may be permanent (protocol modification), which changes the protocol for all remaining subjects, or one-time, which changes the protocol for a specific subject (protocol exception). See *Section 7, Protocol/Research Plan Exceptions* for details on protocol exceptions.

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 generally requires a new study application rather than allow such changes to be made through a modification to the existing protocol/research plan.

Procedures

Investigators must submit documentation to inform the IRB about the proposed changes to the study, including, but necessarily limited to:

- Completed *Modification Request Form*.
- A revised protocol/research plan, application, and/or study materials (in tracked changes or with a detailed summary of changes and the locations of those changes), as applicable.
- Revised consent/parental permission/assent documents (if applicable).
- When the proposed change(s) to the research might relate to current subjects' willingness to continue to participate in the study and they won't be asked to re-consent using the revised consent form, an information sheet, letter, script, or other mechanism of providing information.
- Any other relevant documentation such as cover letters provided by the sponsor or coordinating center.

HRPP/IRB staff 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 IRB 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.

Convened Board Review of Modifications

When a proposed change in a research study is not minor, or when a proposed change to an expedited study renders it no longer eligible for expedited review 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 subjects' continued welfare.

All IRB members are provided with and review all documents provided by the Principal 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 assessment of the regulatory criteria for approval and evaluating whether the modification alters any previous determinations (eg the risk determination) or necessitates any additional determinations (eg for vulnerable populations).

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.

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 performed by the IRB chair and/or experienced designee(s) among the IRB members.

The reviewer(s) completes the *Expedited Review 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 also evaluates whether the modification alters any previous determinations (eg, a Subpart determination), or necessitates any additional determinations (eg, vulnerable populations).

The reviewer also considers 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 and how to provide that information to participants.

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. See *Section 7, Possible IRB Actions* for a detailed description of IRB actions.

- Approval.
- Partial approval.
- Conditions required for approval.
- Deferred.

Additionally, the convened IRB may vote to disapprove the proposed changes. If an IRB member conducting expedited review believes that the proposed modifications should be disapproved, the IRB member refers 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. See *Section 8, Study Suspension, Termination, and Investigator Hold* for a detailed discussion of suspensions and terminations.

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 protocol/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 must get approval from the sponsor and the IRB ahead of time. For sponsored research, prior approval from the sponsor is generally required in addition to IRB approval. Depending on the nature of the

exception, an expedited IRB review may be possible. In order to be approved under expedited review the proposed exception must not adversely affect the risk/benefit analysis, participant's rights, safety, welfare, or the overall integrity of the study data. Review of exceptions that represent more than minor changes are reviewed 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 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 as a deviation.

Closure of Research Studies

The completion or early termination of the study, is a change in study activity and as such must be reported to the IRB. Although subjects are longer deemed to be "at risk" under the study, a final report to the IRB allows the IRB to close its files. A final report also provides 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 the medical school and any sites for which the medical school IRB is the "IRB of record". If the investigator is serving as the lead investigator or the site reviewed by the medical school IRB is the coordinating center, the study must remain open as long as the lead investigator or coordinating center is still receiving, studying, using, or analyzing identifiable private information from other sites even if local site interventions, interactions, observations, and data gathering is complete.

Investigators may submit study closures to the IRB on a *Study Completion or Closure Form*. With closure submissions, the investigator must provide a summary of the research activity and any findings available at that time via the *Study Completion or Closure Form*.

Investigators may maintain the data that they collected, including identifiable private data, if this is consistent with the IRB-approved protocol/research plan. However, investigators may not conduct any additional analysis of identified data without 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 reviews study closure reports, typically by expedited review, and either acknowledges the closure of the study or request additional information, actions, or confirmation of facts from the investigator.

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 letter prepared by the HRPP/IRB staff. For an approval, written notification of approval and the approved consent/assent/permission form(s), if applicable, containing the IRB stamp with the date the approval became effective and the study expiration date, are sent to the investigator. For approval with conditions, the notification includes a listing of the conditions that must be satisfied. For a deferral, the notification includes the basis for deferral and a listing of the required modifications and/or clarifications. For a disapproval, termination or suspension, the notification includes the basis for making that decision.

IRB letters are maintained in the IRB study file.

The IRB reports its findings and actions to the organization in the form of its minutes, which are distributed by HRPP/IRB staff to the assistant dean for Research Compliance and Institutional Official.

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 (eg, a request for modification), the IRB chair or IRB director reviews the circumstances, including any potential impact on human subjects, and contacts 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 must be reviewed in accordance with the procedures in *Section 16, Non-Compliance*. Notice, including an explanation, is sent by HRPP/IRB staff to the investigator. An extension beyond 90 days may be granted by the IRB if the investigator provides sufficient cause.

Appeal of IRB Decisions

When an IRB research study is disapproved or deferred, the IRB notifies 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. Similarly, when research is suspended in part or in full, or terminated, the IRB notifies 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, the investigator may submit an appeal to the IRB to request reconsideration. The investigator may be invited to attend the IRB meeting to discuss the request and provide information, and is required to leave the meeting prior to the IRB's final deliberations and vote. In the event a disagreement cannot be resolved, the investigator and/or the IRB may make an appeal to the assistant dean for Research Compliance or Institutional Official, either of whom may organize a meeting to help facilitate discussion between the IRB and the investigator. While the Institutional Official may provide input and make recommendations to the investigator and IRB for resolution of the matter, final determinations for approval/required modifications/disapproval remain under the purview of the IRB.

Research Previously Approved by another IRB

When an investigator transfers research oversight to the medical school IRB that was previously approved by another IRB, the investigator must notify both IRBs and submit the research for review under the procedures covered by this section. The IRBs work together to determine the effective date of transfer and any steps necessary to avoid a lapse in IRB oversight during the transfer process.

Section VIII: Study Suspension, Termination, and Investigator Hold

Suspension and 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. See *Section 15 Unanticipated Problems Involving Risks to Subjects or Others* and *Section 16 Non-compliance* for further discussion.

The IO or associate dean for Research Compliance has the authority to suspend or terminate the organization's approval for research. Such actions will be promptly reported to the IRB so that the IRB can review the circumstances and take any necessary actions relevant to IRB review and oversight.

Suspension of IRB approval is a directive of the convened IRB or IRB chair to temporarily stop some or all previously approved research activities. The IRB Chair may temporarily suspend IRB approval, in part or in full, when the available information suggests that actions must be taken to protect human subjects or the integrity of the research, prior to the next convened meeting of the IRB. Temporary suspensions by the Chair will be reported to the convened IRB at the next scheduled meeting at which time the convened IRB will determine if the suspension should continue, be lifted, or be modified. Suspended research studies remain open and require continuing review. Investigators must continue to provide reports on adverse events and unanticipated problems to both the IRB and sponsors just as if there had never been a suspension (ie, 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 considers notification of subjects and any actions necessary to ensure that the rights, safety, and welfare of subjects are appropriately protected.

The IRB will notify the investigator of suspensions in writing; a call or email may precede the written notice when appropriate. Written notices of suspensions will include a statement of the reason(s) for the IRB's action and any requirements or conditions associated with the suspension (eg, notification of subjects). The investigator will be provided with an opportunity to respond in person or in writing.

Suspensions of IRB approval must be reported promptly to the assistant dean for Research Compliance, associate dean for Research, Institutional Official, sponsors including federal department or agency heads, and federal oversight agencies according to applicable federal and institutional requirements. See *Section 14, Other Reportable Information* for a detailed discussion of reportable events and reporting 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 will notify the investigator of terminations in writing; a call or email may precede the written notice when appropriate. Written notices of terminations will include a statement of the reasons for the IRB's action and any requirements associated with the termination (eg, 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 assistant dean for Research Compliance, associate dean for Research, Institutional Official, sponsors including federal department or agency heads, and federal oversight agencies according to applicable federal and institutional requirements. See *Section 14, Other Reportable Information* for a detailed discussion of reporting requirements.

Investigator Hold

An investigator may request an investigator hold when the investigator wishes to temporarily or permanently stop 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. Investigator holds are not equivalent to IRB suspensions or terminations.

Investigators must submit a memo and any supporting materials to inform the IRB of the hold. The memo and materials should include:

1. A statement that the investigator is voluntarily placing a study on hold;
 - a. The reason(s) for the hold;
 - b. A description of the research activities that will be stopped;
 - c. Proposed actions to be taken to protect current participants; and
 - d. Any 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 IRB staff places the research on the next available IRB meeting agenda for review.

The IRB chair or vice chair, in consultation with the investigator, determine whether any additional procedures need to be followed to protect the rights and welfare of current participants as described in *Section 8, Protection of Currently Enrolled Participants*.

The IRB chair or vice chair, in consultation with the investigators, determine how and when currently enrolled participants will be notified of the hold.

Protection of Currently Enrolled Participants

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

- 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.
- Notification of former participants.

Section IX: IRB Reliance on an External IRB

Use of an External IRB

Medical school investigators wishing to conduct industry-sponsored biomedical research studies may choose between the IRB services provided locally by the medical school IRB or an external IRB that the medical school has IRB authorization agreements with. A list of IRBs that the medical school has IRB authorization agreements with is available from HRPP/IRB staff.

IRB reliance agreements establish the authorities, roles, and responsibilities of the reviewing IRB and the relying organization. The procedures for reliance, including for communication, information sharing, and reports, may be outlined in the reliance agreement or in companion SOPs or other materials. The HRPP director utilizes a checklist to ensure that reliance agreements and any accompanying materials address all requirements and are consistent with the medical school's standards. To support compliance, the medical school will make every effort to ensure as much consistency as possible across reliance agreements.

The medical school recognizes the use of a single IRB (sIRB) of record for research that is funded by the NIH and carried out at more than one site in the United States. (See *Section 9, NIH Single IRB (sIRB) for Multi-Site Research*).

Other investigator-initiated studies must be reviewed by the medical school's IRB and are not eligible for review by external IRBs. Exceptions may be made by the associate dean for Research on an individual basis.

Investigator Responsibilities

Prior to submitting the application package to the external IRB, the investigator must satisfy medical school application requirements for externally reviewed studies and complete all applicable medical school required training and reviews. The following must be submitted to the IRB:

- A copy of the protocol/research plan.
- A copy of the draft consent document with any applicable medical school or facility required standard language incorporated.
- A copy of the HIPAA Authorization form, if applicable.
- Documentation of other required reviews (eg, conflict of interest and commitment, IBC).

Medical School Responsibilities Prior to Accepting External Oversight for a Study

When the submission packet is received, HRPP/IRB staff review the materials and confirm that the research is eligible for external IRB submission, and that all local requirements have been satisfied. If a Conflict Management Plan is in place, or if other committees such as the IBC have recommendations, the HRPP/IRB staff ensure that the reviewing IRB is provided with the information.

Eligibility to use external IRB review (industry-sponsored, industry-initiated). Review of investigator and research staff (confirmation of training/credentialing, assessment of prior non-compliance or other issues). Once it has been determined that the research is eligible for external IRB submission and that all local requirements have been satisfied, the HRPP director issues an acknowledgment letter to the investigator. Local policies concerning special topics (eg, use of legally-authorized representatives, consent requirements) may also be included in the acknowledgement.

The external IRBs that serve as the IRB of record for the medical school research have the same authority as the medical school IRB and all determinations and requirements of the external IRBs are equally binding. Investigators must be familiar with and comply with the external IRB's policies and procedures and any additional requirements or procedures outlined in the IRB reliance agreement or companion materials (eg, reliance SOPs).

Regardless of which IRB is designated to review a research project, the medical school is responsible for the conduct of the research in which it engages. Research reviewed by external IRBs remains subject to review, approval, and oversight by the medical school and must adhere to all applicable policies, procedures, and requirements, including those of the medical school HRPP.

Post-Approval Requirements

Clinical studies approved through external IRB review still report local unanticipated problems, complaints and noncompliance to the medical school IRB Office via the *Reportable New Information form*.

The Principal Investigator is required to submit the External IRB approval letters to the medical school IRB for study updates/renewals of the External IRB approved research that meet the following criteria:

- Updates to Principal or Sub-Investigators.
- Updates to protocol or consent forms.
- External IRB Continuing review approval of the medical school study site.
- In the event that the Principal Investigator has failed to renew the study with the External IRB by the expiration date, the Principal Investigator must notify the medical school IRB in writing within 24 hours of study expiration.

The medical school IRB Office considers study closure a change in status. Therefore, the Principal Investigator is required to submit the External IRB closure documentation to the medical school IRB.

NIH Single IRB (sIRB) for Multi-Site Research

In June 2016, the National Institutes of Health (NIH) released a final policy requiring domestic awardees and domestic sites of NIH-funded multi-site research to use a single IRB (sIRB) for review of non-exempt human subject research unless there is

justification for an exception. This policy is intended to streamline the IRB review process and reduce inefficiencies and redundancies while maintaining and enhancing subject protections. The policy does not apply to career development, research training, or fellowship awards, nor to sites that are not conducting the same protocol as the other sites (eg, sites providing statistical support or laboratory analysis only) or to foreign sites.

Exceptions to the policy are automatic when local IRB review is required by federal, tribal, or state law/regulation/policy and when the proposed research is the “child” of a grant that predates the requirement for sIRB review. Such exceptions and the basis (and information regarding the “parent” study, when applicable) should be cited in the proposed sIRB plan and, when the exception is based on law/regulation/policy, apply only to the site(s) to which the law/regulation/policy applies. Other exceptions will be considered when there is compelling justification. The site(s) and justification for why the site(s) cannot rely on the single IRB of record should be included in the proposed sIRB plan. The NIH will consider the exception request and inform the applicant of the outcome.

Selection and Designation of a sIRB

The medical school’s investigators submitting applications for NIH-funded multi-site research must be provided to the medical school IRB describing the sIRB plan in the funding proposal (grant application or contract proposal), and, if applicable, may request direct cost funding to cover additional costs related to the requirements of the NIH policy. The sIRB can be the IRB at one of the participating sites or an independent, fee-based IRB. When the sIRB is named in the proposal, the IRB must have agreed to take on this responsibility in advance. Requests for the medical school to rely upon an external IRB as the sIRB should be submitted as early in the process as possible by completing and submitting the HRPP application.

Reliance Agreements for sIRB Studies

A Reliance Agreement (or “Authorization Agreement”) between the sIRB and the participating sites is required. The Reliance Agreement documents the respective authorities, roles, responsibilities, and communication between an organization providing the ethical review and a participating organization relying on a reviewing IRB. Reliance Agreements should describe the responsibilities of all parties and how communication between parties will occur, for example, notifications of the outcome of regulatory review and management of federally-mandated reports such as reports of unanticipated problems, serious or continuing noncompliance, and suspensions or terminations of IRB approval. When IRB certification requirements apply (eg, for NIH Genomic Data Sharing), the agreement or written procedures should indicate who is responsible for meeting the certification requirements.

The agreement or written procedures should also specify points of contact and contact information for the sIRB and relying institution(s).

The institution that is awarded the funding for the research is responsible for maintaining all agreements and for ensuring that adequate and appropriate communication channels between the sIRB and participating sites are in place. Participating sites are responsible for maintaining copies of the site agreement in accordance with the terms of their FWA.

Responsibilities

The sIRB will be responsible for compliance with the regulatory requirements for IRBs specified in the federal regulations (ie, [45 CFR 46](#) and other applicable regulations) and for any other responsibilities outlined in the reliance agreement and/or procedures. Participating sites (Relying institutions) are responsible for providing relevant local context information to the sIRB, ensuring that the research is conducted in accordance with applicable regulations and the determinations and requirements of the sIRB, and for other responsibilities, as outlined in the reliance agreement and/or procedures. When an external IRB serves as the sIRB for a study the medical school is engaged in, investigators must register the study with the medical school's IRB following the procedures outlined in *Section 9, Use of an External IRB*. Post-approval requirements are summarized in *Section 9, Medical School Responsibilities: Post External IRB Approval*.

Research reviewed by external IRBs remains subject to review, approval, and oversight by the medical school and must adhere to all applicable policies, procedures, and requirements, including those of the medical school.

Medical School Responsibilities: Post External IRB Approval

The medical school retains certain on-site responsibilities for all studies reviewed by any external IRB. Reports of site monitoring activities which have any findings that potentially affect human subject protections must be shared between the external IRB and the medical school IRB.

As a general rule, external IRBs copy the HRPP on all documents sent to the Principal Investigator of the study. These documents are reviewed by HRPP/IRB staff to determine if any additional actions or notifications are needed locally. In the event that the external IRB does not provide this service, the investigator may be required to provide such documents to the medical school IRB.

Investigators approved through an external IRB review must still report local unanticipated problems, complaints, non-compliance, suspensions, terminations, and an annual and end-of-study summary to the medical school IRB in compliance with medical school policy, in addition to any external IRB reporting requirements. Changes in investigators or study personnel must be submitted to the medical school IRB and approved prior to the personnel assuming any study responsibilities. If the protocol, consent form, or other key documents are updated during the study, a copy must be provided to the medical school IRB.

Section X: Documentation and Records

The medical school 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.

Medical School IRB Records

Medical school IRB records include, but are not limited to:

- Written operating policies and procedures.
- IRB membership rosters.
- Training records documenting that investigators, IRB members, and HRPP/IRB staff have fulfilled the medical school's human subject training requirements.
- Verification of Research Conflict of Interest Form completion by investigators, IRB members, and HRPP/IRB staff.
- IRB correspondence including reports to regulatory agencies.
- IRB study records (study files) including correspondence with investigators and research staff.
- Documentation of exemptions including exemptions related to emergency uses.
- Convened IRB meeting minutes.
- Documentation of review by another institution's IRB when appropriate.
- Documentation of IRB authorization or cooperative review agreements such as Master Service Agreements, IAAs, and Memoranda of Understanding (MOU).
- Federalwide Assurances.
- IRB Registrations.
- Documentation of complaints and any related findings and/or resolution.

IRB Study Files

The IRB maintains a separate IRB study file for each research application (study) that it receives for review. Research studies are assigned a unique identification number. Accurate records are maintained of all communications to and from the IRB. Copies are filed in the electronic study file. The medical school IRB maintains a separate electronic file for each research study that includes, but is not limited to:

- The application and all other documents submitted as part of a new study application.
- Documents submitted for continuing review or closure.
- Documents submitted and reviewed after the study has been approved, including modification requests, protocol exception requests, proposed advertisements, data and safety monitoring reports, and reports of protocol deviations, complaints, non-compliance, significant new findings, unanticipated adverse device events and unanticipated problems involving risks to subjects or others.
- Copy of IRB-approved Consent/Assent/Permission Forms.

- DHHS-approved sample consent form document and protocol/research plan, when applicable.
- IRB reviewer determinations.
- Documentation of scientific or scholarly review (if available).
- Documentation of type of IRB review. For exempt and expedited review, this includes the category(ies) 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 recorded in the minutes.
- For expedited review, documentation of the risk determination and period of approval. For research reviewed by the convened board, these determinations are 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 approval letters and forms that describe any requirements that the investigator must satisfy before beginning the study.
- IRB correspondence to and from research investigators or otherwise related to the research.
- For devices, documentation of determination by IRB of significant risk/non-significant risk.
- Documentation of audits, inspections, or other similar reports.

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 institutional authority.

A copy of IRB-approved minutes for each IRB meeting is distributed to the assistant dean for Research Compliance, associate dean for Research, and Institutional Official. Minutes of IRB meetings must contain sufficient detail to show:

- Attendance.
 - Names of members or alternates present.
 - 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 materials prior to the meeting and were able to actively and equally participate in all discussions.
 - Names of alternates attending in lieu of specified (named) absent members. (Alternates may substitute for specific absent members or

categories of members only as designated on the official IRB membership roster).

- Names of consultants, investigators, and other guests present.
 - The attendance list shall include those members who attended the meeting, in person or remotely. The minutes must indicate when members enter or leave the meeting. The vote on each action must reflect the numbers of members present for the vote on that item. Members who recuse themselves because of conflict of interest or commitment are listed by name along with the fact that the recusal is due to conflict of interest or commitment.
- 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.
 - Actions taken, including separate deliberations, actions, and votes for each agenda item undergoing review by the convened IRB.
 - Vote counts on these actions (Total number voting; number voting for; number voting against; number abstaining; number recused).
 - Basis or justification for actions disapproving or requiring changes in research.
 - Summary of any controverted issues and their resolution.
 - Approval period for initial and continuing reviews, including identification of research that warrants review more often than annually and the basis for that determination.
 - 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 of the required elements of informed consent, or when waiving the requirement to obtain informed consent altogether.
 - Study-specific findings supporting 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.
 - Significant risk/non-significant risk/ [21 CFR 812](#) exempt device determinations and the basis for those determinations.
 - Determinations of conflict of interest and commitment, 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 of interim reports, eg, unanticipated problems or safety reports; modification requests; report of violations/deviations; serious or continuing non-compliance; suspensions/terminations; etc.

- A list of research approved under expedited review procedures since the time of the last such report.
- Key information provided by consultants will be documented in the minutes or in a report provided by the consultant.

IRB Membership Roster

A list of IRB members is maintained that identifies members sufficiently to describe each member's chief anticipated contributions to IRB deliberations. The list contains the following information about members:

- Name.
- Earned degrees.
- Employment or other relationship between each member and the organization (ie, 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 the medical school.
- 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 sufficient 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, if any, and which IRB members are knowledgeable about or experienced in working with children, pregnant women, cognitively impaired individuals, and other vulnerable populations commonly involved in research reviewed by the medical school IRB.
- Role on the IRB (chair, vice chair, etc.).
- IRB voting status.
- For alternate members, the primary member or class of members for whom the member could substitute.

The HRPP director keeps the IRB membership list current. The HRPP director must report changes in IRB membership to OHRP and FDA within 90 days of the change.

Documentation of Exemptions

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 application satisfies the conditions of the cited exemption category as detailed in *Section 6, Exempt Studies*.

Documentation of Expedited Reviews

IRB records for initial and continuing review by the expedited procedure must include: the specific permissible category; evidence that the activity described by the investigator satisfies all of the criteria for approval; the approval period 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.

Access to IRB Records

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

- All IRB records are kept secure in a locked environment with restricted access.
- Ordinarily, access to all IRB records is limited to the HRPP director, IRB chair, IRB members, IRB manager, HRPP/IRB staff, authorized institutional officials, and officials of federal and state regulatory agencies (eg, 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 Institutional Official and HRPP director.
- Records are accessible for inspection and copying by authorized representatives of federal regulatory agencies or accrediting bodies during regular business hours.
- All other access to IRB study files is prohibited.

Record Retention

In order to comply with the requirements of OHRP, FDA, and HIPAA, IRB records are retained for at least six (6) years after completion of the research.

IRB agendas and minutes are retained for at least six (6) years after completion of each included study.

IRB records for research cancelled without participant enrollment are retained for at least three (3) years after closure.

Section XI: Obtaining Informed Consent from Research Subjects

No investigator conducting research at, or under the auspices of the medical school may involve a human being as a subject in research without obtaining the legally effective 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 *Section 11, Waiver of Informed Consent* of these procedures. Except as provided in *Section 11, Waiver of Documentation of Informed Consent* and *Waiver of Informed Consent for Planned Emergency Research* of these procedures, informed consent must be documented by the use of a written consent form approved by the IRB.

The IRB evaluates 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 at, under the auspices of, or using the services or resources of the medical school.

When the medical school IRB is serving as the IRB of record for external sites or personnel, the below requirements may be adapted as appropriate based upon the local context where the research will occur (eg, who may serve as a LAR).

Definitions

- **Legally Authorized Representative (LAR):** A LAR is an individual or body authorized under applicable law to provide permission on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. For the purposes of this policy, a LAR includes legal guardians.

