Human Research Protection Program

(HRPP)

Policy Manual

June 2024

HRPP Policy Manual Revision Table

Date	Parts	Summary of Changes
August 2010		Formal HRPP manual created
September 2016		Manual revised to address AAHRPP standards and elements
March 2021		2018 Revised Common Rule edits and onboarding of clinical research.
June 2024		Revision to better define clinical research information

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Section 1: Human Subject Protection Program

Central Michigan University (CMU) fosters a research environment that promotes respect for the rights and welfare of individuals recruited for or participating in research conducted by or under the auspices of the University. In reviewing and conducting research, CMU will be guided by the principles of respect for persons, beneficence, and justice set forth in the Ethical Principals and Guidelines for the Protection of Human Subjects of Research (often referred to as the Belmont Report). The actions of CMU will be performed in accordance with the Department of Health and Human Services (DHHS) policy and regulations at 45 CFR 46 (also known as the "Common Rule"), and the Food and Drug Administration regulations at 21 CFR 50 and 21 CFR 56. The actions of CMU will also conform to all applicable federal, state, and local laws and regulations. To conduct this responsibility effectively, the University maintains an Institutional Review Board (IRB), in collaboration with its research community to ensure the ethical and equitable treatment of all human subjects in research conducted at, under the auspices of, or using the services or resources of CMU. This includes research that is externally funded, funded from internal sources, or conducted without direct funding, if CMU faculty, staff, students, or facilities are involved.

Mission

The mission of the HRPP is to:

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

The HRPP includes mechanisms to:

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

Institutional Authority

The CMU HRPP operates under the authority of the Central Michigan University Policy 5-4, Human Subject Research (HSR), adopted April 9, 2024. As stated in Policy 5-4, the Human Subject Protection Program (HRPP) Policy Manual serve as the governing policies for the conduct and review of all human research conducted at, under the auspices of, or using the services or resources of CMU.

IRB approval is necessary for any research conducted that involves human subjects. Prior to any research commencing, all required institutional approvals must be obtained, including IRB approval if needed. To receive an exemption determination, the research is subject to IRB review. A board member is tasked with reviewing and granting exemption status. Research not involving human subjects does not require IRB review.

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

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

The HSR Policy and these HRPP operating policies are made available to all CMU investigators and research staff and are posted on the CMU Office of Research Compliance (ORC) website.

Definitions

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

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 will cite the DHHS regulations.

Employee or Agent: For the purposes of this document, employees or agents refers to individuals who: (1) act on behalf of the organization; (2) exercise institutional authority or responsibility; or (3) perform institutionally designated activities. Employees and agents can include faculty, clinicians, 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).

Institutions are considered "engaged" in a research project when the involvement of their employees or agents in that project includes any of the following:

- Intervention for research purposes with any human subjects of the research by performing invasive or non-invasive procedures or manipulating the environment.
- Interaction for research purposes with any human subject of the research.
- Obtaining the informed consent of human subjects for the research.
- Obtaining for research purposes identifiable private information or identifiable biological specimens. This includes but is not limited to
    - observing or recording private behaviour;
    - using, studying, or analysing for research purposes identifiable private information or identifiable specimens provided by another institution or already in the possession of the investigators.

Additionally, institutions that receive an award through a grant, contract, or cooperative agreement directly from DHHS for non-exempt human subjects research (i.e., awardee institutions), are also considered engaged in research even where all activities involving human subjects are carried out by employees or agents of another institution.

Human subject: A living individual about whom an investigator (whether professional or student) conducting research:

(i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
(ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. [45 CFR 46.102(f)]

For research covered by FDA regulations (21 CFR 50 and 56), "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.

The terms "subject" and "participant" are used interchangeably in this document and have the same meaning.

Human Subjects Research: Human Subjects Research means any activity that meets the definition of "research" and involves "human subjects" as defined by the Common Rule, FDA regulations, or other applicable regulations.

Identifiable Information/Biospecimen: Identifiable information/biospecimen means for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information/biospecimen.

Institution*:* Any public or private entity, or department or agency (including federal, state, and other agencies).

Interaction*:* An interaction means communication or interpersonal contact between investigator and subject.

Intervention: An intervention includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

IRB: An institutional review board established in accord with and for the purposes expressed in this policy.

Private information*:* Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., 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 with the exception of the following 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 (i.e., knowledge gained from a study may be applied to populations outside of the specific study population), inform policy, or generalize findings.

<u>The following activities are not considered research</u>:

- Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individual(s) about whom the information is collected.
- Public health surveillance activities authorized by a public health authority that are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance.

    - Including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority.
    - Including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products.
    - Activities including those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).
- Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
- Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.
- Secondary research involving non-identifiable newborn screening blood spots.

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]. [21CFR 50.3(j)]

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

- **Human drugs**: The primary intended use of the drug is achieved through chemical action or by being metabolized by the body. A drug is defined as a substance recognized by an official pharmacopoeia or formulary; a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; a substance (other than food) intended to affect the structure or any function of the body; a substance intended for use as a component of a medicine but not a device or a component, part, or accessory of a device. Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process).
  http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm
- **Medical Devices**: A device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them; intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051512.htm
- **Biological Products**: Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources —
  human, animal, and microorganism — and may be produced by biotechnology methods and other new technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.
  http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm
- **Food Additives**: A food additive is defined in section 201(s) of the FD&C Act as any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristic of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use); if such substance is not Generally Recognized As Safe (GRAS) or sanctioned prior to 1958 or otherwise excluded from the definition of food

additives.
http://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm

- **Color Additives**: A color additive is any dye, pigment, or substance which when added or applied to a food, drug or cosmetic, or to the human body, is capable (alone or through reactions with other substances) of imparting color. Color additives for use in food, drugs, and cosmetics require premarket approval. Color additives for use in or on a medical device are subject to premarket approval if the color additive comes in direct contact with the body for a significant period of time.
http://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm
- **Dietary Supplements:** A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains one or more "dietary ingredients." The "dietary ingredients" in these products may include vitamins, minerals, herbs or other botanicals, amino acids, and other substances found in the human diet, such as enzymes. When a dietary supplement meets the definition of drug, it is regulated as such.
- **Medical Foods:** A medical food, as defined in section (b) of the Orphan Drug Act [21 U.S.C. 360ee (b) (3)], is a food which is formulated to be consumed or administered internally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.
- **Mobile Medical Apps:** Mobile apps are software programs that run on smartphones and other mobile communication devices. They can also be accessories that attach to a smartphone of other mobile communication devices, or a combination of accessories and software. Mobile medical apps are medical devices that are mobile apps, meet the definition of a medical device and are an accessory to a regulated medical device or transform a mobile platform into a regulated medical device.
- **Radioactive Drugs:** The term radioactive drug means any substance defined as a drug which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles of photons and includes any nonradioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance but does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides. The term "radioactive drug" includes "radioactive biological product".
- **Radiation-Emitting Electronic Products:** A radiation-emitting electronic product as any electrically powered product that can emit any form of radiation on the electromagnetic devices, magnetic resonance imaging (MRI) devices, laser toys, laser pointers, liquid crystal displays (LCDs), and light emitting diodes (LEDs).
- **Infant Formulas**: Infant formulas are liquid foods intended for infants and substitute for mother's milk.

- **Electronic Products**: The FDA regulates certain classes of electronic products including radiation-emitting electronic products such as microwaves and X-rays.

Ethical Principles

Central Michigan University is committed to conducting research with the highest regard for the welfare of human subjects. With the exception of international research, where consideration of alternative ethical principles may apply see Section 26, Special Topics, CMU upholds and adheres to the principles of *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research* by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research (1979).

These principles include:

Respect for Persons, which is ensured by obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations.

Beneficence, which is assured by ensuring that possible benefits are maximized, and possible risks are minimized.

Justice, which is the equitable selection of subjects.

In collaboration our research community, the CMU HRPP program is responsible to insure the ethical and equitable treatment of human subjects in research conducted at, under the auspices of, or using the services of CMU.

Regulatory Compliance

The HRPP is responsible for ensuring compliance with federal regulations, state law, and institutional policies. Human subjects research conducted at, under the auspices of or using the services or resources of CMU 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 Education Rights and Privacy Act (FERPA). The actions of CMU will also conform to all other applicable federal, state, and local laws and regulations.

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

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

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

Research supported by the DOD is reviewed and conducted in compliance with 32 CFR 219, 10 USC 980, applicable parts of title 21 CFR (50, 56, 312, 600, 812), DOD Instruction 3216.02, DOD Instruction 3210.07, and applicable additional requirements from respective DOD component(s). Researchers should consult the applicable DOD regulations, instructions, and directives when designing the research that may be supported by DOD.

