



**Human Research  
Protection Program  
(HRPP)  
and  
Institutional Review  
Board (IRB)  
Handbook**

**September 2016**

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All material in this *Human Research Protection Program (HRPP) and Institutional Review Board (IRB) Handbook* is intended to be consistent with all other medical school policies. In an environment as dynamic as the medical school, changes will periodically occur in the policies and procedures that apply to the Human Research Protection Program and Institutional Review Board. The current *Human Research Protection Program (HRPP) and Institutional Review Board (IRB) Handbook* and all other medical school policies are available online.

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## Abbreviations

AAHRPP	Association for the Accreditation of Human Research Protection Programs
AIDS	Acquired immunodeficiency syndrome
ASL	American Sign Language
BAA	Business Associate Agreement
CBPR	Community-based participatory research
CBR	Community-based research
CFR	Code of Federal Regulations
CITI	Collaborative Institutional Training Initiative
CRO	Contract Research Organization
DHSS	Department of Health and Human Services
DMC	Data Monitoring Committee
DOD	U.S. Department of Defense
DOE	U.S. Department of Education
DOJ	U.S. Department of Justice
DUA	Data Use Agreement
FDA	U.S. Food and Drug Administration
FERPA	Family Educational Rights and Privacy Act of 1974
FWA	Federalwide Assurance
GCP	Good Clinical Practices
HIPAA	Health Insurance and Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus
HRPP	Human Research Protection Program
HUD	Humanitarian Use Device
IAA	Institutional Authorization Agreement
ICH-GCP E6	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use <a href="#"><i>Guideline for Good Clinical Practice</i></a> , June 10, 1996.
IDE	Investigational Device Exemption
IEC	Institutional Ethics Committee
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
MOU	Memorandum of Understanding
NIH	National Institutes of Health
NSR	Non-Significant Risk device
OHRP	Office for Human Research Protections, of the DHHS
PHI	Protected Health Information
PI	Principal Investigator
PRIM&R	Public Responsibility in Medicine and Research
PPRA	Protection of Pupil Rights Amendment
REB	Research Ethics Board
sIRB	single Institutional Review Board of record for research that is funded by NIH and carried out at more than one site in the United States.
SR	Significant Risk device
URL	Universal Resource Locators of the web

## Section 1. 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.

### 1.1 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.

## 1.2 Organizational Authority

The medical school HRPP operates under the authority of the medical school. The *Human Research Protection Program (HRPP) and Institutional Review Board (IRB) Handbook* 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:

1. Fostering, supporting, and maintaining an organizational culture that promotes and facilitates the ethical conduct of all research involving human subjects and the adherence to regulations and organizational policies.
2. 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.
3. Oversight of the Institutional Review Board (IRB).
4. Oversight of the conduct of research conducted by all medical school investigators.
5. Ensuring the IRB members are appropriately knowledgeable to review research in accordance with ethical standards and applicable regulations.
6. Ensuring that all investigators are appropriately knowledgeable to conduct research in accordance with ethical standards and applicable regulations.
7. Oversight of the development and implementation of an educational plan for IRB members, staff, and investigators.
8. Ensuring compliance with institutional policies and all applicable regulations for the protection of human subjects.
9. Serving as the signatory authority and ensuring compliance with the terms of the Federalwide Assurance to the Office of Human Research Protections (OHRP).
10. 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 noncompliance may be published or used for research purposes. Both the IRB and the assistant dean for Research Compliance 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, 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) Handbook*. 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.

### 1.3 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 organizational authority or responsibility; or (3) perform organizationally 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 obtains data through intervention or interaction with the individual or through identifiable private information [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 Subject Research:** Human Subject 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:** Identifiable information means information that is individually identifiable (ie, the identity of the subject is or may readily be ascertained by the investigator or associated with the information).
- **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/Oversight/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>
- **Foods:** Foods include dietary supplements that bear a nutrient content claim or a health claim.
- **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.

## 1.4 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 25), 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.

## 1.5 Regulatory Compliance

The HRPP is responsible for ensuring compliance with federal regulations, state law and organizational 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 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 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.

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

When requested by an industry sponsor, the medical school will adhere to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [Guideline for Good Clinical Practice](#), June 10, 1996 (sometimes referred to as "ICH-GCP E6"), for human subjects research involving

pharmaceuticals. In general, the medical school applies ICH-GCP E6 guidelines only to the extent that they are compatible with DHHS and FDA regulations.

## **1.7 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.

In its FWA, the medical school has opted to limit the application of the FWA to non-exempt human subject research conducted or supported by DHHS or federal agencies that have adopted the Common Rule.

## **1.8 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 monitoring and all other aspects and 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).

An IRB chair or Vice Chair, with the assistance of the HRPP director, IRB manager, and legal counsel as needed, 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 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.

## **1.9 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) Handbook*. 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.

## **1.10 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(s), Institutional Biosafety Committee, Sponsored Programs Administration 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:

### **1.10.1 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 and 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(s) have the resources and support necessary to comply with all organizational policies, laws, and regulations that govern human subject research. Such resources include, but are not limited to:

- Staffing commensurate with the size and complexity of the research program.
- Appropriate office space, equipment, materials, and technology.
- Resources for the production, maintenance, and secure storage of HRPP and IRB records.
- Resources for auditing 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 organizational culture that supports the ethical conduct of all research involving human subjects and the adherence to regulations and organizational policies.
- Oversight of the medical school IRB(s).
- 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(s).
- 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 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.

### **1.10.2 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(s).
- Advising the Institutional Official 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.
- Developing training requirements as required and as appropriate for investigators, subcommittee members and research staff, and ensuring 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.

### **1.10.3 HRPP/IRB Staff**

In addition to the leadership, support staff members for the HRPP and IRB include the IRB manager, IRB specialists, Research QA and Education Specialists, and Quality Coordinators. 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.

### **1.10.4 Institutional Review Board (IRB)**

The medical school supports one or more IRBs 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 organizational policies. (See Section 4 for a detailed discussion of the IRB.)

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.

### **1.10.5 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.

### **1.10.6 Department Chairs**

For human subjects research conducted by medical school-employed investigators, the investigator's department chair, or designee, reviews the proposal before it is submitted to the IRB for review. Approval of the department 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

### **1.10.7 Investigators**

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

### **1.10.8 Sponsored Programs Administration**

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, who has the authority to approve research proposals and to execute research agreements on behalf of the medical school.

Sponsored Programs Administration ensures that required AAHRPP language (see Section 20.2) is included in all contracts. Sponsored Programs Administration has access to the IRB submission to confirm that the contract and the consent documents are consistent in the description of costs to subjects and who pays in case of injury. Sponsored Programs Administration and HRPP/IRB staff coordinate efforts to ensure that all applicable individuals have filed appropriate conflict of interest and commitment disclosures to meet investigator conflict of interest and commitment policies.

A subaward (subcontract) must be executed between the medical school and collaborating institutions for grants and contracts that include human research activities that are conducted by investigators who are not employees of the medical school. The subaward includes the requirement for the collaborating institution to assure compliance with federal regulations for the protection of human subjects in research and provide documentation of current and ongoing IRB approval. The collaborating institution must also ensure that key personnel involved in human subjects research are in compliance with the NIH policy on education in the protection of human research subjects and provide documentation of education of key personnel to the medical school.

### **1.10.9 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.
- Project management.
- 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.

### **1.11 Study-Specific Coordination**

In addition to IRB approval, investigators must obtain and document the approval, support, or permission of other individuals, departments, and entities affected by the research as well as approval by other oversight committees, including, but not limited to:

- 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).
- Other medical school committees, as applicable (eg, Institutional Biosafety Committee).

For any that are indicated, 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 is reviewed by HRPP/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.

## **Section 2. 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 organizational policies and procedures and applicable federal, state, and local laws.

### **2.1 External Monitoring, Audit, and Inspection Reports**

All reports from external monitors (eg, sponsor, CRO, or Coordinating Center reports) must be submitted by investigators to the IRB for review. The IRB chair or designee reviews the reports in order to monitor for issues that could affect the rights or welfare of human subjects, and to identify issues indicative of possible serious or continuing non-compliance. If concerns are identified, the report is forwarded to the convened IRB to determine what additional actions are necessary. When appropriate, the IRB chair or designee may request additional information or clarification from the investigator, or refer the issue to the HRPP/IRB staff for fact-finding or evaluation, prior to forwarding the report to the convened IRB.

### **2.2 Audits and Inspections by Regulatory Agencies and Sponsors**

The HRPP and all potentially affected services (eg, pharmacy) must be notified within two business days 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 sole discretion of the assistant dean for Research Compliance, 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, and appropriate ancillary services. When determined appropriate by the Institutional Official 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, 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.

### **2.3 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 law, and applicable policies; provide recommendations based on existing policies and procedures; and identify areas for improvement. The results of compliance reviews are reported to the HRPP director, study 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. 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 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 RESo4 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.
- Contacting research subjects.
- 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.

## **2.4 IRB Compliance Reviews**

The HRPP QA Research Education & Compliance Specialist and QA Coordinators, 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 (45 CFR46.111) and FDA (21CFR 56.111) 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 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, IRB chair, Institutional Official, and, when appropriate, members of the IRB. If any significant deficiencies are noted in the review, a corrective action plan is developed by the HRPP director and IRB chair and approved by the Institutional Official. 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 and Institutional Official.

## 2.5 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, and Institutional Official meet to review the results, determine whether the respective goals were achieved, and, if needed, develop corrective actions.

## Section 3. Education & Training

### 3.1 Training and Continuing Education of the IRB Chair, IRB Members, and 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.

#### 3.1.1 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) Handbook*, 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
- 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.

#### 3.1.2 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.

#### 3.1.3 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.

### **3.2 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 be reviewed until the Principal Investigator and all investigators and research staff with human subject responsibilities have completed the required modules of CITI courses.

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.

### **3.2.1 *Equivalent Training***

#### *3.2.1.1 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.

#### *3.2.1.2 Refresher Training*

Medical school investigators and research staff who attend a PRIM&R, OHRP, FDA, or other conference 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 4. Institutional Review Board

The medical school has established one or more Institutional Review Boards (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 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.

### 4.1 IRB Authority

The medical school IRB derives its authority from medical school policy, as cited in Section 1.2. Under the federal regulations, 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 also has the authority to determine, with the assistant dean for Research Compliance, whether data or information involving human subjects but gathered without IRB approval or in association with serious noncompliance may be published or used for research purposes. Both the IRB and the assistant dean for

Research Compliance must approve the publication or use of the data or information under these circumstances.

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 4.7. Similarly, the IRB must remain free from the influence of financial and other organizational 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.

## **4.2 Roles and Responsibilities**

### **4.2.1 *Chair of the IRB***

The Institutional Official, in consultation with the assistant dean for Research Compliance 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 task of making the IRB a respected part of the research community falls largely on the shoulders of the chair. 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 and assistant dean for Research Compliance. 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.

#### **4.2.2 Vice Chair of the IRB**

The vice chair serves as the chair of the IRB in the absence of the chair and has the same qualifications, authority, and duties as the chair.

The performance of IRB vice chair is reviewed on an annual basis by the Institutional Official in consultation with the HRPP director, assistant dean for Research Compliance, and IRB chair. Feedback from this review is provided to the 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.

#### **4.2.3 IRB Members**

The role of an 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 education and training requirements, both initial and ongoing (see Section 3.1).
- 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 inform HRPP/IRB staff with sufficient time, 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 HRPP/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 vote 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.

#### **4.2.4 *Alternate members***

The appointment and function of alternate members is the same as that for primary 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 regular member is unavailable to attend a convened meeting. When an alternate member substitutes for a primary 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 primary member(s) and class of members (ie, physician scientist) for whom each alternate member may substitute. The alternate member is not be counted toward meeting quorum as a voting member unless the primary member is absent. The IRB minutes must document when an alternate member replaces a primary member.

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

#### **4.2.5 *Subcommittees of the IRB***

The IRB chair, in consultation with the HRPP director and assistant dean for Research Compliance, 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 and assistant dean for Research Compliance, 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.

### 4.3 Composition of the IRB

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 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 organizational 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 HRPP/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, 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 organizational needs.

#### **4.3.1 Appointment of Members to the IRB**

When a need is identified for a new, replacement, or alternate member for the IRB, the HRPP director, assistant dean for Research Compliance, 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, 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.

#### **4.3.2 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.

#### **4.4 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.

HRPP/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 HRPP/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.

#### **4.5 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.

#### **4.6 Reporting and Investigation of Allegations of Undue Influence**

The medical school Hotline is 269.337.6505.

If the IRB chair, and IRB member, or HRPP/IRB staff person 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, 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 and Research Integrity Officer for investigation and any necessary action.

Undue influence means attempting to interfere with a normal functioning and decision-making of the IRB, or to attempt to influence an IRB member, HRPP/IRB staff, investigator, or research staff outside of 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 HRPP/IRB staff.

## Section 5. 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” and “research” in Section 1.3. 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 HRPP. **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.

Determinations whether an activity constitutes human subject research are made according to the definitions in Section 1.3 using the *Human Subject Research Determination Checklist*. Determinations are made by the IRB chair or vice chair, who may refer the determination request to the convened IRB.

Documentation of all determinations made through HRPP and the IRB are recorded and maintained in HRPP/IRB records. Requests and responses are maintained in HRPP/IRB records.

## Section 6. Exempt Studies

All research using human subjects must be approved by the medical school. However, certain categories of human subject research are exempt from the requirement for IRB approval. Exempt research is subject to review for determination of exemption status. At the medical school, exemptions are reviewed and granted by the IRB chair and vice chair.

Although exempt research is not covered by the Common Rule or FDA regulations, other regulations and requirements, such as HIPAA and disclosure of conflicts of interest and commitment, may apply. Furthermore, exempt research is not exempt from ethical considerations, such as the principles described in the Belmont Report. Determination of exemption must include determination of whether to require protections for subjects in keeping with ethical principles (eg, requiring consent).

### 6.1 Limitations on Exemptions

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

- Research Involving Children
  - The exemption for research involving 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.
- Research Involving Prisoners
  - Exemptions do NOT apply. IRB review is required.

### 6.2 Categories of Exempt Research

Within the limitations outlined in Section 6.1, research activities that are not regulated by the FDA (see Section 6.3 for 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:

- Research conducted in established or commonly accepted educational settings, involving normal educational practices, 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.
- Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless both of the following apply:
  - Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects.
  - Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation.

- Research involving the use of educational tests (cognitive, diagnostic, aptitude, or achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under the preceding, if either of the following apply:
  - The human subjects are elected or appointed public officials or candidates for public office.
  - Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
- Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. In order to be eligible for this exemption, all of the materials have to exist at the time the research is proposed.
- Research and demonstration projects that are conducted by or subject to the approval of federal departments or agency heads, and which are designed to study, evaluate, or otherwise examine one or more of the following:
  - 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 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).

The research demonstration project must be conducted pursuant to specific federal statutory authority, there must be no statutory requirements of IRB review, the research must not involve significant physical invasions or intrusions upon the privacy of subjects, and the exemption must be invoked only with authorization or concurrence by the federal funding agency.