Michigan law does not define who may serve as a LAR for research purposes. Thus, the applicable guidelines for determining the most appropriate LAR for research are based upon the guidelines that apply in the clinical setting.

For legally incompetent adults who are unable to make medical decisions, a legal representative (court appointed guardian) or durable power of attorney for health care must provide informed consent for non-emergent medical treatment. The legal guardian must be authorized by the court to make decisions regarding the types of activities, procedures, or treatments called for in the research to serve as LAR. Investigators should refer to clinical setting guidelines to determine who may serve as LAR for research involving clinical procedures or treatments when a court appointed guardian or durable power of attorney for health care are not in place.

When the medical school IRB serves as the IRB of record for external sites and the use of LARs is proposed, information regarding relevant state law and local policy and clinical setting guidelines will be sought and applied.

LARs should be well informed regarding their roles and responsibilities when asked to provide surrogate consent. In addition to the consent information, LARs should be informed that their obligation is to try to determine what the potential subject would do if able to provide consent, or if the potential subject's wishes cannot be determined, what they think is in the person's best interest.

Investigators must describe the intended use of LARs in their submission to the IRB. The IRB determines whether the use of LARs is appropriate for a given research study.

Further discussion and procedures for assessment of capacity and inclusion of adults with impaired decision-making capacity in research are described in *Section 12, Adults with Impaired Decision-Making Capacity*.

- **Legal guardian:** A person appointed by a court of appropriate jurisdiction.

Basic 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 the medical school IRB. Investigators are required to obtain legally effective informed consent from a subject or the subject's LAR unless the requirement has been waived by the 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 or not 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, discussing, providing answers to any questions, and obtaining signature on 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. Those obtaining informed consent must have received the appropriate training and be knowledgeable about the study in order that they may answer questions to help provide understanding to the study participant or potential study participant. The exchange of information between those obtaining informed consent and study participant can occur via one or more of the following modes of communication, among others: face-to-face dialogue, mail, telephone, video or fax. The process must be conducted in a location that ensures privacy and allows the prospective subject sufficient time to consider the information and ask questions and seek clarification from the investigator. Consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's LAR at the time of consent. Those obtaining informed consent must have a signed and dated written consent form before entering a subject into a study, gathering

study data about a subject, and/or conducting any procedures required by the protocol/research plan, unless consent is waived by the IRB.

If someone other than the investigator conducts the interview and obtains consent, the investigator needs to formally delegate this responsibility, and the person so delegated must have received appropriate training to perform this activity. The person so delegated must be knowledgeable about the research to be conducted and the consenting process, and must have the expertise to be able to answer questions about the study including those regarding risks, procedures, and alternatives. The medical school IRB application solicits information regarding who will obtain consent; proposed changes to the personnel authorized to obtain consent must be submitted to the medical school IRB for approval.

Sample or draft consent documents may be developed by a sponsor, lead investigator, or coordinating center. However, the IRB of record is the final authority on approving the content of the consent document that is presented to the prospective study subjects.

For federally-sponsored clinical trials, a copy of the consent form must be posted to a “publicly available” federal website (clinicaltrials.gov or regulations.gov) post-recruitment and no later than 60 days after the last study visit by any subject.

These informed consent requirements are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed for the informed consent to be legally effective.

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 with appropriate authority to make decisions regarding the activities called for in the research or a LAR.
- The informed consent process provides the prospective subject LAR/guardian with sufficient opportunity to read the consent document, if applicable.
- The informed consent process shall be sought under circumstances that provide the subject (or LAR) with sufficient opportunity to consider whether or not 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 LAR. To the extent possible, the language should be understandable by a person who is educated at an eighth-grade level and layman’s terms shall be used in the description of the research. The IRB may require or allow different readability standards based upon the characteristics of the target subject population.
- For subjects with limited fluency in the English language, informed consent must be obtained in a language that is understandable to the subject or the subject’s

LAR. The IRB requires that informed consent discussions include a reliable 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 investigators, the sponsor, the organization where research activities take place, or medical school 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.

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 his or her own participation in a research activity if s/he demonstrates 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.
- 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. See *Section 12, Adults with Impaired Decision-Making Capacity* for further discussion regarding adults who cannot consent for themselves.

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 subjects' 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 and institutional 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 LAR may be necessary.

In the event that research participants lose or become impaired in decision-making capacity after enrollment, and this is not anticipated in the protocol/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 *Section 11, Documentation of Informed Consent*. When participants lack the capacity to give consent, investigators may obtain consent from the LAR of a subject as described in *Section 12, Adults with Impaired Decision-making Capacity*.

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 videotapes, 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. All materials must be approved by the IRB prior to use.

Basic Elements of Informed Consent

To be valid, the consent process must provide the following basic elements of information to potential subjects:

- A statement that the study involves research, an explanation of the purposes of the research, 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 subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- 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."
- For research that involves the collection of identifiable private information or identifiable biospecimens; (1) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, 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 the legally authorized representative, if this might be a possibility, or (2) The subject'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.

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 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.
- A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions.
- For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (ie, sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

Informed Consent Templates that include the New Common Rule requirements are available and posted to the WMed Website/Forms & Templates. Investigators are strongly urged to begin using the updated ICF templates effective 01/21/2019 to ensure compliance.

In general, “applicable” clinical trials mean controlled clinical investigations, other than Phase 1 clinical investigations, of a drug or biologic; and prospective clinical studies of health outcomes comparing an intervention with a device against a control (other than (i) small clinical trials to determine the feasibility of a device; (ii) a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes; or (iii) mandated pediatric post market surveillance activities).

Documentation of Informed Consent

Except as provided in *Section 11, Waiver of Documentation of Informed Consent*, informed consent must be documented by the use of an IRB approved written consent form.

- Informed consent is documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's LAR at the time of consent and by the person obtaining consent.
- For research conducted in accordance with ICH-GCP E6 or in facilities subject to Joint Commission requirements, the name of the person who obtained consent and the date they did so is documented on the written consent form.
- A copy of the signed and dated consent form must be given to the person signing the form and, as appropriate, their LAR. The investigator should retain the signed original in the research records. When appropriate, a copy of the consent form is uploaded into the electronic health record.
- The 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 LAR, but the subject or representative must be given adequate opportunity to read it before it is signed; or
 - A short form written consent document stating that the elements of informed consent have been presented orally to the subject or the subject's LAR.

When the short form written consent procedure is used, all of the following must be met:

- 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).
- The oral presentation and the short form written document should be in a language understandable to the subject.
- There must be a witness to the oral presentation.
- The short form document is signed by the subject.
- The witness must sign both the short form and a copy of the summary.
- The person actually obtaining consent must sign a copy of the summary.
- A copy of the summary must be given to the subject or representative, in addition to a copy of the short form.

When the short form procedure is used with subjects who do not speak, or read, English, or have limited proficiency in oral or written English, all of the following apply:

- The oral presentation and the short form written document should be in a language understandable to the subject.
- The IRB-approved English language informed consent document may serve as the summary.
- 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 per clinical setting guidelines. 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.

Special Consent Circumstances

Enrollment of Persons with Limited English-language Proficiency

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 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.

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 existing 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 in as described in *Section 11, Documentation of Informed Consent*.

Use of Interpreters in the Consent Process

An interpreter will be necessary to facilitate the consent discussion. Preferably someone who based on clinical setting guidance. This person is independent of the subject (ie, not a family member) assists in presenting the 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) generally 24-48 hours, if possible, before the consent discussion with the subject. If the interpreter also serves as the witness, the interpreter 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.

Braille Consent

The IRB may approve a consent document prepared in Braille for use by blind subjects who read Braille. In order to assure itself that a Braille consent document is accurate, the IRB may require a transcription into printed text, or review of the document by an IRB member or other person who reads Braille. If possible, the subject signs the Braille consent; otherwise, oral consent is obtained, witnessed, and documented as described in *Section 11, Oral Consent*.

Consenting in American Sign Language (ASL)

The IRB may approve a consent process using ASL and the IRB-approved written consent form for deaf subjects who are fluent in ASL. When this process is approved, the individual authorized to consent prospective subjects must use a 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 11, Informed Consent*.

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 research that is no more than minimal risk, documentation of consent may be waived according to the criteria in *Section 11, Waiver of Informed Consent*.

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 audiotape 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 by audio or video recordings.

Telephone Consent

The IRB encourages whenever possible the informed consent process be done in person and not over the telephone. However, when the research cannot reasonably be conducted in person, a telephone consent may be deemed appropriate. When the proposed research poses minimal risk to subjects, and you plan an initial contact with subjects by phone, or if you plan to conduct the research using a phone questionnaire, a telephone consent script is needed. The request for telephone consent is evaluated on a case-by-case basis. When obtaining consent over the phone, the investigator must submit a phone “script” that addresses the key elements of informed consent. The participant or their LAR should receive a copy of the informed consent document in advance of the telephone discussion.

Phone scripts for minimal risk research typically include the following:

- Statement that the study involves research and participation is voluntary.
- Purpose of the phone survey or interview and description of what participants will be asked to do.

- Approximate length of the phone call.
- Description of risks and benefits of the study.
- Information about confidentiality and the use of the study data:
 - Description of who will have access to the data.
 - Description of how data will be used.
 - Description of how long data will be kept.
 - If the survey or interview involves health information, the script must include certain HIPAA statements.
- An invitation to choose whether or not to participate in the research and how to withdraw from study participation without penalty.
- Researcher's contact information in the event the participant should have further questions that may need to be addressed after the phone call.

For some projects, investigators are approved to obtain informed consent over the phone for research that is greater than minimal risk that involves ongoing contact with participants. In those cases, investigators are required to mail a full, written consent document to the potential subject in advance of the phone conversation.

If the participant or LAR agrees to participation, s/he signs and dates the consent form as instructed by the investigator or designee and returns the original signed and dated consent form to the investigator or designee for signature before the subject is enrolled in the study. A fully endorsed consent form will be provided to the participant.

Physically-Challenged Subjects

A person who is physically challenged (eg, physically unable to talk or write) can enroll in research if competent and able to indicate voluntary consent to participate. Whenever possible, the subjects should sign the consent form or make their mark by initialing or making an X. As with oral consent, a witness to the consent process is recommended and the circumstances and consent process should be carefully documented in the research records.

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 managed 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 partial (eg, 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 subsequent to 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, but 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.

Waiver of Informed Consent

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

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

This option applies to both FDA-regulated and DHHS-conducted or supported research. In addition, an IRB may approve a consent procedure that does not include, or that alters, some or all of 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.
 - Possible changes in methods or levels of payment for benefits or services under those programs.
- The research could not practicably be carried out without the waiver or alteration.

This option does not apply to FDA-regulated research except in certain emergency situations.

Use of identifiable information/biospecimen to identify potential subjects (ie, screening for recruitment purposes) is allowed without informed consent under certain circumstances. A waiver of consent will no longer be needed for these screening activities.

Waivers of consent are not permissible for either option for federally funded research using newborn Blood Spots.

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 either that:

- The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. 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).

This option does not apply to FDA-regulated research.

OR

- The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Procedures such as non-sensitive surveys, questionnaires and interviews generally do not require written consent when conducted by non-investigators (eg, marketing surveys, telemarketing).

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 in the application materials, and the IRB will consider whether to require the investigator to provide subjects with a written statement regarding the research.

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 are in need of 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 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 with the exception of the requirements specified in *Section 11, FDA-regulated Planned Emergency Research and Planned Emergency Research Not Subject to FDA Regulations* below. The DHHS waiver is not applicable to research involving prisoners, pregnant women, fetuses, or in vitro fertilization.

Definitions

- **Planned Emergency Research:** It is 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 subjects' medical condition and the unavailability of LARs of the subjects, it is generally not possible to obtain legally effective informed consent.
- **Family Member:** For this section Family Member means any one of the following adult and legally competent persons: spouses; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

Procedures

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 of all of the following:
 - The subjects will not be able to give their informed consent as a result of their medical condition.
 - The intervention under investigation must be administered before consent from the subjects' LARs is feasible.
 - 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 of all of the following:
 - 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.
 - 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 protocol/research plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a LAR for each subject within that window of time and, if feasible, to asking the LAR contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact LARs 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 Sections [46.116](#) and [46.117](#) of [45 CFR 46](#) and Sections [50.20](#), [50.25](#) and [50.27](#) of [21 CFR 50](#). These procedures and the informed consent document are to be used with subjects or their LARs 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 e) 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 sufficient 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.
- If obtaining informed consent is not feasible and a LAR 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 LAR, 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 LAR 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 LAR 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 LAR 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 LAR or family member can be contacted, information about the research is to be provided to the subject's LAR or family member, if feasible.

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 11, Procedures* are satisfied.

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 required in *Section 11, Procedures* and this section 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 [56.115\(b\)](#).

Planned Emergency Research Not Subject to FDA Regulations

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 (i) found and documented that the research *is not subject* to regulations codified by the FDA at [21 CFR Part 50](#), and (ii) found and documented and reported to the OHRP that the conditions required *Section 11, Procedures* have been met relative to the research.

Section XII: Vulnerable Subjects in Research

Research with participants conducted at, or under the auspices of, or using the services or resources of the medical school who are vulnerable to coercion or undue influence or have impaired decision-making capacity 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.

This section describes the requirements for involving vulnerable participants in research conducted at, under the auspices of, or using the services or resources of the medical school.

Definitions

- **Children:** Children are 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.

Michigan law defines the "age of majority" in MCL 722.51. An individual who is eighteen or older is an "adult" and can consent to undergo most medical procedures. Parents or legal guardians generally must consent on behalf of children younger than eighteen, with the following exceptions:

- Emancipated minors (generally those who are married or are on active duty in the U.S. armed forces) (MCL 722.4e(1)(g)).
- Children seeking prenatal and pregnancy-related care (excluding abortions) (MCL 333.9132; MCL 722 .903).
- Children age 14 and above seeking limited outpatient mental health services (MCL 330.1707).
- Children receiving substance abuse treatment (MCL 330.1264); and
- Children seeking treatment for sexually transmitted diseases, including HIV/AIDS (MCL 333.5127).

The latter four exceptions are intended to permit children to seek the listed services confidentially. Generally, if research involves only the listed services or the listed services accompanied only by minimal risk activities (eg, records review, interviews) and the child is accessing those services confidentially, the child may consent for his or her participation in the research. However, if the child is not receiving the services confidentially, or if the research involves experimental procedures, unapproved drugs or devices, or any procedures or activities that might add to the child's risk, parental permission is required.

For research conducted in jurisdictions other than Michigan, the research must comply with the laws regarding the legal age of consent in the relevant jurisdictions. Legal counsel will be consulted about the laws in other jurisdictions or such "local context" information will be sought through other means (eg, according to the terms of a reliance agreement).

- **Guardian:** A guardian is an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care [45 CFR 46.402(e)].

In Michigan, a guardian is a person with specific legal authority (eg, through a court order) to make decisions on behalf of his or her ward. A guardian may consent for research or experimental procedures only to the extent that they are specifically legally empowered to do so (ie, in the durable power of attorney or court documents granting guardianship).

Foster parents may not have the legal authority to independently provide permission for a foster child to participate in research. Investigators should consult with IRB staff for research that may include foster children or wards.

For research conducted in jurisdictions other than Michigan, the research must comply with the laws regarding guardianship in all relevant jurisdictions. Legal counsel will be consulted about the laws in other jurisdictions or such “local context” information will be sought through other means (eg, according to the terms of a reliance agreement).

- **Fetus:** A fetus means the product of conception from implantation until delivery.
- **Dead fetus:** A fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.
- **Delivery:** A delivery is a complete separation of the fetus from the woman by expulsion or extraction or any other means.
- **Neonate:** A neonate is a newborn.
 - **Viable neonate:** A viable neonate means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration.
 - **Nonviable neonate:** A nonviable neonate means a neonate after delivery that, although living, is not viable.
- **Pregnancy:** Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits 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:** Prisoner is 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 statutes or commitment procedures that provide alternatives to

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

Involvement of Persons Vulnerable to Coercion or Undue Influence

When 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 participants. The IRB may include one or more individuals who are knowledgeable about or experienced in working with individuals from these populations or it may seek such expertise through the use of consultants.

[45 CFR 46](#) has additional subparts designed to provide extra protections for special populations, which also state 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.

DHHS conducted or supported research that involves any of these populations must comply with the requirements of the relevant subparts. Research regulated by the FDA includes equivalent protections and obligations when research involves children (Subpart D). Research conducted, supported, or otherwise regulated by other federal agencies may or may not be covered by the subparts.

In its FWA, the medical school limits its commitment to apply Subparts B, C, and D to non-exempt human subjects research conducted or supported by DHHS or any other federal agency that requires compliance with the Subparts B, C, or D applicable to the research.

The following policies and procedures, which are based on Subparts B, C, and D, apply to all research regardless of funding. The individual sections describe how the subparts apply specifically to DHHS-funded research.

Responsibilities

The investigator is responsible for identifying the potential for enrolling vulnerable subjects in the research proposal. This includes the possibility of subjects who are at risk for impaired decisional capacity.

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

The IRB considers the circumstances of the proposed research, including any justifications provided by investigators, when assessing the appropriateness of including vulnerable populations in the research.

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.

Procedures

Initial Review of Research Proposal

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

The investigator describes safeguards to protect the subject's rights and welfare in the research proposal.

The 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 than 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 for subjects, including, if applicable, the proposed plan for identifying, recruiting, and obtaining consent from subjects and or their LARs 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 whether the proposed plan is adequate or if additional protections are needed such as interim monitoring, review more than annually, or the use of a data and safety monitoring board, consent monitor, or research subject advocate.

The IRB considers each of the specific findings discussed in the IRB application forms for research involving vulnerable subjects, as documented by IRB approval. IRB approval also documents that the IRB members acknowledge and agree with the preliminary description of safeguards and risk assessment of the protocol as described in the application by the PI. The IRB staff document in the minutes discussions of controverted issues at convened meetings.

The IRB staff document specific findings in the meeting minutes, or exempt/expedited reviewers document determinations in accord with applicable HRPP and IRB Policies.

The IRB does not reapply the categories during subsequent reviews unless changes to the protocol dictate otherwise.

Continuing Review and Modifications to Research

When an investigator submits a continuing review, they 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.

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.

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 modification of the research plan to ensure protection of the subjects' rights and welfare.

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 than 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 populations(s).

Research Involving Pregnant Women, Human Fetuses and Neonates

The following applies to all research involving pregnant women, human fetuses, and neonates reviewed by the medical school IRB. DHHS-specific requirements are noted in the appropriate sections.

If a woman becomes pregnant while participating in a study that has not been approved for inclusion of pregnant women, the IRB must be notified immediately so that the IRB can determine whether the subject may continue in the research, whether additional safeguards are needed, and to make the determinations required by the regulations and these policies.

Research Involving Pregnant Women or Fetuses

Research Not Conducted or Supported by DHHS

For research not conducted or supported by DHHS where the risk to the pregnant women and fetus is no more than minimal, no additional safeguards are required and there are no restrictions on the involvement of pregnant women in research. However,

the IRB may determine that additional safeguards or restrictions are warranted for a specific study.

Pregnant women or fetuses may be involved in research not conducted or supported by DHHS involving more than minimal risk to pregnant women and/or fetuses 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.
- 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, 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 bullet four (4) or five (5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
- For children see *Section 12, Definitions*, who are pregnant, assent and permission are obtained in accord with the requirements of Michigan 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.
- The IRB may allow individuals whose normal responsibilities include determining the viability of fetuses to be engaged in the research, if their involvement in the determination of viability for an individual fetus cannot be avoided. Confirmation of the determination regarding viability will be sought from a qualified individual who is not otherwise engaged in the research prior to beginning the research. The opinion of the independent qualified individual will be documented and made available upon request to the IRB representative. When advance confirmation is not possible, the investigator will obtain it as soon as s/he can after enrollment, but in all cases within five (5) business days. The circumstances that prohibited prospective confirmation of viability and the outcome of the subsequent consultation will be reported to the IRB within ten (10) business days.

Conducted or Supported by DHHS

For DHHS-conducted or supported research, [45 CFR 46 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 of 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 four (4) or five (5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
- For children see *Section 12 Definitions*, who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in Section 12.
- 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.

Research involving Neonates of Uncertain Viability or Nonviable Neonates

Research Not Conducted or Supported by DHHS

Neonates of uncertain viability and nonviable neonates may be involved in research involving more than minimal risk if all the following conditions listed below are met. The IRB will determine on a case-by-case basis whether safeguards or restrictions should be required for more than minimal risk research.

- Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
- Individuals providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
- The IRB may allow individuals whose normal responsibilities include determining the viability of neonates to be engaged in the research, if their involvement in the determination of viability for an individual neonate cannot be avoided. In such cases, confirmation of the determination regarding viability must be made by a qualified individual who is not otherwise engaged in the research whenever possible prior to involving the subject(s) in the research. The opinion of the independent qualified individual will be documented and made available upon request to the HRPP/IRB representative. When advance confirmation is not possible, the investigator will obtain it as soon as s/he can after enrollment, but in all cases within five (5) business days. The circumstances that prohibited prospective confirmation of viability and the outcome of the subsequent consultation will be reported to the IRB within ten (10) business days.
- The requirements of Neonates of Uncertain Viability or Nonviable Neonates (see below in this section) have been met as applicable.

Until it has been ascertained whether a neonate is viable, the neonate may not be involved in research unless both of the following additional conditions are met. The IRB must determine 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 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 LAR is obtained in accord with the provisions of permission and assent, except

that the consent of the father or his LAR need not be obtained if the pregnancy resulted from rape or incest.

Nonviable neonates after delivery 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 knowledge that cannot be obtained by other means.
- 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, incompetence, or temporary 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 *does not* suffice to meet the requirements of this paragraph.

Research Conducted or Supported by DHHS

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.

Until it has been ascertained whether a neonate is viable, the neonate may not be involved in research unless both of the following additional conditions are met. The IRB must determine that:

- Either 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 that 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 LAR is obtained in accord with the provisions of permission and assent, except that the consent of the father or his LAR need not be obtained if the pregnancy resulted from rape or incest.

Nonviable neonates after delivery may not be involved in research unless all of 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.
- 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 LAR of either or both parents of a nonviable neonate *does not* suffice to meet the requirements of this paragraph.

Viable Neonates

A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements for Research Involving Children (ie, a viable neonate is a child for purposes of applying federal regulations and the medical school HRPP/IRB policies).

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

Research involving, after delivery the: placenta; dead fetus; macerated fetal material; or cells, tissues, or organs excised from a dead fetus, must be conducted only in accord with any applicable federal, state, or local laws 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.

Research Not Otherwise Approvable

Research Not Conducted or Supported by DHHS

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 IRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research based on either:

- That the research in fact satisfies the conditions detailed above, as applicable.
- All the following:
 - 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.
 - The research will be conducted in accord with sound ethical principles.
 - Informed consent will be obtained in accord with the provisions for informed consent and other applicable sections of the *Human Research Protection Program (HRPP) and Institutional Review Board (IRB) Handbook*.

Research Conducted or Supported by DHHS

DHHS conducted or supported research that falls in this category 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.

Research Involving Prisoners

Applicability

For research not conducted or supported by DHHS, where the risk to prisoners is no more than minimal as defined in *Section 12 Minimal Risk*, no additional safeguards are required under this policy. However, the IRB may determine that additional safeguards or restrictions are warranted for a specific study. For research involving more than minimal risk, and for research conducted or supported by DHHS, the requirements outlined in this section apply.

The requirements apply to all biomedical and behavioral research conducted at, under the auspices of, or using the services or resources of the medical school 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 Michigan Department of Corrections and any other applicable State or local laws. [[45 CFR 46.301](#)]

Minimal Risk

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*.