These rules include but are not limited to:

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

Review by the applicable DOD Human Research Protection Program and IRB may be required. CMU 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 CMU FERPA contact. 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 (NIJ) (28 CFR 22). Investigators should consult these regulations and resources provided by NIJ when developing their research protocol. The IRB evaluates the research in accordance with these regulations if applicable.

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

CMU voluntarily applies the International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines (sometimes referred to as ICH-GCP or E6) to certain

types of human subject's research conducted under its HRPP only to the extent that they are compatible with FDA and DHHS regulations.

Federalwide Assurance (FWA)

Federal regulations require that federally conducted or supported human subjects research only be conducted at facilities covered by a Federalwide Assurance (FWA) approved by the DHHS Office for Human Research Protections (OHRP). Federal regulations require IRBs to register with DHHS if they will review human subjects research conducted or supported by DHHS or research subject to FDA regulations.

The FWA is an organization's assurance to the federal government that the listed Institutional Review Boards will review and oversee human subject research conducted at that site is in compliance with ethical principles and federal regulations pertaining to the protection of human subjects. Also, federal regulations require IRBs to register with DHHS if they review human subject research conducted or supported by DHHS or research subjects to FDA regulations.

CMU has an OHRP-approved Federalwide Assurance (FWA 00000755) and has designated three (3) internal IRBs (registered as IRB 00001370, IRB 00009405, IRB 00012496) to review human research conducted under its auspices.

There are twenty (20) federal agencies, including the DHHS, that issued revisions to the Common Rule. These changes went into effect on January 21, 2019, with the exception of a staged implementation on single IRB requirements. In its FWA, CMU has opted to limit the application of the FWA to research funded by DHHS or federal agencies that have adopted the Common Rule.

CMU reserves the right to apply "equivalent protections" to research that is not federally funded or supported by an agency that has adopted the Common Rule and is not subject to FDA regulations. CMU ensures human subjects benefit by applying the Common Rule standards that do not diminish the protections outlined in this document.

Research Covered by the Human Research Protection Program

The CMU Human Research Protection Program (HRPP) covers all research (regardless of funding) involving human subjects that is conducted under one or more of the following conditions:

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

Research conducted at, under the auspices of, or using the services or resources of CMU is subject to quality review, monitoring, inclusion of local research context and all other

requirements of Office of Research Compliance, even when CMU's IRB does not serve as the IRB of record.

As opposed to DHHS regulation which are oriented to institutions, FDA regulations outline the responsibilities of IRBs, investigators, and sponsors. CMU Principal or Sub-Investigators (as defined on the FDA 1572, or equivalent for medical device studies, or delegation log of responsibilities) requires review by an IRB designated by CMU Office of Research Compliance.

A CMU faculty member must be identified and designated to serve as the principal investigator when external organizations and researchers seek to conduct human subjects research under the auspices of CMU for the scope of the research.

Prior to initiating any research activities under the auspices of CMU, the investigator should consult with the Office of Research Compliance or IRB coordinator to understand their responsibility in following all CMU policies and procedures related to the research. The Director of Research Compliance, with the possible assistance of the IRB chair or vice chair, determine whether CMU is engaged in a particular research study.

CMU makes the determination of engagement, not investigators or other institutions. When CMU is engaged in research and an agreement entered into to cede review to an external IRB, it is at the discretion of the Institutional Official or designee. The OHRP guidance, "*Engagement of Institutions in Human Subjects Research (2008)*", provides additional information on determining engagement.

Written Policies and Procedures

The "CMU Human Research Protection Program Policy Manual" details the policies and regulations governing research with human subjects and the requirements for submitting research proposals for review by the CMU IRBs. The Director of Research Compliance (DRC) is responsible for implementing changes in procedures necessary to comply with changes in federal regulations as well as other changes dictated by the IRB. The policies and procedures are reviewed as needed to respond to regulatory changes due to the static nature of this document. The Institutional Official (IO) will approve all revisions of the policies and procedures.

The DRC will keep the Central Michigan University research community apprised on the IRB website and through campus electronic newsletters of new information that may affect the HRPP, including laws, regulations, policies, procedures, and emerging ethical and scientific issues. The policies and procedures will be available on the CMU IRB website.

HRPP Organization

The HRPP is a comprehensive system to ensure the protection of human subjects participating in research. It involves various individuals and committees with

responsibilities to oversee the system, and includes the Institutional Official, Director of Research Compliance, Office of Research Compliance/IRB staff, the IRB, Institutional Biosafety Committee, Radiation Safety Committee, Sponsored Program Director and staff, CMU Clinical Research Institute administration and staff, clinical research staff, legal counsel, investigators, and others. The objective of this system is to assist the institution 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 protection:

Institutional Official

The ultimate responsibility of the HRPP resides with the Vice President for Research and Innovation (VPRI), who serves as the Institutional Official (IO). The Institutional Official is legally authorized to represent CMU, is the signatory of the FWA, and assumes the obligations of the FWA. The IO is responsible for ensuring the CMU's HRPP and IRB has the resources and support necessary to comply with all institutional policies, federal regulations, and state laws that govern human subjects research. Such resources include but are not limited to:

- Communicating the staffing needs to the hiring authority, commensurate with the size and complexity of the research program.
- Appropriate office space, equipment, supplies and technology.
- Access to legal counsel when necessary.
- Support for HRPP/IRB staff, IRB members, investigators and research staff educational opportunities related to human subject protection.
- Resources for maintaining secure storage of HRPP and IRB records.
- Addressing the Compliance Office budgetary needs and allocating resources within the Office of Research and Graduate Studies (ORGS) budget.
- Assist in Conflict of Interest determinations.
- Assistance in developing Quality Improvement plans.

The Institutional Official on at least an annual basis reviews, with the Director of Research Compliance, the HRPP/IRB needs and makes changes as needed.

The Institutional Official is also responsible for:

- Policies and procedures created relating to the HRPP at CMU.
- Supporting the ethical conduct of research involving human subjects by assisting in maintaining an institutional culture to support such research and that institutional polices and federal regulations are respected.
- Ensuring the research review process is independent and free of coercion or undue influence and that CMU officials do not approve research that has not been approved by one of the CMU IRBs.
- Being accessible to IRB chairs and members if they experience undue influences or have IRB administration concerns.

- Appointing IRB members and ensure they have appropriate knowledge to apply the ethical standard and application regulations to studies they review.
- Providing oversight on the research conducted by CMU investigators, ensuring they have appropriate knowledge to apply the ethical standards and application of the regulations to their research.
- Ensuring IRB members, staff and investigators have access to educational opportunities to assist in responsible conduct of research at CMU.

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

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

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

Director of Research Compliance

The Director of Research Compliance (DRC) is appointed by and reports to the IO 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 all aspects of the HRPP program.
- Advising the IO on key matters regarding research conducted at, under the auspices of, or using the services or resources of CMU.
- Implementing the CMU's HRPP policy and procedures.
- Submitting, implementing, and maintaining an approved FWA through the Vice President for Research and Innovation and the DHHS Office of Human Research Protection (OHRP)
- Assisting investigators in their efforts to carry out CMU's research mission 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 and implementing educational plans, in conjunction with IRB Leadership, for IRB members, staff, and investigators.

- Develop training requirements for investigators, subcommittee members, and research staff. DRC will ensure that training is completed on a timely basis.
- Exercising day-to-day responsibility for the operation of the HRPP office, including supervision of HRPP staff.
- Overseeing all aspects of the IRB review process. This includes review of IRB minutes for accuracy and ensures proper documentation of discussions, including controverted issues and actions taken by the IRBs during convened meetings.
- Serving as the primary contact at CMU for DHHS, FDA, ORI and other federal regulatory agencies.
- Acting as liaison to the research community by responding to questions from faculty, students, and staff.
- Working closely with the Chairs of the IRBs on the development of policy and procedures as well as organizing and documenting the review process.
- Managing the budget of the CMU Office of Research Compliance (ORC).

Office of Research Compliance/IRB Staff

Support members for the HRPP and IRB include the Assistant Director of Research Compliance (ADRC), IRB Coordinator and the IBC Coordinator who assist DRC in the operations of the HRPP program. The HRPP/IRB staff must comply with all ethical standards and practices. The CMU Human Resources policies and procedures are followed for all staff who support the IRB program. Their responsibilities are outlined in their position descriptions and their performance are evaluated on an annual basis and as needed. The Office of Research Compliance staff reports to the Director of Research Compliance who is responsible for the office operations.