- Taste and food quality evaluation 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.

### **6.3 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) working days. Any subsequent use of the test article is

subject to IRB review. [21 CFR 56.104(c)] See Section 13.2 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)]

## 6.4 Procedures for Exemption Determination

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

- A completed *Exemption Request Form*.
- All recruitment materials (eg, letter of invitation, recruitment script, flyer).
- Consent form/disclosure/information sheet, if applicable.
- HIPAA authorization form, if applicable.
- All surveys, questionnaires, instruments, and other related information.
- Letter(s) of permission from each non-medical school site of performance.
- Verification of current human research protection training for all investigators and research staff.

The IRB chair or vice chair reviews requests for exemption determinations and determines whether the research qualifies for exempt status. In the event that the IRB chair and vice chair both have a conflict of interest or commitment, an experienced IRB member or consultant is identified by the HRPP director to make the determination.

The chair, vice chair, or designated reviewer uses the *Exemption Determination Checklist* to evaluate the submission and document their determination of whether the study qualifies for exempt status, and if it does, under which category/categories.

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, review form, and determination letter are recorded and maintained in the same manner and for the same length of time as other IRB review documentation.

Once exemption review is completed, HRPP/IRB staff send written notification of the results of the review to the investigator.

Investigators must submit any proposed modifications to the research for a determination of whether or not the modified activity still qualifies for exemption and must notify the HRPP/IRB staff by email or in writing when an exempt research project

is complete so that the organization can maintain an accurate database of active research.

## Section 7. 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.)

### 7.1 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 7.2.2).
  - 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.



## 7.2 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.

### 7.2.1 *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 (21 CFR Part 312) 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 (21 CFR Part 812) 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 nonresearch 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 45 CFR 46 101(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 45 CFR 46.101(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.

- (9) 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.

### **7.2.2 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 will designate a list of IRB members 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.

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 21.2) 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 will determine and document 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 Sections 7.2 and 7.4 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 7.3).

Reviewers will 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.

### **7.2.3 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.

## **7.3 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 below) of the members is present.

### **7.3.1 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.

### **7.3.2 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.

### **7.3.3 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 may be outside of the knowledge base or representative capacity of the IRB members, an outside consultant will be sought (see Section 4.5). Research studies for which appropriate expertise cannot be obtained for a given IRB meeting will be 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 7.4).
- 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 nonapproval, but such recommendation will not be counted as a vote.

### **7.3.4 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.

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.

### **7.3.5 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.

It is generally expected that at least one unaffiliated member and at least one member who represents the general perspective of participants will be 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.

### **7.3.6 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. 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.

### **7.3.7 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 will 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.

## **7.4 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 take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disable 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.

#### **7.4.1 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.

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”).

#### *7.4.1.1 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.

#### **7.4.2 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 will verify that the investigator has followed the subject selection criteria that was originally set forth at the time of the initial IRB review and approval.

#### *7.4.2.1 Recruitment of Subjects*

The investigator will provide the IRB with a plan for recruitment of all potential subjects. All recruiting materials will be submitted to the IRB, including advertisements, flyers, scripts, information sheets and brochures. The IRB should ensure that the recruitment plan and materials appropriately protect the rights and welfare of the

prospective subjects and do not present undue influence. See Section 7.5.10 for a discussion of IRB review of advertisements and Section 7.5.11 for a discussion of IRB review of payments.

### **7.4.3 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 will ensure that informed consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117 and 21 CFR 50.27. The IRB must ensure, 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 for detailed policies on informed consent.

### **7.4.4 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 will consider in determining whether the safety monitoring plan is adequate for the research are as follows:

- Monitoring is commensurate with the nature, complexity, size and risk involved.
- Monitoring is timely. Frequency should be commensurate with risk.
- Conclusions are reported to 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.
- 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.

#### **7.4.5 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.

##### **7.4.5.1 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 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.

#### 7.4.5.2 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 in which an individual will be interacting with an investigator.
- Appropriateness of all personnel present for research activities.
- Methods used to obtain information about participants.
- 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."

#### 7.4.5.3 Confidentiality

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

At the time of initial review, continuing review, and with any requests for modification 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 will provide 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 25.8).

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 organizational requirements and policies regarding the use of information and information security.

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

#### **7.4.6 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 provides additional information about the IRB review and approval process for specific populations of vulnerable subjects.

### **7.5 Additional Considerations**

#### **7.5.1 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 will be 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 *Initial Study Review Checklist*.

### **7.5.2 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 *Initial Study 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.



### **7.5.3 Review More Often Than Annually**

The following factors will be considered when determining which studies 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 *Initial Study Review Checklist*.

### **7.5.4 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 QA 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 will evaluate the issue in accordance with the procedures described in Section 16 (Non-compliance).

### **7.5.5 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 will determine the appropriate action to be taken, if any.

### **7.5.6 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.

### **7.5.7 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 provides additional discussion of conflicts of interest and commitment.

### **7.5.8 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 21.3 provides additional discussion of institutional conflicts of interest.

### **7.5.9 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 will review 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 will communicate 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.

#### **7.5.10 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 for taking part in the investigation.
- Emphasis on payment or the amount to be paid, such as bold type or larger font on printed media.
- Offers for a coupon good for a discount on the purchase price of an investigational product once it has been approved for marketing.
- 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 will be 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://www.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.

The first contact with prospective study subjects may be by a person who follows a script to determine basic eligibility for the specific study. The IRB should review and approve the script and assure the procedures followed adequately protect the rights and welfare of the prospective subjects.

#### **7.5.11 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.

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

The IRB will review all gifts and incentives being particularly sensitive to the potential impact on potential subjects' decision to participate and on existing subjects' decision to continue or withdraw participation.

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

### **7.5.13 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 will ensure that consent forms are consistent with applicable state and local laws.

## **7.6 Possible IRB Actions**

### **7.6.1 Approval**

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.

## 7.6.2 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 will 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) will receive the response 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 will be informed of the outcome of the review of the investigator's response as part of the agenda of the next meeting.

### **7.6.3 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).

### **7.6.4 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 *Initial Study 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.

### **7.6.5 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.

### **7.6.6 Approval in Principle**

As per federal regulations [45CFR46.118], 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 pilots.

## **7.7 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, but not less than once per year. The date by which continuing review must occur will be recorded in the IRB minutes or other IRB records and communicated in writing to the investigator. Continuing review must occur as long as the research remains active including when the remaining research activities are limited to the analysis of private identifiable information.

### **7.7.1 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 (this serves as the protocol/research plan summary).
- The current protocol/research plan.
- The current consent document and the most recent signed consent document with the subject name redacted.
- 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).
- 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.

### **7.7.2 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 organizational issues.
- Research progress.

### **7.7.3 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 7.7.2 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.

### **7.7.4 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 7.2.1. 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.

### **7.7.5 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 7.6 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 will be referred to the convened board for review. If the IRB has significant concerns, the IRB may vote to suspend or terminate the research. See Section 8 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 will specify 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.

#### **7.7.6 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 will review the request and provide a determination regarding what activities, if any, may continue during the lapse. Such a determination may include a time limit or other conditions or restrictions. If the IRB decides that 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 will review the request and provide 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 will notify the 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.

## **7.8 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 make changes to the protocol for all remaining subjects or one-time changes for a specific subject (protocol exception). See Section 7.8.5 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 will typically require a new study application rather than allow such changes to be made through a modification to the existing protocol/research plan.

### **7.8.1 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.

### **7.8.2 Convened Board Review of Modifications**

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

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

At the meeting, the Primary Reviewer presents an overview of the proposed modifications and assists the IRB chair in leading the IRB through the assessment of the regulatory criteria for approval.

When the IRB reviews modifications to previously approved research, the IRB considers whether information about those modifications might relate to participants' willingness

to continue to take part in the research and if so, whether to provide that information to future/current/past participants.

### **7.8.3 Expedited Review of Modifications**

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

The reviewer(s) completes the *Initial Study 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 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.

### **7.8.4 Possible IRB Actions After Modification Review**

As with Initial Review, at the time of Continuing Review, the Convened IRB or IRB Member(s) conducting expedited review may take any of the following actions. See Section 7.6 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, they will refer the proposed modification to the convened board for review. If the proposed changes raise significant concerns on the part of the IRB, the IRB may vote to suspend or terminate the research. See Section 8 for a detailed discussion of suspensions and terminations.

### **7.8.5 Protocol/Research Plan Exceptions**

Protocol/research plan exceptions are circumstances in which the investigator wishes to deviate from eligibility criteria or one or more of the specific procedures called for in a 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.

## 7.9 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 will no longer be "at risk" under the study, a final report to the IRB allows it to close its files as well as providing information that may be used by the IRB in the evaluation and approval of related studies.

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

For multi-center research, the study may be closed once all research activities (as above) are complete at 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.

## **7.10 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 dates approval became effective and the study expiration date are sent to the investigator. For approval with conditions, the notification will include a listing of the conditions that must be satisfied. For a deferral, the notification 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.

## **7.11 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 will be reviewed in accordance with the procedures in Section 16. 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.

## **7.12 Appeal of IRB Decisions**

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



or terminated, the IRB will notify the investigator in writing of the suspension or termination and the reasons for its decision.

In cases where there is disagreement between the IRB and the investigator regarding the nature and extent of requested changes or the necessity of or basis for a suspension or termination, the investigator may submit an appeal to the IRB to request reconsideration. 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.

### **7.13 Research Previously Approved by Another IRB**

When an investigator transfers research to the medical school 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 8. Study Suspension, Termination, and Investigator Hold**

### **8.1 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 for a discussion of unanticipated problems and Section 16 for a discussion of non-compliance.

Suspension of IRB approval is a directive of the convened IRB or IRB chair to temporarily stop some or all previously approved research activities. Suspensions made by the IRB chair must be reported to a meeting of the convened IRB. Suspended research studies remain open and require continuing review. Investigators must continue to provide reports on adverse events and 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 shall notify the investigator in writing of suspensions and shall include a statement of the reasons for the IRB's actions and any requirements or conditions associated with the suspension (eg, notification of subjects). The investigator shall be provided with an opportunity to respond in person or in writing.

Suspensions of IRB approval must be reported promptly to the assistant dean for Research Compliance, Institutional Official, sponsors including federal department or agency heads, and federal oversight agencies according to applicable federal and organizational requirements. See Section 14 for a detailed discussion of 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 shall notify the investigator in writing of a study termination and shall include a statement of the reasons for the IRB's actions and any requirements associated with the termination (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, Institutional Official, sponsors including federal department or agency heads, and federal oversight agencies according to applicable federal and organizational requirements. See Section 14 for a detailed discussion of reporting requirements.

Suspension or termination of research studies approved by the IRB can also be issued by sponsors or funding agencies, senior leaders at the medical school (associate dean for Research, and Institutional Official), and senior leaders of the facilities where research takes place. The investigator must immediately report any such suspension or termination to the IRB of record. The IRB will then determine if steps must be taken to protect the rights and welfare of existing subjects and whether suspension or termination of IRB approval is warranted.

## **8.2 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.

To implement an investigator hold, the investigator must notify the IRB in writing that:

- They are voluntarily placing a study on hold requested by the investigator.
- A description of the research activities that will be stopped.
- Proposed actions to be taken to protect current participants.
- 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 HRPP/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 8.3, 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.

Investigators may request a modification of the research on hold by submitting a *Modification Request Form* to previously approved research.

### **8.3 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 9. Off-site IRB Policies and Procedures

### 9.1 Use of Independent or 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 independent or 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.

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. 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.

#### 9.1.1 *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:

- *Institutional Approval to Submit* to the medical school IRB.
- A copy of the external IRB initial application.
- Medical school and facility research approvals.
- A copy of the external IRB cover page or equivalent.
- Documentation of other required reviews (eg, conflict of interest and commitment, IBC).
- 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.

#### 9.1.2 *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 investigator will be notified that they may move forward with their submission to the external IRB. If the reviewing IRB requires documentation of this approval via a signed form or other form of documentation, it will be provided. Local policies concerning special topics (eg, use of legally-authorized representatives, consent requirements) may also be included in the notification.

### **9.1.3 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 10. 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.

### 10.1 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.
- 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.

### 10.2 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 study file. The medical school IRB maintains a separate 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 they exist.

- IRB reviewer forms (when expedited review procedures are used).
- Documentation of scientific or scholarly review (if available).
- Documentation of type of IRB review. For 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.

### **10.3 IRB Minutes**

Proceedings are written and available for review by the next regularly scheduled IRB meeting. Once accepted by the members, the minutes must not be altered by anyone including a higher organizational authority.

A copy of IRB-approved minutes for each IRB meeting is distributed to the assistant dean for Research Compliance 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 material 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/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, e.g., 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.

## 10.4 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.

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

## 10.5 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.

## 10.6 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.

## 10.7 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 organizational 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.

## 10.8 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 11. Obtaining Informed Consent from Research Subjects

No investigator conducting research conducted at, under the auspices of, or using the services or resources 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 11.9 of these procedures. Except as provided in Sections 11.10 and 11.11 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.

### 11.1 Definitions

- **Legally Authorized Representative:** A legally authorized representative 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 legally authorized representative includes legal guardians.
- **Legal guardian:** A person appointed by a court of appropriate jurisdiction.

### 11.2 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 Legally Authorized Representative 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; or fax; however, obtaining informed consent must allow for a dialogue so that the potential subject has the opportunity to ask questions and receive responses. Those obtaining consent must do so prior to entering a subject into a study, gathering 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 be able to answer questions about the study including those regarding risks, procedures, and alternatives.

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 the content of the consent document that is presented to the prospective study subjects.

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

### **11.3 Informed Consent Process**

Informed consent must be obtained under the following circumstances:

- Informed consent may only be obtained from subjects who have the legal and mental capacity to give consent. For subjects without that capacity, permission must be obtained from a legal guardian or a legally authorized representative.
- The informed consent process provides the prospective subject (or legally authorized representative) with sufficient opportunity to read the consent document, if applicable.
- The informed consent process shall be sought under circumstances that provide the subject (or legally authorized representative) 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 legally authorized representative). To the extent possible, the language should be understandable by a person who is educated to eighth-grade level and layman's terms shall be used in the description of the research.

- For subjects with limited fluency in the English language, informed consent must be obtained in a language that is understandable to the subject (or the subject's legally authorized representative). In accordance with this policy, the IRB requires that informed consent discussions include 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.

#### **11.4 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 12.8 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 organizational 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 audio-taping of

consent interviews, second opinions, use of independent consent observers, allowing a waiting period before enrollment, or involvement of a trusted family member or friend in the disclosure and decision making process.

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

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 11.6 above. When participants lack the capacity to give consent, investigators may obtain consent from the legally authorized representative of a subject as described in Section 12.8.

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.

## **11.5 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 at [ClinicalTrials.gov](http://ClinicalTrials.gov), as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the study results. You can search this website at any time."

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).

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.