Composition of the IRB

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 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 research project is reviewed by more than one IRB, only one IRB need satisfy this requirement.
- 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 involving prisoners.

Review of Research Involving Prisoners

Initial Review

The prisoner representative must review research involving prisoners, focusing on the requirements outlined in Subpart C and these policies.

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, if the representative is able to participate in the meeting as if they were present in person at the meeting.

The IRB must be familiar with the specific conditions in the local prison(s) or jail sites(s) that are pertinent to subject protections, before approving the proposal for local site (45 CFR 45.107(a)).

Modifications

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).

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).

Minor modifications to research may be reviewed using the expedited review procedure.

- Research involving interaction with prisoners 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 and the research falls within the categories of research eligible for expedited review. Whenever possible, the prisoner representative will be consulted to verify that they agree that the research is minimal risk and to conduct (if designated by the IRB chair as an expedited reviewer) or participate in the expedited review as a consultant. Review of modifications and continuing review will follow the initial review using the expedited procedure.
- Research that does not involve interaction with prisoners (eg, 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.

Incarceration of Enrolled Subjects

If a subject is incarcerated temporarily while enrolled in a study, and the temporary incarceration has no effect on the study (ie, there is no need for study activities to take place during the temporary incarceration), the participant may continue study enrollment. If the temporary incarceration influences the study, the guidelines below should be followed.

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 applying the standards and requirements for research involving prisoners.
- If the participant should continue, one of two options are available:
 - Keep the participant enrolled in the study and review the research applying the standards and requirements for research involving prisoners.

If some of the requirements cannot be met or are not applicable (eg, 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.

Additional Duties of the IRB

In addition to all other responsibilities prescribed for IRB in other sections of the *Human Research Protection Program (HRPP) and Institutional Review Board (IRB) Policy Manual*, the IRB reviews research involving prisoners and approves 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 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 intent to approve the research.
 - The research qualifies under the HHS Secretarial waiver that applies to certain epidemiological research (68 FR 36929, June 20, 2003). 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.
- 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 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.
- 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.

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, the medical school 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 the medical school 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 Federalwide Assurance (FWA) number.
- The IRB registration number for the designated IRB.
- 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.
 - The date of subpart C review, if not done at the time of initial IRB review.

Research Involving Children

The following applies to all research involving children, regardless of funding source. 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.

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 (eg, 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:

- [\[45 CFR 46.404/21 CFR 50.51\]](#) 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 as set forth in *Section 12, Parental Permission and Assent*.
- [\[45 CFR 46.405/21 CFR 50.52\]](#) 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 all the following:

- 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.
- Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in *Section 12, Parental Permission and Assent*.
- [\[45 CFR 46.406/21 CFR 50.53\]](#) 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 all of the following:
 - 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 subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition.
 - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in *Section 12, Parental Permission and Assent*.
- [\[45 CFR 46.407/21 CFR 50.54\]](#) 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:
 - DHHS -conducted or supported research in this category is 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 is referred for review by the Commissioner of Food and Drugs.
 - For research that is not DHHS conducted or supported and not FDA-regulated, the IRB consults with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, and law). Based on the recommendation of the panel, the IRB may approve the research because it satisfies the conditions of the previous categories, as applicable; or all the following:
 - The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.

- The research will be conducted in accord with sound ethical principles.
- Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in *Section 12, Parent Permission and Assent*.

Parental Permission and Assent

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, as described in *Section 11, Basic Elements of Informed Consent*.

The IRB may find that the permission of one parent is sufficient for research to be conducted under Bullet Points 1 [[45 CFR 46.404/21 CFR 50.51](#)] and 2 [[45 CFR 46.405/21 CFR 50.52](#)] in *Section 12, Allowable Categories*. 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 Bullet Points 3 [[45 CFR 46.406/21 CFR 50.53](#)] and 4 [[45 CFR 46.407/21 CFR 50.54](#)] of *Section 12, Allowable Categories* unless one of the following apply:

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

For research not covered by the FDA regulations, the IRB may waive the requirement for obtaining permission from a parent or legal guardian if one of the following apply:

- The research meets the provisions for waiver in *Section 11, Waiver of Informed Consent*.
- 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, 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.

Permission from parents or legal guardians must be documented in accordance with and to the extent required by *Section 11, Documentation of Informed Consent*.

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 can provide 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 all the following:

- 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.
- 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 similar to 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 in order

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.

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 the very young child or 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's up to the child to participate and that it's 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.
- 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.

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](#) (Bullet Points 3 and 4 in *Section 12 Allowable Categories*, only if such research is at least one of the following:

- Related to their status as wards.
- Conducted in schools, camps, hospitals, institutions, or similar settings in which most 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.

Adults with Impaired Decision-Making Capacity, Economically or Educationally Disadvantaged

The requirements in this section apply to all research involving adults who cannot provide consent or with impaired decision-making capacity, economically or educationally disadvantaged regardless of funding source.

When vulnerable populations are included in research, regulations require that additional safeguards are put in place to protect the rights and welfare of these subjects. [\[45 CFR 46.111\(b\)/21 CFR 56.111\(b\)\]](#) Adults who lack or who have impaired, fluctuating, or diminishing decision-making capacity (collectively referred to as “adults with impaired decision-making capacity” in this section) or are economically or educationally disadvantaged are particularly vulnerable. Investigators and IRBs must carefully consider whether inclusion of such subjects in a research study is appropriate; and when it is, must consider how best to ensure that these subjects are adequately protected. The principals and procedures outlined in this section are intended to assist the medical school investigators and the IRB with the development and review of research involving adults with impaired decision-making capacity, economically or educationally disadvantaged.

Decision-Making Capacity

“Decision-making capacity” refers to a potential subject’s ability to make a rationale and meaningful decision about whether to participate in a research study. This ability is generally thought to include at least the following four elements:

- Understanding, ie, the ability to comprehend the disclosed information about the nature and purpose of the study, the procedures involved, the risks and benefits of participating versus not participating, and the voluntary nature of participating.
- Appreciation, ie, the ability to appreciate the significance of the disclosed information and the potential risks and benefits for one’s own situation and condition.
- Reasoning, ie, the ability to engage in a reasoning process about the risks and benefits of participating versus alternatives.

- Choice, ie, the ability to express a choice about whether to participate.

“Decision-making capacity” should not be confused with the legal concept of “competence.” While the court may consider information about a person’s decision-making capacity in making a competency determination, the terms are not synonymous. Incompetence is a legal determination made by a court of law. For example, someone who is judged legally incompetent to manage their financial affairs may retain sufficient decision-making capacity to make meaningful decisions about participating in a research protocol. Likewise, people who have normal cognitive functioning and are considered legally competent may be put into circumstances where their decision-making capacity is temporarily impaired by a physical or mental condition or by alcohol or drugs.

Decision-making capacity is protocol and situation-specific. Thus, a person may have capacity to consent to participate in low risk research in usual circumstances, but not have the capacity to consent to a higher risk protocol when s/he is under significant stress or faced with unfamiliar circumstances.

Inclusion of Adults with Impaired Decision-Making Capacity in Research

Research involving adult 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.

Investigators must disclose to the IRB both plans and justification for including adults with impaired decision-making capacity in a given research proposal. If adults with questionable or fluctuating capacity will be included, investigators must specify procedures for assessing capacity prior to providing informed consent and, if appropriate, for re-evaluating capacity during study participation. If a prospective subject’s capacity to consent is expected to diminish, the investigator should consider requesting that the subject designate a future LAR prior to enrollment in the research, including the future LAR in the initial consent process, and obtaining written documentation of the subject’s wishes regarding participation in the research. When the study includes subjects likely to regain capacity to consent while the research is ongoing, the investigator should include provisions to inform them of their participation and seek consent for ongoing participation.

Plans for evaluation of capacity should be tailored to the subject population and the risks and nature of the research. In some instances, assessment by a qualified investigator may be appropriate. However, an independent, qualified assessor should evaluate subjects’ capacity when the risks of the research are more than a minor increase over minimal or the investigator is in a position of authority over a prospective subject. In all cases, the person(s) evaluating capacity must be qualified to do so and use appropriate, validated tools and methods (eg, University of California, San Diego Brief Assessment of Capacity to Consent [UBACC], MacArthur Competence Assessment Tool for Clinical Research [MacCAT-CR]). Assessments of capacity should be documented in the research record, and when appropriate, in the medical record.

Under some circumstances, it may be possible for investigators to enable adults with a degree of decisional impairment to make voluntary and informed decisions to consent, assent, or refuse participation in research. Potential measures include repetitive teaching, audiovisual presentations, and oral or written recall tests. Other measures might include follow-up questions to assess subject understanding, videotaping or audio-taping of consent discussions, use of waiting periods to allow more time for the potential subject to consider the information that has been presented, or involvement of a trusted family member or friend in the disclosure and decision-making process. Audio or videotapes, electronic presentations, or written materials used to promote understanding must be provided to the IRB for review and approval prior to use.

When a prospective subject is deemed to lack capacity to consent to participate in research, investigators may obtain informed consent from the individuals' surrogate or LAR see *Section 11, Obtaining Consent from Research Subjects*. Under these circumstances, the prospective subject should still be informed about the research in a manner compatible with the subjects' likely understanding and, if possible, be asked to assent to participate. Potential subjects who express resistance or dissent (by word, gesture, or action) to either participation or use of surrogate consent, should be excluded from the study. Some subjects may initially assent but later resist participation. Under no circumstances may an investigator or caregiver override a subject's dissent or resistance. 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, how assent will be documented, and a copy of the assent form. 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.

When inclusion of adults with impaired decision-making capacity is not anticipated and a plan for inclusion of such subjects has not been reviewed and approved by the IRB, and an enrolled subject becomes unable to provide consent or impaired in decision-making capacity, the investigator is responsible for promptly notifying the IRB (as soon as possible but within five (5) business days). The investigator should consider whether continuing participation is appropriate and, if so, present a plan for surrogate consent from a LAR and, if appropriate, a plan to periodically evaluate capacity and re-obtain consent if possible.

Informed Consent

Obtaining legally effective informed consent before involving human subjects in research is one of the central ethical principles described in the Belmont Report and provided for by federal regulations governing research.

As discussed previously, the informed consent process involves three key features: (1) providing the prospective subject the information needed to make an informed decision (in language understandable to him or her); (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether to participate in the research.

Among other requirements, for consent to be legally effective, the potential subject or their LAR must have the necessary decision-making capacity to make a rational and meaningful choice about whether to participate (or continue participating) in a study.

IRB Review

The IRB review process will include at least one member, or a consultant, who is experienced with or otherwise knowledgeable about the population when the research involves greater than minimal risk, or the research is minimal risk but includes interactions with subjects, and the proposed subject population includes adults with impaired decision-making capacity.

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 adults with impaired decision-making capacity, the IRB should consider whether any components of the research involve risks that are greater for participants with diminished capacity. For example, whether subjects 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 to the research, the IRB will consider the following in 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 periodic re-evaluation of capacity and/or periodic re-consent should be required.
- Whether a research subject advocate or consent monitor should be required, for some or all subjects.

In general, the IRB will only approve research involving subjects unable to provide consent or with impaired decision-making capacity when the aims of the research cannot reasonably be achieved without inclusion of the population, and there are appropriate provisions to: (1) evaluate capacity, (2) obtain consent (and assent if possible), and (3) otherwise protect subjects.

Research Involving Students, Residents or Employees

Students, residents and employees are potentially a vulnerable population due to perceived undue influences especially if the investigator(s) is their supervisor, or instructor, or someone who might be able to influence their future. The potential undue influence should be minimized by additional safeguards included in the protocol to protect the rights and welfare of these subjects. Some measures that could be taken to minimizing the potential for them to experience undue influences are:

- Recruitment should not be conducted in ways that students, residents and employees may reasonably perceive to be coercive.
- Ensure that students, residents and employees understand that they may choose not to participate in the research.
- If incentives for participation are offered, the incentive should not be so large to significantly increase an overall grade.
- Provide an equal alternative to participation, which should be comparable in terms of effort, time commitment of any incentives.
- Outline procedures in the research protocol to ensure that students or residents will not be subject to undue influences or coercion and to ensure that each student's or resident's privacy will be respected.
- The use of a neutral third party, sometime known as an "Honest Broker".
- Conduct the research procedures out of sight of other employees whenever possible. This avoids the employee being identified as a research participant to their superiors and co-workers.
- Ensure that steps are taken to avoid informing supervisors whenever possible of employees who decline to participate.

An "honest broker" is a neutral third party who is not part of the research team. This person acts on the behalf of the researcher or institution to provide information in such a manner whereby it would not be reasonably possible for the investigators or others to identify the student, resident, or employee directly or indirectly. The honest broker

collects and collates pertinent information from the protocol measurements, removes identifiers, and releases only coded information to the researcher. An honest broker may not provide researchers with the code or any other means to re-identify participants.

Researchers Recruiting from Their Own Courses

One circumstance that may raise special ethical concerns involves researchers recruiting students from courses that they are teaching. The primary issue with gathering data from one's own course is the potential for perceived coercion.

Potential for Coercion

Faculty have inherent power over students or residents (eg, performance evaluation or grades). Because of this power relationship, it is likely that some will feel pressure. It may not be truly voluntary because of the desire on the part of the students or residents to appear cooperative, or highly motivated, or because participation in research is a course requirement.

There are cases in which the research cannot be feasibly completed without recruiting students or residents from a course. If the project has a reasonable chance of yielding benefits, and the only feasible way to complete the study is to recruit in the faculty's course, the research may be permissible if the researcher is able to sufficiently reduce the potential for students to feel pressured to participate.

Reducing the Potential for Students to Experience Coercion

In the instances in which a Faculty member(s) recruits from one's own class, researchers are expected to minimize the potential for students to feel pressured to participate. There are various strategies for minimizing the potential pressure to participate. One way that researchers can reduce the potential for perceived coercion is to design the study so that the faculty is blinded to the identity of the participants. If a researcher designs a study this way, several points are crucial:

- Before being asked to participate, potential participants should be informed that the instructor will not know who did and who did not participate.
- The research should be designed so that the faculty cannot infer who participated through indirect means.
- Include an "opt-out" statement allowing the student to decline to participate in the research portion if the data is required for curriculum purposes.
- Incorporate an honest broker into the study design.

In summary, due to the potential for undue influence, researchers generally should avoid recruiting participants from their own classes. If recruiting from their own class is the only feasible way to do a study, researchers are expected to design the research in such a way that the potential for students to feel pressured is minimized. When employees are the participants, ensure that data given to the employer is either in the

aggregate or is stripped of identifiers so that the employee participant's identity is protected.

Section 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 institutional policy or a 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 at, under the auspices of, or using the services or resources of the medical school.

Definitions

- **Biologic:** Biological products include a wide range of products such as vaccines, blood and blood components, allergens, 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.
- **Clinical Investigation:** Clinical investigation means any experiment that involves a test article and on or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 506(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies. [21 CFR 50.3(c)]
- **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 sufficient time to obtain IRB approval. [[21 CFR 56.102](#) (d)]

- **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 not more than 8,000 individuals in the United States per year.
- **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 for a new indication or use.
- **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.
- **IND:** IND means an investigational new drug application in accordance with [21 CFR Part 312](#).
- **IDE:** IDE means 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.
 - 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.
 - 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.
 - Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. [[21 CFR 812.3\(m\)](#)]

FDA Exemptions

The following categories of clinical investigations are exempt from the requirements of FDA regulations for IRB review:

- Emergency use of a test article, provided that such emergency use is reported to the IRB within **five (5) business days**. Any subsequent use of the test article at the institution is subject to IRB review. [[21 CFR §56.104\(c\)](#)]

- Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [[21 CFR §56.104\(d\)](#)]

Procedures

At initial submission, the investigator must indicate on the electronic *application form* whether the research involves a test article and is a clinical investigation involving human subjects. The investigator may use the IDE/IND Decision help link to assist in making this determination.

During the pre-review process, HRPP/IRB staff will assess whether FDA regulations are applicable using the IDE/IND Decision Worksheet. If FDA regulations apply and the research is not exempt, HRPP/IRB staff will notify reviewers that the study is FDA-regulated.

If the study involves investigational drugs and is industry sponsored and ICH-GCP E6 compliance is required by the sponsor, the investigator will indicate on the *application form* that ICH-GCP E6 compliance is required and provide an affirmation of compliance. The medical school follows ICH-GCP E6 to the extent it is consistent with FDA regulations. If the study involves investigational drugs and is industry sponsored and the PI has not indicated ICH-GCP E6 compliance, HRPP/IRB staff reviews the study to determine if ICH-GCP E6 applies and obtain investigator affirmation of compliance, if needed.

Investigator Responsibilities

The investigator holds additional responsibilities when conducting a clinical investigation subject to FDA regulations. These responsibilities include, but are not limited to, the following:

- The investigator is responsible for indicating on the IRB application that the proposed research is FDA-regulated and for providing relevant information regarding the test article.
- 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 FDA or IRB.
- 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 (eg, 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. A separate list should be maintained 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 about the test articles being used for investigational purposes and ensuring that the requirements relating to obtaining informed consent are met.
 - Providing or arranging for 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 (eg, when the investigator is unavailable, or when specialized care is needed).
 - Adhering to the protocol/investigational plan so that study subjects are not exposed to unreasonable risks.
 - 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 brochure, 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 retained 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, institutional 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.
- For research reviewed by the medical school IRB, 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 include storage, security, dispensing,

administration, return, disposition, and records of accountability. Such details will be provided in the IRB submission and reviewed by the IRB for acceptability.

- The investigator may delegate writing, as part of the IRB submission, the responsibility detailed in above bullet point to the Pharmacy Service.
- Investigational drugs and devices must be labeled in accordance with federal and state standards.
- All devices received for a study must be stored in a locked environment under secure control with limited access. When applicable, 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 clinical investigation 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, HRPP/IRB staff, FDA, accrediting bodies, and any other agencies or individuals entitled to inspect such records under regulation, institutional policy, or contractual agreement.

Dietary Supplements

Research involving dietary supplements may or may not fall under FDA regulations. Under the Dietary Supplement Health and Education Act (DSHEA) of 1994, a dietary supplement is not considered a drug and is not subject to the premarket approval requirements for drugs if the intended use for which it is marketed is only to affect the structure or any function of the body (ie, not intended to be used for a therapeutic purpose). Whether a study falls under FDA oversight is determined by the intent of the clinical investigation. If the clinical investigation is intended only to evaluate the dietary supplement's effect on the structure or function of the body, FDA research regulations do not apply. However, if the study is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, then FDA regulations do apply. Studies involving the ingestion of dietary supplements that are not subject to FDA oversight are still research, and therefore must be reviewed by the IRB.

Similarly, whether an IND is needed for a study evaluating a dietary supplement is determined by the intent of the study. If the study is intended only to evaluate the dietary supplement's effect on the structure or function of the body, an IND is not required. However, if the study is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required under part 312.

As with any research involving a test article, the investigator must supply the IRB with sufficient information to determine that the criteria for approval are satisfied and to determine or verify whether or not the research requires an IND. Applications should provide detail consistent with that expected on a drug protocol/research plan and

consistent with the level of risk associated or anticipated with the research. At a minimum, the protocol/research plan should provide the following information regarding the supplement: Name, Manufacturer, Formulation, Dosage, Method/Route of Administration, Mechanism of Action, Known Drug Interactions, Risk Profile, IND number (or justification for why an IND is unnecessary), documentation of approval for use in humans, documentation or certification of Quality or Purity. As with drugs and devices there should be an accountability plan for the product describing where and how the product will be stored, how it will be dispensed, how usage is tracked, and how it will be disposed of or returned. If the study entails greater than minimal risk, a plan for Data and Safety Monitoring must be included.

Clinical Investigations of Drugs and Devices

IND/IDE Requirements

For studies submitted to medical school IRB evaluating the safety or effectiveness of medical devices or experiments using drugs, biologics, dietary supplements, and other compounds that may be considered a drug or device under FDA regulations, the investigator must indicate on the *Initial Study Review Form* whether or not an IDE or IND is in place, and, if not, the basis for why an IDE or IND is not needed. Complete *Supplement Form H, Research Involving Drugs or Biologics*, for studies of drugs and biologics. Complete *Supplement Form I, Research Involving Medical Devices* for medical device studies.

Documentation must be provided by the sponsor or the sponsor-investigator. Documentation of the IND/IDE could be any of the following:

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

For investigational devices, the study may be exempt from IDE requirements (IDE-exempt) 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 study as IDE-exempt or NSR, then the investigator should include documentation with the submission providing the basis for exempt or NSR categorization for the IRB's consideration. If the FDA has determined that the study is IDE-exempt or NSR, documentation of that determination must be provided.

The IRB will review the application and, based upon the documentation provided, determine: (1) that there is an approved IND/IDE in place; (2) that the FDA has determined that an IND is not required or that a device study is exempt or NSR; or, (3) if neither of the above, whether or not an IND is necessary, or that a device study is exempt or NSR, using the criteria below.

The IRB cannot grant approval to the research until the IND/IDE status is determined, and, if necessary, an approved IND or IDE is in place.

IND Exemptions

For drugs, an IND is not necessary if the research falls in one of the following seven (7) categories ([FDA Guidance](#)):

- **Category One:** [21 CFR 321.2\(b\)\(1\)](#) The drug being used in the research is lawfully marketed in the United States and all of the following conditions are met:
 - 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.
 - In the case of a prescription drug, the research is 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 and informed consent [21 CFR parts [56](#) and [50](#), respectively].
 - The research is conducted in compliance with the requirements of [21 CFR 312.7](#) (ie, the research is not intended to promote or commercialize the drug product).
 - The research does not intend to invoke FDA regulations for planned emergency research [[21 CFR 50.24](#)].
- **Category Two:** [21 CFR 312.2\(b\)\(2\)](#) The research involves an *in vitro* diagnostic biological product (blood grouping serum, reagent red blood cells, or anti-human globulin) if both the following conditions are met:
 - The product is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and
 - The product is shipped in compliance with 21 CFR 321.160.
- **Category Three:** [21 CFR 320.31\(b\)and\(d\)](#) The research involves Bioavailability or Bioequivalence (BA/BE) studies if all of the following conditions are met:
 - The drug product does not contain a new chemical entity [[21 CFR 314.108](#)], is not radioactively labeled, and is not cytotoxic.
 - The dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product.
 - The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts [56](#) and [50](#), respectively].
 - The sponsor meets the requirements for retention of test article samples [[21 CFR 320.31\(d\)\(1\)](#)] and safety reporting [[21 CFR 320.31\(d\)\(3\)](#)].
- **Category Four:** [21 CFR 361.1](#) The research involves using a radioactive drug or biological product if all of the following conditions are met:

- It involves basic research not intended for immediate therapeutic, diagnostic, or similar purposes, or otherwise to determine the safety and efficacy of the product.
- The use in humans is approved by a Radioactive Drug Research Committee (RDRC) that is composed and approved by the FDA.
- The dose to be administered is known not to cause any clinically detectable pharmacological effect in humans.
- The total amount of radiation to be administered as part of the study is the smallest radiation dose practical to perform the study without jeopardizing the benefits of the study and is within specified limits.
- **Category Five: ([FDA Guidance](#))** FDA practices enforcement discretion for research using cold isotopes of unapproved drugs if all of the following conditions are met:
 - The research is intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a drug labeled with a cold isotope or regarding human physiology, pathophysiology, or biochemistry.
 - The research is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject.
 - The dose to be administered is known not to cause any clinically detectable pharmacologic effect in humans based on clinical data from published literature or other valid human studies.
 - The quality of the cold isotope meets relevant quality standards.
 - The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts [56](#) and [50](#), respectively].
- **Category Six: ([FDA Guidance](#))** The research involves studies of marketed drugs to treat cancers if all of the following conditions are met:
 - The study is not intended to support FDA approval of a new indication or a significant change in the product labeling.
 - The study is not intended to support a significant change in the advertising for the product.
 - Based on the scientific literature and generally known clinical experience, there is no significant increase in the risk associated with the used of the drug product.
 - The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts [56](#) and [50](#), respectively].
 - The studies will not be used to promote unapproved indications, in compliance with [21 CFR 312.7](#).
- **Category Seven:** A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.