Institutional Review Board (IRB)

CMU support three IRBs, the Mt. Pleasant Campus IRB, an Ad Hoc IRB for Mt. Pleasant Campus, and the Pediatric IRB located at Children's Hospital of Michigan in Detroit. IRB members are appointed by the Institutional Official. The IRBs prospectively reviews and make decisions concerning all human subject research conducted at, under the auspices of or using CMU facilities, services or resources to do so. The IRBs is responsible for protecting the rights and welfare of human research subjects at the CMU. They discharge this duty by complying with the requirements of the Common Rule, federal and state regulations, the FWA, and applicable institutional policies. See *Section 1, Human Subject Protection Program*.

The IRB makes independent determinations on whether to approve or disapprove research based upon whether or not human subjects are adequately protected, and regulatory requirements are satisfied. This can be done in coordination with other committees and officials with responsibilities related to human subject research.

Research that has been reviewed and approved by the IRBs are subject to review and

disapproval by officials of CMU or organizations that rely upon the CMU IRBs. However, those officials may not approve human research that has not been approved or has been disapproved by the IRB.

CMU also uses the services of external IRBs. External IRBs are primarily relied upon for the review and oversight of industry-sponsored clinical studies. CMU may enter into reliance agreements with other institutions to follow the NIH and OHRP single IRB mandate when federally funded grants or contracts are involved.

Principle Investigator

The Principal Investigator (PI) is the ultimate protector of the human subjects who participate in research. The PI must abide by the highest ethical standards when developing a research protocol and to incorporate the principles of the *Belmont Report*. The PI is expected to conduct research in accordance with the IRB approved research protocol and to oversee all aspects of the research, including informed consent and by providing supervision of support staff, including oversight of the informed consent process. In addition to complying with all the policies and standards of the governing regulatory bodies, the investigator must comply with institutional and administrative requirements for conducting research. The investigator is responsible for ensuring that all research staff complete appropriate training and must obtain all required approvals prior to initiating research. When investigational drugs or devices are used, the PI is responsible for providing and following written procedures for their storage, security, dispensing, and disposal. See *Section 19 Investigator Responsibilities*.

Office of Research Compliance follows the Office of Sponsor Project's policy "*Eligibility to serve as CMU Principal Investigator/Project Director on Sponsored Projects*" which has designated individuals in the following categories as being eligible to serve as PI:

- All CMU tenure or tenure-track faculty
- All non-tenure College of Medicine faculty with a CMU paid appointment
- All professional staff with CMU permanent appointments
- CMU Medical Education Partners (CMEP) employees: submissions must also include a project Lead who is a paid CMU employee or faculty member, who meets the PI eligibility criteria. See the first three bullet point above.

Each study must have a PI and may have one or more additional investigators. Only an individual with a paid faculty appointment at CMU is eligible to serve the PI. The IRB will assess investigator qualifications and affirms that the proposed PI and investigators are qualified and appropriate for their roles on the study. The IRB may require additional investigators as part of the study to strengthen the expertise available on the research team or to conduct or oversee certain aspects of the research. Approval of a study by the IRB includes approval of the PI and the investigators, as affirmed or modified in the final approval by the IRB.

Individuals who are debarred, disqualified, or otherwise restricted from participation in research or as a recipient of grant funds for research by a federal, state, or other agency

may not serve as PI.

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

Office of General Counsel

The CMU HRPP relies on Central Michigan University Office of General Counsel for the interpretations and applications of Michigan law and the laws of any other jurisdiction where research is conducted as they apply to human subjects research. Counsel is available to provide guidance on other relevant topics as needed.

Office of Sponsored Programs

The Office of Sponsored Programs' (OSP) staff review externally funded grants and contracts with a wide variety of sponsors including federal, state, foundation, and not-for-profit. This institutional review ensures that the terms of an award are in compliance with institutional, federal, and state regulations and policies. The Vice President for Research and Innovation (VPRI), as well as the Executive Director for Research and Innovation (EDRI), within the Office of Research and Graduate Studies, have the authority to approve proposals and to execute most contract and grant agreements on behalf of the institution. Contract and grant agreements exceeding $250,000 are executed by the university's Provost. Industry sponsored clinical trials may be executed by the VPRI, the Vice President for Health Affairs, or the Provost.

When the grant or contract agreement includes activities that will be conducted by investigators who are not employees or agents of CMU, and where funding will be provided to the collaborating institution, a subaward is executed by the OSP between CMU and the collaborating entity. If human subject research is involved, the subaward includes the requirement for the collaborating institution to assure compliance with federal regulations for the protection of human subjects in research, including any training requirements for personnel. The collaborating institution must maintain documentation of compliance fulfilment of all federal, sponsor, and institutional requirements and provide it to CMU upon request.

The Office of Sponsored Programs maintains copies of the following items: proposal and award documents, proposal, and award budgets, including any budget justifications, proposal and award Cayuse shells, including documentation of senior leadership reviews and approvals, Cayuse financial disclosure forms, including any associated management plans, reporting, training, and specialized compliance requirements, and expenditure tracking.

Office of Information Technology

The HRPP has established a very close working relationship with the Office of Information Technology. OIT Directors from various academic units sit on the IRB and actively participate in protocol review. They also offer technical assistance to investigators developing applications to conduct research involving human subjects and conducts educational presentations to the board.

Office of Risk Management

The IRB consults the Office of Risk Management when questions arise about indemnification and liability of investigators when conducting research in other states or countries.

Clinical Research Institute

CMU College of Medicine's Clinical Research Institute (CRI) mission is to service as a center for pediatric research that will advance clinical care, provide children and their families with access to cutting-edge treatment options, and improve the lives of children in Detroit and beyond. The CRI is dedicated to providing a comprehensive and seamless network of support to clinician-scientists and trainees who practice at the Children's Hospital of Michigan.

CRI supports physicians and research investigators through the following services that may include, but not limited to, the following:

- Grants administration.
- Regulatory management.
- Research Design and analysis.
- Support of clinical and basic science research.
- Research mentorship education and training.
- Liaison with sponsors, contract research organization, and monitors.

Study-Specific Coordination

Investigators conducting non-industry sponsored studies may need to obtain and document the approval, support, or permission of specific individuals, departments, and entities affected by the conduct of the research, besides having IRB approval. This information is provided via the electronic application and could encompass the following:

- Sites where research activities will take place (e.g., hospitals, outside institutions, schools, community centers).
- Departments or units that will perform testing or provide services for the research (e.g., pathology, pharmacy, radiology, nursing).
- Departments or units from which data will be requested (e.g., medical records, registries, databases, registrar).

- Studies that use student or faculty data (e.g., surveys, opinions, academic information, etc.)
- Other CMU committees, as applicable (e.g., Institutional Biosafety Committee).

When applicable, a letter of support, collaboration, permission, or approval from the designated authority, should be included in the electronic application to the IRB. The application will be reviewed by the IRB coordinator to ensure that all necessary letters are included.

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

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

Section 2: Quality Assurance and Improvement

The objective of Central Michigan University's HRPP Quality Assurance and Quality Improvement activities are to measure and improve human research protection effectiveness, efficacy, and compliance with organizational policies and procedures and applicable federal, state, and local laws. The Quality Assurance and Quality Improvement activities will be managed and implemented by the Director of Research Compliance.

Audits and Inspections by Regulatory Agencies and Sponsors

When investigators receive an audit or inspection communication from a regulatory agency, the investigators need to inform the HRPP and any associated service areas (e.g., CRI, pharmacy). Assistance will be provided to the Investigator in preparing for such audits and the Director of Research Compliance, Vice President of Research and Innovation or designee may attend the entrance and exit interviews. Prompt reporting of all reports from the regulatory audits must be provided to the HRPP who will provide the report to the appropriate IRB, Director of Research Compliance, and the associated service areas. The HRPP/IRB coordinator may assist in preparing a response to the findings if the Institutional Official or Director of Research Compliance deems it appropriate.

If the Director of Research Compliance receives notification a CMU IRB is to be audited by an external regulatory agency, the Institutional Official and all appropriate persons with CMU will be notified. The IRB provides the regulatory agency with full access to all requested information and is fully responsive to requests and required actions.

All reports from an external agency's audit or inspection will be provided to an external IRB, to review, in which CMU has entered into a Reliance Agreement to oversee the research. The overseeing IRB may require corrective and preventative action (CAPA), a follow-up report, or other actions as needed to support compliance and ensure the protection of human subjects.