## 11.6 Documentation of Informed Consent

Except as provided in Section 11.10 of this document, 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 legally-authorized representative at the time of consent.
- A copy of the signed and dated consent form must be given to the person signing the form and, as appropriate, their legally-authorized representative. The investigator should retain the signed original in the research records.
- 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 legally authorized representative, but the subject or representative must be given adequate opportunity to read it before it is signed.
  - A short form written consent document stating that the elements of informed consent have been presented orally to the subject or the subject's legally-authorized representative.

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 this 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.

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.

## **11.7 Special Consent Circumstances**

### **11.7.1 Enrollment of Persons with Limited English-language Proficiency**

#### *11.7.1.1 Expected Enrollment*

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

#### *11.7.1.2 Unexpected Enrollment*

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

If an investigator decides to enroll a subject into a study for which there is not an extant IRB-approved consent document in the prospective subject's language, the investigator must receive IRB approval to follow the procedures for a “short form” written consent in as described in Section 11.6.

#### *11.7.1.3 Use of interpreters in the consent process*

Unless the person obtaining consent is fluent in the prospective subject's language, an interpreter will be necessary to facilitate the consent discussion. Preferably someone who is independent of the subject (ie, not a family member) should assist in presenting information and obtaining consent. Whenever possible, interpreters should be provided copies of the translated consent, or short form and the IRB-approved consent script (typically the English-language version of the consent document) 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.

### **11.7.2 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 under “Oral Consent” (see Section 11.7.4).

### **11.7.3 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 11.6.

### **11.7.4 Oral Consent**

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

For research that is no more than minimal risk, documentation of consent may be waived according to the criteria in Section 11.9.

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.

## 11.8 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.

## 11.9 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 the waiver or alteration.
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

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 one of the following apply:

- 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.

FDA regulations do not provide for waivers of informed consent except in certain emergency situations. Additionally, waivers of consent are not permissible for federally-funded research using newborn blood Spots.

## 11.10 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 that either of the following apply:

- 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.) In order to waive written documentation of consent where the only record linking the participant and the research would be the consent document, the IRB has to determine that the research was not FDA-regulated.

- The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. The FDA does permit a waiver of documentation of consent if this condition is otherwise satisfied. This is most commonly applied in the context of minimal risk screening activities that are necessary to determine eligibility for enrollment in the full trial.

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.

### **11.11 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 legally authorized representatives.

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 Sections 11.11.2.1 and 11.11.2.2 below. The DHHS waiver is not applicable to research involving prisoners, pregnant women, fetuses, or in vitro fertilization.

#### **11.11.1 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 legally authorized representatives 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.

### **11.11.2 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:

- 1) 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.
- 2) Obtaining informed consent is not feasible because of all of the following:
  - a. The subjects will not be able to give their informed consent as a result of their medical condition.
  - b. The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible.
  - c. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.
- 3) Participation in the research holds out the prospect of direct benefit to the subjects because of all of the following:
  - a. Subjects are facing a life-threatening situation that necessitates intervention.
  - b. 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.
  - c. 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.
- 4) The research could not practicably be carried out without the waiver.
- 5) 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 legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.
- 6) 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 legally authorized representatives in situations where use of such procedures and

documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the research consistent with paragraph (7)(v) of this section.

- 7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:
  - a. 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.
  - b. 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.
  - c. 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.
  - d. Establishment of an independent data monitoring committee to exercise oversight of the research.
  - e. If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the research. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

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



### *11.11.2.1 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 11.11.2 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 11.11.2 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).

### *11.11.2.2 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 11.11.2 have been met relative to the research.

## Section 12. Vulnerable Subjects in Research

When some or all of the participants in research conducted at, under the auspices of, or using the services or resources of the medical school are likely to be vulnerable to coercion or undue influence or have diminished decision-making capacity, the research must include additional safeguards to protect the rights and welfare of these participants. The IRB must ensure that all of 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.

### 12.1 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 is able to 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 with regard to the laws in other jurisdictions.

- **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.

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 HRPP/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 with regard to the laws in other jurisdictions.

- **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:** A 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:** A 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 virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

## 12.2 Involvement of Vulnerable Populations

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

Research that is conducted or supported by DHHS and that involves any of these populations must comply with the requirements of the relevant subparts. Research funded 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.

## 12.3 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 through the use of consultants, of individual(s) who are knowledgeable about or experienced working with the vulnerable populations involved in the research proposal under review.

The IRB 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.

## **12.4 Procedures**

### **12.4.1 Initial Review of Research Proposal**

The investigator identifies the potential to enroll vulnerable subjects in the proposed research at initial review and, when asked, 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 evaluates the proposed safeguards for subjects, including, if applicable, the proposed plan for obtaining consent from legally authorized representatives and the plans for assent of children and adults unable to provide consent.

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

### **12.4.2 Continuing Review and Monitoring**

At Continuing Review, the investigator should identify the number and categories of vulnerable subjects enrolled and any problems that arose relevant to their rights and welfare.

## **12.5 Research Involving Pregnant Women, Human Fetuses and Neonates**

### **12.5.1 Research Involving Pregnant Women or Fetuses**

#### **12.5.1.1 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.

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 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.
- 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 paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
- For children (as defined in Section 12.1) who are pregnant, assent and permission are obtained in accord with the requirements of state law and the IRB.
- No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
- Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
- 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 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 3 business days. The circumstances that prohibited prospective confirmation of viability and the outcome of the subsequent consultation will be reported to the IRB within five (5) working days.

#### *12.5.1.2 Research Conducted or Supported by DHHS*

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

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

1. 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.

2. 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.
3. Any risk is the least possible for achieving the objectives of the research.
4. 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.
5. 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.
6. Each individual providing consent under paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
7. For children (as defined in Section 12.1) who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in Section 12.7.2.
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
10. Individuals engaged in the research will have no part in determining the viability of a neonate.

### **12.5.2 Research Involving Neonates of Uncertain Viability or Nonviable Neonates**

#### **12.5.2.1 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 of 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.
- 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 beginning 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 three (3) working days. The circumstances that prohibited prospective confirmation of viability and the outcome of the subsequent consultation will be reported to the IRB within five (5) working 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 or not 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 knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research.
- The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with the provisions of permission and assent, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

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 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 of the parents of a nonviable neonate *does not* suffice to meet the requirements of this paragraph.



### 12.5.2.2 Research Conducted or Supported by DHHS

Neonates of uncertain viability and nonviable neonates may be involved in research if all of 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 or not 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.
- The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with the provisions of permission and assent, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

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 legally

authorized representative of either or both of the parents of a nonviable neonate *does not* suffice to meet the requirements of this paragraph.

### **12.5.3 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).

### **12.5.4 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.

### **12.5.5 Research Not Otherwise Approvable**

#### **12.5.5.1 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 of 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*.

### 12.5.5.2 *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.

## **12.6 Research Involving Prisoners**

### **12.6.1 *Applicability***

This policy applies 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]

### **12.6.2 *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*.

### **12.6.3 *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 particular 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 covered by subpart C.

## **12.6.4 Review of Research Involving Prisoners**

### *12.6.4.1 Initial Review*

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

The prisoner representative must receive all review materials pertaining to the research (same as primary reviewer).

The prisoner representative must be present at a convened meeting when the research involving prisoners is reviewed. If the prisoner representative is not present, research involving prisoners cannot be reviewed or approved. The prisoner representative may attend the meeting by phone, video-conference, or webinar, as long as the representative is able to participate in the meeting as if they were present in person at the meeting.

### *12.6.4.2 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.

### **12.6.5 Incarceration of Enrolled Subjects**

If a study participant 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 has an effect on 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 study under Subpart C.
- If the participant should continue, one of two options are available:
  - Keep the participant enrolled in the study and review the research under Subpart C. If some of the requirements of Subpart C cannot be met or are not applicable (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.

### **12.6.6 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) Handbook*, 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.
- Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired.
- The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers.
- Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the investigator provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project.
- The information is presented in language which is understandable to the subject population.
- Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole.
- 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, taking into account the varying lengths of individual prisoners' sentences, and for informing subjects of this fact.

### **12.6.7 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.

### **12.6.8 Waiver for Epidemiology Research**

The DHHS Secretarial waiver for certain epidemiological research conducted or supported by DHHS functions as a fifth [category of permissible research](#) [68 FR 36929]. The criteria for this category are that the research must have as its sole purpose (i) to describe the prevalence or incidence of a disease by identifying all cases, or (ii) to study potential risk factor associations for a disease. The organization still must review the research under subpart C and certify to OHRP that an appropriately constituted IRB has reviewed the proposal and made all other required findings under DHHS regulations at [45 CFR 46.305\(a\)](#) and receive OHRP authorization prior to initiating any research involving prisoners. All of the other requirements of subpart C apply to research in this category.

## **12.7 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.

### **12.7.1 Allowable Categories**

In addition to the IRB's normal duties, research involving children must be reviewed by the IRB to determine if it fits within and is permissible under one or more federally-defined categories (OHRP/FDA). Each procedure or intervention that the child will undergo for the research must be taken into consideration, and, if the research includes more than one study group assignment (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 12.7.2.
- [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 of 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 12.7.2.
- [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 12.7.2.



- [45 CFR 46.407/21 CFR 50.54] Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children. When the IRB does not believe that the research meets the requirements of any of the above categories, and the IRB finds and documents that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, the IRB shall refer the research for further review as follows:
  - HHS conducted or supported research in this category 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 of 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 of 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 12.7.2.

## **12.7.2 Parental Permission and Assent**

### *12.7.2.1 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 11.5.

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

Permission from both parents is required for research to be conducted under Categories 3 [45 CFR 46.406/21 CFR 50.53] & 4 [45 CFR 46.407/21 CFR 50.54] above 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 11.9.
- 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 11.6.

#### *12.7.2.2 Assent from Children*

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

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

### *12.7.2.3 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, taking into account 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.

#### *12.7.2.4 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 (Categories 3 & 4 in Section 12.7.1), 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 the majority of children involved as subjects are not wards.

If the research meets the condition(s) above, an advocate must be appointed for each child who is a ward (one individual may serve as advocate for more than one child), in addition to any other individual acting on behalf of the child as legal guardian or in loco parentis.

The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

## **12.8 Adults with Impaired Decision-Making Capacity**

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

Research involving subjects without the ability to provide consent or with impaired decision-making capacity should only be conducted when the aims of the research cannot reasonably be achieved without their participation. Participation of such subjects in research cannot be justified solely on their availability or the convenience for the investigator.

When an investigator seeks to include such subjects in research, they must disclose this to the IRB and provide justification for why inclusion is necessary. If capacity to consent is questionable, or may fluctuate, investigators should include provisions for determining capacity to provide informed consent (see Section 11.4), and, if appropriate to reevaluate capacity during participation. When capacity to consent may diminish, the procedures should include, when possible and appropriate, designation of a legally-authorized representative, inclusion of the future legally-authorized representative in the initial consent discussion and process, and memorialization of the participant's wishes regarding the research in writing. When the research includes subjects likely to regain capacity to consent, the investigator should include provisions to inform the subject regarding their participation and to seek consent for ongoing participation, if applicable.

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

In evaluating research, the IRB must be able to determine that the risks to subjects are reasonable not only in relation to any benefits, but also in relation to the importance of the knowledge that may reasonably be expected to result. In considering the risks of research involving subjects unable to provide informed consent or with diminished capacity to do so, the IRB should consider whether any components of the research involve risks that are greater for participants with diminished capacity. For example, the population might experience increased sensitivity or discomfort to certain stimuli or may not be able to verbalize or otherwise demonstrate when they are experiencing discomfort or pain.

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

- Whether the aims of the research cannot reasonably be achieved without inclusion of the population.
- Whether the research is likely to improve the understanding of the condition, disease, or issue affecting the subject population.
- Whether any experimental procedure or interventions have undergone pre-clinical testing or human testing on other populations and whether the data from that testing supports its use in the proposed research.
- Whether the procedures or interventions that the subject will undergo in the research place them at increased risk and if appropriate mechanisms are in place to minimize risks, when possible.
- Whether the data and safety monitoring plan, including any stopping rules, is appropriate given the risks of the research and the vulnerability of the population.
- Whether the procedures for withdrawing individual subjects from the research are appropriate.

- Whether the recruitment procedures, consent process, and any plans for financial compensation support voluntariness and minimize the likelihood of undue influence or coercion.
- Whether the subjects will be exposed to financial or other risks that they might not consider acceptable if they had the capacity to provide consent, and whether appropriate mechanisms have been put into place to minimize these risks.
- Whether the procedures for determining capacity to provide consent, and for evaluating capacity on an ongoing basis, if applicable, are appropriate.
- Whether the procedures for informing subjects who regain capacity about their involvement in the research, and for obtaining consent for on-going participation, if applicable, are appropriate.
- Whether assent should be required when possible, and, if so, if the proposed procedures to obtain and document assent are appropriate.
- Whether a research subject advocate or consent monitor should be required, for some or all subjects.

## Section 13. FDA-Regulated Research

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

### 13.1 Definitions

- **Biologic:** Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other technologies. In general, the term "drugs" includes therapeutic biological products.
- **Dietary Supplement:** A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains a dietary ingredient. The dietary ingredients in these products can include vitamins, minerals, herbs and other botanicals, amino acids, other dietary substances intended to supplement the diet, and concentrates, metabolites, constituents, extracts, or combinations of the preceding types of ingredients. See section 201(ff) of the FD&C Act [21 U.S.C. 321(ff)].
- **Investigational Drug:** Investigational or experimental drugs are new drugs that have not yet been approved by the FDA or approved drugs that are being studied in a clinical investigation.
- **Investigational 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:** 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)]
- **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. [21CFR 56.102(d)]
- **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.

**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.

**Humanitarian Use Device (HUD):** A Humanitarian Use Device is a device intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.

## 13.2 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) working 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)]

### **13.3 Procedures**

At initial submission, the investigator must indicate on the 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 Worksheet 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.

### **13.4 Investigator Responsibilities**

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

- The investigator is responsible for ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs (including biological products) or agreement for clinical investigations of medical devices, the investigational plan and other applicable regulations, and any requirements imposed by the IRB or FDA.
- The investigator is responsible for personally conducting or supervising the investigation. When certain study-related tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.
- The investigator must maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks (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. An investigator should maintain separate lists for each study conducted by the investigator.

- The investigator is responsible for protecting the rights, safety, and welfare of subjects under their care during a clinical trial. This responsibility includes:
  - Informing subjects about the test articles being used for investigational purposes and ensuring that the requirements relating to obtaining informed consent are met.
  - Providing reasonable medical care for study subjects for medical problems arising during participation in the trial that are, or could be, related to the study intervention.
  - Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (eg, when the investigator is unavailable, or when specialized care is needed).
  - Adhering to the protocol/research plan so that study subjects are not exposed to unreasonable risks.
  - 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 obtained for a minimum of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such. Other regulations, such as HIPAA, organizational policies, or contractual agreements with sponsors may necessitate retention for a longer period of time.
- The investigator is responsible for controlling drugs, biological products, and devices according to FDA regulations and the Controlled Substances Act, if applicable.
- The investigator proposing the clinical investigation will be required to provide a plan to be evaluated by the IRB that includes storage, security, dispensing, and tracking (accountability) of the test article which may include delegation of such responsibilities to the pharmacy when the test article is a drug.
- The investigator shall furnish all reports required by the sponsor of the research including adverse events, progress reports, safety reports, final reports, and financial disclosure reports.
- The investigator will permit inspection of research records by the sponsor, sponsor representatives, HRPP/IRB staff, FDA, accrediting bodies, and any other agencies or individuals entitled to inspect such records under regulation, organizational policy, or contractual agreement.