IDE Exemptions

For clinical investigations of devices, an IDE ([21 CFR 812.2\(c\)](#)) is not necessary if:

- 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).
- The research involves a 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.
 - Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- The research involves a 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.
- 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 is labeled in accordance with [21 CFR 812.5\(c\)](#).
- The research involves 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.

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.
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

If the FDA has already determined a study to be SR or NSR, documentation evidencing such should be provided to the IRB as described in *Section 13, IND/IDE Requirements*. The FDA's determination is final and the IRB does not have to make the device risk determination.

Unless the FDA has already made a device risk determination for the study, the IRB will review studies that the sponsor or investigator have put forth as NSR at a convened meeting to determine if the device represents SR or NSR.

The sponsor or 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 (eg, reports of prior investigations of the device).

The IRB will review the information provided by the sponsor and investigator including, but not limited to: the sponsor's or investigator's NSR assessment, the description of the device, reports of prior investigations of the device (if applicable), the proposed investigational plan, and subject selection criteria.

The NSR/SR determination made by the IRB will be based on the proposed use of the device in the investigation, not on the device alone. The IRB will consider the nature of any harms that may result from use of the device, including potential harms from additional procedures subjects would need to undergo as part of the investigation (eg, procedures for inserting, implanting, or deploying the device). 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, and sponsor, if applicable, 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 the FDA has notified a sponsor under 812.20(a) that approval of an application is required: Labels the device in accordance with [812.5](#).

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):

- Obtains IRB approval of the investigation after presenting the reviewing IRB with an explanation of why the device is not a SR 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), and (7).
- Complies with the prohibitions in [812.7](#) against promotion and other practices.

When the FDA or IRB determines that a study is SR, the IRB may approve the study, but the study cannot begin until an IDE is obtained.

Humanitarian Use Devices

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 not more than 8,000 individuals in the United States per year [[21 CFR 814.3](#)(n)]. Federal law requires that IRBs approve the use of an HUD at the medical school or affiliated institutions. 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.

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 the 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 taking into account 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 the approval of an HDE from the FDA.

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 an HUD is provided only to facilities having an IRB constituted and acting in accordance with FDA regulations governing IRBs ([21 CFR Part 56](#)), including continuing review of use of the device.

When an HUD is used in a clinical investigation (ie, 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 SR device.

Procedures

The relevant requirements and procedures for investigators and for IRB review described elsewhere in the *Human Research Protection Program (HRPP) and Institutional Review Board (IRB) Handbook* apply to clinical investigations of HUDs. The policies and procedures in this section applies to diagnostic and treatment uses of HUDs (non-research use).

The qualified health care clinician seeking approval for diagnostic or treatment use of an HUD is responsible for obtaining IRB approval prior to use of the HUD at the medical school or affiliated institutions and for complying with the applicable regulations, including those for medical device reporting, institutional policies, and the requirements of the IRB.

Qualified health care clinicians seeking initial IRB approval for diagnostic or treatment use of an HUD for the indication(s) in the HUDs approved labeling should submit the following materials to the IRB:

- Application Form – Humanitarian Use Devices (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, and draft consent form if one is to be used.
- Other relevant materials (eg, training certificates) as identified in the Application Form.

The IRB reviews 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 reviews 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 medical school or affiliated institutions. The IRB evaluates 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 require the use of a consent form to document consent for the use of the HUD.

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 medical school or affiliated institutions.

Once use of the HUD is approved, the qualified health care clinician 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 with Exceptions* 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 qualified health care clinician is responsible for submitting reports to the FDA, the IRB, and the manufacturer/HDE Holder whenever an 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 an 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 qualified health care clinician 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 *Humanitarian Use Device Continuing Review (Non-Research Use)* form.
- 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.
- Any other new relevant information or materials.

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

Uses of HUDs

If an appropriately trained and licensed health care clinician in an emergency situation determines that IRB approval for the use of the HUD at the medical school or affiliated institutions cannot be obtained in time to prevent serious harm or death to a patient, an HUD may be used without prior IRB approval. The qualified health care clinician must, within **five (5) business days** after the emergency use of the device, provide written notification of the use to the IRB including the identification of the patient involved, date of use, and reason for use. [21 CFR 812.124]

If an HUD is approved for use in a the medical school or affiliated institutions, but an appropriately trained and licensed health care clinician 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 clinician 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 requirements, as appropriate given the specifics of the situation.

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 the use of investigational or unapproved/not cleared medical products (all referred to as “investigational” throughout this section) outside of a clinical trial, where the primary intent is treatment, rather than research. Because the 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 LAR and to monitor for safety.

Charging for expanded access use of investigational products is discussed in *Section 13, Charging Subjects for Investigational Products*.

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. Expanded access is sometimes referred to as compassionate use, or treatment use.

For the purpose of expanded access to investigational drugs, immediately life-threatening disease or condition means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. Serious disease or condition means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a

disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. [21 CFR 312.300(b)]

Expanded access may also apply to (1) situations when a drug has been withdrawn for safety reasons, but there exists a patient population for whom the benefits of the withdrawn drug continue to outweigh the risks; (2) use of a similar, but unapproved drug (eg, foreign-approved drug product) to provide treatment during a drug shortage; (3) use of an approved drug where availability is limited by a risk evaluation and mitigation strategy (REMS); and (4) use for other reasons. All are referred to as “investigational drugs” for the purposes of these SOPs.

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](#)].
- Widespread use 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 [(a)].
- Provide criteria for charging for an investigational drug in a clinical trial [(b)].

Set forth criteria for charging for an investigational drug under the following sections address expanded access for individual patients. Investigators seeking expanded access for intermediate-size populations or widespread use should consult with the HRPP/IRB office. Convened IRB review is generally required for intermediate or widespread expanded access unless the FDA has issued a waiver.

Physicians seeking access to investigational drugs under expanded access should work closely with the sponsor or manufacturer, the FDA, and the medical school HRPP, to determine the appropriate access mechanism and ensure that proper regulatory procedures are followed. The FDA provides information about the procedures and requirements for expanded access on a [website](#), including a link to [contact information](#).

Expanded Access for Individual Patients

Expanded access to investigational drugs may be sought under an “Access Protocol” or an “Access IND”. FDA generally encourages Access Protocols, which are managed and submitted by the sponsor of an existing IND, because it facilitates the review of safety and other information. However, Access INDs for the treatment of individual patients are also available and commonly used when: (1) a sponsor holding an existing IND declines to be the sponsor for the individual patient use (eg, because they prefer that the physician take on the role of sponsor-investigator); or (2) there is no existing IND.

Sponsor or Manufacturer Approval

Prior to submitting to the FDA or IRB, physicians seeking expanded access to an investigational drug should contact the sponsor (eg, for investigational drugs under a commercial IND) or manufacturer (eg, for approved drugs under a REMS) to: (1) ensure that the investigational drug can be obtained; (2) determine whether the patient may be treated under an existing IND study, sponsor-held Access Protocol, or if the physician should seek an Access IND; and (3) determine if the drug will be provided free or if there will be a charge. A Letter of Authorization (LOA) from the sponsor or manufacturer should be obtained.

FDA Approval

When a commercial sponsor agrees to provide access under an Access Protocol, the sponsor is responsible for managing and obtaining FDA approval and all other sponsor responsibilities. A licensed physician under whose immediate direction an investigational drug is administered or dispensed for expanded access is considered an “investigator” under FDA regulations and is responsible for all investigator responsibilities under [21 CFR 312](#), to the extent they are applicable to expanded access.

If the sponsor or manufacturer declines treatment of the patient under an existing IND study or Access Protocol but agrees to make the investigational drug available for the patient, physicians may apply to the FDA for an individual patient Access IND using Form *FDA 3926*, a streamlined IND application specifically designed for such requests. Form *FDA 3926*, and [related guidance](#), is available on a FDA [website](#). Form *FDA 3926* includes a section where an investigator can request approval from the FDA for alternative IRB review procedures; these alternative procedures enable review by the IRB Chair (or a Chair-designated IRB member) in lieu of review by the convened IRB. This alternative review procedure is referred to as a “concurrence review” in FDA guidance; however, the IRB Chair must review the same materials and make the same determinations as the convened board would. IRB Chair review can also be used for any post-approval reviews (eg, unanticipated problems, continuing review, closure, etc.).

When there is an emergency situation and insufficient time to submit a written application to the FDA prior to treatment, a request to FDA for emergency use may be made by telephone (or other rapid means). A written expanded access application must be submitted within 15 days of the FDA’s authorization. For more information on emergency use, see (*Emergency Use of Investigational Drugs and Devices*).

A physician who obtains an Access IND is considered a “sponsor-investigator” and is responsible for the responsibilities of both sponsors and investigators under [21 CFR 312](#), as applicable, including IND safety reports, annual reports, and maintenance of adequate drug accountability records.

IRB Review

Unless the conditions that permit an emergency use exemption (see *Emergency use Exemption from Prospective IRB Approval*) are satisfied, prospective IRB review and approval is required for all expanded access uses, including clinical patient use. This requires, among other things, that the IRB review the expanded access use at a convened meeting at which a majority of IRB members are present. IRB approval must be obtained prior to initiating treatment with the investigational drug. When the FDA has authorized the use of alternative IRB review procedures (which can be presumed when the request is made on Form *FDA 3926* unless the FDA specifically states that the request is denied), the review may be conducted by the IRB Chair (or designee). Otherwise, the review must be conducted by the convened IRB.

Physicians using investigational drugs under compassionate use should develop and submit an appropriate plan and schedule for treating and monitoring the patient, taking into consideration the nature of the drug and the needs of the patient. The plan should include monitoring to detect any possible problems arising from the use of the drug.

To request IRB approval for single patient expanded access, investigators should contact the IRB office and submit the following:

- A summary of the request and any associated documents for a single-patient expanded access use.
- A copy of the Letter of Authorization (LOA) from the Commercial Sponsor or Manufacturer or other documentation supporting sponsor/manufacturer approval.
- A copy of the information submitted to the FDA (and FDA approval, if available).
- A copy of the Investigator’s Brochure or similar documentation that provides information regarding the potential risks and benefits of the investigational drug.
- A copy of the plan for treating and monitoring the patient.
- A copy of the draft informed consent document.

The IRB may review the expanded access application prior to FDA approval being received but cannot finalize approval until documentation of FDA approval is provided. The IRB will provide the investigator with written documentation of its review.

The medical school will consider reliance upon an external IRB for expanded access when the IND is held by a commercial sponsor and an external IRB has approved the protocol and is willing to accept review and oversight of additional investigators/sites. Investigators should contact the HRPP/IRB office for consult with the assistant dean for Research Compliance for consideration of request.

Post-Approval Requirements

Investigators are responsible for complying with any sponsor or FDA reporting requirements. The post-approval requirements for research described throughout this manual apply, including, but not limited to, prospective IRB approval of any proposed modifications to the plan or materials approved by the IRB unless the change is necessary to eliminate apparent immediate hazard to the subject (in which case it must be promptly reported), reporting of unanticipated problems, noncompliance, complaints, and other reportable information, and for continuing review and study closure, as applicable. Additionally, copies of any [follow-up submissions](#) to the FDA related to the expanded access use must be submitted to the IRB within seven (7) business days of the date of submission to the FDA.

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 are circumstances under which a health care provider may use an unapproved device outside of a clinical study when it is not possible to enroll a patient in a clinical study and the 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
- Compassionate Use (or Single Patient/Small Group Access)
- Treatment Use

Investigators 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 medical school HRPP, to ensure that proper regulatory procedures are followed. FDA has made information about expanded access to medical devices available on a [website](#).

Compassionate Use of Investigational/Unapproved Medical Devices

The compassionate use provision under expanded access provides a mechanism for accessing investigational devices for an individual patient or small groups of patients when the treating physician believes the device may provide a diagnostic or treatment benefit. Compassionate use can be used for devices being studied in a clinical trial under an IDE for patients who do not qualify for inclusion in the trial, and for devices for which an IDE does not exist. The following criteria must be satisfied:

- The patient has a life-threatening or serious disease or condition.
- No generally acceptable alternative treatment for the condition exists.

The medical device company must agree to make the medical device available for the proposed compassionate use. FDA and IRB approval are required before the device may be used under the compassionate use provision.

FDA Approval

When there is an IDE for the device, the IDE sponsor submits an IDE supplement requesting approval for the compassionate use under [21 CFR 812.35\(a\)](#).

When there is not an IDE for the device, the physician or manufacturer submits the following information to the FDA:

- A description of the device (provided by the manufacturer).
- Authorization from the device manufacturer for the use.
- A description of the patient's condition and the circumstances necessitating treatment or diagnostics (when seeking small group access, the number of patients to be treated).
- A discussion of why alternative therapies/diagnostics are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition.
- The patient protection measures that will be followed, including:
 - A draft of the informed consent document that will be used;
 - Clearance from the institution as specified by their policies (see below);
 - Concurrence (approval) of the IRB Chair or Chair-designated IRB member (prior to FDA request when possible).
 - An independent assessment from an uninvolved physician.

When IRB Chair approval cannot be obtained in advance of the submission to the FDA, the request should indicate that approval from the IRB Chair will be obtained prior to use of the device. Proof of IRB Chair approval must be submitted with the follow-up report to the FDA after the patient is treated (or the diagnostic is used).

When the compassionate use is conducted under an IDE, a licensed provider who receives an investigational device is an “investigator” under FDA regulations and is responsible and accountable for all applicable investigator responsibilities under [21 CFR 812](#) (IDE regulations), [21 CFR 50](#) (Informed Consent), and [21 CFR 56](#) (IRB).

When the provider obtains an IDE for compassionate use, the provider is considered a “sponsor-investigator” and is responsible for the responsibilities of both sponsors and investigators under [21 CFR 812](#), as applicable, including medical device reports and progress reports.

IRB Review

Unless the conditions that permit an emergency use exemption are satisfied as outlined in (see *Emergency Use of Investigational Drugs and Devices* below). IRB approval must be obtained prior to initiating treatment with the investigational device. When the

request is for single-patient compassionate use, the review may be conducted by the IRB Chair (or designee). Otherwise, the review must be conducted by the convened IRB.

Physicians using medical devices under compassionate use should develop and submit an appropriate plan and schedule for treating and monitoring the patient, taking into consideration the nature of the device and the needs of the patient. The plan should include monitoring to detect any possible problems arising from the use of the device.

To request IRB approval for compassionate use, investigators should contact the IRB office and submit the following:

- Provide for IRB review a summary of the request and any associated documents to do a single-patient expanded access use.
- A copy of the information submitted to the FDA (and FDA approval, if available).
- A copy of the device brochure, Instructions for Use, or other similar documentation that provides information regarding the potential risks and benefits of the device.
- A copy of the plan for treating and monitoring the patient.
- A copy of the draft informed consent document.

The IRB may review the expanded access application prior to FDA approval being received but may condition approval upon receipt of FDA approval. The IRB will provide the investigator with written documentation of its review.

The medical school will consider reliance upon an external IRB for Compassionate Use protocols on a case-by-case basis when the IDE is held by a commercial sponsor and an external IRB has already approved the protocol and is willing to accept review and oversight of additional investigators/sites. Investigators should contact the HRPP/IRB office for consult with the assistant dean for Research Compliance for consideration of request.

Post-Approval Requirements

Investigators are responsible for complying with any sponsor or FDA reporting requirements. The post-approval requirements for research described throughout this manual apply, including, but not limited to, prospective IRB approval of any proposed modifications to the plan or materials approved by the IRB unless the change is necessary to eliminate apparent immediate hazard to the subject (in which case it must be promptly reported), reporting of unanticipated problems, noncompliance, complaints, and other reportable information, and for continuing review and study closure, as applicable. Additionally, a follow-up report to the FDA is required following a compassionate use by whomever submitted the original request to the FDA. The report should include summary information regarding patient outcome and any problems that occurred as a result of the device. A copy of the follow-up report to the FDA and any other post-approval submissions or reports to the FDA must be submitted to the IRB within seven (7) business days of the date of submission to the FDA.

Treatment Use of Investigational/Unapproved Devices

During the course of a clinical trial under an IDE, if the data suggest that the device under study is effective, the trial may be expanded to include additional patients with life-threatening or serious diseases under the Treatment Use provision for expanded access. “Treatment Use” also applies to the use of a device for diagnostic purposes under these same conditions. [[21 CFR 812.36](#)]

The following criteria must be satisfied for Treatment Use to apply:

- The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition.
- There is no comparable or satisfactory alternative device available to treat or diagnose the disease or condition in the intended patient population.
- The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or all clinical trials have been completed.
- The sponsor of the controlled clinical trial is pursuing marketing approval/clearance of the investigational device with due diligence.

The IDE sponsor is responsible for applying for a Treatment Use IDE.

A licensed provider who receives an investigational device for treatment use under a Treatment Use IDE is an “investigator” under FDA regulations and is responsible and accountable for all applicable investigator responsibilities under [21 CFR 812](#) (IDE regulations), [21 CFR 50](#) (Informed Consent), and [21 CFR 56](#) (IRB).

IRB Review:

IRB approval is required before the investigational device/diagnostic is used. To request IRB approval for treatment use access, investigators should contact the IRB office and submit the following:

- A summary of the request and any associated documents for a treatment use access use.
- A copy of the Letter of Authorization (LOA) from the Commercial Sponsor or Manufacturer or other documentation supporting sponsor/manufacturer approval.
- A copy of the information submitted to the FDA (and FDA approval, if available).
- A copy of the Investigator’s Brochure or similar documentation that provides information regarding the potential risks and benefits of the investigational device/diagnostic.
- A copy of the plan for treating and monitoring the patient.
- A copy of the draft informed consent document.

The IRB may review the expanded access application prior to the FDA approval being received but cannot finalize approval until documentation of FDA approval is provided. The IRB will provide the investigator with written documentation of its review.

The medical school will consider reliance upon an external IRB for Treatment Use IDE protocols on a case-by-case basis when an external IRB has already approved the protocol and is willing to accept review and oversight of additional investigators/sites. Investigators should contact the HRPP/IRB office to consult with the assistant dean for Research Compliance for consideration of request.

Post-Approval Requirements

Investigators are responsible for complying with any sponsor or FDA reporting requirements. The post-approval requirements for research described throughout this manual apply, including, but not limited to, prospective IRB approval of any proposed modifications to the plan or materials approved by the IRB unless the change is necessary to eliminate apparent immediate hazard to the subject (in which case it must be promptly reported), for reporting of unanticipated problems, noncompliance, complaints, and other reportable information, and for continuing review and study closure, as applicable. Additionally, the semi-annual (applicable until the marketing application is filed) or annual (applicable after the marketing application is filed) progress report from the sponsor must be submitted to the IRB within seven (7) business days of receipt.

Emergency Use of Investigational Drugs and Devices

FDA regulations permit the use of an investigational drug or device without IRB approval when an appropriately trained and licensed health care provider determines that IRB approval for the use of the drug or device cannot be obtained in time to prevent serious harm or death to a patient. The provider is expected to assess the potential for benefit from the use of the drug or device and to have substantial reason to believe that benefits will exist. The criteria and requirements for this Emergency Use Exemption are explained below.

Sponsor/Manufacturer approval must be obtained prior to initiating treatment with the drug or device.

For emergency use of drugs, FDA approval must be obtained prior to initiating treatment. For emergency use of devices, prior FDA approval is not required if the provider determines and documents that: (1) the patient has a life-threatening or serious disease or condition that needs immediate treatment; (2) no generally acceptable alternative treatment for the condition exists; and (3) because of the immediate need to use the device, there is no time to use existing procedures to obtain FDA approval for the use.

Providers invoking the emergency use exemption must comply with any applicable FDA follow-up requirements. Information regarding follow-up report requirements for investigational [drugs](#) and [devices](#) is available on the respective FDA websites.

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.

Emergency Use 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 (5) business 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 sufficient time to convene a meeting to review the issue. If in the review of the emergency use, it appears likely that the test article may be used again, the IRB may request that a study application is submitted which would cover future uses.

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 sufficient 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 (see *Emergency Exception from the Informed Consent Requirement*) below, 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 (5) business days when an emergency exemption is invoked via the submission of an *Emergency Use Report*. The IRB chair or their designee will review the report to verify that circumstances of the emergency exception conformed to FDA regulations. This must not be construed as IRB approval, 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 prior to the emergency use, the IRB Chair or designee will review the proposed use, and, if appropriate, 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\(c\)](#).

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

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 drug or device without informed consent when the investigator and an independent physician who is not otherwise participating in the clinical investigation (the emergency use) certify in writing all four (4) of the following conditions:

1. The subject is confronted by a life-threatening situation necessitating the use of the test article.
2. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
3. Time is not sufficient to obtain consent from the subject's LAR.
4. 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 (5) business 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 (5) business days when an emergency exception is invoked via the submission of an *Emergency Use Report* and documentation of the independent physician evaluation. The IRB Chair or designated IRB member will review the report to verify that circumstances of the emergency exception conformed to FDA regulations.

Waiver of Informed Consent for Planned Emergency Research

The medical school IRB follows FDA regulations, 21 CFR 50.24., and any applicable state requirements which permit waiver of informed consent requirements for emergency research when human subjects in need of emergency medical intervention cannot provide legally effective informed consent and their legally-authorized representatives are also unable or unavailable to give informed consent on their behalf.

See *Section 11, Obtaining Informed Consent from Research Subjects* for additional detail on Planned Emergency Research.

Charging Subjects for Investigational Products

FDA regulations do not prohibit charging subjects or their insurers for investigational products so long as those charges comply with specified criteria. FDA approval of such charges does not obviate the investigators and IRB's responsibility to minimize risks to subjects. To ensure that the risks and burdens associated with research are equitably distributed, and to ensure that subjects are properly informed and not unduly influenced to accept and otherwise unacceptable risk or cost in order to access a benefit. Any costs to subjects or insurers must be described in the IRB application and informed consent

document. The use of and any costs must also be approved by the institution where the HUD will be used prior to deployment.

Charging for Investigational Medical Devices and Radiological Health Products

IDE regulations allow sponsors to charge for an investigational device, however, the charge may not exceed the amount necessary to recover the costs of manufacture, research, development, and handling of the investigational device [[21 CFR 812.7\(b\)](#)]. Sponsors must justify the proposed charges for the device in the IDR application, state the amount to be charged, and explain why the charge does not constitute commercialization [[21 CFR 812.20\(b\)\(8\)](#)].

Charging for Investigational Drugs and Biologics

In 2009, FDA updated its rules at 21 CFR 312 regarding charging for Investigational Drugs under an IND. These rules:

- 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 for an expanded access for treatment use [[21 CFR 312.8\(c\)](#)].
- Establish criteria for determining what costs can be recovered when charging for an investigational drug [[21 CFR 312.8\(d\)](#)].

Additional information is available in FDA guidance: [Charging for Investigational Drugs Under an IND – Questions and Answers](#).

Section XIV: Other Reportable Information

When research is under the oversight of the medical school IRB, in addition to UAPs, noncompliance, and complaints, any change to the research implemented without IRB approval and any information that may impact the rights, safety, or welfare of subjects or inform the IRB's oversight of the research must be reported to the IRB within seven (7) business days of discovery using the *Interim/Event Reporting Form*, as applicable. Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in *Section 9, External IRB Review of Medical School Research*.