Investigator Audits and Compliance Reviews

The Assistant Director of Research Compliance, or designee, is responsible for directed ("for cause") audits and periodic ("not for cause") compliance reviews of research conducted at, under the auspices of, or using the services or resources of CMU. Directed audits of IRB-approved research studies are requested by the DRC and/or IRB Chair in response to identified concerns. In collaboration with the IRB Chair and/or IO, the ADRC compiles the results and the written report is reviewed by the IO. External directed audits and periodic compliance reviews will be conducted, as needed, at non-Central Michigan University sites, where the CMU IRB serves as the "IRB of Record". Periodic compliance reviews are conducted using a systematic method to review IRB-approved research on a regular basis.

Compliance reviews are conducted to:

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

The results of compliance reviews are reported to the DRC, investigator, and others as appropriate. If an audit or review finds that subjects in a research project have been exposed to unexpected serious risk, the reviewer will promptly report such findings to the DRC and the IRB Chair for immediate action.

The Director of Research Compliance will provide to the IRB the report or summary when appropriate. Any non-compliance is managed according to the procedures in *Section 16, Non-compliance*.

The Office of Research Compliance will advise the investigator to report the compliance review to the external IRB, where CMU has ceded oversight/jurisdiction, in accordance with the external IRB's policies and procedures.

If issues are identified that indicate possible misconduct in research, the procedures in CMU Policy 3-29, *Research Integrity and Misconduct*, are followed.

Directed audits and periodic compliance reviews may include, but are not limited to:

- Requesting progress reports from researchers.
- Evaluating the integrity of data security.
- Examining investigator-held research records.
- Contacting research subjects.
- Observing research sites where research involving human research subjects and/or the informed consent process is being conducted.
- Evaluating advertisements and other recruiting materials as deemed appropriate by the IRB.
- Reviewing projects to verify that no unapproved changes have occurred since previous review.
- Monitoring conflict of interest concerns to assure the consent documents include the appropriate information and disclosures.
- Monitoring HIPAA or FERPA authorizations.
- Conducting other monitoring or auditing activities as deemed appropriate by the IRB.

IRB Internal Compliance Reviews

Internal directed audits and random internal compliance reviews will be conducted. The results may impact current practices, may require additional educational activities, and will be reported to the IO. The Assistant Director of Research Compliance or designee will:

- Review the IRB minutes to determine that adequate documentation of the meeting discussion has occurred. This review is based on the OHRP and FDA regulations "111" criteria. Additional criteria like the specifics of the protocol (e.g., subparts, device determinations), level of risk, protection of vulnerable populations, waivers or alteration of consent, HIPAA authorization and period of approval should be present, as required.
- Assess the IRB minutes to assure that a quorum was met and maintained.
- Evaluate the continuing review discussions to assure they are substantive and meaningful. Verify that no approval lapse has occurred since the previous IRB review.
- Observe IRB meetings or other related activities.
- Review of expedited review documentation to determine that adequate documentation of the review has occurred. Verifying the study qualifies for expedited review and the "111" criteria are addressed. The protections of vulnerable populations, waivers or alterations of consent, documentation of consent, HIPAA authorization, and the period of approval are noted, as required.
- Verify the consent forms has all required elements included.
- Review the IRB database to assure tasks are completed accurately and whether adequate documentation of exemptions, expedited review, and other outside of committee reviews has occurred.
- Verify IRB approvals for collaborating institutions or external performance sites.
- Review the appropriate metrics (e.g., time from submission to first review) to evaluate the quality, efficiency, and effectiveness of the IRB review process.
- Review the emergency/disaster preparedness plan.
- Perform other monitoring or auditing activities deemed appropriate.

The DRC will review the results of internal compliance reviews with the IO and when appropriate IRB Chair and members of the IRB. If any significant deficiencies are noted in the review, a corrective action plan will be developed by the DRC. The DRC will be responsible for implementing the corrective action plan, the results of which will be evaluated by the IO.

Quality Assessment and Improvement

The Director and Assistant Director of Research Compliance are developing a quality assessment and improvement plan. In developing a plan, the goals will be to achieve and maintain one measure of compliance and at least having one objective achieved. This will be done by targeting the levels of quality, efficiency, and effectiveness of the HRPP by using defined objectives, measures and methods to assess them.

All quality assurance reports, both research-related and HRPP-related, will be reviewed by the DRC and the IO to determine if systemic changes are required in the HRPP to prevent re-occurrence of noncompliance. If so, a corrective action plan will be developed, implemented, and evaluated by the DRC and IO.

Section 3: Education and Training

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

A vital component of a comprehensive Human Research Protection Program is an education program for IRB Chairs, IRB members, HRPP/IRB staff and investigators and their research staff. CMU is committed to providing training and an on-going educational process for IRB members and the HRPP/IRB staff related to ethical concerns and regulatory and institutional requirements for the protection of human subjects.

Orientation

New IRB members, including alternate members will meet with the DRC and/or IRB Chair for an orientation session. At the session, an overview of the federal regulations is reviewed and an orientation to the IRB process is provided. Also, the new member is provided with access to:

- CMU's *Human Research Protection Program (HRPP) Policy Manual*
- The Belmont Report
- Federal Regulations for protection of human subjects
- Comparable Resources
  - A resource list from OHRP website.
  - Tools such as checklists used by IRB reviewers.

Initial Training and Education

New IRB members and HRPP/IRB staff must complete the CITI training modules that are required by CMU Office Research Compliance for the campus where the research they will review will be conducted: Central Michigan University, Central Michigan University- Detroit or Central Michigan University- Saginaw. Prior to serving as primary or independent reviewers, new members are to be orientated to review procedures with the DRC and/or IRB Chair; work with the IRB Coordinator on the use of the electronic management system for conducting reviews; and work with an experienced IRB member to conduct expedited reviews.

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 is continuous for IRB members throughout their service on the IRB. Educational activities include, but are not limited to,

- In-service education training at IRB meetings.
- Education and training workshops.
- Copies of appropriate publications.

- Identification and dissemination by the DRC of 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, mail, or during IRB meetings.
- Providing support for webinars and conferences.

IRB members and HRPP/IRB staff are also required to complete the modules of CITI courses that are required by CMU every three years as part of the continuing education requirements.

The activities for continuing education vary on a yearly basis depending on ORGS/ORC budget and areas of need, as determined by the Director of Research Compliance. The DRC in collaboration with the IRB chair determine which continuing education activities are mandatory for IRB members and staff in a given year. 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 (e.g., a webinar or conference), then an equivalent educational opportunity may be offered at the discretion of the DRC.

Training and Ongoing Education of Investigators and Research Team

One component of a comprehensive HRPP is an education program for all individuals involved with research subjects. 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 CMU. CMU is committed to providing training and an on-going educational process for investigators and their research team related to ethical concerns and regulatory and institutional requirements for the protection of human subjects.

Evidence of current training for each investigator and their research staff with the date of completion within three 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 IRB staff at the time of initial application and continuing review.

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.

Investigators or members of their research staff can affiliate another institution's CITI training to CMU to show that they have successfully completed human subjects research training equivalent to that required by CMU. If their certification is current, the IRB staff will determine to accept the other institutions certification until the expiration date. If certification has expired, CMU CITI course needs to be completed.

All investigators and their research staff must meet CMU continuing education requirement every three (3) years after certification of Initial Education through the

review of appropriate refresher modules at the CITI web-based training site for as long as they are involved in human subject research. There is no exception to this requirement. Other training may be acceptable as determined by the DRC.

Investigators must submit evidence of continuing education prior to the expiration of their training certification. New research protocols and applications for continuing review will not be accepted from PIs who have not submitted satisfactory evidence of continuing education.

Investigators who are also IRB Chair, IRB members, or IRB staff will also need to satisfy the training requirements for IRB members and staff described in this policy.

Equivalent Training

External Investigators

If external investigators or research staff believe they have successfully completed human subject research training equivalent to that required by CMU, they may request that the CMU accept their training as equivalent to the required CITI courses. The DRC or designee reviews the documentation and determines if it satisfies CMU's requirements.

Refresher Training

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

Section 4: Institutional Review Board

CMU has established three Institutional Review Boards (IRB) to ensure the protection of human subjects in research conducted under the auspices of Central Michigan University. All non-exempt human subjects research conducted under the auspices of Central Michigan University must be reviewed and approved by a CMU IRB prior to the initiation of the research. The reference to the Institutional Review Board (singular) is meant to refer to all Institutional Review Boards registered to CMU and noted on the most current version of the CMU IRB Registration approved by the Office of Human Research Protections.

Majority of the human subject research conducted on the Mt. Pleasant campus have a behavioral science or education focus. These protocols are reviewed by IRB #1 or the *ad hoc* board, IRB#2. The pediatric board, IRB #3, review mainly biomedical studies and clinical trials done by the pediatric faculty of the College of Medicine.