## 13.5 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 the product will be stored and how it will be dispensed, usage tracked, and disposal or return. If the study entails greater than minimal risk, a plan for Data and Safety Monitoring must be included.

## 13.6 Clinical Investigations of Drugs and Devices

### 13.6.1 IND/IDE Requirements

For studies evaluating the safety or effectiveness of medical devices or experiments using drugs, biologics, dietary supplements, and other compounds that may be considered a drug under FDA regulations, the investigator must indicate on the IRB application whether or not an IDE or IND is in place, and, if not, the basis for why an IDE or IND is not needed. Documentation must be provided by the sponsor or the sponsor-investigator. Documentation of the IND/IDE could be 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 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 exempt or NSR, then the investigator should include documentation with the submission providing the basis for exempt or NSR categorization. If the FDA has determined that the study is 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.

#### *13.6.1.1 IND Exemptions*

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

- The drug being used in the research is lawfully marketed in the United States and all of the following requirements 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].
- The research only involves one or more of the following:
  - Blood grouping serum.

- Reagent red blood cells.
  - Anti-human globulin.
- For clinical investigations involving an in vitro diagnostic biological product, an IND is not necessary if a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and b) it is shipped in compliance with 312.160
- 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.
- 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)].
- Research 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.
- 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].

### 13.6.1.2 IDE Exemptions

For clinical investigations of devices, an IDE 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 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.

### 13.6.1.3 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 13.6.1. 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, unless the FDA has informed a sponsor that an application to the FDA is required, devices that are not significant risk and are not banned are considered to have approved applications for IDE's so long as the sponsor (or sponsor-investigator):

- Labels the device in accordance with 812.5.
- Obtains IRB approval of the investigation after presenting the reviewing IRB with an explanation of why the device is not a significant risk device, and maintains such approval.
- Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under 56.109(c).
- Complies with the requirements of 812.46 with respect to monitoring investigations.

- Maintains the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10).
- Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), 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.

## 13.7 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 fewer than 4,000 individuals in the United States per year [21 CFR 814.3(n)]. Federal law requires that IRBs approve the use of an HUD at a facility. Once approved, the clinical use of the HUD may be considered as any other approved device, with the caution that effectiveness has not been shown in clinical trials.

### 13.7.1 Definitions

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

### 13.7.2 IRB Review Requirements

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

When a 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 a FDA-approved IDE before starting the clinical investigation of a Significant Risk device.

### **13.7.3 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.

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

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

- Application Form – 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 facility. 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 facility.

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

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

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

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

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

#### **13.7.4 Emergency Uses of HUDs**

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

If a HUD is approved for use in a facility, but an appropriately trained and licensed health care provider wants to use the HUD outside its approved indication(s) in an emergency or determines that there is no alternative device for a patient's condition, the physician should consult with the HDE holder and IRB in advance if possible, obtain informed consent if possible, and ensure that reasonable measures are taken to protect the well-being of the patient such as a schedule and plan for follow up examinations and procedures to monitor the patient, taking into consideration the patient's specific needs and what is known about the risks and benefits of the device. The provider should submit a follow up report to the HDE holder and the IRB and must comply with medical device reporting requirements.

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

### **13.8 Expanded Access to Investigational Drugs, Biologics, and Devices**

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

#### **13.8.1 Expanded Access to Investigational Drugs and Biologics**

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

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

- Individual patients, including in emergencies [21 CFR 312.310].
- Intermediate-size patient populations [21 CFR 312.315].
- Larger populations under a treatment protocol or treatment IND [21 CFR 312.320].

Expanded access submissions are categorized by FDA as either “Access Protocols,” which involve a protocol amendment to an existing IND, or “Access INDs,” which are managed separately from any existing INDs.

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

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

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

Unless the conditions that permit an emergency use exemption (see Section 13.9) 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.

When the expanded access use is time-sensitive but does not satisfy the emergency use exemption criteria, and the medical school IRB may not be able to convene within sufficient time to meet the needs of the patient(s), the investigator should consult with the medical school HRPP director to determine if use of an external IRB is acceptable.

### **13.8.2 Expanded Access to Investigational and Unapproved Medical Devices**

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

The FDA has made the following mechanisms available for these circumstances:

- Emergency use.
- Planned emergency research (see Section 11.11.1).
- Compassionate use (or single patient/small group access).
- Treatment use.
- Continued access.

Investigators, when seeking access to investigational or unapproved devices under one of the above provisions, should work closely with the sponsor or manufacturer, the FDA, and the medical school HRPP director or IRB manager, to ensure that proper regulatory procedures are followed.

Unless the conditions that permit an emergency use exemption are satisfied (see Section 13.9), prospective IRB review and approval is required. This requires, among other things, that the IRB review the proposed use at a convened meeting at which a majority of IRB members are present.

When the expanded access use is time-sensitive but does not satisfy the emergency use exemption criteria, and the medical school IRB may not be able to convene within sufficient time to meet the needs of the patient(s), the investigator should consult with the medical school HRPP director or IRB manager, to determine if use of an external IRB is possible.

## **13.9 Emergency Use**

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

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.

### **13.9.1 Emergency Exemption from Prospective IRB Approval**

Under FDA regulations [21 CFR 56.104(c)], FDA exempts the emergency use of a test article from the requirement for prospective IRB approval, provided that such emergency use is reported to the IRB within five (5) working days. Any subsequent use of the test article in the facility requires IRB review. However, FDA acknowledges that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

FDA defines emergency use as the use of a test article in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not 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 Section 13.9.2), 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) working days when an emergency exemption is used. The IRB chair or designee will review the report to verify that circumstances of the emergency use conformed to FDA regulations. This must not be construed as an approval for the emergency use by the IRB, as an exemption from the requirement for prospective IRB approval has been invoked. When appropriate, in the event a manufacturer requires documentation from the IRB, the IRB will provide a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c).

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

### **13.9.2 *Emergency Exception from the Informed Consent Requirement***

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

- The subject is confronted by a life-threatening situation necessitating the use of the test article.
- Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
- Time is not sufficient to obtain consent from the subject's legally authorized representative.
- 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) working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

The IRB must be notified within five (5) working days when an emergency exception is used. The IRB chair or designee will review the report to verify that circumstances of the emergency exception conformed to FDA regulations.

### **13.9.3 *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 11.11.1 for additional detail on Planned Emergency Research.

## Section 14. Reportable Events

The medical school complies with DHHS and FDA regulations that require organizations to have written policies and procedures to ensure prompt reporting of: changes in research activity; unanticipated problems involving risk to subjects or others; and any instances of serious or continuing non-compliance to the IRB, organizational officials, and applicable federal agencies.

This section provides definitions and the policies and procedures regarding issues that arise during the conduct of research that must be reported.

### 14.1 Definitions

- **Unanticipated problems involving risk to participants or others:** Unanticipated problems involving risks to subjects or others refers to any incident, experience, outcome, or new information that:
  - Is unexpected.
  - Is related or 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.
- **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 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 (UADE):** An Unanticipated Adverse Device Effect 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)].

- **Protocol Deviations:** A protocol deviation is defined as a variation from the IRB-approved protocol/research plan that happens without prior review and approval of the IRB (eg, study visit outside protocol/research plan window, blood work drawn outside protocol/research plan window, etc.). Depending on the details, protocol/research plan deviations may be determined to be non-compliance (serious, continuing, or otherwise).
- **Protocol Exceptions:** Protocol exceptions are planned deviations from the protocol/research plan. Exceptions are anticipated and must occur with prior agreement from the sponsor, if applicable, and approval by the IRB. If an exception is implemented without IRB approval, it is a deviation, even when the sponsor has approved.

## 14.2 Procedures

### 14.2.1 Reporting

Adverse events in clinical trials must be reported to the sponsor in compliance with FDA regulations and sponsor requirements. Unless specifically required by the IRB as a condition of approval (eg, for first in human clinical trials), the medical school IRB does not accept reports of adverse events and IND Safety Reports that do not meet the definition of an unanticipated problem involving risks to subjects or others.

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

Unanticipated deaths and unanticipated life-threatening serious adverse events must be reported to the IRB immediately after the investigator first learns of the event.

Investigators must report the following events or issues to the IRB as soon as possible, but in no event later than seven (7) working days after the investigator first learns of the event.

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (eg, tendon rupture, progressive multifocal leukoencephalopathy).
- Multiple occurrences of an adverse event that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of adverse events represents a signal that the adverse events 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 adverse event 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 adverse event that is described or addressed in the investigator’s brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). A discussion of the divergence from the expected rate should accompany the report.
- Changes made to the research without prior IRB approval to eliminate apparent immediate hazards to the subject(s).
- Adverse events involving direct harm to subjects enrolled by the investigator (ie, local adverse events), which in the opinion of the investigator or sponsor, may represent an unanticipated problem involving risk to subjects or others.
- An unanticipated event related to the research that exposes subjects to potential risk but that does not involve direct harm to subjects (e.g. lost laptop).
- An unanticipated event related to the research that results in actual harm or exposes individuals *other than the research participants* (eg, investigators, research assistants, students, the public, etc.) to potential risk.
- IND Safety Reports from sponsors that meet the criteria for an unanticipated problem involving risk to subjects.
- Data and Safety Monitoring Reports that indicate that risks are greater than previously known or that indicate that the study requires modification or should be suspended or terminated.
- New information that indicates an increase to the risks or decrease to potential benefits of the research. Examples include:
  - An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB
  - A paper is published from another study that shows that the risks or potential benefits of the research may be different than initially presented to the IRB.
- New information that may impact the willingness of participants to continue in the research.
- A breach of confidentiality.
- Incarceration of a participant in a study not approved to enroll prisoners.
- Complaint of a subject when the complaint involves the health, safety, or rights of the subject or indicates unexpected risks, possible non-compliance, or cannot be resolved by the investigators and research staff.
- Protocol deviations.

- Sponsor or lead investigator/coordinating center imposed suspension or termination of some or all research activities.
- Unanticipated adverse device effects (UADEs). Regulations require that UADEs be reported to the sponsor and IRB as soon as possible but in no event later than ten (10) working days after the investigator first learns of the event [21 CFR 812.150(a)(1)].
- Any other adverse event or safety finding (e.g. based on animal or epidemiologic data) that indicates subjects or others might be at risk of serious, unanticipated harms that are reasonably related to the research. These would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects. An explanation of the conclusion should accompany the report.

### **14.2.2 Submission of Reports**

Investigators and research staff must report possible problems or issues with the research to HRPP/IRB staff in writing using the *Event Reporting Form*. The written report should contain the following:

- Detailed information about the event or issue, including relevant dates.
- Any corrective and preventative actions, planned or already taken, to ensure that the issue or problem is corrected and will not occur again.
- An assessment of whether any subjects or others were placed at risk as a result of the event or suffered any harm (eg, physical, social, financial, legal or psychological) and any plan to address these consequences.
- If a report from a sponsor is the basis for the report of a possible unanticipated problem involving risks to subjects or others, or a sponsor has requested the submission to the IRB, the report should be accompanied by an analysis from the sponsor detailing:
  - How the event or problem satisfies the definition of an unanticipated problem.
  - Proposed study-wide corrective actions or modifications to the research along with a timeline for anticipated completion of the actions.
  - Whether or not the problem has been reported as an unanticipated problem to any relevant federal agencies.
- If a sponsor or lead investigator or coordinating center suspends or terminates some or all research activities, the report should be accompanied by information from the sponsor detailing:
  - Why the suspension or termination was enacted.
  - If it was because of a possible a unanticipated problem (in which case the information in the bullet above must be included).
  - Any impact on subjects or actions to be taken to protect subjects.
  - Any plan to inform subjects of the suspension or termination and other pertinent information.
  - Whether the suspension or termination has been reported to any relevant federal agencies.
- Any other relevant information.

- Any other information requested by HRPP/IRB staff.

Reports are screened by HRPP/IRB staff and immediately forwarded to the IRB chair or vice chair if HRPP/IRB staff believes that immediate intervention may be required to protect participants or others from serious harm.

Upon receipt of a report or complaint from someone other than the investigator or research staff on behalf of the investigator, the IRB chair or vice chair notifies the investigator as appropriate.

### **14.2.3 IRB Procedures for Handling Reportable Events**

Upon receipt of the *Event Reporting Form* from an investigator, HRPP/IRB staff checks the form for completeness. If any applicable sections of the form are incomplete or have been answered unsatisfactorily, HRPP/IRB staff contacts the investigator or the designated contact person to obtain additional information. Corrections are documented in the IRB file, indicating the date, the person spoken with, and HRPP/IRB staff making the correction.

The IRB chair and/or other experienced member(s) designated by the IRB chair receives and reviews the report. The IRB chair (or designee) will make the initial determination as to whether the event is to be regarded as an unanticipated problem and/or non-compliance. (See Section 15 for procedures for unanticipated problems, and Section 16 for serious or continuing non-compliance.)

Based on the information received from the investigator, the IRB chair or designee may suspend research to ensure protection of the rights and welfare of participants. Suspension directives made by the IRB chair or designee must be reported to a meeting of the convened IRB and must follow notification procedures for IRB suspensions.

The IRB or the IRB chair (or designee) has authority to require submission of more detailed contextual information by the investigator, the sponsor, the study coordinating center, or DSMB/DMC about any event occurring in a research study as a condition of the continuation of the IRB's approval of the research.

If the IRB chair or designee determines that the problem does not possibly meet the definition of an unanticipated problem or serious or continuing non-compliance, the reviewer will consider whether any corrective or preventative actions are sufficient and whether modifications to the protocol/research plan, consent, or corrective action plan may be necessary, and refer the matter to the convened IRB for review if appropriate. The results of the review will be recorded in the study record and communicated to the investigator.

If the reviewer determines that the event is a possible unanticipated problem, the report is reviewed at a convened IRB meeting and must follow notification procedures for addressing unanticipated problems.

## **Section 15. Unanticipated Problems Involving Risks to Subjects or Others**

The medical school complies with DHHS and FDA regulations that require organizations to have written policies and procedures for reporting unanticipated problems involving risks to subjects or others to the IRB, organizational officials, and relevant federal agencies and departments.

This section provides the policies and procedures of how unanticipated problems are managed for research for which the medical school IRB serves as the IRB of record. Unless specifically required by the IRB, the medical school IRB does not accept reports of adverse events that do not meet the definition of an unanticipated problem.

### **15.1 IRB Review**

After a determination of a possible unanticipated problem involving risk to subjects or others, the report is placed on the agenda for the next convened IRB meeting and a primary reviewer assigned.