Other reportable information includes, but is not limited to, the following:

- Changes made to the research without prior IRB approval to eliminate apparent immediate hazards to the subject(s).
- Protocol Deviations - any variation from the IRB approved research plan that happens without prior review and approval of the IRB and isn't necessary to eliminate apparent immediate hazards to the subject(s).
- Monitoring, audit, and inspection reports in accordance with *Section 2, Audits and Inspections by Regulatory Agencies and Sponsors*, of this manual.
- Sponsor or coordinating center reports.
- Data Safety Monitoring reports, including reports from DSMBs, DMCs, and others.
- Enrollment or inclusion of vulnerable populations not previously approved by the IRB for the study (eg, prisoner, pregnant woman, neonate, child, adult with impaired decision-making capacity).
- When an existing subject becomes a member of a vulnerable population not previously approved by the IRB for inclusion in the study (eg, incarceration, pregnancy, or change in decision-making capacity of an already enrolled subject).
- Holds, suspensions, or terminations of a study, in part or in full, by an investigator, sponsor, or others.
- Changes that impact the ability of the PI to conduct or supervise the study, temporarily or permanently.
- Changes that impact the qualifications of investigators or research staff members such as actions taken by regulatory authorities, licensing boards, or credentialing committees.
- New information that may impact the rights, welfare, or willingness of subjects to continue in the research.

Review Procedures

- Upon receipt of the report, the IRB staff pre-reviews the submission and, if needed, contacts the investigator for corrections or additional information. If the information provided suggests that subjects may be at risk of harm without immediate intervention or that research misconduct may have occurred, the HRPP Director, IRB Chair, and, when appropriate, the IO and/or Research

Integrity Officer, will be notified so that they can take any necessary steps to ensure the safety of subjects or investigate the matter.

- The IRB Chair or designated reviewer receives and reviews the report and if the report may represent an UAP or noncompliance, reviews the report as described in *Section 15, Unanticipated Problems Involving Risks to Subjects or Section 16, Non-Compliance*. When circumstances warrant, the HRPP Director or IRB Manager may bypass this step and assign the report for convened board review.
- If the reviewer determines that the event or issue is not noncompliance or an UAP, they will review the event or issue, any proposed corrective and preventative action plans, and determine if any additional actions are needed to ensure the protection of human subjects. As warranted, the reviewer may refer the matter to the convened IRB for review. The results of the review will be documented and communicated to the investigator.

Section XV: Unanticipated Problems Involving Risks to Subjects or Others

Regulations require an organization to have written procedures for ensuring prompt reporting of “unanticipated problems involving risk to subjects or others” (also referred to as UPs, UAPs, and UPIRTSOs).

This section provides definitions and procedures for the reporting of UAPs to the medical school IRB. Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in *Section 9, External IRB Review of the Medical School Research*.

In conducting its review of protocol deviations, noncompliance, subject complaints, and other reportable events, the IRB will also consider whether the event or issue was caused by, contributed to, or otherwise related to an UAP.

Definitions

Unanticipated problems involving risk to participants or others:

Unanticipated problems involving risks to subjects or others (UAPs) refer to any incident, experience, outcome, or new information that:

- Is unexpected.
- Is at least possibly related to participation in the research.
- 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.

UAPs also encompass Unanticipated Adverse Device Effects, as defined below.

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.

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

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 or not 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.

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\(s\)](#)].

Procedures

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 for a given protocol, the medical school IRB does not accept reports of adverse events that are not UAPs.

Investigators must report the following events or issues to the IRB as soon as possible but within seven (7) business days after the investigator first learns of the event using the *Interim/Event Reporting Form*.

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

Examples of UAPs include:

- 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 (eg, tendon rupture, progressive multifocal leukoencephalopathy).
- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. 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 (eg, 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 an unanticipated problem 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.

- AEs involving direct harm to subjects enrolled by the local investigator which in the opinion of the investigator or sponsor, may represent an UAP;
- IND Safety Reports from sponsors that meet the criteria for an UAP. Such reports must be accompanied by an analysis from the sponsor explaining why the report represents an UAP and whether it has been reported to the FDA as such.
- Unanticipated adverse device effects (UADEs).
- Any other AE or safety finding (eg 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.
- Reports (including reports from DSMBs/DMCs) that indicate that risks are greater than previously known or that indicate that the research should be modified, suspended, or halted.
- Sponsor or lead investigator/coordinating center imposed suspension or termination of some or all research activities.
- An unanticipated event related to the research that exposes subjects to potential risk but that does not involve direct harm to subjects.
- A breach of confidentiality or loss of research data (eg, a laptop or thumb drive is lost or stolen).
- An unanticipated event related to the research that results in actual harm or exposes individuals other than the research subjects (eg, investigators, research assistants, students, the public, etc.) to potential risk.
- New information that indicates increased risk, new risk(s), or decrease to potential benefit from what was previously understood. Examples include:
 - An interim analysis or safety monitoring report indicates that the frequency or magnitude of harms or benefits may be different than initially presented to the IRB.
 - A report or publication that indicates the risks, benefits, or merit of the research are different from what was previously understood.

Review Procedures

- Upon receipt of the *Interim/Event Reporting Form*, the IRB staff pre-reviews the submission and, if needed, contacts the investigator for corrections or additional information.
- The IRB Chair or designated reviewer receives and reviews the report and makes an initial determination as to whether the event represents an UAP. If needed, the Chair or designee may request additional information from the investigator, sponsor, or others (including study committees, such as data monitoring committees, data safety monitoring boards, or steering committees).

- If the reviewer determines that the problem does not meet the definition of an UAP, they will determine whether any additional actions are necessary to ensure the protection of human subjects. As warranted, the reviewer may refer the matter to the convened IRB for review. The results of the review will be documented and communicated to the investigator.
- If the reviewer determines that the event may be an UAP, the report will be referred for review by the convened IRB. The convened IRB will determine whether the event is a UAP and whether any additional actions, such as those outlined below, are necessary to ensure the protection of human subjects. If needed, the IRB may request additional information from the investigator, sponsor, or others (including study committees, such as data monitoring committees, data safety monitoring boards, or steering committees). The results of the review will be recorded in the IRB minutes and communicated to the investigator.
- Based upon the circumstances, the IRB may take any of the following actions, or others, to ensure the protection of human subjects:
 - Requiring modifications to the protocol or plan or procedures for implantation of the research (Research Plan) as described in the application and other materials submitted to the IRB.
 - Revising the continuing review timetable.
 - Modifying the consent process.
 - Modifying the consent document.
 - Providing additional information to current participants (eg, whenever the information may relate to the subject's rights, welfare, or willingness to continue participation).
 - Providing additional information to past participants.
 - Requiring additional training of the investigator and/or study staff.
 - Requiring that current subjects re-consent to participation.
 - Monitoring the research.
 - Monitoring consent.
 - Reporting or referral to appropriate parties (eg, assistant dean for Research Compliance, associate dean of Research).
 - Suspending IRB approval.
 - Terminating IRB approval.
 - Other actions as appropriate given the specific circumstances.

When the IRB determines that an event is an UAP, the IRB staff will follow the procedures for reporting to regulatory agencies, sponsors, and institutional officials in *Section 15, Reporting*. When appropriate, a preliminary report may be submitted while more information is obtained to inform the determination or actions.

Section XVI: Non-Compliance

This section provides definitions and procedures for the reporting and review of known or suspected noncompliance for research under the oversight of the medical school IRB. Research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in *Section 9, External IRB Review of Medical School Research*.

In conducting its review of protocol deviations, unanticipated problems, subject complaints, and other reportable events, the IRB will also consider whether the event or issue was caused by, contributed to, or otherwise related to noncompliance.

Definitions

- **Non-compliance:** Non-compliance is defined as failure to adhere to federal, state, or local regulations governing human subject research, institutional policies related to human subject research, or the requirements or determinations of the IRB. Non-compliance may be minor or sporadic or it may be serious or continuing.
- **Serious non-compliance:** Serious non-compliance is defined as 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, policies, or procedures may also constitute serious non-compliance.
- **Continuing non-compliance:** Continuing non-compliance is defined as a pattern of non-compliance that, in the judgment of the convened IRB, suggests a likelihood that instances of non-compliance will continue unless the IRB or organization intervenes.
- **Allegation of Non-Compliance:** Allegation of non-compliance is defined as an unproved assertion of non-compliance.
- **Finding of Non-Compliance:** Finding of non-compliance is defined as an allegation of non-compliance that is proven true or a report of non-compliance that is clearly true. For example, a finding on an audit of an unsigned consent document, or an admission of an investigator of that the protocol/research plan was willfully not followed, represent reports of non-compliance that would require no further action to determine their truth and would therefore represent findings of non-compliance. Once a finding of non-compliance is proven, it must be categorized as non-compliance, serious non-compliance, or continuing non-compliance.

Reporting

Investigators and research staff are required to report instances of possible non-compliance within seven (7) business days of discovery using the Report of New Information. The investigator is responsible for reporting any possible non-compliance by research staff to the IRB. However, any individual or employee may report observed or apparent instances of non-compliance to the medical school 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 institutional review of these reports.

If an individual, whether investigator, research staff, or other individual, is uncertain whether there is cause to report non-compliance, the individual may contact the HRPP Director, IRB manager or IRB chair directly to discuss the situation informally.

Reports of non-compliance must be submitted to the IRB within seven (7) business 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 by using the *Research Compliance Violation Report Form*.

Review of Allegations of Non-compliance

All allegations of non-compliance are reviewed by the IRB chair or designee, who reviews the report or allegation and may request additional information or a review/audit of the research in question.

When the IRB chair or designee determines that non-compliance did not occur because the event 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 is copied to the Institutional Official, associate dean for Research, and assistant dean for Research Compliance in cases where the Institutional Official and any other parties had been notified previously of the allegation or event

If in the judgment of the IRB chair or designee, the report or allegation does represent non-compliance, the non-compliance is processed according to *Section 16, 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, Study Suspension, Termination or Investigator Hold*, with subsequent review by the IRB.

The IRB chair or designee may determine that additional expertise or assistance is required to make these determinations and may request assistance from HRPP/IRB staff 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 IRB Chair or designee is responsible for assuring that minutes of the meetings are generated and kept to help support any determinations or findings made by the ad hoc committee.

Review of Findings of Non-compliance

Non-compliance that is Not Serious or Continuing

If the IRB Chair or designee determines that the non-compliance occurred, but the non-compliance does not meet definition of serious or continuing non-compliance, the determination is reported in writing to the investigator and, if applicable, the reporting party. The IRB chair reviews 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. In the event that additional actions may be warranted, the matter is referred to the convened IRB for review.

Serious or Continuing Non-compliance

If 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 IRB 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 is 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.
- Find that additional information is required to make a final determination. In this instance, the IRB will request additional information, and indicate whether such information will be reviewed by the full committee or a subcommittee. If by a subcommittee, a report is written by the subcommittee for review by the convened IRB for final determination.

Final Review

The IRB makes a final determination as to whether the non-compliance is serious or continuing. Upon a finding of serious or continuing non-compliance, possible actions by the IRB 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 assessment/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 (eg, 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.
- Terminate the study.

In cases where the IRB determines that the event of non-compliance also meets the definition of unanticipated problem involving risks to subjects or others, it is managed according to *Section 15, Unanticipated Problems Involving Risks to Subjects or Others*.

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 17, Reporting to Regulatory Agencies and Institutional Officials*.

Section XVII: Complaints

The phone number for the medical school Compliance Hotline is 269.337.6505.

The HRPP & IRB will be responsive and sensitive to the complaints or concerns expressed by subjects or others and will respond to all complaints or concerns in a confidential and timely manner. The PI and all other research team members are responsible for the safety and welfare of all subjects enrolled in their studies. When investigators or team members hear complaints or concerns from subjects, he or she will try to resolve them.

Investigators conducting research under the auspices of the medical school must report complaints to the medical school HRPP regardless of who serves as the IRB of record. Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in *Section 9, NIH Single IRB (sIRB) for Multi-Site Research*. Investigators conducting research under the oversight of the medical school IRB report complaints using the *Interim/Event Reporting Form*. Investigators are encouraged to contact the HRPP Director or IRB Manager when they are having difficulty resolving a complaint or concern, and whenever circumstances warrant (eg, immediate attention is needed).

When the HRPP or IRB office is the direct recipient of complaints or concerns, the staff will do the following:

- Document the complaint or allegation. When appropriate, the staff may request that the subject submit the complaint in writing.
- Reassure the subject that the HRPP/IRB will take all necessary measures to inquire into the circumstances and to address the issue.
- Provide written confirmation of receipt of the complaint to the subject, if the subject is willing to provide contact information.
- Convey the information to the IRB of record in a timely manner.
- When appropriate, contact the investigator for additional information or to assist with resolution.
- When appropriate, contact other resources (eg, Research Compliance, Patient Relations) to assist with information-gathering or resolution.

For research under the oversight of the medical school IRB, the IRB Chair or designee will consider the complaint or concern and take any reasonable steps necessary to investigate and/or resolve the issue, if appropriate, prior to review and consideration by the IRB. A report will be provided to the IRB at the next available meeting if the research is subject to convened IRB review, or provided to the designated expedited reviewer if the research is eligible for expedited review. When reviewing complaints, the IRB will consider whether the complaint was the result of, or related to, an UAP or noncompliance, and, if so, will follow the relevant procedures. The IRB Chair or designated expedited reviewer may refer any complaint for review by the convened IRB.

The IRB minutes, or reviewer comments for expedited reviews, will reflect the action(s) taken and, if necessary, notice to the appropriate officials and/or agencies.

The HRPP will maintain written copies of complaints and concerns and will document the investigation and resolution. The complainant will be notified promptly following resolution of the complaint or concern, when appropriate, and if contact information has been provided. If the HRPP or IRB receives a complaint, or identifies information while investigating a complaint, that is indicative of possible misconduct in research, the medical school's Research Integrity Officer will be notified immediately.

Within five (5) business days of receipt of the complaint, IRB staff generates a letter to acknowledge that the complaint has been received and is being investigated, if the person making the complaint provided contact information.

Section XVIII: Reporting to Regulatory Agencies & Institutional Officials

Federal regulations require prompt reporting to appropriate institutional officials and, as applicable, the federal department or agency (eg, OHRP, FDA), of (i) any unanticipated problems involving risks to subjects or others; (ii) any serious or continuing noncompliance with the applicable federal regulations or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval. When research is under the oversight of an external IRB, the terms of the agreement with that IRB will guide reporting.

Procedures

HRPP/IRB staff initiate these procedures as soon as the IRB takes any of the following actions:

- Determines that an event may be considered an unanticipated problem involving risks to participants or others.
- Determines that non-compliance was serious or continuing.
- Suspends or terminates approval of research.

The HRPP director is responsible for preparing reports and letters that include the following information:

- The nature of the event (unanticipated problem 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 sponsored program if applicable, in which the problem occurred.
- Name of the investigator on the project.
- Study number of the research project assigned by the IRB and the award 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 action.
- Actions the institution is taking or plans to take to address the problem (eg, revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.).
- 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, assistant dean for Research Compliance, associate dean for Research, and Institutional Official review the letter and make modifications as needed.
- The affiliated institution's designee reviews and makes comments if applicable.

- The IO is the signatory.

The HRPP Director or designee sends a copy of the report to:

- The IRB Chair.
- The IRB by including the letter in the next meeting agenda as an information item.
- The IO, associate dean for Research, and assistant dean for Research Compliance.
- Federal agencies, as follows:
 - OHRP, if the study is subject to DHHS regulations or subject to a DHHS FWA.
 - If the study is conducted or supported by a Common Rule agency other than DHHS, the report is sent to OHRP or the head of the federal agency, as required by the agency.
 - If the study is conducted or supported by a federal agency that has not adopted the Common Rule, and reporting is required, the report is sent to the party identified by the agency.
 - FDA, if the study is subject to FDA regulations.
 - Note: Reporting to a regulatory agency is not required if the event occurred at a site that was not subject to the direct oversight of the organization, and the agency has been notified of the event by another party (eg, sponsor).
- Sponsor, if the study is sponsored.
- Sponsored Programs Administration, if there is an award or the study is otherwise tracked by Sponsored Programs Administration.
- Investigator.
- The affiliated institution's designee, if applicable.
- Others as deemed appropriate by the IO.

The Institutional Official or designee is the signatory for all correspondence from the medical school.

The HRPP director ensures that all steps of this policy are completed within thirty (30) business days of the determination. For actions that are more serious, the HRPP director expedites reporting. If additional time is needed to gather facts, or determine corrective actions, a preliminary report will be submitted within 30 days, to be followed by a final report as described above.

Section XIX: Investigator Responsibilities

Principal Investigators (PIs) are ultimately responsible for the conduct of research however, they may delegate tasks to appropriately trained and qualified investigators and research staff. PIs must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibilities.

Investigators

The various roles of “Investigators” are differentiated based on their responsibilities in the conduct of research involving human participants.

Within the regulations, the term ‘investigator’ refers to individuals involved in the design, conduct, or reporting of the research. Such involvement may include one or more of the following:

- Designing the research.
- 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.
- Studying, interpreting, or analyzing identifiable private information or data for research purposes.

Principal Investigators (PI)

At the medical school, only individuals with a faculty appointment at the rank of assistant, associate, or full professor are eligible to serve as the PI. The medical school may establish more stringent qualifications for individuals to serve as the PI, regardless of a finding by the IRB, whether it is the medical school IRB or an external IRB. The associate dean for Research or the IRB (either the medical school IRB or an external IRB), may determine that an individual may not serve as PI for any given project based on factors such as expertise, training, experience, licensing, credentials, conflict of interest or commitment, or a history of non-compliance related to research or any medical school policy.

Students, residents, fellows, and others whose status is considered as “in-training” may not serve as a PI but may serve as a sub-investigator. The PI must ensure that the elements of the research protocol conducted in part by trainees has sound research design and that trainees are appropriately supervised at all times.

The IRB recognizes a single individual as the PI for each study. The PI has ultimate responsibility for the oversight of research activities.

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 sub-investigators.

Sub-Investigators

A sub-investigator is any investigator other than the PI who is involved in the conduct of a research study. Sub-investigators may be faculty appointed at any rank, including at the rank of instructors. Students may not serve as sub-investigators but may serve as research staff. Involvement of sub-investigators may include:

Responsibilities

In order to satisfy the requirements of the medical school under these policies and procedures, 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 protocol/research plan that is scientifically sound and minimizes risk to the subjects.
- Incorporate into the protocol/research plan steps to ensure the just, fair, and equitable recruitment and selection of subjects.
- When some or all of the subjects are likely to be vulnerable to coercion or undue influence (eg, children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons), include additional safeguards in the study to protect the rights and welfare of these subjects.
- Ensure that the protocol/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, and other support that subjects might require during or as a consequence of their participation in the research.
- Assure 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 Michigan state law (or the laws where the research is conducted), and that the policies are followed of the organizations or facilities where the procedures are performed.

- Assure that all study personnel are educated in the regulatory requirements regarding the conduct of research and the ethical principles upon which they are based.
- Assure 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. (Investigators and staff may not begin work on the research until there is IRB approval).
- Protect the rights, safety, and welfare of participants.
- Ensure that when protected health information is used, legally effective HIPAA authorization is obtained for each subject unless the Privacy Board or 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, any associated grant or contract, and, if 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 authorized representative (LAR), 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 unanticipated problems, deviations, complaints, non-compliance, suspensions, terminations, and any other reportable events to the IRB.
- Notify the IRB if information becomes available that indicates a change to the potential risks or benefits, merit, or feasibility 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 HRPP or IRB assistance when in doubt about whether proposed research requires IRB review.
- Retain records for the time period and in the manner described to and approved by the IRB and as required by applicable regulations, agreements, and medical school policies.

Additional investigator responsibilities, including specific responsibilities for investigators engaged in FDA-regulated research are described throughout this policy manual.

Investigator Records

Investigators or designee must maintain, at a minimum but not limited to, the following research records. If applicable, investigators must also comply with all sponsor and ICH-GCP E6 requirements.

- Study Records
 - Individual subject records or case histories.
 - Materials provided to or completed by subjects.
 - Documentation of the consent process (addressing who, what, when, and how), if applicable.
 - Signed consent forms and HIPAA authorizations, if applicable.
 - Adverse events.
 - Subject complaint reports.
 - Results of all research exams, procedures, and visits.
 - Test article records.
 - Records of payment or reimbursement.
 - Records related to the withdrawal of subjects, in part or in full.
- Regulatory Records
 - All versions of the IRB-approved protocol/research plan.
 - All versions of IRB-approved consents, parental permission, and assent forms, scripts, or information sheets, if applicable.
 - All versions of the HIPAA authorization form, if applicable.
 - All submissions to and correspondence (ie, approvals, reporting forms and responses) with the IRB.
 - All correspondence with the sponsor and others regarding the study.
 - Investigational product accountability records, if applicable.

Investigator records must be retained in accordance with all applicable regulatory, institutional, and sponsor or grantor requirements. All records must be maintained securely with limited access. Disposal of investigator records must be performed in such a manner that no identifying information can be linked to research data. When research is sponsored or grant-supported, consult the contract, grant terms, or other relevant agreements prior to destroying or transferring any records. If there are questions or allegations about the validity of the data or allegations have been completely resolved. Information regarding record retention requirements is available from the HRPP and Sponsored Programs Administration.

Investigator Concerns

As needed, the HRPP director, assistant dean for Research Compliance, associate dean for Research, and IRB chair are available to address investigators' questions, concerns, and suggestions.

Investigators who have concerns or suggestions regarding the medical school HRPP or IRB(s) that require greater attention should also convey them to the Institutional Official, or to associate dean for Research, assistant dean for Research Compliance, or Research Integrity Officer, who then forward these to the Institutional Official. The Institutional Official considers the issue, and when deemed necessary, seeks additional information and convenes the appropriate parties to formulate a response for the investigator or make necessary procedural or policy modifications, as warranted.

Anyone with concerns may also report anonymously via the Compliance Hotline is 269-337-6505. There will be no retaliation against those who report concerns in good faith.

In addition to these policies and procedures, which are made available on the medical school website for investigators and research staff, investigators are also made aware of the process for expressing their concerns via statement on approval letters, as well as the link on the medical school website for submitting concerns or complaints.

Section XX: Conflicts of Interest and Commitment in Research

It is medical school policy to preserve public trust in the integrity and quality of research by reducing actual or perceived conflicts of interest and commitment in the conduct of research.

Conflicts of interest and commitment in research can be broadly described as any interest that competes with an organization's or individual's obligation to protect the rights and welfare of research subjects, the integrity of a research study, or the credibility of the research program. Conflicts of interest and commitment can be financial or non-financial.

In the environment of research, openness and honesty are indicators of integrity and responsibility, which are characteristics that promote quality research and strengthen the research process. Therefore, conflicts of interest and commitment should be eliminated when possible and effectively managed and disclosed when they cannot be eliminated.

Disclosure of Researcher Conflicts of Interest and Commitment

Definitions

- **Clinical Investigator:** For purposes of [21 CFR 54](#), “clinical investigator” means a “listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects,” including the spouse and each dependent child of the investigator or subinvestigator. Clinical investigators are included in the definition even if they did not participate for the entire length of the study. If a clinical investigator did not participate in the entire study, information collected should be in the period of time he or she participated in the study and for one year following the end of his or her participation.
- **Covered clinical study:** [21 CFR 54](#) regulations define “covered clinical study” to mean “any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, not include phase I tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, treatment protocols, and parallel track protocols.” ([See 21 CFR 54.2](#)).
- **Applicant:** “Applicant” means the party who submits a marketing application to the FDA for approval of a drug, device, or biologic product or who submits a reclassification petition. The applicant is responsible for submitting the required certification and disclosure statements. ([See 21 CFR 54.2\(g\)](#)). Note that for the purposes of financial disclosure, the term “applicant” includes “submitter” and the term “application” includes “510(k) submission.”