CMU 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 CMU IRB as the IRB of Record and delineating the responsibilities of each organization, or the CMU IRB and the investigator will be evaluated during the review process and executed prior to the final approval of such research.

The Institutional Official may also authorize use of external IRBs through master research agreements. The authorized external IRBs that serve as the IRB of Record for CMU have the same authority as the CMU IRB and as such all determinations and findings of the external IRBs are binding.

IRB Authority and Independence

The CMU IRB derives its authority from the CMU HRPP policy, as cited in Section 1, *Institutional Authority*. Under the federal regulations, the CMU IRB authority includes:

- To approve, require modifications to secure approval, or disapprove all research activities overseen and conducted under the auspices of, or using the services or resources of CMU or for which the CMU 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 suspend or terminate approval of research not being conducted in accordance with the 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.

The IRB functions independently. If an IRB chair, member, or staff person feels that there was an attempt to coerce or unduly influence by any party, they shall make a confidential report to the IO, depending on the circumstances. Issues or concerns involving the IO will be reported to the Provost, and other appropriate institutional official(s) or the CMU ethics hotline. The IO or other official receiving the report will investigate, and if necessary, prescribe corrective action to prevent additional occurrences. Similarly, the IRB must remain free from the influence of financial and other institutional interests. No individual with primary responsibility for the business and financial interests of the organization may serve on the IRB.

Research that has been reviewed and approved by the IRB may be subject to further review and approval or disapproval by officials of the institution. However, those officials may NOT approve research involving human subjects if it has not been approved by the IRB. CMU officials may strengthen requirements and/or conditions, add other modifications to secure CMU approval or approval by another CMU committee. Any changes required by CMU officials of previously IRB approved research proposals and/or consent forms must be reviewed and re-approved by the IRB before the changes or modifications may be initiated unless the change is necessary to eliminate an immediate hazard to human subjects.

The number of active IRBs registered to CMU is specified in the FWA. The IO and the DRC will review the activity of the IRB on at least an annual basis and determine the appropriate number of IRBs that are needed for the institution.

CMU has three separately constituted and registered IRBs:

- IRB1 is located on the Mt. Pleasant campus and meets during the academic year (OHRP registration # IRB00001370)
- IRB2 is located on the Mt. Pleasant campus and meets when an ad hoc meeting is necessary usually during summer months. (OHRP registration # IRB00009405)
- IRB3- Peds/Children's Hospital of Michigan located in Detroit, MI at the Detroit Medical Center- Children's Hospital of Michigan campus and meets year-round. (OHRP registration # IRB00012496)

Roles and Responsibilities

IRB Chair

The Institutional Official, in consultation with the Director of Research Compliance, Chair of University Pediatrics and current IRB Chairs, appoints a Chair of the IRB to serve for renewable three-year terms. Any change in appointment, including reappointment or removal, requires written notification.

The IRB Chair should be a highly respected individual, from within Central Michigan University, capable of ensuring the matters brought before it is managed with fairness and impartiality. The IRB must be perceived to be fair, impartial, and immune to pressure by the institution's administration, the investigators whose protocols are

brought before it, other committees, and other professional and nonprofessional sources and entities.

The IRB Chair is responsible for:

- conducting IRB meetings.
- conducting expedited reviews, determining if research fits into the exempt categories and if the research involves research and/or human subjects.
- designating other experienced IRB members to perform expedited and exempt reviews and other IRB functions.
- delegating responsibilities to IRB members or HRPP staff as appropriate.
- advising the IO and the DRC about IRB member performance and competence.

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 performance of IRB Chair will be reviewed annually by the Director of Research Compliance, in consultation with the IO. Feedback from this evaluation will be provided to the Chair. If the Chair is not acting in accordance with the IRB's mission, following institutional policies and procedures, has an undue number of absences, or is not fulfilling the responsibilities of the Chair, he/she may be removed by the IO.

IRB Vice Chair

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

The performance of IRB Vice Chair will be reviewed annually by the Director of Research Compliance, in consultation with the IRB Chair. Feedback from this evaluation will be provided to the Vice Chair. If the Vice Chair is not acting in accordance with the IRB's mission, following institutional policies and procedures, has an undue number of absences, or is not fulfilling the responsibilities of the Vice Chair, he/she may be removed by the IO.

Voting IRB Members

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

- Completing initial and ongoing education and training requirements see *Section 3, Training and Continuing Education of the IRB Chairs, IRB Members and Staff*.
- Maintaining the confidentiality of IRB deliberations and research reviewed by the IRB.
- Conducting and documenting reviews of assigned research in a timely fashion.

- Attending IRB meetings as scheduled.
- If a member is unable to attend a scheduled meeting, he/she should inform the IRB Chair, Vice Chair, or IRB Coordinator. They should provide IRB Coordinator with sufficient notice, whenever possible, for the coordinator to arrange for an alternate member to attend.
- If an IRB member is to be absent for an extended period of time, he or she must notify IRB staff at least 30 days in advance so that an appropriate alternate member can be scheduled to attend. If the member has a designated alternate, the alternate can serve during the primary member's absence.
- Recusing oneself from final deliberations and voting when the IRB member has a conflict of interest or commitment.
- Conducting themselves in a professional and collegial manner.

The IRB Chair, in consultation with the Director of Research Compliance, designate experienced IRB members to conduct expedited and exempt reviews.

Alternate IRB Members

The appointment, qualifications, and responsibilities of alternate members (non-voting member) are the same as those of voting IRB members. Alternate members' expertise and perspective are comparable to those of voting members.

The term "alternate" and "voting" are used for the roster that is filed with OHRP, IORG registration. CMU records voting members for a convened meeting on the agenda. This allows for any member listed on the roster to serve as a voting member at a convened meeting when their expertise is needed.

An alternate member is encouraged to attend convened meetings but will not be counted towards quorum unless a voting member is absent or recuses. The IRB minutes will document when an alternate member replaces a voting member at a convened meeting.

To ensure a quorum at a convened meeting, the IRB coordinator determine approximately 1-2 weeks in advance which members will be present and will serve as voting members. Voting members noted on the agenda and in the minutes.

Experienced alternate members may be designated to conduct expedited reviews.

IRB Leadership

The IRB Chair, Vice Chair(s) of the Mt. Pleasant and the Pediatric board each meet with the staff of the Office of Research Compliance, monthly, to discuss various topics that could improve efficiency of operations, quality of reviews and effectiveness of members and investigators. The upcoming convened IRB meeting protocols are discussed to identify if specific regulations may need to be covered at the meeting.

IRB Composition

The IRB is designed to be diverse and multidisciplinary to ensure its advice and counsel is respected and the rights, safety, and well-being of human participants involved in research studies are safeguarded. The membership must possess the professional competence necessary to review the research projects submitted. The structure composition of the IRB assures that research involving human participants is conducted in compliance with relevant regulations and the areas of specialty that encompasses most research performed at CMU. A member of the IRB may fill multiple membership position requirements (e.g., nonscientific and unaffiliated).

- The IRB will have at least five members with varying backgrounds to promote adequate review of research activities commonly conducted by the organization.
- The IRB will be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.
- In addition to possessing the professional competence necessary to review specific research activities, the IRB will be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB will therefore include persons knowledgeable in these areas.
- If the IRB regularly reviews research that involves a vulnerable category of subjects (e.g., 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.
- No IRB has members who are all males or all females. The IRB shall not consist entirely of members of one profession or department. Every effort will be made to ensure that CMU considers the qualifications of persons of both sexes, so long as no selection is made to the IRB solely on the basis of gender.
- The IRB includes at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in non-scientific 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.

Scientific members of the boards are drawn from colleges or clinical departments that submit most of the protocols. In recognition of the increasing importance of data security in research, the information technology directors of the various colleges are appointed to Mt. Pleasant campus boards. These IT directors are also available to consult on issues encountered on protocols.

One member may satisfy more than one membership category. The Director of Research Compliance and IRB coordinator may be appointed to serve as an alternate members of the IRB. Per institutional policy, the CMU Privacy Officer may serve on the IRB as a voting member.

No one from the CMU Office of Sponsored Programs, the Office of Development, or the CMU Research Corporation shall serve as members of the IRB or carry out day-to-day operations of the review process. Individuals from these offices may provide information to the IRB and attend IRB meetings as guests.

On an annual basis, the DRC, IRB Chairs and Chair of University Pediatrics shall evaluate the membership and composition of the IRB to determine if they continue to meet regulatory and Institutional requirements. The Institutional Official will review the recommended adjustments and decide to accept the recommendations.