The primary reviewer is given the study file, current approved consent document (if applicable), previous reports of unanticipated problems, investigator's brochure (if one exists), event report, and recommendations from the IRB chair, or designee. All IRB members receive the event report and have full access to all materials upon request.

After review of the study and event report, the full IRB makes findings and recommendations based on the following considerations:

- Whether the reported event is an unanticipated problem according to the definition in this policy.
- The appropriate action(s), if any, in response to the report.
- Whether suspension or termination of study approval is warranted.

If the IRB finds that the event is not an unanticipated problem according to the definition in this policy, the IRB may recommend any of the following actions:

- No action.
- Requiring modifications to the protocol/research plan.
- Revising the continuing review timetable.
- Modifying the consent process.
- Modifying the consent document.
- Providing additional information to current participants (eg, whenever the information may relate to the subject's willingness to continue participation).
- Providing additional information to past subjects.
- Requiring additional training of the investigator and research staff.
- Other actions as appropriate given the specific circumstances.

If the IRB finds that the event is an unanticipated problem, according to the definition in the policy, the IRB may recommend any of the following actions:

- Requiring modifications to the protocol/research plan.
- Revising the continuing review timetable.
- Modifying the consent process.
- Modifying the consent document.
- Providing additional information to current participants (eg, whenever the information may relate to the subject's willingness to continue participation).
- Providing additional information to past participants.
- Requiring additional training of the investigator and research staff.
- Reconsidering approval.
- Requiring that current subjects re-consent to participation.
- Monitoring the research.
- Monitoring consent.
- Referral to other organizational officials and entities (eg, legal counsel, risk management, Institutional Official).
- Suspending the research approval.
- Terminating the research approval.
- Other actions as appropriate given the specific circumstances.

If a report suggests that participant safety is at risk, the IRB may immediately suspend or terminate the research. Any suspension or termination of research by the IRB must be promptly reported to the Institutional Official and relevant federal regulatory agencies through the Institutional Official. This should be done in writing.

If, after reviewing a report, the IRB finds that the event is an unanticipated problem, or that suspension or termination of approval is warranted, the IRB:

- Notifies the investigator in writing of its findings, with copies to the chair of the investigator's department, the investigator's immediate supervisor, and directors of other affected units
- Reports its findings and recommendations to the assistant dean for Research Compliance for further reporting to the appropriate federal officials, when required (see Section 18).

## Section 16. Non-compliance

As part of its commitment to protecting the rights and welfare of human subjects in research, the medical school reviews all reports and allegations of non-compliance and takes any necessary action to ensure the ethical conduct of research.

All Investigators and other study personnel involved in human subject research are required to comply with all laws and regulations governing their research activities, as well as with requirements and determinations of the IRB.

This section provides definitions and the policies and procedures of how complaints and allegations of non-compliance are managed by the IRB.

### 16.1 Definitions

- **Non-compliance:** Non-compliance is defined as failure to adhere to federal, state, or local regulations governing human subject research, organizational 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.

## **16.2 Reporting**

Investigators and research staff are required to report instances of possible non-compliance. 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 organizational 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 IRB manager or IRB chair directly to discuss the situation informally.

Reports of non-compliance must be submitted to the IRB within seven (7) working days of discovery of this non-compliance. The report must include a complete description of the non-compliance including any personnel involved.

Complainants may choose to remain anonymous.

## **16.3 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 an audit of the research in question.

When the 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 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 16.4 (Review of Findings of Non-compliance).

If in the judgment of the IRB chair or designee, any allegation or findings of non-compliance warrants suspension of the research before completion of any review or investigation to ensure protection of the rights and welfare of participants, the IRB chair may suspend the research as described in Section 8 with subsequent review by the IRB.

The 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.

## **16.4 Review of Findings of Non-compliance**

### **16.4.1 *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.

### **16.4.2 *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 committee 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.

### **16.4.3 *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 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.

The investigator is informed of the IRB determination and the basis for the determination in writing. If the IRB determines that the non-compliance was serious or continuing, the results of the final review will be reported as described below in Section 18.

## Section 17. Complaints

The medical school Hotline is 269.337.6505.

The IRB manager shall promptly address and, if appropriate, investigate all complaints, concerns, and appeals received by HRPP/IRB staff. This includes complaints, concerns, and appeals from investigators, research staff, participants, and any others, by any means of communication.

All complaints, written or oral (including telephone complaints), and regardless of point of origin, are recorded in writing and forwarded to the IRB manager and IRB chair. The IRB manager maintains a log of complaints, and provides regular reports to the IRB director and associate dean for Research Compliance, and a report at least annually to the Institutional Official.

Upon receipt of the complaint, the IRB chair or vice chair makes a preliminary assessment whether the complaint warrants immediate suspension of the research project. If a suspension is warranted, the procedures in Section 8 are followed.

If the complaint meets, or may meet, the definition of non-compliance, it is managed as an allegation of non-compliance according to Section 16.

If the complaint meets, or may meet, the definition of an unanticipated problem involving risk to subjects or others, it is managed according to Section 15.

If the complaint is actually an inquiry from a subject regarding study procedures, such as not receiving a payment, the complaint may be forwarded to the investigator and research staff to address. The investigator and research are required to inform the IRB within two weeks of the management plan, and also when the matter is considered closed including whether the subject is satisfied with the response.

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

## **Section 18. Reporting to Regulatory Agencies and Organizational Officials**

Federal regulations require prompt reporting to appropriate organizational officials and, as applicable, the federal department or agency head or the FDA, of (i) any unanticipated problems involving risks to subjects or others; (ii) any serious or continuing non-compliance with this policy or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval.

This section provides definitions and the policies and procedures to ensure prompt reporting to appropriate organizational officials and, as applicable, the federal department or agency head or the FDA.

### **18.1 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/research plan, 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, and Institutional Official review the letter and make modifications as needed.

The Institutional Official or the Associate Dean for Research is the signatory for all correspondence from the medical school.

The HRPP director sends a copy of the report to:

- The IRB by including the letter in the next meeting agenda as an information item.
- The Institutional Official and assistant dean for Research Compliance.
- The following federal agencies:
  - OHRP, if the study is subject to DHHS regulations or subject to a DHHS FWA.
  - FDA, if the study is subject to FDA regulations.
  - If the study is conducted or funded by any Federal Agency other than DHHS that is subject to “The Common Rule,” the report is sent to OHRP or the head of the federal agency as required by the agency.
  - 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 the investigator, sponsor, another organization, or other mechanisms.
- Investigator.
- Sponsored Programs Administration, if there is an award or the study is otherwise tracked by Sponsored Programs Administration.
- Sponsor, if the study is sponsored.
- Others as required by IRB agreement or as deemed appropriate by the assistant dean for Research Compliance or Institutional Official

The HRPP director ensures that all steps of this policy are completed within 30 working days of the determination. For actions that are more serious, the HRPP director expedites reporting.

## Section 19. Investigator Responsibilities

Principal Investigators are ultimately responsible for the conduct of research for the studies for which they serve as the Principal Investigator. Principal investigators may delegate tasks to appropriately trained and qualified investigators and research staff. However, investigators must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibilities.

### 19.1 Investigators

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

#### 19.1.1 *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 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 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.

#### 19.1.2 *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 could include:

- Obtaining information about living individuals by intervening or interacting with them for research purposes.
- Obtaining identifiable private information about living individuals for research purposes.

- Obtaining the voluntary informed consent of individuals to be subjects in research.
- Studying, interpreting, or analyzing identifiable private information or data for research purposes.

## 19.2 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 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, 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 of the research.
- Obtain IRB review and approval before changes are made to the research unless a change is necessary 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 required by applicable regulations, contractual agreements, and medical school policies.

Additional investigator responsibilities, including specific responsibilities for investigators engaged in FDA-regulated research are described elsewhere in the *Human Research Protection Program (HRPP) and Institutional Review Board (IRB) Handbook*.



### 19.3 Investigator Records

Investigators 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.
  - 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, organizational, 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. Information regarding record retention requirements is available from the HRPP and Sponsored Programs Administration.

### 19.4 Investigator Concerns

As needed, the HRPP director, assistant dean for Research Compliance, 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.

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 20. Sponsored Research

It is medical school policy that any sponsored research conducted at, under the auspices of, or using the services or resources of the medical school is conducted in accordance with federal guidelines and ethical standards.

This section provides definitions and the policies and procedures to ensure that all sponsored research meets these requirements.

### 20.1 Definitions

- **Sponsor:** Sponsor means the company, institution, individual donor, or organization responsible for the initiation, management or financing of a research study.
- **Sponsored Research:** Sponsored research means research funded by external entities (public, industry, or private) through a grant or contract that involves a specified statement of work (eg, the research proposal), including clinical trials involving investigational drugs, devices or biologics.

### 20.2 Responsibility

Sponsor grants, contracts, and other written agreements will be reviewed for the following by the Sponsored Programs Administration, with consultation with the IRB, as necessary:

- Inclusion of a written agreement with the Sponsor that addresses medical care for research participants with a research-related injury, if applicable.
- In studies where Sponsors conduct research site monitoring visits or conduct monitoring activities remotely, inclusion of a written agreement with the Sponsor that the Sponsor promptly reports findings to the medical school 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, inclusion of 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.
- Inclusion of a written agreement with the Sponsor about plans for disseminating findings from the research and the roles that investigators and Sponsors will play in the publication or disclosure of results.
- When participant safety could be directly affected by study results after the study has ended, inclusion of a written agreement with the Sponsor that the investigator or the medical school will be notified of the results in order to consider informing participants
- Payment in exchange for referrals of prospective participants (“finder’s fees”) are 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 21. 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.

### 21.1 Disclosure of Researcher Conflicts of Interest and Commitment

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 IRB purposes, review of researcher 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 conflicts disclosure indicating a new or changed interest. For FDA studies, the clinical investigator(s) shall supply to the sponsor the completed DHHS forms 3454 and 3455 one year following the completion of the study. For the medical school IRB, the completed medical school *Conflict of Interest – Significant Financial Interests Disclosure* form must be completed. HRPP/IRB staff notify 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 and HRPP/IRB staff that no researcher conflict was identified 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 prohibit participation by the researcher with a potential conflict until the review process is completed and the results are made available to the IRB.

## 21.2 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 effectively protects research subjects and the integrity and credibility of the research and the research program.

The IRB considers:

- 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.

## 21.3 Management of Conflicts of Interest and Commitment

The 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 IRB may either affirm or add additional stipulations. The 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 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 conflict lessens or resolves, the Research Integrity Officer and IRB adjust 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.

## 21.4 IRB Member Conflicts of Interest

No IRB member or alternate may participate in the review of any research project in which the member has a conflict of interest or commitment, except to provide information as requested. It is the responsibility of each IRB member to disclose any conflict of interest 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 an *IRB Member Research Conflict of Interest Assessment Form* when first appointed and annually thereafter, or sooner if there is a change in their conflicts. These forms may be submitted via mail, email, or in person and reviewed by the HRPP director, who determines if a conflict of interest exists. HRPP/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. HRPP/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 an immediate member of their family, 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.

## 21.5 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.

## **21.6 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 participants (“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.

## **Section 22. Participant Outreach**

The medical school is committed to ensuring that educational opportunities are offered to research participants, prospective research participants, and community members.

### **22.1 Responsibility**

The assistant dean for Research Compliance, IRB director, and HRPP/IRB staff are responsible for implementing, facilitating, and promoting educational opportunities to research participants, prospective research participants, and community members that will enhance their understanding of research involving human participants at the medical school and provide them the opportunity to provide input and express concerns.

### **22.2 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, brochures designed and developed by the medical school (eg, Volunteering in Research), and a listing of relevant research-related links.

The “Participant Outreach Corner” includes information regarding how to contact the medical school with any questions or concerns about specific research projects or research in general.

The “Participant Outreach Corner” includes a “Contact Us” 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.

#### **22.2.1 Evaluation**

On an annual basis, the medical school evaluates its community outreach activities and makes changes as appropriate. In order to formally evaluate its outreach activities, the assistant dean for Research Compliance and IRB 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 annual review are provided to the Institutional Official, and used to establish both the adequacy of current outreach activities and identify any additional resources that may be needed to meet the needs of the research community regarding research participant outreach.

## Section 23. 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 defines individually identifiable health information transmitted or maintained by a covered entity in any form (electronic, written, or oral) as Protected Health Information (PHI) and establishes the conditions under which investigators may access and use this information in the conduct of research.

Except as otherwise permitted, the Privacy Rule requires that a research subject “authorize” the use or disclosure of his/her PHI to be used in research. This authorization is distinct from the subject’s consent to participate in research, which is required under the Common Rule and FDA regulations.

Under the Privacy Rule, a HIPAA Authorization may be combined with the consent document for research. When the consent document is combined with an Authorization, 45 CFR part 46 and 21 CFR part 56 require IRB review of the combined document.

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.

### 23.1 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. However, PHI disclosures made before the compliance date for a covered entity are not part of the accounting requirement.
- **Authorization:** An individual’s written permission to allow a covered entity to use or disclose specified PHI for a particular purpose. Except as otherwise

permitted by the Privacy Rule, a covered entity may not use or disclose PHI for research purposes without a valid Authorization.

- **Covered entity:** A health plan, a health care clearinghouse, or a health care provider who transmits health information in electronic form in connection with a transaction for which DHHS has adopted a standard.
- **Data Use Agreement:** An agreement into which the covered entity enters with the intended recipient of a limited data set that establishes the ways in which the information in the limited data set may be used and how it will be protected.
- **Designated Record Set:** A group of records maintained by or for a covered entity that includes: (1) medical and billing records about individuals maintained by or for a covered health care provider; (2) enrollment, payment, claims adjudication, and case or medical management record systems maintained by or for a health plan; or (3) used, in whole or in part, by or for the covered entity to make decisions about individuals. A record is any item, collection, or grouping of information that includes PHI and is maintained, collected, used, or disseminated by or for a covered entity.
- **Disclosure:** The release, transfer, access to, or divulging of information in any other manner *outside* the entity holding the information.
- **Health Information:** Health Information means any information, whether oral or recorded in any form or medium, that: (1) is created or received by a health care provider, health plan, public health authority, employer, life insurer, school or university, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual.
- **Individually Identifiable Health Information:** Information that is a subset of health information, including demographic information collected from an individual, and (1) is created or received by a health care provider, health plan, employer, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; and (a) that identifies the individual; or (b) with respect to which there is a reasonable basis to believe the information can be used to identify the individual.
- **Limited Data Set:** Refers to PHI that excludes 16 categories of direct identifiers and may be used or disclosed, for purposes of research, public health, or health care operations, without obtaining either an individual's Authorization or a waiver or an alteration of Authorization for its use and disclosure, with a data use agreement.