- **Sponsor of covered clinical study:** For purposes of part 54, “sponsor of the covered clinical study” means “a party supporting a particular study at the time it was carried out.” ([See 21 CFR 54.2\(h\).](#)) A covered clinical study may have more than one sponsor for whom financial information will need to be collected. For example, if one party designed and conducted the covered clinical study, a second party provided funding, and a third party provided the test product, there would be three sponsors of the covered clinical study. However, if the third party in this example was reimbursed for a test product, it would not be considered a sponsor of the covered clinical study and the study would be considered to have two sponsors. Note also that the definition of “sponsor” for purposes of part 54 is different from the definition of “sponsor” for the purposes of investigational new drug applications (INDs) and investigational device exemptions applications (IDEs) ([see 21 CFR 312.3\(b\)](#))

Pursuant to medical school policy GENo4, *Conflicts of Interest and Commitment*, which serves as the IRB research conflict of interest policy, the medical school IRB collaborates with the Research Integrity Officer to ensure that conflicts of investigators and research staff are identified and managed before the IRB completes its review of any research application. For WMed studies, each study team member listed on the IRB application is required to complete a *Project/Research Conflict of Interest Form* in the electronic database before the application can be submitted for IRB review. For covered clinical studies, the clinical investigators (PI and subinvestigators) listed on the Statement of Investigator, Form *FDA 1572*, are required to complete a Project/Research Conflict of Interest Form in the electronic database before the application can be submitted to the designated IRB for review. If a disclosure is made on the COI completed by the clinical investigator(s)/investigator(s)/study team member(s), the electronic database alerts the Research Integrity Officer who ensures that such conflicts are identified and managed before the IRB application is submitted to the IRB for review of any research.

For IRB purposes, review of clinical investigator(s), investigator(s), and study team member(s) conflicts occurs at the time of new study submission, continuing review, with the addition of a new researcher, and whenever a researcher updates their medical school IRB conflicts disclosure indicating a new or changed interest.

For a covered clinical study, the clinical investigator(s) shall supply to the sponsor the completed Financial Disclosure Forms for the period of time that he or she participated in the study and for one year following the end of his or her participation.

For covered clinical studies, the applicant completes DHHS *CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS*, Form *FDA 3454*, and DHHS *DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS*, *FDA Form 3455*, and one year following the completion of the study.

For the medical school IRB, all study team members listed on the IRB application must complete the medical school *Conflict of Interest – Significant Financial Interests Disclosure* form whenever an interest is disclosed. The electronic database alerts the Research Integrity Officer whenever a submission requiring conflict review is received.

The Research Integrity Officer reviews the researcher(s) disclosures and notifies the researcher(s) and HRPP/IRB staff that either no researcher conflict was identified and/or that one or more researchers has an interest that requires further review. In the event a conflict that requires disclosure or management is identified, the Research Integrity Officer provides to the IRB in writing a summary of the conflict, and also the conflict management plan approved by the associate dean for research and the Research Integrity Officer. If the associate dean for research, associate dean for finance administration, and the Research Integrity Officer have not completed the review, the IRB defers the research study review or prohibits participation by the researcher with a potential conflict until the review process is completed and the results are made available to the IRB.

Evaluation of Conflicts of Interest and Commitment

The IRB reviews conflicts of interest and conflict management plans to determine:

- Whether the conflict affects the rights or welfare of research subjects.
- Whether the conflict might adversely affect the integrity or credibility of the research or the research program.
- Whether the conflict management plan (CMP) effectively protects research subjects and the integrity and credibility of the research and the research program.

In evaluating COIs and CMPs, among other factors, the IRB will consider:

- The support and financing of the research.
- The nature and extent of the conflict.
- The role and responsibilities of the conflicted individual in the design, conduct, and reporting of the research.
- The ability of the conflicted individual to influence the outcome of the research.

Management of Conflicts of Interest and Commitment

The convened IRB has final authority to determine whether the research, the conflicts of interest and commitment, and the conflict management plan, if any, allow the research to be approved. With regard to the conflict management plan issued by the medical school or another organization, the convened IRB may either affirm or add additional stipulations. The convened IRB can require additional measures to manage a conflict of interest so that the research may be approved. However, the IRB must adhere to, at a minimum, the conflict management plan approved by the medical school or a relying organization. If additional conflict management is required by the IRB, the convened IRB shall provide the management plan to the researcher and Research Integrity Officer. This management plan then constitutes the medical school conflict management plan for the research, and remains subject to additional stipulations, as appropriate, by either the Research Integrity Officer or IRB. If the significant financial interest or commitment changes, the Research Integrity Officer and IRB adjusts the management plan accordingly.

For example, in addition to the conflict management plan, the IRB may require:

- Disclosure of the conflict of interest to subjects through the consent process.
- Modification of the protocol/research plan or safety monitoring plan.
- Monitoring of research by a third party.
- Disqualification of the conflicted party from participation in all or a portion of the research.
- Appointment of a non-conflicted PI.
- Divestiture of significant financial interests or conflicts of commitment.
- Severance of relationships that create actual or potential conflicts.

In the event the conflict cannot be effectively managed, the IRB may disapprove the research.

IRB Member Conflict of Interest (COI)

No IRB member or alternate may participate in the review of any research project in which the member has a COI or commitment, except to provide information as requested. It is the responsibility of each IRB member to disclose any COI or commitment related to a study submitted for review in a timely manner, and recuse himself/herself from both the discussion and vote by leaving the room.

IRB members and alternate members of the IRB complete *General Conflict of Interest Form* when first appointed and annually thereafter, or when there is a change in the conflict status to disclose. If there is a disclosure, these forms are reviewed by the Research Integrity Officer, who determines if a conflict of interest exists. IRB staff are notified when a conflict of interest exists and will not assign members or alternates to review studies for which the member or alternate has a conflict. IRB staff may consult with the IRB chair to clarify whether a specific study poses a member conflict.

IRB members, alternates, and consultants *may* be considered to have a conflicting interest requiring recusal when they, or a person whom they have a Personal Relationship with, have any of the following:

- Involvement in the design, conduct, and reporting of the research.
- Significant financial interests. Medical school policy GEN04, *Conflicts of Interest and Commitment*, defines significant financial interests related to research, including research being reviewed by the IRB.
- A reporting relationship with the Principal Investigator.
- 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 must ask IRB members at the beginning of each convened meeting if any members have a conflict of interest 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 concludes and the call disconnected for both the discussion and vote. If the IRB

requests, the conflicted member may remain or return in order to provide information or answer questions, but will leave or disconnect before final IRB deliberations and vote.

IRB members with a conflicting interest are excluded from being counted towards quorum during the review of the item for which they have a conflict. Recusals of members with conflicts of interest are recorded in the minutes.

Institutional Conflict of Interest

The medical school has established principles and procedures to ensure that research involving human subjects under the auspices of the medical school is conducted without untoward influence resulting from either medical school financial investments or holdings or the personal financial interests or holdings of key institutional leaders.

Endowment funds that financially support the medical school are independently held and managed by the Western Michigan University Foundation. The medical school does not control the investment strategies or holdings of the endowment funds.

Recruitment Incentives

Payment arrangements among sponsors, organizations, investigators, and those referring research participants present a conflict of interest and may place participants at risk of coercion or undue influence or cause inequitable selection. Payment in exchange for referrals of prospective study subjects (“finder’s fees”) is not permitted. Similarly, payments designed to accelerate recruitment that is tied to the rate or timing of study enrollment (“bonus payments”) also are not permitted. Bonus payments do not include payments for bona fide items or services.

Section XXI: Participant Outreach

The medical school is committed to ensuring that educational opportunities are offered to research participants, prospective research participants, and community members, which will enhance their understanding of human subjects research at the medical school and provide them the opportunity to provide input, seek information, and express concerns.

Outreach Resources and Educational Materials

HRPP dedicates a section of the website to research participants entitled “Participant Outreach Corner.” This website includes resources, such as Frequently Asked Questions (FAQs), a brochure designed and developed by the medical school (eg, Volunteering in Research), and a listing of relevant research-related links.

The website includes information regarding how to contact the medical school with any questions or concerns about specific research projects or research in general.

The website includes contact numbers and a link that allows members of the community to ask questions, express concerns, or provide feedback. Provision of contact information by the person is optional.

The medical school periodically provides presentations related to research to community organizations.

The medical school sponsors an annual Kalamazoo Community Medical and Health Sciences Research Day to which members of the public are invited.

Evaluation

On an annual basis, the medical school evaluates its outreach activities and makes changes as appropriate. In order to formally evaluate its outreach activities, the assistant dean for Research Compliance and HRPP director review:

- The specific community outreach activities being used.
- Whether or not these community outreach activities have an evaluative component (eg, evaluation instrument distributed to participants), and, if so whether the feedback was positive, negative, or neutral and if any suggestions were made that could be used to enhance future activities.
- The number of times the “Participant Outreach Corner” is visited.
- Feedback provided via the “Contact Us” mechanism on the “Participant Outreach Corner.”
- Feedback provided from other sources including but not limited to unaffiliated IRB members, investigators, research staff, faculty, residents/fellows, and students.

The results of the review will be used to establish both the adequacy of current outreach activities and any additional resources that may be needed to meet the needs of the research community regarding research participant outreach.

Section XXII: Health Insurance Portability and Accountability Act (HIPAA)

The *Health Insurance Portability and Accountability Act of 1996* (HIPAA) requires 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 Privacy Rule also affects the conduct and oversight of research.

The Privacy Rule ([45 CFR 160](#)) 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 if the research is subject to the Common Rule, FDA regulations, and/or state laws that provide additional protection for research involving certain categories of health information (such as information derived from HIV/AIDS testing, genetic testing, and mental health records). When research consent is not required by regulation or law (eg, for exempt research) or the requirement for research consent has been waived by an IRB, the requirements for authorization still apply unless an IRB or Privacy Board has determined that the criteria for a waiver of the authorization requirement are satisfied.

At the medical school, for exempt projects and other research that does not require IRB review, the IRB chair or designee may act on requests for waivers and alterations of the HIPAA Authorization requirement for research purposes.

Definitions

These definitions are adapted from [Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule](#), published by DHHS.

- **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.
- **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 that includes all of the required elements under the Privacy Rule.

- **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.
- **De-identified.** Data is considered de-identified under HIPAA when they do not identify an individual, and there is no reasonable basis to believe that the data can be used to identify an individual. The Privacy Rule defines two methods for de-identifying PHI: (1) when the PHI is stripped of all 18 HIPAA-defined identifying elements and the covered entity does not have actual knowledge that the information could be used alone or in combination with other information to identify an individual who is a subject of the information (Safe Harbor method); or (2) when an appropriate expert determines that the risk is very small that the information could be used, alone or in combination with other reasonably available information, by an anticipated recipient to identify an individual who is a subject of the information (Expert Determination method).
- **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, provision of access to, or divulging in any manner, of information outside the entity holding the information.
- **Genetic Information:** Genetic information means, with respect to an individual, information about: (i) The individual's genetic tests; (ii) The genetic tests of family members of the individual; (iii) The manifestation of a disease or disorder in family members of such individual; or iv) Any request for, or receipt of, genetic services, or participation in clinical research which includes genetic services, by the individual or any family member of the individual.
Genetic information concerning an individual or family member of an individual includes the genetic information of: (i) A fetus carried by the individual or family member who is a pregnant woman; and (ii) Any embryo legally held by an individual or family member utilizing an assisted reproductive technology. Genetic information excludes information about the sex or age of any individual.
- **Genetic services:** A genetic test; genetic counseling (including obtaining, interpreting, or assessing genetic information); or genetic education.
- **Genetic test:** Means an analysis of human DNA, RNA, chromosomes, proteins, or metabolites, if the analysis detects genotypes, mutations, or chromosomal

changes. Genetic test does not include an analysis of proteins or metabolites that is directly related to a manifested disease, disorder, or pathological condition.

- **Health Information:** Health Information means any information, including genetic 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; the provision of health care to an individual; or the past, present, or future payment for 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 data sets that exclude 16 categories of direct identifiers that are specified in the Privacy Rule. Limited Data Sets 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, only if the covered entity obtains satisfactory assurances in the form of a Data Use Agreement. Limited Data Sets are not de-identified information under the Privacy Rule.
- **Minimum Necessary:** The least PHI 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 PHI 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 protocol/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 or commitment.

- **Protected Health Information:** Protected Health Information (PHI) means individually identifiable health information that is 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 (FERPA), as amended, [20 U.S.C. 1232g](#); in records described at 20 U.S.C. 1232g(a)(4)(B)(iv); in employment records held by a covered entity in its role as employer; and regarding a person who has been deceased for more than 50 years.
- **Psychotherapy Notes:** Psychotherapy notes means notes recorded (in any medium) by a health care provider who is a mental health professional documenting or analyzing the contents of conversation during a private counseling session or a group, joint, or family counseling session and that are separated from the rest of the individual's medical record. Psychotherapy notes excludes medication prescription and monitoring, counseling session start and stop times, the modalities and frequencies of treatment furnished, results of clinical tests, and any summary of the following items: Diagnosis, functional status, the treatment plan, symptoms, prognosis, and progress to date.
- **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 covered 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, trainees, and other persons whose conduct, in the performance of work for a covered entity, is under the direct control of the covered entity, whether or not they are paid by the covered entity.

The Role of the IRB under the Privacy Rule

Under the Privacy Rule, IRBs have 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 the Common Rule and FDA regulations include protections to help ensure the privacy of subjects and the confidentiality of information (as applicable, to research activities that are regulated under those sets of regulations), the Privacy Rule supplements these protections where HIPAA is applicable, 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.

The medical school's internal IRB and, when mutually agreed, the external IRBs it relies upon, fulfill the functions of a Privacy Board for human subject research.

The Privacy Rule does not change the composition of an IRB. When acting upon a request to waive or alter the Authorization requirement, an IRB must follow the procedural requirements of the Common Rule and, if applicable, FDA regulations, including using either the normal review procedures (review by the convened IRB) or, as appropriate, 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. In order 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 conflict of interest or commitment 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 IRB review or approval. DHHS has 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 if the research study qualifies for expedited review under DHHS requirements. A modification to a previously approved protocol/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 considered to be 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 conflict of interest or commitment may not participate in an expedited review. If an IRB uses expedited review procedures, it must adopt methods for keeping all of 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 the alteration or waiver or authorization, in whole or in part, satisfies the three criteria in the Rule.
- 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.
- The required signature of the IRB chair or designee.

The medical school does not release PHI to investigators or other third parties 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 medical school standards, the medical school does not accept waivers or alterations approved by an external Privacy Board or IRB without review and approval of the requested disclosure by the assistant dean for Research Compliance.

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 for research to which the Common Rule, FDA regulations, and/or state laws regarding certain categories of health information apply (although certain research that is subject to the Privacy Rule may be exempt from Common Rule requirements). Just as a valid consent under Common Rule and FDA regulations must meet certain requirements, a valid authorization must be written in plain language and contain certain statements and core elements [[45 CFR 164.508.6\(c\)](#)].

Once executed, a signed copy must be provided to the individual providing authorization. Signed authorizations must be retained by the covered entity for six (6) 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. See Section Accounting of Disclosures for more information regarding an individual’s right to revoke, procedures, and exceptions.

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 laws 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 Common Rule or the FDA regulations, an IRB may impose further restrictions on the use or disclosure of research information to protect subjects.

Authorization core elements include:

- 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 (A statement that there is “no expiration date or event” or that authorization expires at the “end of the research study” or “unless and until revoked” by the individual are permissible for research, including authorizations for future research).
- Signature of the individual and date. If the individual’s LAR 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 (if such condition is permitted under the Privacy Rule), 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.

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 six (6) years from the date of its creation or the date it was last in effect, whichever is later. This is in addition to any other documentation requirements that might apply.

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 contemplated to be used or disclosed for that particular research project. A partial waiver of authorization occurs when the IRB or Privacy Board determines that a covered entity does not need authorization for all PHI uses and disclosures for research purposes for some defined group of research purposes, such as accessing PHI for research recruitment purposes. An IRB or Privacy Board may also approve a request that removes some, but not all, required elements or statements of an authorization (an alteration).

In order for an IRB or Privacy Board to waive or alter authorization, the Privacy Rule ([45 CFR 164.512\(i\)\(2\)\(ii\)](#)) requires the IRB or Privacy Board 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, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.
 - Adequate written assurances that the PHI will not be reused or disclosed to (or 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 to be used to obtain or release PHI in connection with a multi-site project.

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 protocol, or identifying potential subjects.

The covered entity must obtain from an investigator representations, either in writing or orally, that (1) the use or disclosure is requested solely to review PHI as necessary to prepare a protocol/research plan or for similar purposes preparatory to research, (2) that the investigator will not remove any PHI from the covered entity (eg, physically taken out of a facility, or downloaded and retained on the investigator's device) in the course of review, and (3) the PHI for which access is sought is necessary for the research purpose. [45 CFR 164.512(i)(1)(ii)]

At the medical school, this is accomplished by the investigator submitting a request for waiver of consent and authorization for screening purposes to the IRB.

Federal guidance has drawn a distinction between activities that may be undertaken by a researcher who is a member of the covered entity's workforce, eg, an employee of the covered entity, and a researcher who is not part of the covered entity's workforce. This guidance indicates that researchers may use PHI under the preparatory to research provision to *identify* potential study subjects, so long as no PHI is removed from the covered entity and the remaining two representations set forth above can be made. However, the guidance also indicates that researchers may not use PHI obtained pursuant to the "preparatory to research" provision to *contact* potential study subjects unless (i) the researcher is a member of the covered entity's workforce, or (ii) the

researcher enters into a BAA with the covered entity. Therefore, if the researcher is not a workforce member or business associate of the covered entity, then the researcher may contact potential subjects only pursuant to a partial waiver of authorization from the cognizant IRB or privacy board, or pursuant to the Authorization of the subject.

Research Using Decedent's Information

The HIPAA Privacy Rule protects the individually identifiable health information about a decedent for 50 years following the date of death of the individual. When a researcher seeks to use PHI from decedents for a research protocol, the researcher must (1) obtain authorization from the personal representative of the decedent (ie, the person under applicable law with authority to act on behalf of the decedent or the decedent's estate), (2) obtain a waiver of the requirement to obtain authorization from an IRB or Privacy Board, or (3) attest to the covered entity holding the PHI that the use or disclosure is solely for research on the PHI of decedents, that the PHI being sought is necessary for the research, and, if requested by the covered entity, provide documentation of the death of the individuals about whom information is being sought.

At the medical school, the attestation option referenced above is accomplished by the investigator submitting a Research Use of Decedents' PHI Attestation to the IRB Chair or HRPP director.

Storage and Use of PHI for Future Research

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. When researchers establish a database or repository containing PHI for the purposes of future research, or intend to maintain PHI following completion of a primary study for potential future research use, individual authorization for the storage of PHI for such future research must be sought unless the IRB has determined that the criteria for a waiver of the authorization requirement are satisfied. See *Section 22, Waiver or Alteration of the Authorization Requirement* of this policy manual for a discussion of waivers of authorization.

An authorization for use and/or disclosure of the stored PHI for future research must describe the future research uses and/or disclosures in sufficient detail to allow the potential subject to make an informed decision. The Rule does not require that an authorization describe each specific future study if the particular studies to be conducted are not yet determined. Instead, the authorization must adequately describe future purposes such that it would be reasonable for the subject to expect that their PHI could be used or disclosed for such research. When developing the description of potential future research uses, the investigator should be cognizant of uses of information/specimens that the community may consider particularly sensitive, such as genetics, mental health, studies of origin, and use of tissues that may have cultural significance, including whether any state laws may impose additional consent requirements with respect to any of these sensitive categories of information.

The authorization for future research can be a stand-alone document or may be incorporated into authorization for the establishment of the database or repository or for the primary study, 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 authorization for future research is combined with consent/authorization for another research activity (eg, a clinical trial), the consent/authorization must clearly differentiate between the research activities and allow the individual to opt-in to the future research. The use of 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 PHI for future research, and may be viewed as coercive.

It is important to note that securing a HIPAA authorization for unspecified future research activities may not, by itself, satisfy all applicable legal consent requirements. The Common Rule, FDA regulations, and state laws also must be considered, as applicable, in evaluating whether the information (including PHI) or identifiable biospecimens may be used for future research projects.

Corollary and Sub-studies

Consistent with the discussion above relating to future uses of research databases or repositories, the Privacy Rule mandates that subject participation in corollary or sub-studies not essential to the primary aims of the research, such as when PHI from an interventional clinical trial is used to create or to contribute to a central research repository, must be on a voluntary, “opt-in” basis. This is particularly important when the primary research offers a potential direct benefit to the research subject, such as treatment, that might compel the potential subject to agree to an ancillary study, even if the subject would prefer not to do so.

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 involves 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 (which is one form of “unconditioned activity”), it is acceptable to combine in a single document the authorization for a conditioned activity, such as a clinical trial, with authorization for other forms of 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-in to the unconditioned research activities.
- Sufficient 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.

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, because information that has been de-identified consistent with the Privacy Rule requirements is not considered individually identifiable health information. The “Safe Harbor” method permits a covered entity to de-identify data by removing all 18 data elements specified in the Privacy Rule that could be used to identify the individual or the individual’s relatives, employers, or household members. To satisfy the Safe Harbor method of de-identification, 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 Safe Harbor method, the identifiers of the individual or his or her relatives, employers, or household members 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 containing 20,000 or fewer people are changed to “000.”
- All elements of dates except the year for dates:
 - Directly related to an individual, including birth date, admission date, discharge date, and date of death.
 - All ages over 89 years and all elements of dates (including year) indicative of such ages; such ages and elements may be aggregated into a single category of age 90 years and 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 very small and 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 six (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 are considered de-identified under HIPAA may still be considered human subject data under the Common Rule and may require IRB review and approval. Removal of HIPAA-identifying elements does not necessarily mean that the identity of the subject is not or may not readily be ascertained by the investigator or associated with the information and thus be considered identifiable private information under the Common Rule. The reverse can also be true (and, in practice, is more likely to occur): information may not be “identifiable” under the Common Rule but, because it contains certain HIPAA identifiers, it is considered identifiable under HIPAA.

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, PHI 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 and license numbers.
- Vehicle identifiers and license plate numbers.
- Device identifiers and serial numbers.
- Web universal resource locators (URLs).
- Internet protocol (IP) addresses.
- Biometric identifiers.
- 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 DUA 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 or disclosure will be made other than as permitted by the DUA or as otherwise required by law, 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 or disclosure, that any agents, including subcontractors, to whom the recipient provides the LDS will agree to the same restrictions and conditions that apply to the recipient, and that the recipient will report any uses or disclosures of the information that they become aware of that are not in keeping with the terms of the DUA. Data Use Agreements for the purposes of research are available through the medical school. Contact the IRB to determine who must authorize a DUA for a specific project.

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.

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 (6) years prior to their request for an accounting. A covered entity must therefore keep records of such PHI disclosures for six (6) years.

It is important to understand the difference between a *use* and a *disclosure* of PHI. In general, the *use* of PHI means use of that information within the covered entity. A disclosure of PHI means “the release, transfer, provision of access to, or divulging in any manner of information outside of the entity holding the information.” 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 (eg, under public health authority, to regulatory agencies, to persons with FDA-related responsibilities) with limited exceptions (eg, law enforcement, national security).
- 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 himself or herself.
- As part of a limited data set under a data use agreement.