IRB Member Appointment

When the need for a new, replacement, or alternate member for the IRB, the DRC, IRB Chair and/or Vice Chair shall collaborate to identify such need. The DRC will solicit nominations from Deans and Chairs and sends the names of the nominees to IO for consideration. Department Chairs and others may forward nominations to the IO, the Office of Research Compliance, or the IRB Chair. The final decision in selecting a new member is made by the IO in consultation with the DRC and IRB Chair.

Appointments are made for an initial one-year term. Subsequent appointments may be made for one to three years period of service and may be renewed. The appointment letter explicitly states performance expectations and members explicitly acknowledge the expectations in signing their agreement to serve.

Any change in appointment, including reappointment or removal, requires written notification. Members may resign by written notification to the IRB Chair or DRC. The DRC, IRB Chair, and/or Chair of University Pediatrics review the membership and composition of the IRB to annually to determine if they continue to meet regulatory and institutional requirements.

Evaluations of IRB Members

Members are evaluated on their ability to conduct expedited and full board reviews accurately and in a timely manner. The IRB Chair and DRC or designee will discuss any issues that might negatively affect a members' ability to complete reviews in a timely manner. The performance of IRB members is reviewed annually. If the board member is not acting in accordance with the IRB's mission, following institutional policies and procedures, has an undue number of absences, or is not fulfilling the responsibilities of the full member, he/she may be removed by the IO. In deference to stated concerns from the CMU Faculty Association (collective bargaining unit), the IRB does not maintain comprehensive evaluation reports of individual member and presents performance data only in aggregated from. The DRC has at minimum, a monthly meeting with the IO in which feedback on performance of the IRB Chairs and Vice Chairs is provided.

IRB Registration Updates

Changes that affect the CMU's federal IRB registration must be reported to FDA and OHRP within the following time periods:

- Within 90 days of a change in the Institutional Official.
- 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 an 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 (e.g., to review device studies if it only reviewed drug studies previously) or to discontinue reviewing clinical investigations regulated by FDA.

Use of Consulting Reviewer

The IRB Chair or the DRC may solicit individuals with competence in special areas to assist in the review of issues or protocols that require appropriate scientific or scholarly expertise beyond or in addition to that available on the IRB.

Prospective consulting reviewers must sign a COI disclosure form prior to conducting a review. The DRC reviews the conflict of interest disclosure form. Individuals who have a conflicting interest or whose family members have a conflicting interest in the sponsor of the research will generally not be invited to provide consultation.

IRB coordinator ensures 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 reviewer must be available for discussion if needed.

Written statements of consulting reviewers will be kept in the IRB records. Key information provided orally by consulting reviewer at meetings must be documented in the minutes.

Ad hoc or informal consultations requested by individual IRB members, rather than the convened board, must be requested in a manner that protects the researcher's confidentiality and complies with the IRB conflict of interest policy.

Information from consultations is disseminated to other members prior to or during convened IRB reviews, or for expedited reviews, documented in the reviewer's notes.

Liability Coverage for IRB Members

Central Michigan University's insurance coverage applies to employees and any other person, including members of the IRB, authorized to act on behalf of Central Michigan University within the scope of their employment or authorized activity.

Reporting and Investigating Allegations of Undue Influence

If an IRB chair, member, or staff person feels that the IRB has been unduly influenced by any party, they shall make a confidential report to the IO, depending on the circumstances. Issues or concerns involving the IO will be reported to the Provost, and other appropriate institutional official(s) or the CMU ethics hotline. The IO or other official receiving the report will conduct an investigation, and if necessary, prescribe corrective action to prevent additional occurrences.

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

Section 5: Human Subject Research Determination

The investigator is responsible for initial determination of whether an activity constitutes human subjects research. The investigator should make this determination based on the definitions of "human subject, research, and clinical investigation" as provided by the Common Rule and FDA regulations, respectively. Central Michigan University will hold investigators responsible if the determination is not correct, investigators are urged to request a confirmation that an activity does not constitute human subjects research from the IRB.

Making the initial determination of whether research involves "human subjects" also is the responsibility of the investigator. Under the Common Rule, information is considered identifiable, and thus involving human subjects, when the identity of the subject is or may readily be ascertained by the investigator or associated with the information. It should be noted that this definition differs significantly from deidentified in accordance with HIPAA standards. The concept of "identifiability" in the evaluation of an activity as a clinical investigation or clinical research is not integrated into the FDA regulations. For example, the use of deidentified human specimens to evaluate the safety or effectiveness of a diagnostic device is considered human subjects research subject to FDA regulations. If an investigator is unsure if a research study involves "human subjects" as defined by the Common Rule, the IRB urges them to submit "IRB Does My Project Need IRB Review" application to request a determination. *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 by submitting a "IRB Does My Project Need IRB Review".* By using the IRB electronic application system, the questions will guide the investigator to provide sufficient description of the activity and the rationale for the investigator's initial determination.

The only exception to this policy is when the research is not subject to FDA regulations and the coded private information or specimens are to be obtained from an IRB approved repository and the rules of that repository forbid the release of identifiable information, the key or code that would enable re-identification, or the release of sufficient information that investigators could readily ascertain the identity of subjects. Human Subjects Research Determinations must be submitted, and determined, prospectively (i.e. before the proposed activity or research begins). Conducting human subjects research without IRB approval or exemption is noncompliance.

Determinations whether an activity constitutes human subject research are made according to the definitions in *Section 1, Human Research Protection Program*. A determination letter will be issued to document the determination. Investigators *may not* rely upon determinations made by other organizations or through the use of electronic or other determination tools if the research is conducted under the auspices of CMU.

IRB determinations are documented and maintained within the IRB electronic records. An investigator's request and responses to a determination are maintained in the IRB electric record.

Section 6: Exempt Studies

All research using human subjects conducted at, under the auspices of, or using the services or resources of CMU must be approved by CMU. However, OHRP regulations define several categories of "exempt research" which refers to research that does not fall under the full regulatory oversight and approval process typically required for human subject research. The CMU IRB requires exempt studies to be reviewed and be issued a determination or confirmation of exempt status. The IRB Chair, Director of Research Compliance or a qualified IRB member designated by the IRB Chair review exempt study submissions and grant a determination. CMU may also choose to accept an exempt determination made by an external IRB and will consider such requests on a case-by-case basis.

A determination is granted for exempt studies, rather than being approved. Exempt studies are exempt from the requirements of subpart A, also known as the "Common Rule" (i.e., IRB approval and full consent of research participant are not required). A determination or confirmation of exemption status is required by CMU. Although exempt research is not covered by the federal regulations, it is not exempt from the ethical guidelines of the Belmont Report. Other regulations, such as HIPAA, FERPA, and CMU requirements may need to be applied. Besides making a determination of exemption, the IRB Chair or designee will also decide whether to require additional protections in keeping with ethical principles (e.g., consent, disclosure, etc.) of the Belmont Report.

The ethical standards of CMU are fulfilled with exempt research:

- The research holds out no more than minimal risk to participants.
- Selection of participants is equitable.
- If there is recording of identifiable information, there are adequate provisions to maintain the confidentiality of the data.
- If there are interactions with participants, the IRB should determine whether there should be a consent process that will disclose such information as:
    - That the activity involves research.
    - A description of the procedures.
    - That participation is voluntary.
    - Name and contact information for the researcher.
    - There are adequate provisions to maintain the privacy interests of participants.

Limitations on Exemptions

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

- Research involving Children.

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

Categories of Exemption Research

Research activities in which the only involvement of human subjects are determined to be in one or more of the following categories qualify for exempt status. Note in *Section 6, Limitation on Exemptions and FDA Exemption put limitations on the use of the exemption categories.*

When following DHHS regulations, the criteria allowing exemptions are:

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

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

iii. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review of the research under §46.111(a)(7).
    - There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of identifiable data.
    - The research meets the ethical standards as follows:
        - The research holds out no more than minimal risk to subjects.
        - Selection of subjects is equitable.
        - If there are interactions with subjects there is a consent process.

- **Category 3:** Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:

    i. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects.
    ii. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation.
    iii. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7): "When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data."

For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing.

- Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

- **Category 4:** Secondary research without consent involving the use of identifiable private information or identifiable biospecimens if at least one of the following criteria is met:

    i. The identifiable private information or identifiable biospecimens are publicly available.

ii. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects.
iii. The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164 ['HIPAA'], subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b).
iv. The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.

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

- **Category 6:** Taste and food quality evaluation and consumer acceptance studies:
    i. If wholesome foods without additives are consumed, or
    ii. If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or

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

- **Category 7:** Collection of Data for Secondary Research with Consent- CMU is not implementing this Exemption currently.

- **Category 8:** Use of Data for Secondary Research with Consent- CMU is not implementing this Exemption currently.