- **Minimum Necessary:** The standard that uses the least information reasonably necessary to accomplish the intended purpose of the use, disclosure, or request. Unless an exception applies, this standard applies to a covered entity when using or disclosing PHI or when requesting PHI from another covered entity. A covered entity that is using or disclosing PHI for research without Authorization must make reasonable efforts to limit PHI to the minimum necessary. A covered entity may rely, if reasonable under the circumstances, on documentation of IRB or Privacy Board approval or other appropriate representations and documentation under section 164.512(i) as establishing that the request for protected health information for the research meets the minimum necessary requirements.
- **Privacy Board:** A board that is established to review and approve requests for waivers or alterations of Authorization in connection with a use or disclosure of PHI as an alternative to obtaining such waivers or alterations from an IRB. A Privacy Board consists of members with varying backgrounds and appropriate professional competencies as necessary to review the effect of the 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:** PHI is individually identifiable health information transmitted by electronic media, maintained in electronic media, or transmitted or maintained in any other form or medium. PHI excludes individually identifiable health information in education records covered by the Family Educational Rights and Privacy Act, as amended, 20 U.S.C. 1232g, records described at 20 U.S.C. 1232g(a)(4)(B)(iv), and employment records held by a covered entity in its role as employer.
- **Research:** A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. This includes the development of research repositories and databases for research.
- **Use:** With respect to individually identifiable health information, the sharing, employment, application, utilization, examination, or analysis of such information within the entity or health care component (for hybrid entities) that maintains such information.
- **Waiver or Alteration of Authorization:** The documentation that the covered entity obtains from an investigator or an IRB or a Privacy Board that states that the IRB or Privacy Board has waived or altered the Privacy Rule's requirement that an individual must authorize a covered entity to use or disclose the individual's PHI for research purposes.

- **Workforce:** Employees, volunteers, 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.

## 23.2 The Role of the IRB under the Privacy Rule

Under the Privacy Rule, IRBs gained authority to consider, and act upon, requests for a partial or complete waiver or alteration of the Privacy Rule's Authorization requirement for uses and disclosures of PHI for research. Although DHHS and FDA Protection of Human Subjects Regulations include protections to help ensure the privacy of subjects and the confidentiality of information, the Privacy Rule supplements these protections by requiring covered entities to implement specific measures to safeguard the privacy of PHI. If certain conditions are met, an IRB may grant a waiver or an alteration of the Authorization requirement for research uses or disclosures of PHI.

The medical school has designated the medical school IRB to fulfill the functions of a Privacy Board for human subject research.

The Privacy Rule does not change the composition of an IRB. The Privacy Rule permits a covered entity to accept documentation of waiver or alteration approval from any qualified IRB or Privacy Board -- not only the IRB overseeing the organization's research.

When acting upon a request to waive or alter the Authorization requirement, an IRB must follow the procedural requirements of the DHHS Protection of Human Subjects regulations and, if applicable, FDA regulations, including using either the normal review procedures (review by the convened IRB) or the expedited review procedures.

When a request for a waiver or an alteration of the Authorization requirement is considered by the convened IRB, a majority of the IRB members must be present at the meeting, including at least one member whose primary concerns are in nonscientific areas. 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. DHHS and FDA have established categories of research that may be reviewed by an IRB through an expedited review procedure. Expedited review of a request for a waiver or an alteration of the Authorization requirement is permitted where the research activity is on the DHHS or FDA list of approved categories and involves no more than minimal risks. In addition, 45 CFR 46.110 and 21 CFR 56.110 permit an IRB to use an expedited review procedure to review minor changes in previously approved research. 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 all the specified criteria for a waiver or an alteration were met.
- A brief description of the PHI for which use or access has been determined by the IRB to be necessary in connection with the specific research activity.
- A statement that the waiver or alteration was reviewed and approved under either normal or expedited review procedures.
- The required signature of the IRB chair or designee.

The medical school does not release PHI to investigators without individual authorization or proper documentation of an IRB or Privacy Board approval of a waiver or alteration of the requirement. In order to ensure that appropriate approvals are in place and that uses of patient information for research are in accordance with 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 medical school HRPP.

### **23.3 Authorization**

Except as otherwise permitted, the Privacy Rule requires that a research subject “authorize” the use or disclosure of his/her PHI to be used in research. This authorization is distinct from the subject’s consent to participate in research, which is required under the Common Rule and FDA regulations. Just as a valid consent under Common Rule and FDA regulations must meet certain requirements, a valid authorization must contain certain statements and core elements [45 CFR 164.508(c)]. At the medical school, authorization is typically a stand-alone document. Template HIPAA authorization forms are available from the HRPP.

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. Investigators are not required to retrieve information that was disclosed under the authorization before learning of the revocation. Additionally, investigators may continue to use and disclosure PHI that was already obtained for the research under an authorization to the extent necessary to protect the integrity of the research.

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 DHHS Protection of Human Subjects regulations or the FDA Protection of Human Subjects 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 (“end of the research study” or “none” are permissible for research, including for the creation and maintenance of a research database or repository).
- Signature of the individual and date. If the individual’s legally authorized representative signs the Authorization, a description of the representative’s authority to act for the individual must also be provided.

The Authorization must include the following required statements.

- A statement of the individual’s right to revoke his/her Authorization and how to do so, and, if applicable, the exceptions to the right to revoke his/her Authorization or reference to the corresponding section of the covered entity’s notice of privacy practices.
- Whether treatment, payment, enrollment, or eligibility of benefits can be conditioned on Authorization, including research-related treatment and consequences of refusing to sign the Authorization, if applicable.
- A statement of the potential risk that PHI will be re-disclosed by the recipient. This may be a general statement that the Privacy Rule may no longer protect health information disclosed to the recipient.

### **23.4 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.

For research uses and disclosures of PHI, an IRB or Privacy Board may approve a waiver or an alteration of the authorization requirement in whole or in part. A complete waiver occurs when the IRB or Privacy Board determines that no authorization will be required for a covered entity to use and disclose PHI for a particular research project. A partial waiver of authorization occurs when the IRB or Privacy Board determines that a covered entity does not need authorization for all PHI uses and disclosures for research purposes, such as accessing PHI for research recruitment purposes. An IRB or Privacy Board may also approve a request that removes some PHI, but not all, or alters the requirements for 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 (absent a healthcare or research justification for retaining them or a legal requirement to do so).
  - Adequate written assurances that the PHI will not be reused or disclosed to (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. However, DHHS also recognizes that “covered entities may elect to require duplicate Privacy Board reviews before disclosing [PHI] to requesting researchers” (67 Federal Register 53232, August 14, 2002). At the medical school, PHI may not be disclosed for the purposes of research pursuant to a waiver provided by an external Privacy Board without the approval of the HRPP or IRB.

### **23.5 Activities Preparatory to Research**

Under the preparatory to research provision of the Privacy Rule, a covered entity may permit a investigator who works for that covered entity to use PHI for purposes preparatory to research such as assessing the feasibility of conducting a research project, developing a grant application, or identifying potential subjects. A covered entity may also permit, as a disclosure of PHI, a researcher who is not a workforce member of that covered entity to review PHI (within that covered entity) for purposes preparatory to research.



The covered entity must obtain from a investigator representations 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) the PHI will not be removed from the covered entity in the course of review, and (3) the PHI for which use or access is requested is necessary for the research.

At the medical school, this is accomplished by the investigator submitting either a *Preparatory to Research* form, for projects in development, or a request for waiver of consent and authorization for screening purposes to the HRPP.

### **23.6 Research Using Decedent's Information**

For research using decedent's information, HRPP/IRB staff obtains all of the following from the investigator:

- Representation that the use or disclosure sought is solely for research on the protected health information of decedents.
- Documentation, at the request of the covered entity, of the death of such individuals.
- Representation that the protected health information for which use or disclosure is sought is necessary for the research purposes.

### **23.7 Future Uses: Databases and Repositories**

The Privacy Rule recognizes the creation of a research database or a specimen repository to be a research activity if the data/specimens to be stored contain PHI. There are two separate activities that the covered entity must consider: (1) the use or disclosure of PHI for creating a research database or repository; and (2) the subsequent use or disclosure of PHI in the database for a particular protocol/research plan.

Individual authorization for the storage of PHI for future research must be sought unless the IRB has determined that the criteria for a waiver of the authorization requirement are satisfied. See Section 23.4 for a discussion of waivers of authorization.

For medical school investigators, consent for research and authorization for use and/or disclosure of PHI may be combined in one document. As with any research activity, the combined consent/authorization for future research must describe the future research uses in sufficient detail to allow the potential subject to make an informed decision. The investigator and IRB should be cognizant of uses of information/specimens that the target community may consider particularly sensitive, such as genetics, mental health, studies of origin, and use of tissues that may have cultural significance.

The authorization for future research can be a stand-alone document or may be incorporated into another consent/authorization if the information/specimens will originate from another research activity, such as a clinical trial, unless the research involves the use or disclosure of psychotherapy notes. Authorizations for the use or disclosure of psychotherapy notes can only be combined with another authorization for a use or disclosure of psychotherapy notes.

If the 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.

### **23.8 Corollary and Sub-studies**

As with any other research, subject participation in corollary or sub-studies not essential to the primary aims of the research should be on a voluntary basis. This is particularly important when the primary research offers a potential benefit, such as treatment, that might compel the potential subject to agree to something that they otherwise would not.

HIPAA reinforces this ethical principle by explicitly stating that authorization for “unconditioned” activities, for which there is no associated treatment, benefit, or other effect on the individual subject associated with participation, cannot be required. The published preamble to HIPAA Omnibus clarifies the basis for this position, and the requirement that authorization for unconditioned activities involve a clear opt-in mechanism, stating:

“This limitation on certain compound authorizations was intended to help ensure that individuals understand that they may decline the activity described in the unconditioned authorization yet still receive treatment or other benefits or services by agreeing to the conditioned authorization.”

and

“...an opt out option does not provide individuals with a clear ability to authorize the optional research activity, and may be viewed as coercive by individuals.”

As with authorization for future research, it is acceptable to combine in a single document the authorization for a conditioned activity, such as a clinical trial, with authorization for an unconditioned activity such as a corollary or sub-study that does not directly benefit or effect the individual participant, provided that:

- The authorization clearly differentiates between the conditioned and unconditioned research activities.
- The authorization clearly allows the individual the option to opt 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.

### **23.9 De-identification of PHI under the Privacy Rule**

Covered entities may use or disclose health information that is de-identified without restriction under the Privacy Rule. The “Safe Harbor” method permits a covered entity to de-identify data by removing all 18 data elements that could be used to identify the individual or the individual’s relatives, employers, or household members. The covered entity also must have no actual knowledge that the remaining information could be used alone or in combination with other information to identify individuals. Under this method, the identifiers that must be removed are the following:

- Names.
- All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP Code, and their equivalent geographical codes, except for the initial three digits of a ZIP Code if, according to the current publicly available data from the Bureau of the Census:
  - The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people.
  - The initial three digits of a ZIP Code 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 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.

Data that is considered de-identified under HIPAA may still be considered human subject data under the Common Rule, particularly when working with a small data set or a data set that contains sufficient detail that investigators can readily ascertain the identity of individual subjects using the data set alone or combining it with other data sources. Additionally, while coded information may be de-identified under HIPAA, if the investigator holds or has the ability to access both the code and the data, the information is considered identifiable private information under the Common Rule.

### **23.10 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 will be made of the data, no attempt will be made to identify or contact individuals whose data are included in the limited data set, that appropriate safeguards are in place to protect the data from unauthorized use, and that the recipient will report any uses or disclosures of the PHI that they become aware of that not in keeping with the terms of the DUA. DUAs for the purposes of research are available through HRPP. DUAs should be submitted to the IRB along with the other project materials so that the medical school has a record of the agreement.

### **23.11 Research Subject Access to PHI**

With few exceptions, the Privacy Rule guarantees individuals access to their medical records and other types of health information. One exception is during a clinical trial, when the subject's right of access can be suspended while the research is in progress. The subject must have been notified of and agreed to the temporary denial of access when providing consent and authorization. Any such notice must also inform the individual that the right to access will be restored upon conclusion of the clinical trial. Language accommodating this exclusion is included in the applicable medical school research authorization templates.

### **23.12 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 communicating that information within the covered entity. A *disclosure* of PHI means communicating that information to a person or entity outside the covered entity. The Privacy Rule restricts both uses and disclosures of PHI, but it requires an accounting only for certain PHI disclosures.

Generally, an Accounting of Disclosures is required for:

- Routinely Permitted Disclosures (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 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 Policy*, for a detailed discussion on accounting of disclosures.

## **Section 24. Additional Protections for Information/Records Under Michigan Law**

### **24.1 HIV/AIDS and Other Serious Communicable Diseases (MCL 333.5131)**

Michigan Public Health Code defines a “communicable disease” in MCL 333.5101 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.”

A “serious communicable disease or infection” is defined as “a communicable disease or infection that is designated as serious by the [Michigan Department of Community Health]. Serious communicable disease or infection includes, but is not limited to, HIV infection, acquired immunodeficiency syndrome, venereal disease, and tuberculosis.”

Any report, record, or data related to HIV/AIDS or other serious communicable disease testing, care, treatment, reporting, or research is confidential and may be disclosed only in response to a court order, but only if: (1) the court determines that other ways of obtaining the information are not available or would not be effective; and (2) the public interest in and the need for the disclosure outweigh the potential for injury to the subject. The court order must:

- Limit disclosure to those parts of the subject's record that are determined to be essential to fulfill the objective of the order.
- Limit disclosure to those individuals whose need for the information is the basis of the order.
- Include other measures necessary to limit disclosure for the protection of the subject.

## Section 25. 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, Borgess Health, Bronson Healthcare) 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 User Agreement is completed.

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 both the IRB 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 Information Technology and the IRB

Investigators and research staff working with or at Borgess Health, Bronson Healthcare, 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.

## **25.1 NIH GRANTS**

The NIH has specific requirements about ensuring data security when collecting identifiable research data, as described in NIH Grants Policy Statement section 2.3.12, [\*Protecting Sensitive Data and Information in Research\*](#).

“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 26. Special Topics

### 26.1 Community-Based Research

Wherever research is being conducted in communities, investigators are encouraged to actively engage members of the community in the research process.

Community-based research (CBR) is research that is conducted as an equal partnership between academic investigators and members of a community. In CBR projects, the community participates fully in all aspects of the research process. Community is often self-defined, but general categories of community include geographic community, a community of individuals with a common problem or issue, or a community of individuals with a common interest or goal.

The most substantive community involvement is a subset of CBR called community-based participatory research (CBPR), which represents 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 studies, include:

- 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 protocol/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)?
- 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 staff, 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, such as specifically when the investigator/research staff is a friend, peer, service provider, doctor, nurse, social worker, educator, funder, or has another conflict?
- How will the research outcomes be disseminated to the community?
- Is there a partnership agreement or memorandum of understanding to be signed by the investigators and community partners that describes how they will work together?

## 26.2 Collaborative Research Projects

Multiple institutions may be engaged in the same non-exempt human subjects research project, commonly referred to as cooperative or collaborative research. For such research, the medical school acknowledges that each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with applicable federal regulations, and state and local laws. The medical school IRB is responsible for review of those aspects of the research in which the medical school or an organization that relies upon the medical school IRB is engaged, but may choose to review the research in its entirety.