The Privacy Rule allows three (3) 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 50 or more individuals. Whichever 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 medical school policy HIM27, *Accounting of Disclosure of Protected Health Information*, for a detailed discussion on accounting of disclosures.

Section XXIII: Additional Protections for Information/Records under Michigan Law

HIV/AIDS and Other Serious Communicable Diseases (MCL 333.5131)

Michigan Public Health Code defines a “communicable disease” as “an illness due to a specific infectious agent or its toxic products that results from transmission of that infectious agent or its products from a reservoir to a susceptible host, directly as from an infected individual or animal, or indirectly through the agency of an intermediate plant or animal host, vector, or the inanimate environment.” MCL 333.5101(1)(b)

A “serious communicable disease or infection” is defined as “a communicable disease or infection that is designated as serious by the department [of Community Health pursuant to PA 368 of 1978]... Serious communicable disease or infection includes, but is not limited to, HIV infection, acquired immunodeficiency syndrome, sexually transmitted infection, and tuberculosis.” MCL 333.5101(1)(g).

Any report, record, or data related to HIV/AIDS, or other serious communicable disease, (i.e. testing, care, treatment, reporting, or research, and information related to partner notifications under MCL 333.5114a) are confidential and subject to the physician patient privilege. MCL 333.5131 (referring to MCL 600.2157). However, information on a positive test result MUST be disclosed to the local health department/ Michigan Department of Community Health pursuant to MCL 333.5114 and if assistance with partner notification is required, with the requirements of MCL 333.5114a.

In response to a court order and subpoena, HIV/AIDS information is limited only to cases in which (a) the court is petitioned for an order to disclose, or (b) the court issues an order to disclose. MCL 333.5131(3)(a) and (b).

If the court is petitioned for the records, the court must determine: (1) “that other ways of obtaining the information are not available or would not be effective”; and (2) “the public interest and need for the disclosure outweigh the potential for injury to the patient”. MCL 333.5131(3)(a).

If the court issues an order for disclosure, the order must: (1) limit “disclosure to those parts of the patient’s record that are determined by the court to be essential to fulfill the objective of the order”; (2) limit “disclosure to those individuals whose need for the information is the basis of the order”; and (3) include “such other measures as considered necessary by the court to limit the disclosure for the protection of the patient.” MCL 333.5131(3)(b).

Section XXIV: Information Security

The medical school has established standards and safeguards to protect patient information and to ensure compliance with federal and state information security regulations. There may be additional requirements of an external research site (eg, a hospital or other covered entity), and the sponsor, depending on the study and type of data (eg, PHI) being stored or transmitted. It is the responsibility of investigators and research staff to understand and comply with all required standards for information security.

Medical school information security standards and requirements must be met if the medical school IRB is the IRB of record, or if the research is conducted at, under the auspices of, or using the services or resources of the medical school.

The use of personal computers and devices (eg, laptops, desktops, tablets, smartphones, portable/USB drives) for storing research data is prohibited.

The use of computers and devices owned and managed by another entity (eg, Ascension Borgess, Bronson Methodist Hospital) for storing, even temporarily, or transmitting PHI or PII (Personally Identifiable Information) for research requires that medical school Information Technology verify the safeguards of the computer or device, and also that a “Business Associates Agreement” has been completed between WMed and the other entities.

Any potential or known breach of a device used in the research study, whether the device is owned by the medical school or not, or breach of study data must be immediately reported to the IRB, Information Technology (IT) and the medical school Research Integrity Officer, who is also part of corporate compliance, so that appropriate steps can be taken to assess the situation, protect the information, and comply with regulations and reporting requirements.

Lost or stolen devices that are used for research, whether owned by the medical school or not, must be reported immediately to Information Technology.

Research data that is shared or transmitted between devices or covered entities must be encrypted when transmitted.

Provisions for data security must be described in the study application to the IRB and updated as necessary. When information containing PHI or direct identifiers such as Social Security numbers, including sensitive data that may not be PHI, is to be transferred outside of medical school or computers or devices that have been approved by the IRB, the provisions for data security for the study are subject to further review and approval by medical school IT and the IRB.

Investigators and research staff working with or at Ascension Borgess, Bronson Methodist Hospital, and other covered entities are subject to the separate HIPAA privacy and security policies of the covered entity. Thus, a study may be subject to

policies of the medical school and also other covered entities. Regardless of the site or the owner of the computer or device, the storage and transmission of research data must meet medical school security standards and requirements at all times.

Medical School Information Technology staff provide extensive guidance to assist investigators and research staff with standards and safeguards to protect patient information and to ensure compliance with federal and state information security regulations.

NIH GRANTS

The NIH has specific requirements about ensuring data security when collecting identifiable research data, as described in [NIH Grants Policy Statement](#) as follows:

“Recipients of NIH funds are reminded of their vital responsibility to protect sensitive and confidential data as part of proper stewardship of federally funded research, and take all reasonable and appropriate actions to prevent the inadvertent disclosure, release or loss of sensitive personal information. NIH advises that personally identifiable, sensitive and confidential information about NIH-supported research or research participants not be housed on portable electronic devices. If portable electronic devices must be used, they should be encrypted to safeguard data and information. These devices include laptops, CDs, disc drives, flash drives, etc. Researchers and institutions also should limit access to personally identifiable information through proper access controls such as password protection and other means. Research data should be transmitted only when the security of the recipient's system is known and is satisfactory to the transmitter.”

Section XXV: Sponsored Projects

It is medical school's policy that any sponsored research conducted under the auspices of the medical school 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.

Definitions

Sponsor: Sponsor means the company, institution, individual donor, or organization responsible for the initiation, management or financing of a research study (see Departmental Policy and Procedure Number SPA09 for addition guidance).

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 (eg, the research proposal), including clinical trials involving investigational drugs, devices or biologics (see Organizational Policy and Procedure Number DEVO2 for additional guidance).

Responsibility

Sponsor grants, contracts, and other written agreements will be reviewed for the following by the Sponsored Projects Administration (SPA), utilizing Departmental Policy and Procedure Number SPA09, 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 medical school 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 the medical school.
- 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 of medical school 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.

Section XXVI: Special Topics

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, Michigan law mandates that certain persons who suspect child or elder abuse or neglect report this to Children's Protective Services, at 855-444-3911.

Medical school policy requires the solicitation of informed consent from all adult research subjects and, where appropriate, assent 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. See Act No. 238, Public Acts of 1975, as amended, being Sections 722.621 –722.638, Michigan Compiled Laws.

Mandated reporter guides may be found at:

<http://chanceatchildhood.msu.edu/pub.html>

Certificates of Confidentiality

Certificates of Confidentiality (CoC) protect research information by prohibiting certain disclosures and conditioning others upon consent from the subject. The protections and requirements of CoCs are outlined in [42 U.S.C. 241\(d\)](#) and [NIH policy](#) (when applicable), and summarized below.

CoC's 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](#).

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 other research and:

- Through which an individual is identified.
- 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.

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.
- To any other person not connected with the research, unless:
 - Required by Federal, State, or local laws (eg, adverse event reporting to the FDA, transmissible disease reporting required under State law), but excluding proceedings as described in “1” 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.
 - Made for the purposes of other scientific research that complies with applicable Federal regulations governing the protection of human subjects in research.

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 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.

NIH Policy

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 subjects 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 a very small risk that some combination of the biospecimen, a request for the biospecimen, and other available data sources could be used to deduce the identity of an individual.
- Research that involves the generation of individual level, human genomic data from biospecimens, or the use of such data, **regardless of whether the data is recorded in such a manner that human subjects can be identified or the identity of the human subjects can readily be ascertained.**
- 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.

NIH CoC Policy Determination

At the medical school, Sponsored Programs Administration (SPA) staff 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 doesn't apply, investigators (or Program or Project Directors, if applicable) are responsible for consulting with SPA 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.

Application Procedures for non-NIH Research

Any person engaged in human subjects 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](#).

IRB Review

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 Form* 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 medical school 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](#).

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 subjects' privacy and the confidentiality of subjects' information or specimens.

Case Reports Requiring IRB Review

Federal regulations at [45 CFR 46.102\(d\)](#) and [45 CFR 164.501](#) define research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. The medical school IRB does not consider the retrospective review and analysis of medical records for publication of a single case report or a case series involving data from two or three

patients to be research, and therefore such a report of 1-3 medical cases does not need to be submitted to the IRB. This is because reporting on such a small number of patients does not involve a systematic investigation, including defining a hypothesis that is then investigated prospectively and systematically, to develop or contribute to generalizable knowledge. The medical school regards such limited case report preparation as an educational activity, not research, and thus it is permissible under the Privacy Rule (HIPAA) as a part of health care operations ([45 CFR 164.501](#)) when the case report will be used internally, or in other learning environments, for educational purposes. When a larger series of patients is being evaluated for presentation or publication, the commonalities of those patients are typically explored and conclusions are drawn (ie, a systematic investigation). Such a systematic investigation more closely resembles prospectively designed clinical research and as such requires IRB review and approval. While drawing such a “bright line” to distinguish non-research from research may seem arbitrary, it serves as a guide to those who would prepare case reports. If a researcher ever does intend a report of 1-3 medical cases to develop or contribute to generalizable knowledge, or to otherwise constitute research, the report should be submitted to the IRB with a request for a determination whether the case report constitutes research using the procedures outlined in Section 5 (Human Subjects Research Determination). As always, anyone who is unsure whether a project requires IRB review should contact the IRB staff for assistance.

Regardless of the number of cases, providers must comply with all applicable laws, hospital, and medical school policies related to the use and release of health information. Permission from the patients who will be included in the report should be sought whenever possible, and journals may require such as a condition of publication. Providers should consult with the IRB staff for guidance on patient privacy and HIPAA.

A copy of this policy can be provided to journal editors or others who request confirmation of IRB review or waiver. If needed, the IRB office can provide a letter confirming that submission of single case reports or series of up to three cases is not required.

Databases, Registries, & Repositories

Databases, registries, and biospecimen repositories (all referred to as repositories throughout this section) are used to store data and/or biospecimens for future use.

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

(eg, through the addition of data fields not necessary for the core purpose of the repository) are considered research repositories.

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 approval is required for the research use of identifiable private information or identifiable human specimens from non-research repositories, and, regardless of identifiability, when specimens will be used to evaluate the safety or effectiveness of a medical device. Research under the auspices either of the medical school that includes the use of coded private information or specimens, must be submitted for IRB review or for a “Human Subjects Research Determination” (see Section 5).

Researchers submitting an application for research using data or specimens from non-research repositories must describe the source of the data/specimens and any terms, conditions, or restrictions on use. Data/specimens cannot be used for research if the person from whom the data/specimens originated objected to its use for research. Informed consent and HIPAA authorization (when applicable) must be obtained unless the IRB determines that the criteria for a waiver are satisfied.

Research Repositories

Research repositories involve three (3) distinct activities:

1. Collection of data/specimens.
2. Storage and management of data/specimens.
3. Distribution of data/specimens.

Collection

Informed consent and HIPAA authorization (when applicable) must be obtained unless the IRB determines that the criteria for a waiver are satisfied.

Informed Consent information should include:

- A clear description of
 - What data/specimens will be collected.
 - Where the data/specimens will be stored, who will have access, and how the data/specimens will be secured.
 - Whether the data/specimens will be identifiable, coded, or deidentified.
 - The types of research to be conducted and any limitations or restrictions on such.
 - The conditions under which data/specimens will be released to recipient-investigators.

- A statement regarding future withdrawal of the data from the study (ie, state whether subjects may, in the future, request that their data be destroyed or that all personal identifiers be removed from data and how to make such a request).
- When appropriate, the plan for management of incidental findings and sharing of results.

Storage and Management

Repositories should have written policies describing:

- The conditions under which data/specimens will be accepted (eg, inclusion criteria).
- Informed consent.
- IRB review.
- The sources of data/specimens.
- Whether data/specimens will be identifiable, coded, or de-identified, and, if coded, management of the linkage key.
- Physical and procedural mechanisms for the secure receipt, storage, and distribution of data/specimens.

Distribution

Repositories should have written policies describing:

- How data/specimens may be requested and by whom.
- Any requirements associated with a request for data/specimens (eg, verification of IRB approval or that approval is not required).
- Any limitations or restrictions on how data/specimens may be used.
- Whether released data/specimens will be identifiable, coded, or de-identified, and, if coded, any circumstances under which recipient investigators will access to or be provided with the key or other means to re-identify.
- Agreements with recipient investigators specifying the terms of use.

IRB Oversight

IRB approval is required for the establishment and operation of a research repository when the data/specimens that are accessed, received, stored, or distributed are identifiable. In general, private information or specimens are considered individually identifiable when investigators/repository operators or when the data/specimens can be linked to specific individuals directly or indirectly through coding systems knows the identities of the subjects.

Separate IRB approval is required for the use of data/specimens from a repository when the recipient investigator(s) know or may readily ascertain the identity of individual subjects, and, regardless of identifiability, when specimens will be used to evaluate the safety or effectiveness of a medical device. Research under the auspices either of the medical school that includes the use of coded private information or specimens, must be

submitted for IRB review or for a “*Human Subjects Determination*” (See Section 5). The only exception to this policy is when the coded private information or specimens are to be obtained from an IRB-approved repository and the rules of that repository forbid the release of identifiable information, the release of the key to the code or other means that would allow re-identification, or the release of sufficient information that investigators could readily ascertain the identity of subjects.

Research Involving or Generating Genetic Information

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 his/her genetic material?^{26.5}

Genomic Data Sharing

THIS SECTION IS UNDER DEVELOPMENT.

Community Based Research

Community based research (CBR) is research that is based in a community and conducted in collaboration with members of that community. *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.

Questions to be considered as CBR studies are developed, and issues that the IRB will consider when reviewing CBR, are as follows:

- How was the community involved or consulted in defining the need for the proposed research (ie, getting the community's agreement to conduct the research)?
- How was the community involved or consulted in generating the study research plan?
- How will the research procedures, including recruitment strategies and consent processes be assessed to ensure sensitivity and appropriateness to various communities (eg, literacy issues, language barriers, cultural sensitivities, etc.)?
- How will the community be involved in the conduct of the proposed research?
- How will community members who participate in the implementation of the research be trained and supervised?
- How have "power" relationships between investigators and community members on the research team, and in subject recruitment strategies been considered to minimize coercion and undue influence?
- What are the risks and benefits of the research for the community as a whole?
- How will boundaries between multiple roles (eg, investigator, counselor, peer) be maintained, ie, what happens when the investigator/research staff is the friend, peer, service provider, doctor, nurse, social worker, educator, funder, etc.)?
- How will the research outcomes be disseminated to the community?
- Is there a partnership agreement or memorandum of understanding to be signed by the investigator and community partners that describes how they will work together?

Department of Defense

Research conducted or supported by the Department of Defense (DoD Research) 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). Support of a study generally means the provision of funding, personnel (both military and civilian DoD employees), facilities, and any other resources.

DoD components (eg, Army, Navy) may have additional requirements. The PI and a representative of the HRPP or IRB should contact the Human Research Protection Official (HRPO) for the DoD Component conducting or supporting the research. In most cases, protocols will also require review, approval and oversight by the DoD component HRPP. DoD review must be conducted before research involving human subjects can begin. The HRPO provides administrative review and approval to confirm the research is compliant with federal and DoD requirements.

The medical school assures that DoD supported research complies with all relevant DoD human subjects protection requirements, including but not limited to:

- The Belmont Report.
- Title 32 Code of Federal Regulations Part 219 ([32 CFR 219](#)), Department of Defense Regulations, “Protection of Human Subjects” (DoD adoption of the “Common Rule”)
- Title 45 Code of Federal Regulations Part 46, ([45 CFR 46](#)) Department of Health and Human Services Regulations, “Protection of Human Subjects,” Subparts B, C, and D as made applicable by [DoD Directive \(DoDD\) 3216.02](#).
- Title [21 Code of Federal Regulations 50, 56, 312, and 812](#), Food and Drug Administration (FDA) Regulations.
- [DoDD 3216.02](#), “Protection of Human Subjects and Adherence to Ethical Standards in DoD-supported Research”.
- Title 10 United States Code Section 980 ([10 USC 980](#)), “Limitation on Use of Humans as Experimental Subjects”.
- [DoDD 3210.7](#), “Research Integrity and Misconduct”.
- [DoDD 6200.2](#), “Use of Investigational New Drugs in Force Health Protection”.

It is the responsibility of the PI to ensure compliance with DoD requirements for human subject protection. IRB staff, chairs and members will use these SOPs, DoDD 3216.02, and any relevant DoD component-specific instructions or materials to guide the IRB review and oversight of DoD research.

Key DoD Standards and Requirements

Minimal Risk

The definition of minimal risk based on the phrase “*ordinarily encountered in daily life or during the performance of routine physical or physiological examination or tests*” may not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (eg, emergency responder, pilot, soldier in a combat zone) or having a medical condition (eg, frequent medical tests or constant pain).

Education and Training

All personnel involved in the conduct of DoD research must complete initial and continuing education in the protection of human subjects as described in this manual. Personnel must also familiarize themselves with DoD's specific requirements by reviewing these SOPs, DoDD 3216.02, and any relevant materials specific to the DoD component. The DoD component may require additional education and/or certification to ensure that personnel are qualified to perform the research. The DoD component may evaluate the training policies of the medical school IRB to ensure the personnel are qualified to perform the research, based on the complexity and risk of the research.

Appointment of a Research Monitor

When DoD research involves **more than minimal risk**, the IRB **will** require and approve an independent research monitor by name. When research involves no more than minimal risk, an investigator may identify a research monitor or the IRB or IO may appoint a monitor. There may be more than one research monitor (eg if different skills or experience are needed). The monitor may be an ombudsman or a member of the data safety monitoring board.

The IRB must approve a written summary of the monitors' duties, authorities, and responsibilities and the IRB or a HRPP official shall communicate with research monitors to confirm their duties, authorities, and responsibilities.

The duties of the research monitor are determined based on specific risks or concerns about the research. The monitor:

- May perform oversight functions (eg observe recruitment, enrollment procedures, and the consent process, oversee study interventions and interactions, review monitoring plans and reports of unanticipated problems involving risks to participants or others, oversee data matching, data collection and analysis).
- May discuss the research protocol with researchers, interview human subjects, and consult with others outside of the study.
- The research monitor has the authority to stop a research study in progress, remove individual subjects from the study, and to take whatever steps are necessary to protect the safety and well-being of participants until the IRB can assess the monitor's report.
- Research monitors are obligated to promptly report their observations and findings to the IRB or other designated official.

Additional protections for vulnerable subjects

Non-exempt research involving **pregnant women, fetuses, or neonates** as subjects must meet the requirements of Subpart B of the Common Rule, with the following modifications:

- The applicability of Subpart B is limited to non-exempt research involving:

- Pregnant women as human subjects involved in research that is more than minimal risk and that includes interventions or invasive procedures to the woman or the fetus.
- Involving fetuses or neonates as subjects.
- For purposes of applying Subpart B, the phrase “biomedical knowledge” will be replaced with “generalizable knowledge.”
- Fetal research must comply with the US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g.

Research involving **prisoners** as subjects must meet the requirements of Subpart C of the Common Rule, with the following modifications:

- Research involving prisoners cannot be reviewed by the expedited procedure.
- When the IRB reviews research involving prisoners, at least one prisoner representative must be present for quorum. The prisoner representative may be a prisoner, an employee of the prison, or an individual not affiliated with the prison
- In addition to the four allowable categories of research involving prisoners in Subpart C, two (2) additional categories are allowable:
 - Epidemiological research that meets the following criteria:
 - The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor association for a disease.
 - The research presents no more than minimal risk.
 - The research presents no more than an inconvenience to the participant.
 - Prisoners are not a particular focus of the research.
 - Research that would meet the criteria for exemption described at 32 CFR 219.101(b), can be conducted but must be approved by a convened IRB and meet the requirements of subpart C, DoDD 3216.02, and other applicable requirements.
- When a previously enrolled human subject becomes a prisoner and the research was not previously approved for the inclusion of prisoners:
 - The PI must promptly notify the IRB.
 - If the PI asserts to the IRB that it is in the best interest of the prisoner to continue to participate in the research while a prisoner, the IRB Chair may determine that the prisoner may continue to participate until the convened IRB can review the request to approve a change in the research protocol and until the IO and DoD Component office review the IRB’s approval to change the research protocol. Otherwise, the IRB Chair will require that all research interactions and interventions with the prisoner (including obtaining identifiable private information) cease until the convened IRB can review the request to approve a change in the research protocol.
 - The convened IRB, upon receipt of notification that a previously enrolled human subject has become a prisoner, will promptly re-review the research protocol to ensure that the rights and wellbeing of the human subject, now a prisoner, are not in jeopardy. The IRB should consult with a subject matter expert having the expertise of a prisoner representative if

the IRB reviewing the research protocol does not have a prisoner representative. If the prisoner can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner's confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research from continuing as approved, the convened IRB may approve a change in the study to allow the prisoner to continue to participate in the research. This approval is limited to the individual prisoner-subject and does not allow recruitment of prisoners as participants.

- This type of request for change in the research protocol cannot be reviewed and approved by expedited review. The research does not have to meet one of the six allowable DoD categories for research involving prisoners.
- The medical school IRB will promptly report all decisions in this matter to the director, HRPP and/or the assistant dean for Research Compliance. The HRPP and/or assistant dean for Research Compliance must concur with the IRB decisions before the human subject can continue to participate while a prisoner.

Research involving **Children** as subjects must meet the requirements of Subpart D of the Common Rule, including that:

- The exemption for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

Research involving **Military Personnel** as subjects must meet the following requirements:

- Service members must follow their command policies regarding the requirement to obtain command permission to participate in research involving human subjects while on-duty and for approving off-duty employment or activities.
- Superiors (eg, military and civilian supervisors, unit officers, and noncommissioned officers (NCOs)) are prohibited from influencing the decisions of their subordinates (eg, junior enlisted personnel and equivalent civilians) regarding participation as subjects in research.
- Superiors of Service members (eg, unit officers, senior NCOs, and equivalent civilians) in the chain of command must not be present at any human subject recruitment sessions or during the consent process in which members of units under their command are afforded the opportunity to participate as research subjects. When applicable, the superiors so excluded shall be afforded the opportunity to participate as research subjects in a separate recruitment session.
- When research involving Service members is greater than minimal risk and recruitment occurs in a group setting, the IRB will appoint an ombudsman. The

ombudsman must not be associated in any way to the research and must be present during the recruitment to monitor that the voluntary involvement or recruitment of the Service members is clearly and adequately stressed and that the information provided about the research is clear, adequate, and accurate. The ombudsman may also be the research monitor.

Research involving **DoD Civilians** as subjects must meet the following requirements:

- DoD Civilians must follow their organization’s policies regarding the requirement to obtain permission to participate in research.
- Supervisors (eg, military and civilian supervisors or anyone in the supervisory structure) are prohibited from influencing the decisions of their subordinates regarding participation as subjects in research.
- Supervisors (eg, military and civilian supervisors or anyone in the supervisory structure) must not be present at any human subject recruitment sessions or during the consent process in which DoD civilians under their supervision are afforded the opportunity to participate as human subjects. When applicable, supervisors so excluded shall be afforded the opportunity to participate as human subjects in a separate recruitment session.
- For research involving civilians as human subjects when recruitment occurs in a group setting, the IRB will discuss appointing an ombudsman. The decision to require the appointment of an ombudsman should be based in part on the human subject population, the consent process, and the recruitment strategy.