FDA Exemptions

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

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

Procedure for Exemption Determination

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

- A completed IRB Application to Conduct Exempt Research.
- Recruitment materials (e.g., letter of invitation, recruitment script, flyer)
- Consent form, information sheet, etc.
- Request for a waiver of HIPAA authorization or HIPAA authorization as applicable
- All surveys, questionnaires, instruments, and other related information
- Letter of Permission/Support from each non-Central Michigan University (non-affiliated) performance site(s).
- Verification of current human research protection training for all investigators, research staff, including the faculty advisor.

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

If applicable, the reviewer also evaluates and takes any actions necessary under other

regulations, such as HIPAA and FERPA. The reviewer determines whether to require additional protections for subjects in keeping with the guidelines of the Belmont Report.

Investigators will be given feedback by email via the electronic IRB application system as to the qualification of the application for exempt status. Once institutional review is completed, an email notification to the PI of the results of the review is sent via the electronic IRB application system. Documentation must include the specific categories justifying the exemption.

Investigators must submit proposed modifications to the research for a determination of whether or not the modified activity still qualifies for exemption. The IRB should be notified when an exempt research project is complete so an accurate database of active research can be maintained.

Status Reports

For research given an exemption determination, the CMU IRB requires a yearly Status Report indicating the project is still active and affirming that there have been no changes in procedures that have not been approved by the IRB. For research projects involving vulnerable subjects or supported by internal or external grants or contracts, the Status Report will collect information about the number of research participants. The status report will be due by the anniversary of the original determination. If a status report is not submitted within 90 days of the anniversary of the determination date, the protocol will be administratively closed.

Section 7: IRB Review Process

The CMU IRB reviews and ensures that the research involving human subjects meets all required ethical and regulatory criteria for initial and continuing review as well as any modifications of approved research. The IRB may conduct an expedited review, or a convened IRB review.

The IRB procedures described below are required for the review of human subject research by the CMU IRB. Procedures for research that is reviewed by external IRBs are described in *Section 9, Multi-Site and Collaborative Research*.

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 change that, 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 methodology. Adding procedures that are not eligible for expedited review would be considered more than a minor change. See *Section 7, Expedited Review Procedure* for further information.
    - 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 or an authorized individual to temporarily stop some or all research activities that have been previously approved by the IRB. Suspended research studies remain open and require continuing review by the IRB.

- **Termination of IRB approval** Termination of IRB approval is a directive of the convened IRB to permanently stop all activities that have been previously approved by the IRB. Terminated research studies are closed and no longer require continuing review by the IRB.

Expedited Review

An IRB may use the expedited review procedure to review studies presenting minimal risk to research subjects. CMU uses the following to determine how a study will be reviewed:

- Research funded or supported by an agency that subscribes to the Common Rule.
- Research not supported or regulated by a Common Rule agency and CMU IRB has created a Flexibility Criterion.
- Minor changes in previously approved research during the period of one year or less for which approval is authorized. Review of minor changes does not alter the end-date of study approval.

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

Categories of Research Eligible Expedited Review

CMU 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 for research funded or supported by an agency that subscribes to the Common Rule.

The categories of research listed below 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 when 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 that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.
(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 labelling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(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) Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.
(i) Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings.
(j) Sputum collected after saline mist nebulization.

(4) Collection of data through noninvasive procedures, not involving general anesthesia or sedation, routinely employed in clinical practice, excluding

procedures involving x-rays or microwaves. Where medical devices are employed, they must be approved for marketing. Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of approved medical devices for new indications. Examples include:

(a) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy.
(b) Weighing or testing sensory acuity.
(c) Magnetic resonance imaging.
(d) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography.
(e) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

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

- Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 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 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.
- The CMU IRB has determined that research involving brief episodes of intense exercise, such as that involved in maximum oxygen uptake testing, is eligible for inclusion in this category provided that the subject population meets the following criteria:
  - (i) Non-pregnant.
  - (ii) 18-45 years of age.
  - (iii) in good health, with no medical indication(s) that would otherwise preclude them from engaging in vigorous exercise.

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 at 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 (e.g., 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.

The CMU IRB has determined that certain categories of research, beyond those described in *Section 7, Expedite Reviewed*, present minimal risk to subjects and can be reviewed by expedited procedures, provided the research is not supported or regulated by a Common Rule agency.

Flexibility Criterion

- Flex 1: Research involving low levels of ionizing radiation (not to exceed 0.1 mSv per exposure) qualifies for expedited review if the following conditions are met:
  - (i) Subjects are 18 years of age or over.
  - (ii) Subjects are not pregnant.
  - (iii) The use of multiple exposures is justified as being necessary to evaluate a study hypothesis, and the exposures are separated by a reasonable interval of time considered sufficient for hypothesis testing.
- Flex 2: Any research that the IRB Chair determines to present minimal risk to subjects may be reviewed by expedited procedures.

Expedited Review Procedure

Expedited review may be carried out by the IRB Chair or by one or more reviewers designated by the Chair from among members of the IRB. On at least an annual basis, the IRB chair designates IRB members who are eligible to conduct expedited reviews. Selected reviewers will have the qualifications, experience, and knowledge in the content of the protocol to be reviewed as well as be knowledgeable of the requirements to approve research under expedited review.

IRB coordinator selects 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 (e.g., minor administrative changes), as well as be knowledgeable of the requirements to approve research under expedited review. IRB members with a conflict of interest with the research see *Section 20, IRB Member Conflict of Interest* 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. Using the *Reviewer Checklist for Expediated Review*, the reviewer(s) document the research meets the regulatory criteria for approval by expedited review.

If the research meets the criteria allowing review using the expedited procedure, the reviewer conducting initial or continuing review completes the 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 agenda for an IRB meeting.
In reviewing the research, the reviewers must follow the review procedures described in *Section 7, Expedited Review* and *Criteria for IRB Approval of Research* and may exercise all of the authorities of the IRB except that the reviewers may not disapprove

the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure by the IORG IRB see *Section 7, Convened IRB Meetings*.

Reviewers will document approval, required modifications, or requirement for convened board review. If modifications are required, the IRB Office staff will inform the investigator by e-mail. If expedited review is carried out by more than one IRB member and the expedited reviewers cannot agree, the IRB Chair may make a final determination or refer the study to the convened IRB for review.

Informing the IRB

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

Convened IRB Meetings

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

IRB Meeting Schedule

The Mt. Pleasant IRB meets in-person, as needed, within 3 weeks of receiving an application which qualifies for convened board review. The schedule for Pediatrics' IRB virtual meetings and deadlines for submitting applications is posted on the Pediatrics IRB website due to the type of studies received and reviewed. Special meetings may be called at any time by the IRB Chair or the DRC.

Preliminary Review

The IRB Coordinator performs a preliminary review of all protocol submitted to determination of completeness and accuracy. Only complete submissions are placed on the IRB agenda for review. The Principal Investigator will be informed either by e-mail, phone, or in person of missing materials and the necessary date of receipt for inclusion on that agenda. IRB consultations with the IRB coordinator, DRC and/or IRB Chair can be arranged for principal investigators and study team members at any step in the review process.

Primary and Secondary Reviewers

After determining that the submission is complete, the DRC or IRB Coordinator, in consultation with the IRB Chair as needed, assigns submissions for review taking into account the subject matter of the research, potential reviewer's area of expertise, and representation for vulnerable populations involved in the research. One "primary reviewer" is assigned to each submission and conducts an in-depth review of all

submission material. A single reviewer may be assigned several submissions or other items for review. When the IRB is presented with a protocol that is considered outside the knowledge base or representative capacity of any of the IRB members, a consultant is sought see *Section 4, Liability Coverage for IRB Members*. Protocols for which appropriate expertise cannot be obtained for a given meeting are deferred to another meeting when appropriate expertise is procurable.

Primary reviewers are responsible for:

- Having a thorough knowledge of the details of the proposed research.
- Performing an in-depth review of the proposed research.
- Lead the discussion of the proposed research at the convened meeting, by
- summarizing the proposed research presenting both positive and negative aspects of the research.
- Making suggestions for changes to the proposed research, where applicable.

One or more "secondary reviewers" are 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 (e.g., the consent/assent/permission forms).

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

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

Material received by the IRB

All required materials must be submitted 15 business days before the convened meeting for inclusion on the IRB meeting agenda. The meeting agenda will be prepared by the IRB Coordinator in consultation as needed with the IRB chair. All IRB members receive access to the IRB agenda, prior meeting minutes, applicable business items, continuing education materials and research submission materials no later than 5 business days before the scheduled meeting to allow sufficient time for review. When review time is sensitive and as long as there still is sufficient time for review by IRB members, the IRB coordinator in consultation with the DRC and IRB Chair, may make an exception to the 5 business day rule.