However, when the medical school is the direct recipient (ie, primary awardee) of a HHS grant, contract, or cooperative agreement for the research, the medical school is responsible for review of the research even when all activities involving human subjects are carried out by employees or agents of another institution. In these circumstances, the medical school may choose to enter into a joint review arrangement, rely on the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort. A formal relationship must be established between the medical school and the other institution through an IRB Authorization Agreement, a Memorandum of Understanding, or other written agreement. This relationship must be formalized before the medical school may accept human research proposals from the other institution or rely on the IRB review of another institution. Similarly, when human subjects' research is HHS conducted or supported, regardless of whether the medical school is the primary awardee, a written agreement must be established if the medical school chooses to rely in whole or in part on the review of another qualified IRB, or to serve as the IRB of record for human subjects activities conducted by another organization.

When the medical school IRB reviews research conducted in whole or in part at another institution, the particular characteristics of each institution's local research context must be considered: (i) through knowledge of its local research context by the medical school IRB; (ii) through information gathering by appropriate designated medical school representatives, such as the IRB chair and/or other IRB members; or (iii) through the use of consultants.

## 26.3 The Medical School as Coordinating Center

It is the policy of the medical school to assure that all facilities participating in a human subjects study receive adequate information about the study in order to protect the interests of study subjects. Before a study can begin, it must be approved by the IRB of record for each participating organization, and, where appropriate, the IRB of record for the coordinating center.

When the medical school is the coordinating center for research occurring at multiple organizations, the PI must identify all institutions participating in the research, the responsible IRB(s), and the procedures for dissemination of protocol information (IRB initial and continuing approvals, relevant reports of unanticipated problems, protocol modifications, and interim reports) between all participating organizations. The PI is

responsible for serving as the liaison with other participating organizations and with regulatory and funding agencies. The PI is responsible for ensuring that all participating organizations obtain review and approval from their IRB of record and adopt all protocol modifications in a timely fashion. The PI is responsible for ensuring that the research study is reviewed and approved by any other appropriate committees at the coordinating center and at the participating organizations prior to enrollment of subjects.

The PI must follow these procedures when the medical school is the coordinating center:

- During the initial IRB submission of the multi-site study, the PI indicates in writing on the application form or in an application letter that the medical school is the coordinating center of a multi-site study.
- The PI includes the following information in their IRB application materials:
  - Name of each participating organization.
  - Name of PI at each participating organization.
  - Name of the IRB of record for each participating organization.
  - Summary description of human subjects' activities occurring at each participating organization.
  - Confirmation that each participating organization has an FWA (including FWA number).
  - Name of the IRB of record for each participating organization.
  - Method for assuring all participating organizations have the most current version of the protocol.
  - Method for confirming that all amendments and modifications in the protocol have been communicated to participating organizations.
  - Method for communicating to participating organizations any serious adverse events and unanticipated problems involving risks to subjects or others.
  - Method of communicating regularly with participating organizations about study events.
- The PI submits approval letters to the medical school IRB from the IRBs of record for all participating organizations.
- The PI maintains documentation of approvals and other correspondence between participating organizations and their IRBs of record.

## **26.4 Transnational Research**

The IRB reviews all transnational research involving human participants to assure adequate provisions are in place to protect the rights and welfare of the participants. Approval of research is permitted if “the procedures prescribed by the foreign institution afford protections that are at least equivalent to those provided in 45 CFR 46.”

All policies and procedures that apply to research conducted domestically is applied to research conducted in other countries, as appropriate.

For transnational research, 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 registered with OHRP) and/or local letters of support. The source of this information will depend on the nature of the study, on the country and on the resources available to the investigator. Where there is a local IRB/IEC/REB, the medical school IRB must receive and review the foreign institution or site's IRB/IEC/REB review and approval of each study prior to beginning the research at the foreign institution or site.

In some circumstances where research may be performed internationally and/or in settings where there are no IRBs, the medical school IRB may, prior to approval of the research, require additional verification and information from people outside the particular research project who are familiar with the customs, practices, or standards of care where the research will be taking place, such as local IRBs or ethics committees, other investigators with knowledge of the region, or a consultant who is an expert on the region. These individuals may either provide a written review of a particular protocol/research plan or attend an IRB meeting to provide the medical school IRB with recommendations based on his or her expertise.

For Federally funded research, approval of research for foreign institutions or sites "engaged" in research is only permitted if the foreign institution or site holds an Assurance with OHRP and local IRB review and approval is obtained.

Approval of research for foreign institutions or sites "not engaged" in research is only permitted if one or more of the following circumstances exist:

- When the foreign institution or site has an established IRB/IEC/REB, the investigator must obtain approval to conduct the research at the "not engaged" site from the site's IRB/IEC/REB or provide documentation that the site's IRB/IEC/REB 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/REB, a letter of cooperation must be obtained demonstrating that the appropriate institutional or oversight officials permit the research to be conducted at the performance site.
- IRB approval to conduct research at the foreign institution or site is contingent upon receiving documentation of the performance site's IRB/IEC/REB determination, or letter of cooperation, as applicable.

#### *26.4.1.1 IRB Responsibilities*

In addition to the usual considerations that are part of IRB review, the IRB considers the following issues in the review of transnational research:

- That the investigator and research staff are qualified to conduct research in that country including knowledge of relevant laws, regulations, guidance, and customs.
- That the consent process and consent documents are appropriate for the languages of the subjects and communication with the subject population.

Arrangements are considered to communicate with the subjects throughout the study (eg, to answer questions).

- How modifications to the research are to be managed. The IRB and investigators should consider as many contingencies (eg, survey questions) as possible when research is reviewed and approved.
- How complaints, non-compliance, protocol/research plan deviations, and unanticipated problems involving risks to participants or other are to be managed.
- How post-approval monitoring is to be conducted.
- If 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 IRB/IEC/REB.
- The mechanisms for communicating with the investigators and research staff when they are conducting the research in other countries.
- How to assure that adequate resources are available for data and safety monitoring, including taking into consideration that a foreign IRB/IEC/REB may not require continuing review of approved research.
- That the medical school may develop an Authorization Agreement (IAA) with a transnational entity only if the entity is an AAHRPP-accredited organization, or if the IRB of record has adopted the International Conference on Harmonization Good Clinical Practices (ICH-GCP) for human subjects research.

#### *26.4.1.2 Investigator Responsibilities*

It is the responsibility of the investigator and the foreign institution or site to assure that the resources and facilities are appropriate for the nature of the research.

It is the responsibility of the investigator and the foreign institution or site to confirm the qualifications of the investigators and research staff for conducting research in that country (or those countries).

Investigators obtain all appropriate host country permissions to conduct research (eg, institutional, governmental, ministerial, IRB, local, or tribal).

It is the responsibility of the investigator and the foreign institution or site to ensure that the consent process and consent document are appropriate for the languages of the subjects and communication with the subject population. Arrangements are considered to communicate with the subjects throughout the study (eg, to answer questions).

It is the responsibility of the investigator and the foreign institution or site to ensure that the following activities occur.

- Initial review, continuing review, and review of modifications.
- Post-approval monitoring.
- Handling of complaints, non-compliance and unanticipated problems involving risk to subjects or others.

The IRB will not rely on a local IRB/IEC/REB that does not have policies and procedures for all of the requisite activities.

Investigators must consider how complaints, non-compliance, protocol/research plan deviations, and unanticipated problems involving risks to participants or others are communicated to the IRB.

It is the responsibility of the investigator and the foreign institution or site to notify the IRB promptly if a change in research activities alters the performance site's engagement in the research (eg, a performance site that is "not engaged" begins to obtain consent of research participants).

Investigators must cooperate with the IRB regarding how and when post-approval monitoring will be conducted.

Investigators must establish mechanisms for communicating with the IRB when they are conducting the research in other countries.

#### *26.4.1.3 Consent Documents*

The informed consent documents must be in a language understandable to the proposed participants. Therefore, the IRB reviews the document and a back-translation of the exact content contained in the foreign language informed consent document, which must be provided by the investigator, along with the credentials of the translator, as part of the IRB application or Modification Request form. Verification of the back-translation must be placed in the IRB study file.

#### *26.4.1.4 Monitoring of Approved Transnational Research*

The medical school 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 medical school IRB and a local IRB/IEC/REB will both be involved in the review of research, there must be a plan for coordination and communication with the local IRB/IEC/REB.

The medical school 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 substantial changes in the research since the most recent review.

## **26.5 Research Repositories and Research Involving Coded Private Information or Biological Specimens**

### **26.5.1 Biological Specimens**

All activities involving the collection of human biological specimens for research purposes, as well as the research use of specimens collected for clinical care, must be conducted under the terms of an IRB-approved research protocol. The collection and use of human biological specimens, both identifiable and de-identified, must comply with all applicable laws and regulations for research involving human biological specimens or superseding requirements.

### **26.5.2 Regulatory Oversight**

Under HHS regulations, a human subject is a living individual about whom an investigator conducting research obtains either or both:

- Data through intervention or interaction with the individual.
- Identifiable private information.

Whether research involving biological specimens meets the definition of human subjects research is based on a) how the specimens were obtained and b) whether the specimens include identifiable private information.

If the specimens are obtained specifically for research purposes, then they have been collected through intervention or interaction with the individual and, thus, the research meets the definition of human subjects research. If the specimens were not collected for research purposes but as part of routine clinical care or other non-research purpose, then the research only meets the definition of human subjects research if the specimens include identifiable private information, with (see Section 26.5.4 regarding coded specimens).

An exception to this is federally-funded research involving Newborn Blood Spots. Based on the Newborn Screening Saves Lives Reauthorization Act of 2014 (Public Law No: 113-240), federally-funded research funded using newborn dried spots is considered human subjects' research regardless of whether the specimens are identifiable. Furthermore, the law eliminates the ability of the IRB to approve alterations or waivers of informed consent under 45 CFR 46.116(c) and 116(d) for research involving newborn dried blood spots.

FDA regulations do not apply to biological specimens unless they are gathered as part of a clinical investigation involving human subjects or being used to test a medical device (see Section 13 for more detail on FDA regulations). HIPAA does not cover biological specimens but does cover PHI linked to the specimens (see Section 23 for more detail on HIPAA).

If the research meets the definition of human subjects research, then all of the requirements of this document apply.



### **26.5.3 IRB Review**

Research involving only biological specimens may be exempt under the following exemption Category 4: “Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.” However, in order to qualify for exemption under this category, all of the specimens must exist prior to the research being submitted for IRB review. Additionally, this exemption cannot be applied to federally-funded research involving newborn blood spots.

Non-exempt research involving biological specimens only may be eligible for expedited review if it is minimal risk and falls within one of the following categories:

- (2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture [with restrictions]
- (3) Prospective collection of biological specimens for research purposes by noninvasive means.
- (5) Research involving materials...that have been collected, or will be collected solely for non-research purposes

All non-exempt research involving biological specimens that are not eligible for expedited review must be reviewed at a convened IRB meeting.

For all non-exempt research involving biological specimens, informed consent and documentation of consent is required unless waived by the IRB. Informed consent is required for all federally-funded research using newborn blood spots.

### **26.5.4 Coded Human Data and Biological Specimens**

The medical school IRB policies and procedures for coded human data and biological specimens are based on the OHRP guidance document entitled [Guidance on Research Involving Coded Private Information or Biological Specimens](#) (October 16, 2008). This document:

- Provides guidance as to when research involving coded private information or specimens is or is not research involving human subjects, as defined under HHS regulations for the protection of human research subjects (45 CFR part 46).
- Reaffirms OHRP policy that, under certain limited conditions, research involving only coded private information or specimens is not human subjects research.
- Clarifies the distinction between (a) research involving coded private information or specimens that does not involve human subjects and (b) human subjects research that is exempt from the requirements of the HHS regulations.
- References pertinent requirements of the HIPAA Privacy Rule that may be applicable to research involving coded private information or specimens.

The FDA definition of human subjects differs from the Common Rule definition. Use of coded specimens for FDA-regulated research such as research on in vitro diagnostic devices requires assessment according to the FDA regulations and guidelines. Investigators should contact HRPP/IRB staff for guidance.

For purposes of medical school policy, “coded” means that: (1) identifying information such as name or social security number that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (ie, the “code”); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

Obtaining identifiable private information or identifiable specimens for research purposes constitutes human subjects research. Obtaining identifiable private information or identifiable specimens includes, but is not limited to:  
Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that have been provided to the investigator from any source.  
Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that were already in the possession of the investigator.

In general, private information or specimens are considered to be individually identifiable when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Private information or specimens are not considered to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Research involving only coded private information or specimens (other than federally-funded research using newborn blood spots) do not involve human subjects per the Common Rule definition if both of the following conditions are met:

- The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals.
- The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
  - The investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased. HHS regulations do not require the IRB to review and approve this agreement.
  - There are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased.
  - There are other legal requirements prohibiting the release of the key to the investigators until the individuals are deceased.

In some cases, an investigator who obtains coded private information or specimens about living individuals under one of the conditions cited in 2(a)-(c) above may (1) unexpectedly learn the identity of one or more living individuals, or (2) for previously unforeseen reasons now believe that it is important to identify the individual(s). If, as a result, the investigator knows, or may be able to readily ascertain, the identity of the individuals to whom the previously obtained private information or specimens pertain, then the research activity now would involve human subjects. Unless this human subjects research is determined to be exempt (see Section 5), IRB review of the research would be required. Informed consent of the subjects also would be required unless the IRB approved a waiver of informed consent (see Section 11.9).

### **26.5.5 *Who Should Determine Whether Coded Private Information or Specimens Constitutes Human Subjects Research***

The investigator in consultation with the HRPP director or IRB chair determine if the research involving coded information or specimens requires IRB review, following the procedures for Human Subjects Research Determinations described in Section 5.

### **26.5.6 *Data or Biological Sample Repositories***

These policies and procedures apply to both data and biological sample repositories. For simplicity, both are referred to as “samples.”

A repository is a collection of data or biological specimens whose organizers:

- Receive data or specimens from multiple sources.
- Maintain the data or specimens over time.
- Control access to and use of data or specimens by multiple individuals and/or for multiple purposes, which may evolve over time.

There are two type of repositories:

- Non-research repositories created and maintained for purposes that are totally 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.

#### **26.5.6.1 *Non-research Repositories***

Even though repositories were not created for research purposes, they may contain information that is of great interest to researchers. The creation (or operation) of non-research databases or repositories does not involve human subject research and does not require IRB oversight. However, IRB oversight is required for use in research of

identifiable private information or identifiable human specimens from non-research databases and repositories (including data/tissue banks and registries). When research involves identifiable private information or identifiable human specimens each research use must receive prospective IRB review and approval and continuing IRB oversight.

Researchers should submit an application for IRB review and receive IRB approval before initiating the research.

Where available, the application should include any available information about the circumstances under which the information or specimens were originally collected.

Investigators who believe their research may be exempt from the human subject regulations should include a request for exemption under category 4 with the IRB application.