Research involving **other vulnerable populations** must meet the following requirements:

- Investigators, IRBs, and IOs will consider the need for appropriate similar safeguards for other vulnerable populations, such as: research involving human subjects and investigators in supervisor-subordinate relationships, human subjects with decisional or mental impairments, human subjects with a physical disability, or any other kind of human subjects in circumstances that may warrant provision of additional protections. As appropriate, qualified individuals (eg, research monitors, ombudsmen, advocates) may be appointed to perform oversight functions or assist the human subjects.

Limitation of Waivers and Exceptions from Informed Consent

For DoD-funded research, if the research meets the definition of “*research involving a human being as an experimental subject*,” informed consent must be obtained in advance from the experimental subject or their LAR if the subject cannot consent. If consent is to be obtained from a LAR, the IRB must determine that the research intends to benefit the individual subject.

The Assistant Secretary of Defense for Research and Engineering may waive the requirements for consent when all of the following are met:

- The research is necessarily to advance the development of a medical product for the Military Services.
- The research may directly benefit the individual experimental subject.
- The research is conducted in compliance with all other applicable laws and regulations.

Research involving a human being as an experimental subject is an activity, for research purposes, where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction. If the research participant does not meet the definition of “experimental subject,” policies and procedure allow the IRB to waive the consent process.

For classified research, waivers of consent are prohibited.

An exception from consent in emergency medicine research is prohibited unless a waiver is obtained from the Secretary of Defense.

Limitations on Compensation for Human Subjects in Research

DoDD 3216.02 describes allowable and prohibited compensation for human subjects participating in DoD research and for Federal personnel such as civil servants and Service members. These provisions are intended to ensure compliance with the Dual Compensation Act and 24 U.S.C. 30. Summarized:

- Federal personnel while on duty and non-Federal personnel may be compensated for blood collections for research up to \$50 for each blood collection.
- Federal personnel are prohibited from receiving pay or compensation for research during duty hours (except for blood collection as noted above).
- Non-Federal personnel may be compensated for research participation other than blood collections in a reasonable amount, as approved by the IRB according to local prevailing rates and the nature of the research.
- Federal personnel may be compensated for research if the participant is involved in the research when not on duty in the same way as human subjects who are not Federal personnel (ie, compensated for participation in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research). However, payment to off-duty Federal personnel for research participation other than blood draws must not be directly from a Federal source (payment from a Federal contractor or other non-Federal source is permissible).

Additional detail is available in DoDD 3216.02 or by consulting the HRPP or assistant dean for Research Compliance.

Reporting Requirements

The Institution must promptly (no longer than within 30 days) notify the HRPP of the following: when significant changes to the research protocol are approved by the IRB, the results of the IRB continuing review, if the IRB used to review and approve the research changes to a different IRB, when the institution is notified by any Federal

department or agency or national organization that any part of its HRPP is under investigation for cause involving a DoD-supported research protocol, and all unanticipated problems involving risks to subjects or others, suspensions, terminations, and serious or continuing noncompliance regarding DoD-supported research involving human subjects.

Recordkeeping Requirements

Recordkeeping requirements for DOD-supported research with human subjects are longer than the Common Rule's requirement. DOD may require submitting records to DOD for archiving. Investigators should consult with the HRPO regarding record-keeping requirements for their research.

Records must be made accessible for inspection and copying by representatives of the DoD at reasonable times and in a reasonable manner as determined by the supporting DoD component. The fact that DoD may inspect records should be disclosed in the consent process.

Addressing and Reporting Allegations of Non-Compliance with Human Research Protections

The medical school IRB must report the initiation of all investigations of allegations of non-compliance and report the results of all such investigations (regardless of the funding) to the director, HRPP and/or assistant dean for Research Compliance.

Addressing and Reporting Allegations of Research Misconduct

The medical school IRB will adhere to the requirements of DOD 3210.7 and the terms of any DoD award when allegations or findings of research misconduct arise.

Additional Requirements for DoD Research

IRB review must consider the scientific merit of the research. The IRB may rely on outside experts to provide an evaluation of scientific merit.

When conducting research with international populations, additional safeguards for research conducted with international populations the organization, researcher must have permission to conduct research in that country by certification, or local ethics review. Researchers must follow all local laws, regulations, customs, and practices.

Disclosure regarding the provisions for research-related injury must follow the requirements of the DoD component.

Surveys performed on DoD personnel must be submitted, reviewed, and approved by the DoD component HRPO after the research protocol is reviewed by the IRB. When a survey crosses DoD components, additional review may be required by DoD.

When any institution relies upon another institution's IRB for DoD research, there must be a written agreement defining the responsibilities and authorities of each organization in complying with the terms of each institution's Federal assurance and DoDD 3216.02.

When conducting multi-site or collaborative research, a formal agreement between organizations is required to specify the roles and responsibilities of each party.

Civilian researchers attempting to access military subjects should seek collaboration with a military researcher familiar with service-specific requirements.

Department of Education

The U.S. Department of Education (ED) is a signatory to the Common Rule with regulations equivalent to 45 CFR 46 published under [34 CFR 97](#). Research conducted or supported by ED is reviewed by the medical school IRB in accordance with the Common Rule as described throughout this manual with the following variations and additional requirements.

ED has not adopted Subpart B (Pregnant Women, Fetuses, or Neonates) or Subpart C (Prisoners) of the Common Rule.

ED requires reporting of **alleged** (1) unanticipated problems involving risks to subjects or others; and, (2) serious or continuing noncompliance with the Common Rule or Subpart D (protection of children in research). Other mandated reports, as described in Section 18, *Reporting to Regulatory Agencies and Institutional Officials* are submitted to ED instead of OHRP when the research is funded or sponsored by ED. When applicable, the medical school IRB will follow the directions for incident reporting provided on [ED's Protection of Human Subjects in Research](#) website.

Family Educational Rights and Privacy Act (FERPA)

The [Family Educational Rights and Privacy Act](#) (FERPA) is a Federal law that protects the privacy of student education records at educational entities that receive funds from the ED. In general, schools must have written permission from the parent or eligible student to release any information from a student's education record. However, FERPA allows schools to disclose personally identifiable information from an education record of a student without consent if the disclosure is to organizations conducting studies for, or on behalf of, educational agencies or institutions to:

- Develop, validate, or administer predictive tests.
- Administer student aid programs.
- Improve instruction. [[34 CFR 99.31\(a\)\(6\)](#)]

A written agreement with the receiving organization is required, including:

- The purpose, scope, and duration of the study(ies).
- The information to be disclosed.

- A requirement that the receiving organization uses the personally identifiable information from the educational records only for the purpose(s) of the study as stated in the agreement.
- A requirement that the receiving organization conducts the study in a manner that does not permit personal identification of students and parents by anyone other than representatives of the organization with legitimate interests.
- A requirement that the receiving organization destroys or returns all personally identifiable information when the information is no longer needed for the purposes for which the study was conducted and that specified the time period in which the information must be returned or destroyed.

Education records may be released without consent under FERPA if all personally, identifiable information has been removed including:

- Students' names and other direct identifiers, such as students' Social Security Numbers or student numbers.
- Indirect identifiers, such as the name of students' parents or other family members, the students' or families addresses, and personal characteristics or other information that would make the students' identities easily traceable, and dates and places of birth and mothers' maiden names.
- Biometric records, including measurable biological or behavioral characteristics that can be used for automated recognition of an individual, including fingerprints, retina and iris patterns, voiceprints, DNA sequence, facial characteristics, and handwriting.
- Other information that, alone, or in combination, is linked or linkable to a student that would allow a reasonable person in the school community, who does not have personal knowledge of the relevant circumstances, to identify to student with reasonable certainty.

At the medical school, when FERPA applies, investigators must provide the IRB with information describing how they will ensure compliance with the rule. A letter of support or other documentation from the school supporting the conduct of the research should be provided. The IRB will review the information provided to verify compliance, including verification that permission for the use of the records will be obtained or that it is not required under an allowed use or exception.

Protection of Pupil Rights Amendment (PPRA)

The [Protection of Pupil Rights Amendment](#) (PPRA) affords parents of elementary and secondary students certain rights regarding the conduct of survey, collection and use of information for marketing purposes, and certain physical exams. PPRA applies to the programs and activities of a state educational agency (SEA), local educational agency (LEA), and any other recipient of ED funds. These rights transfer from parents to students when they reach the age of 18 or are an emancipated minor. This section is not intended to address PPRA as a whole; rather it addresses PPRA requirements as they most commonly relate to research.

Definitions:

Instructional Material: Means instructional content that is provided to a student, regardless of its format, including printed or representational materials, audio-visual materials, and materials in electronic or digital formats (such as materials accessible through the Internet). The term does not include academic tests or academic assessments.

Invasive Physical Examination: Means any medical examination that involves the exposure of private body parts, or any act during such examination that includes incision, insertion, or injection into the body, but does not include a hearing, vision, or scoliosis screening.

Personal Information: Means individually identifiable information including: (1) a student's or parent's first and last name; (2) a home or other physical address (including a street name and the name of a city or town); (3) a telephone number; or, (4) a Social Security Number.

Research or Experimentation Program or Project: Means any program or project in any program that is designed to explore or develop new or unproven teaching methods or techniques.

Rights under PPRA

When **research is funded by ED**, no student can be required to submit **without prior consent** to a survey that concerns one or more of the following protected areas:

- Political affiliations or beliefs of the student or the student's parent.
- Mental and psychological problems of the student or his or her family.
- Sex behavior and attitudes.
- Illegal, anti-social, self-incriminating, and demeaning behavior.
- Critical appraisals of other individuals with whom the student has close family relationships.
- Legally recognized privileged and analogous relationships, such as those of lawyers, physicians, and ministers.
- Religious practices, affiliations, or beliefs of the student or student's parent.
- Income, other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under a program.

Parents have the right to **receive notice and an opportunity to opt a student out** of:

- Any other survey that concerns any of the above protected areas, **regardless of funding**.
- Any non-emergency, invasive physical exam or screening required as a condition of attendance, administered by the school or its agent, that is not necessary to protect the health and safety of a student, except for hearing, vision, or scoliosis

screenings, or any physical exam or screening permitted or required under state law.

- Activities involving collection, disclosure, or use of personal information collected from students for marketing or to sell or otherwise distribute the information to others. (This does not apply to the collection, disclosure, or use of personal information collected from students for the exclusive purpose of developing, evaluating, or providing educational products or services for, or to, students or educational institutions).

Parents also have the **right to inspect** upon request and before administration or use:

- Surveys that concern any of the protected areas and surveys created by third parties.
- Instruments used to collect personal information from students for any of the above marketing, sales, or other distribution purposes.
- Any instructional material used as part of the educational curriculum for the student.
- Instructional material, including teachers' manuals, films, tapes, or other supplementary instructional material, which will be used in conjunction with any research or experimentation program or project.

Procedures

At the medical school, when PPRA applies, investigators should review the school's PPRA policies and must provide the IRB with information describing how they will ensure compliance with the rule and the school's policies. A letter of support or other documentation from the school supporting the conduct of the research and its compliance with PPRA should be provided. The IRB will review the information provided to verify compliance.

Department of Justice

The U.S. Department of Justice (DoJ) is a signatory to the Common Rule with regulations equivalent to 45 CFR 46 published under [28 CFR 46](#); however, DOJ has chosen not to adopt Subparts B, C and D. The National Institute of Justice (NIJ) serves as DoJ's research arm. Confidentiality regulations for DoJ/NIJ research are described at [28 CFR 22](#). Research conducted within the Federal Bureau of Prisons is subject to the requirements described at [28 CFR Part 512](#).

This section summarizes additional requirements for the conduct and IRB review of human subjects research conducted or supported by DoJ/NIJ (including funding through grants, subgrants, contracts, subcontracts, cooperative agreements, and interagency agreements) and human subjects research conducted in the Federal Bureau of Prisons.

Principal Investigator Responsibilities

In addition to complying with the Common Rule requirements outlined by DoJ at [28 CFR 46](#), PIs conducting research supported by DoJ/NIJ have the following responsibilities. PIs must:

- Submit a Privacy Certificate to NIJ to document understanding of investigator's obligations under the confidentiality regulations found in [28 CFR 22](#). NIJ provides guidelines for the certificate on its [website](#).
- Inform subjects (in the confidentiality section of the consent form) that private, identifiable information will be kept confidential and will only be used for research and statistical purposes. If, due to sample size or some unique feature, the identity of the individual cannot be maintained, the subjects need to be explicitly notified. If the investigator intends to disclose any information, the subject needs to be explicitly informed what information would be disclosed, under what circumstances, and to whom. The subject must be informed of any potential risks which may result from this disclosure and must explicitly provide prior written consent.
- Submit a copy of the IRB approval as well as supporting documentation of the IRB's institutional affiliation, assurance, etc. to the NIJ prior to initiation of any research activities that are not exempt from the requirements of 28 CFR 46; or
 - Submit supporting documentation of the IRB's determination that the research qualifies for exemption under 28 CFR 46.101(b).
- Comply with [NIJ's policy](#) for the protection of the privacy and well-being of participants in NIJ research studies through the statutory protection provided to private information under the authority of [42 U.S.C. § 3789g](#) and the other DOJ regulations on the Confidentiality of Identifiable Research and Statistical Information found in [28 CFR 22](#).
- Sign and maintain an Employee Confidentiality Statement for themselves and their research staff. A model employee confidentiality statement can be found at <https://www.nij.gov/funding/humansubjects/employee-confidentiality.htm>.
- Send a copy of all de-identified data, including copies of the informed consent document, data collection instruments, surveys and other relevant research materials to the National Archive of Criminal Justice Data.

ICH-GCP E6

When the medical school commits to comply with ICH-GCP E6 as a term of a grant or contract, investigators and the IRB take on additional responsibilities. Investigators are responsible for clearly indicating within their IRB application materials that proposed research is subject to ICH-GCP E6 and for attesting to compliance with ICH-GCP E6 requirements. The medical school IRB will evaluate compliance with the aid of a checklist and by consulting the current [ICH-GCP E6 guidance](#) posted by the FDA on its website. The medical school IRB does not require or evaluate compliance with ICH-GCP E6 requirements that are not consistent with FDA regulations (for example, requiring the reporting to the IRB of all adverse drug reactions that are both serious and unexpected instead of requiring the reporting of unanticipated problems involving risks

to subjects or others). Center for Clinical Research protocols submitted to an external IRB are not evaluated for compliance with ICH-GCP guidance by the medical school IRB.

IRB Responsibilities

In addition to the IRB responsibilities, functions, and procedures outlined elsewhere in this manual, ICH-GCP E6 specifically requires that:

- The IRB obtain and review written information that will be provided to subjects and the investigator's current curriculum vitae and/or other documentation evidencing the investigator's qualifications.
- The IRB's written determination letter must clearly identify the trial, the documents reviewed, and the dates that actions were taken.

Investigator Responsibilities

In addition to the investigator responsibilities outlined elsewhere in this manual, ICH-GCP E6 specifically requires that:

- The investigator should be aware of, and should comply with GCP.
- The investigator should permit monitoring and auditing by the sponsor, and inspection by appropriate regulatory authorities.
- The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.
- The investigator must have adequate resources to conduct the trial, including:
 - Being able to demonstrate (eg, based on retrospective data) the potential for recruiting the required number of subjects within the agreed upon recruitment period.
 - Sufficient time to properly conduct and complete the trial within the agreed trial period.
 - Adequate number of qualified staff and adequate facilities to the foreseen duration of the trial to conduct the trial properly and safely.
 - Ensuring that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.
- A qualified physician (or dentist, when appropriate), who is an investigator or sub-investigator on the trial, should be responsible for all trial-related medical (or dental) decisions.
- During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.
- The investigator should inform the subject's primary physician about the subject's participation in the trial if the subject agrees to the primary physician being informed.

- The investigator should make a reasonable effort to ascertain the reason(s) when a subject withdraws prematurely from a trial, while fully respecting the subject's rights.
- The investigator should sign the protocol, or an alternative contract, to confirm their agreement to comply with the approved protocol.
- The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.
- In addition to reporting to the IRB, when the investigator implements a deviation from or change in the protocol to eliminate an immediate hazard(s) to subject(s) without prior approval, this must be reported as soon as possible to the sponsor.
- The investigator is ultimately responsible for investigational product accountability and for all of the responsibilities outlined in section 4.6 of ICH-GCP E6.
- The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor (and IRB) any premature unblinding.
- Additional requirements for Informed Consent -
 - When subjects or LARs are informed on any new information that may be relevant to the subject's willingness to continue participating in the trial, the communication of this information should be documented.
 - In addition to the subject signature and date on the written informed consent form, the form should be personally signed and dated by the person who conducted the informed consent discussion.
 - Prior to participation in the trial, the subject or LAR should receive a copy of the signed and dated consent form and any other written information provided to the subjects. During the trial, the subject or LAR should receive a signed and dated copy of any updated consent forms and any other updated written information.
 - If a subject is unable to read or if a LAR is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects is read and explained to the subject or the subject's LAR, and after the subject or the subject's LAR has orally consented to the subject's participation in the trial, and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's LAR and that informed consent was freely given by the subject or the subject's LAR.
 - The consent discussion and written informed consent form should include the following additional elements:
 - An explanation of the trial treatment(s) and the probability for random assignment to each treatment.
 - An explanation that the monitor(s), auditor(s), the IRB, and the regulatory authorities will be granted direct access to the subject's

original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or LAR is authorizing such access.

- An explanation of the anticipated prorated payment, if any, to the subject for participating in the trial.
- An explanation of the reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- A statement that the trial has the approval of the IR.;
- Investigators must comply with the requirements for records and reports outlined in section 4.9 of ICH-GCP E6 including the requirements for accuracy, completeness, legibility, and timeliness.
- Investigators must comply with the requirements for safety reporting outlined in Section 4.11 of ICH-GCP E6 including the redaction of personally identifying information.
- Investigators must comply with the requirements for premature termination or suspension of a trial outlined in section 4.12 including the requirements for sponsor (and IRB) reporting.

Transnational Research

The medical school IRB reviews transnational research involving human subjects to ensure that adequate provisions are in place to protect the rights and welfare of the subjects. All policies and procedures that are applied to research conducted domestically are applied to research in international settings, as appropriate. 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.”*

For federally conducted or supported research, approval of research for foreign institutions or sites “engaged” in research is only permitted if the foreign institution or site holds a FWA 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/EC, 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 is IRB/EC 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/EC determination, or letter of cooperation, as applicable.

The medical school IRB seeks sufficient 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/EC, the medical school IRB must receive and review the foreign institution or site's IRB/EC review and approval of each study prior to beginning the research at the foreign institution or site.

In settings where there are no IRBs/ECs, the medical school IRB may 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, including other IRBs or committees with experience reviewing research in the region, other medical school investigators with knowledge of the region, or a consultant who is an expert on the region, prior to approval. These individuals may either provide a written review of the research protocol or attend an IRB meeting to provide the medical school IRB with recommendations based on his or her expertise.

IRB Responsibilities

In addition to the IRB review considerations discussed elsewhere in this manual, the IRB will consider the following when reviewing transnational research:

- The qualifications of the investigator and research staff to conduct research in that country including knowledge of relevant laws, regulations, guidance and custom.
- Whether the consent process and consent documents are appropriate for the language(s) of the subjects and the subject population, and that arrangements are made to be able to communicate with subjects throughout the study (eg, to ask and answer questions).
- How modifications to the research will be handled.
- How complaints, noncompliance, protocol deviations and unanticipated problems involving risks to subjects or others are handled.
- How post-approval monitoring will be managed.
- Whether the investigator has obtained the appropriate host country permissions to conduct research (eg, institutional, governmental or ministerial, IRB, local, or tribal). When appropriate, the IRB communicates and coordinates with the local institutions or ethics committees.
- Mechanisms for communicating with the investigators and research staff when they are conducting the research in other countries.

Investigator Responsibilities

The investigator conducting transnational research is responsible for:

- Ensuring that the resources and facilities are appropriate for the nature of the research.
- Verifying the qualifications of the investigators and research staff for conducting research in the country(ies).
- Obtaining all appropriate host country permissions to conduct research (eg, institutional, governmental or ministerial, IRB, local, or tribal).
- Ensuring that the consent process and consent document are appropriate for the language(s) of the subjects and the subject population, and that arrangements are made to be able to communicate with subjects throughout the study (eg, to ask and answer questions).
- Ensuring that the following activities will occur:
 - Initial review, continuing review, and review of modifications.
 - Post-approval monitoring of the conduct of the research in accordance with the plan approved by the IRB.
 - Handling of complaints, noncompliance and unanticipated problems involving risk to subjects or others.
 - Not relying upon an IRB or EC that does not have policies and procedures for the activities listed above.
 - Ensuring that reportable information such as complaints, noncompliance, protocol deviations and unanticipated problems involving risks to participants or other are communicated to the IRB.
 - Notifying the IRB promptly if a change in research activities alters the performance site's engagement in the research (eg, performance site "not engaged" begins to obtain consent of research participants, etc.).
 - Ensuring that there are mechanisms for communicating with the IRB when they are conducting the research in other countries.

Consent Documents

The informed consent documents must be appropriate for and in a language understandable to the proposed subjects. The IRB will review the proposed document *and* a back translation of the exact content contained in the foreign language informed consent document, with the credentials of the translator detailed in the IRB application or *Modification Request Form*. All documents, including verification of the back translation, are maintained in the IRB file.

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 are both involved in the review of research, there is a plan for coordination and communication with the local IRB/ECs.

The IRB requires documentation of regular correspondence between the investigator and the foreign institution or site and may require verification from sources other than

the investigator that there have been no changes made to the research since its last review.

Student Research

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 of 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 (eg, cannot be made available on the internet, cannot be published in a journal, etc.).
- Research procedures are no more than minimal risk.
- Permissions are obtained from any facilities or organizations where research activities, including recruitment, will take place.
- Vulnerable populations are not targeted (eg, 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 videotapes and photographs and voices on audiotape are identifiable).
- When appropriate, an informed consent process is in place.

Responsibility of the Course Instructor:

The course instructor is responsible for ensuring the protection of human subjects (including a process for obtaining voluntary informed consent from research subjects when appropriate), and for monitoring the students' 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. In particular, instructors and students should:

- Understand the principles of the Belmont Report and their application.
- Develop appropriate consent documents.
- Plan appropriate strategies for recruitment.
- Identify and minimize potential risks to subjects or others.
- Assess the risk-benefit ratio for the project.
- Establish and maintain strict guidelines for protecting privacy and confidentiality.
- Allow sufficient time for IRB review, if applicable, and completion of the project.

In making a determination of whether or not a class research project requires IRB review, the instructor is encouraged to contact the HRPP/IRB office for assistance or to submit a for a determination following the procedures outlined in Section 5 (*Human Subjects Research Determination*).

Individual Research Projects Conducted by Students

When students conduct, or participate as a research team member, in human subjects research other than class work as described above, they must follow the standard procedures for research described throughout this manual, as applicable to the research. As described in Section 19.1.1 (Principal Investigator [PI]), students may not serve as PI on human subjects research conducted under the auspices of the medical school but may serve as a sub-investigator or member of the research team. When students of the medical school conduct, or participate as a research team member, in research at or with another organization, they must contact the medical school HRPP/IRB office to determine if review by the medical school IRB is required, or if a reliance agreement is needed, prior to engaging in the activity. It is important to keep in mind that any human subject research activity that will ultimately contribute to part or all of a thesis, dissertation, or other type of publication or presentation must go through the IRB review process prior to enrolling subjects and collecting data. IRB review/approval cannot occur after a study has begun.

Students and advisors should contact the IRB Office with any questions.