The IRB may require researchers to obtain the informed consent of subjects for research involving information or specimens contained in non-research databases or repositories. The IRB can waive the requirement for informed consent if the research meets the criteria cited in the regulations.

#### *26.5.6.2 Research Repositories*

Research repositories involve three components:

- Sample collection.
- Sample storage and data management.
- The recipient investigators.

##### *26.5.6.2.1 Sample Collection*

If the samples were collected for research purposes or are associated with information that can identify the donor, then informed consent must be obtained from the donor unless appropriately waived by the IRB.

Informed Consent information should include, in addition to the basic elements of consent described in Section 11, the following additional elements:

- A clear description of the:
  - Operation of the database.
  - Specific types of research to be conducted.
  - Conditions under which data will be released to recipient investigators.
  - Procedures for protecting the privacy of subjects and maintaining the confidentiality of data.
- A statement regarding future withdrawal of the data from the study (ie, state whether subjects may, in the future, request that their data be destroyed or that all personal identifiers be removed from data).

- Other information, such as the length of time that data will be stored, subjects' access to information learned from the research, and secondary uses of the samples should be considered as appropriate.

Repositories should have data submission policies to ensure that the data was collected in an ethical manner, such as informed consent and IRB approval.

#### 26.5.6.2.2 *Sample Storage and Data Management*

Repositories should have written policies on:

- Data and tissue submission requirements.
  - Informed consent.
  - IRB review.
- Physical and procedural mechanisms for the secure receipt, storage, and transmission of information and specimens.
- Policies on release of information and specimens.
  - Coding.
  - Release of identifiers.
  - Certificates of confidentiality.

#### 26.5.6.2.3 *Recipient Investigators*

Recipient investigators should have a written agreement with the repository. The agreement should specify the conditions under which the data is released to the recipient investigator(s). The terms under which the data is released determine whether the research requires IRB oversight.

#### 26.5.6.3 *IRB Oversight*

Operation of a research repository and its data or specimen management center at, under the auspices of, or using the services or resources of the medical school is subject to oversight by the medical school IRB unless the medical school has authorized another IRB to serve as the IRB of record. Proposals to establish a repository must be submitted to the IRB using the *Establishment of a Repository* form, specifying the conditions under which data and specimens may be accepted and shared, and ensuring adequate provisions to protect the privacy of subjects and maintain the confidentiality of data. The IRB also reviews and approves a sample collection protocol and informed consent document for distribution to sample collectors and their local IRB.

## 26.6 **Certificate of Confidentiality**

Certificates of confidentiality are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. A certificate of confidentiality does not protect against voluntary disclosures by the investigator, but

those disclosures must be specified in the informed consent form. An investigator may not use the existence of a certificate to withhold data if the participant consents in writing to the disclosure.

Generally, any research project that collects personally identifiable, sensitive information and that has been approved by an IRB operating under either an approved Federal-Wide Assurance issued by OHRP or the approval of the FDA is eligible for a certificate of confidentiality. Federal funding is not a prerequisite for an NIH-issued Certificate, but the subject matter of the study must fall within a mission area of the National Institutes of Health, including its Institutes, Centers, and the National Library of Medicine.

### **26.6.1 Statutory Basis for Protection**

Protection against compelled disclosure of identifying information about subjects of biomedical, behavioral, clinical, and other research is provided by the Public Health Service Act §301(d), 42 U.S.C. §241(d):

“The Secretary may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, including research on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals.”

### **26.6.2 Usage**

Certificates of confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. By protecting investigators and institutions from being compelled to disclose information that would identify research subjects, certificates of confidentiality help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to subjects.

Any investigator engaged in research in which sensitive information is gathered from human subjects (or any person who intends to engage in such research) may apply for a certificate of confidentiality. Research may be considered “sensitive” if it involves the collection of, for example, any of the following:

- Information about HIV, AIDS, and STDs.
- Information about sexual attitudes, preferences, and practices.
- Information about personal use of alcohol, drugs, and other addictive products.
- Information about illegal conduct.
- Information that could damage an individual's financial standing, employability, or reputation within the community.

- Information in a subject's medical record that could lead to social stigmatization or discrimination.
- Information about a subject's psychological well-being or mental health.
- Genetic studies, including those that collect and store biological samples for future use.
- Research on behavioral interventions and epidemiologic studies.

This list is not exhaustive. Investigators contemplating research on a topic that might qualify as sensitive should contact HRPP/IRB staff for help in applying for a certificate.

In the consent process and form, investigators should tell research subjects that a certificate of confidentiality is in effect. Subjects should be given a fair and clear explanation of the protection that it affords, including the limitations and exceptions. Every research project that includes human research subjects should explain how identifiable information will be used or disclosed, regardless of whether or not a certificate of confidentiality is in effect.

### **26.6.3 Limitations**

The protection offered by a certificate of confidentiality is not absolute. A certificate of confidentiality protects research subjects only from legally compelled disclosure of their identity. It does not restrict voluntary disclosures by subjects or investigators.

For example, a certificate of confidentiality does not prevent investigators from voluntarily disclosing to appropriate authorities such matters as child abuse, a subject's threatened violence to self or others, or from reporting a communicable disease. However, if investigators intend to make such disclosures, this should be clearly stated in the consent process and the form which research subjects are asked to sign.

In addition, a certificate of confidentiality does not authorize the person to whom it is issued to refuse to reveal the name or other identifying characteristics of a research subject if:

- The subject (or, if he or she is legally incompetent, his or her legal guardian) consents, in writing, to the disclosure of such information.
- Authorized personnel of the Department of Health and Human Services (DHHS) request such information for audit or program evaluation, or for investigation of DHHS grantees or contractors and their employees.
- Release of such information is required by the federal Food, Drug, and Cosmetic Act or regulations implementing that Act.

### **26.6.4 Application Procedures**

Any investigator engaged in research collecting sensitive information from human research subjects may apply for a certificate of confidentiality. For most research, certificates are obtained from NIH. If NIH funds the research project, the investigator may apply through the funding Institute. However, even if the research is not supported

with NIH funding, the investigator may apply for a certificate 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 299a-1(c) entitled “Limitation on Use of Certain Information”) or the Department of Justice (DOJ) confidentiality statute (42 USC section 3789g), then a certificate of confidentiality is not required.

If there is an Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE), the sponsor can request a certificate of confidentiality from the FDA.

For more information, see the [NIH Certificates of Confidentiality kiosk](#).

## **26.7 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>.

Investigators should consult these sources to determine if potential subjects should be advised of mandatory reporting requirements during the informed consent process.

## **26.8 Medical school Students and Employees as Subjects**

When medical school students and/or employees are being recruited as potential subjects, investigators must ensure that there are additional safeguards for these subjects. The voluntary nature of their participation must be primary and without undue influence on their decision. Investigators must emphasize to subjects that neither their academic status or grades, or their employment, will be affected by their participation decision.

To minimize coercion, investigators should avoid, whenever possible, the use of their students and employees in procedures which are neither therapeutic nor diagnostic. In these latter situations, investigators should solicit subjects through means such as bulletin board notices, flyers, advertisements in newspapers, and announcements in classes or laboratories other than their own. When entering a classroom to recruit



students and conduct research, e.g., administer a survey, investigators must do so at the end of the class period to allow non-participating students the option of leaving the classroom, thereby alleviating pressure to participate.

## **26.9 Student Research**

### **26.9.1 Human Subject Research and Course/Clerkship Projects**

Learning how to conduct ethical human subject research is an important part of a medical student's and graduate student's educational experience. Research activities that are designed as part of a course/clerkship 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 met:

- The research is discussed only within the course/clerkship for teaching and learning purposes, and the research results are reviewed only by the course/clerkship instructor for teaching 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, not presented in a public forum, made available on the internet, or published in any form in a journal).
- Research procedures are no more than minimal risk.
- Vulnerable populations are not studied (eg, children under age of 18 years, students, prisoners, persons who are cognitively impaired, etc.).
- Data collected are recorded in such a manner that the subjects are not identifiable (images in photographs and videotapes, and recorded voices are, by definition, identifiable).
- When appropriate, an informed consent process is in place.

In making a determination of whether or not a course/clerkship research project requires IRB review, the faculty instructor must contact HRPP/IRB staff for assistance. Any human subjects research activity that will ultimately contribute to part or all of a public presentation or publication must be reviewed and approved by the IRB prior to enrolling subjects and collecting data. IRB review and approval cannot occur after a study has begun.

#### **26.9.1.1 Responsibility of the Course/Clerkship Instructor**

When students participate in research activities as part of a curriculum, the faculty course/clerkship instructors are responsible for all aspects of the activities, including ensuring the protection of human subjects and compliance with all regulations and requirements. The faculty serving as course/clerkship instructors are responsible for communicating to students the ethics of human subject research, ensuring the protection of human subjects (including that a process is in place for obtaining voluntary informed consent from research subjects when appropriate), and monitoring the students' progress.

When participating in designing and/or implementing a research activity, students should be instructed on the ethical conduct of research and on the preparation of the IRB application if it is required. In particular, faculty instructors and students should both:

- Understand the elements of informed consent.
- Develop appropriate consent documents.
- Plan appropriate strategies for recruiting subjects.
- Identify and minimize potential risks to subjects.
- Assess the risk-benefit ratio for participating in the project.
- Establish and maintain strict guidelines for protecting privacy and confidentiality.
- Allow sufficient time for IRB review, if necessary, and completion of the project.

Faculty and students should contact HRPP/IRB staff with any questions.

### **26.9.2 Independent Study, Theses, and Dissertations**

Research activities for independent study, theses, and dissertations frequently meet the federal definition of human subjects research and must be submitted to the IRB for review and approval. Faculty advisers assume the responsibility for students engaged in independent research, and faculty instructors are responsible for research that is conducted as part of a course/clerkship. Any human subjects research activity that ultimately contributes to part or all of a thesis, dissertation, or other type of presentation or publication must be reviewed and approved by the IRB prior to enrolling subjects and collecting data. IRB review and approval cannot occur after a study has begun.

Students may not serve as principal investigators or investigators. There must be a faculty sponsor who is qualified to serve as PI, and who serves the PI on the study. Qualified students may serve as research staff.

### **26.10 Oral History**

A decision whether oral history or other activities solely consisting of open-ended, qualitative interviews are subject to the policies and regulations outlined in an institution's FWA and DHHS regulations for the protection of human research subjects (45 CFR 46) is based on the prospective intent of the investigator and the definition of "research" under DHHS regulations at 45 CFR 46.102(d): "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."

Specifically, for the purposes of this policy, the activity must meet both of the following standards (see Section 5) to be considered subject to human research protections policies:

- The activity involves a prospective protocol/research plan that incorporates data collection, including qualitative data, and data analysis to answer a research question.
- The activity is 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 following general principles apply for evaluating activities involving oral histories:

- Oral history activities, such as open ended interviews, that ONLY document a specific historical event or the experiences of individuals without intent to draw conclusions or generalize findings do not constitute "research" as defined by DHHS regulations 45 CFR 46.

Example: An oral history video recording of interviews with holocaust survivors is created for viewing in the Holocaust Museum. The creation of the video tape does not intend to draw conclusions, inform policy, or generalize findings. The sole purpose is to create a historical record of specific personal events and experiences related to the Holocaust and provide a venue for Holocaust survivors to tell their stories.

- Systematic investigations involving open-ended interviews that are designed to develop or contribute to generalizable knowledge (eg, designed to draw conclusions, inform policy, or generalize findings) would constitute "research" as defined by DHHS regulations at 45 CFR 46.

Example: An open ended interview of surviving Gulf War veterans to document their experiences and to draw conclusions about their experiences, inform policy, or generalize findings.

- Oral historians and qualitative investigators may want to create archives for the purpose of providing a resource for others to do research. Because the intent of the archive is to create a repository of information for other investigators to conduct research as defined by 45 CFR 46, the creation of such an archive would constitute research under 45 CFR 46.

Example: Open ended interviews are conducted with surviving Negro League Baseball players to create an archive for future research. The creation of such an archive would constitute research under 45 CFR part 46 because the intent is to collect data for future research.

Investigators should consult with HRPP/IRB staff regarding whether their oral history project requires IRB review.

## 26.11 Genetic Studies

Genetic research studies may create special risks to human subjects and their relatives. These involve medical, psychosocial, legal and economic risks, such as the possible loss of privacy, insurability, and employability, change in immigration status and limits on

education options, and may create a social stigma. Knowledge of one's genetic make-up may also affect one's knowledge of the disease risk status of family members.

In studies involving genetic testing, the IRB considers several questions, including:

- Will test results be provided?
- 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, the IRB considers several questions, including:

- Will DNA be stored or shared? If shared, will the subject's identity be known by the 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?

## **26.12 Case Reports Requiring IRB Review**

In general, an anecdotal report on one or a series of one (1) to three (3) patients seen in one's own clinical activities, and a comparison of these patients to existing reports in the literature, is not research and does not require IRB approval. A series of more than three (3) patients seen in one's own clinical activities, or gathering information on patients beyond one's own clinical activities such as by seeking out patients and reporting cases seen by other clinicians, creates the appearance of a systematic investigation with the intent to contribute to generalizable knowledge and therefore is considered research and requires IRB approval.

### **26.12.1 Definitions**

- **Single Case Report:** The external reporting (eg, publication, poster, or oral presentation) of an interesting clinical situation or medical condition of a single patient. Case reports normally contain detailed information about an individual patient and may include demographic information and information on diagnosis, treatment, response to treatment, follow-up after treatment, as well as a discussion of existing relevant literature. The patient information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience. Single case reports are not required to be

submitted for review by the IRB but investigators must still comply with all applicable patient privacy policies and requirements.

- **Case Series:** The external reporting (eg, publication, poster, or oral presentation) of an interesting clinical situation or medical condition in a series of patients (ie, more than one patient). Case series usually contain detailed information about each patient and may include demographic information and information on diagnosis, treatment, response to treatment, follow-up after treatment, as well as a discussion of existing relevant literature. The information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience. Case series of more than 3 patients must be submitted for IRB review or determination of exemption.

## **Section 27. Changes to the *Human Research Protection Program (HRPP) and Institutional Review Board (IRB) Handbook***

In an environment as dynamic as the medical school, change periodically occurs in the policies and procedures that apply to the HRPP and IRB. The *Human Research Protection Program (HRPP) and Institutional Review Board (IRB) Handbook*, which serves as the policies and standard operating procedures for the HRPP and medical school IRB(s), is incorporated by reference as part of the policies of Western Michigan University Homer Stryker M.D. School of Medicine. All medical school policies are available online.

Western Michigan University Homer Stryker M.D. School of Medicine reserves the right to change, at any time, without notice, the policies and procedures announced in the *Human Research Protection Program (HRPP) and Institutional Review Board (IRB) Handbook*. Such changes supersede any and all prior *Human Research Protection Program (HRPP) and Institutional Review Board (IRB) Handbook* policies, procedures, and practices implemented by the medical school. Notice of the implementation of the revised *Human Research Protection Program (HRPP) and Institutional Review Board (IRB) Handbook* is distributed to all investigators and HRPP/IRB staff.