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.
- Data collection instruments, including surveys and questionnaires.

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 an 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.
(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.

Protocol reviewers have available a Reviewer Checklist Worksheet as a guide for their review.

Quorum

A quorum 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 or device is on the agenda for review, a physician should be included in the quorum. At meetings of the IRB, a quorum must be established and maintained for the deliberation and vote on all matters requiring a vote.

The IRB Chair, with the assistance of the IRB Coordinator, will confirm that an appropriate quorum is present before calling the meeting to order. The IRB Chair will be responsible to ensure that the meetings remain appropriately convened. If a quorum is not maintained, either by losing a majority of the members, or losing all nonscientific members or another required member, the pending item cannot have any action taken or vote on regulatory determinations until quorum is restored. If quorum cannot be restored, study(ies) is placed on the next IRB agenda. The IRB Coordinator will note the arrival and departure of all IRB members during the meeting and notify the IRB Chair when quorum is lost.

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. The same individual can serve in both capacities. The IRB may, on occasion, meet without this representation, individuals serving in these roles should be present routinely, though.

IRB members are considered present and participating at a duly convened IRB meeting when they are either physically present or participating through means such as teleconferencing or videoconferencing that permits them to listen to and speak during IRB deliberations and voting. When not physically present, the IRB member must have had access to all pertinent materials prior to the meeting and must be able to participate actively and equally in discussions.

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

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

Meeting Procedures

The IRB Chair, or Vice-Chair in the event that the IRB Chair is absent, will:

- Call the meeting to order once it has been determined that a quorum is established.
- Announce the voting members that are listed on the agenda. Identify which of the member's present will occupy voting seats and which of the members will not be voting.
- Remind IRB members to recuse themselves from the discussion and vote by leaving the room where they have a conflict of interest.
- Indicate the ORC staff members, consultants, and guest that are present.

The IRB will review and discuss the IRB minutes from the prior meeting and determine if there are any revisions/corrections to be made. If there are no changes to be made, the minutes will be accepted as presented and considered final. If it is determined that substantive revisions/corrections are necessary, the minutes will be amended and presented at the next IRB meeting. Minor revisions and corrections may be verified by the IRB chair or DRC 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 and continuing review, as well as requests for modifications. The Primary present an overview of the research. The IRB Chair and/or IRB Coordinator leads the IRB through consideration of the regulatory criteria for approval. For the research to be approved, it must receive the approval of a majority of those voting members present at the meeting.

It is the responsibility of the IRB Coordinator to record the proceedings and to take minutes at each IRB meeting.

Guests

At the discretion of the IRB Chair, the Principal Investigator and research staff may be invited to the IRB meeting to make a brief presentation or answer questions about

proposed or ongoing research. The Principal Investigator and research staff may not be present for the discussion or vote on the proposal.

The Director of Research Compliance and IRB Coordinator 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 Director of Research Compliance. Guests may be asked to sign a confidentiality agreement and may not participate in discussion unless requested by the IRB Chair or Vice Chair, and under no circumstances may they vote on any action of the IRB.

Criteria for IRB Approval of Research

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

1- 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.

2- 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.

3- Selection of subjects is equitable. In making this assessment the IRB should consider the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disable persons, or economically or educationally disadvantaged persons.

4- 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].

5- 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].

6- When appropriate, the protocol/research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

7- When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

8- For purpose of conduction the limited IRB review required by [45 CFR 46.104(d)(7)], the IRB need not make the determinations at paragraphs (a)(1) through (7) of this section, and shall make the following determinations:

(i) Broad consent for storage, maintenance, and secondary research use of identifiable private information of identifiable biospecimens is obtained in accordance with the requirements of 45 CFR 46.116(a)(1)-(4), (a)(6), and (d).

(ii) Broad consent is appropriately documented or waiver of documentation is appropriate, in accordance with 45 CFR 46.117, and

(iii) If there is a change made for research purposes in the way the identifiable private information or identifiable biospecimens are stored or maintained, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Risk/Benefit Assessment

The goal of the assessment is to ensure that the risks to research subjects posed by participation in the research are justified by the anticipated benefits to the subjects or society. Toward that end, the IRB must:

- Judge whether the anticipated benefit, either of new knowledge or of improved health or other direct benefit for the research subjects, justifies asking any person to undertake the risks; and
- Disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits.

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

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

In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research, as distinguished from risks and benefits subjects would receive even if not participating in the research.

The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks and benefits that fall within the purview of its responsibility.

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

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

Scientific or Scholarly Review

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, IRB reviewers may draw on their own knowledge and disciplinary expertise, or the they may draw on the knowledge and disciplinary expertise of others, such as reviews by an external reviewer, funding agency, departmental review or research committee. When scientific review or scholarly review is conducted by an individual or entity external to the IRB, documentation of the scientific review or scholarly review must be provided to the IRB for review and consideration.

The Investigator may provide the documentation of an individual or entity external to the IRB, that bullet points above were considered, to the IRB for review and consideration. For example, when a protocol is the subject of a masters or doctoral thesis, evidence of scientific merit may be provided in the form of a statement of approval from the advisory committee. When a protocol is reviewed for scientific merit as part of an internal funding application, evidence of the review may be provided to the IRB.

Equitable Selection of Subjects

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

- 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.

The IRB will not approve a study that proposes to recruit subjects because they are disadvantaged economically and would be likely to participate solely in response to economic inducements.

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

Recruitment of Subjects

The investigator will provide the IRB with a recruitment plan that outlines the process of identifying, selecting, and enrolling potential participants. All recruiting materials must be submitted to the IRB, including advertisements, flyers, scripts, information sheets, and brochures. The IRB ensures that the recruitment plan and materials appropriately protect the rights and welfare of the prospective subjects and do not present undue influence.

See *Section 7, Advertisements and Recruitment Materials* for a discussion of IRB review of advertisements and *Section 7, Payments for Research Subjects* for a discussion of IRB review of payments.

Informed Consent

The IRB must ensure that informed consent is sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116 and 21 CFR 50.20. In addition, the IRB ensures that informed consent is appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117 and 21 CFR 50.27. The IRB ensures, as part of its review, that the information in the consent document and process is consistent with the protocol/research plan, and, if applicable, the HIPAA authorization. See *Section 11, Obtaining Informed Consent from Research Subjects* for detailed policies on informed consent.

Data and Safety Monitoring

Data and safety monitoring are critical components to ensure the integrity of study process and the safety of participants. 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 elements of a safety monitoring plan may vary depending on the risks, complexity, and nature of the research. Monitoring may be conducted in various ways or by various individuals or groups, depending on the size and scope of the research effort. These exist on a continuum from monitoring by the principal investigator in a small, low-risk study to the establishment of an independent data- and safety-monitoring board for a large phase III clinical trial.

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 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 of monitoring should be commensurate with risk.
- Conclusions are reported to investigators, sponsors, regulatory authorities, and the IRB, as applicable. For lower risk studies, continuous, close monitoring by the study investigator or an independent individual may be adequate and appropriate, with prompt reporting of problems to the IRB, sponsor, and regulatory bodies as appropriate.
- For greater than minimal risk studies that do not include a plan for monitoring by a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), and that are blinded, multi-site, involve vulnerable populations, or involve high-risk interventions or procedures, the IRB carefully evaluates the proposed DSM plan and may require establishment of a DSMB, DMC, or other methods to enhance the monitoring and management of safety.
- Data and Safety Monitoring plans should specify:
    - The entity or person(s) who will perform the monitoring, and the independence or affiliation that the entity or person(s) has with the sponsor or investigator.
    - The safety information that will be collected and monitored, including serious adverse events and unanticipated problems.
    - The frequency or periodicity of review of safety data.
    - The procedures for analysis and interpretation of the data.

    - The procedures for review of scientific literature and data from other sources that may inform the safety or conduct of the study.
    - The conditions that trigger a suspension or termination of the research (ie, stopping rules), if applicable.
    - The procedures for reporting to the IRB and others, including a summary description of what information, or the types of information, will be provided, when, and to whom.
- For a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), the plan should also describe:
    - The name of the DSMB or DMC. Their charter should be provided, if available.
    - 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 patient safety. Clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease/conditions and treatment under study should be part of the monitoring group or be available if warranted.
    - Frequency and character of monitoring meetings (e.g., open or closed, public or private) and availability of written reports.

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 to require a DSMB or DMC as a condition for approval of research when it determines that such monitoring is needed. When a DSMB or DMC are utilized, the IRB conducting continuing review of research may rely on a current statement from the DSMB or DMC indicating that it has and will continue to review study-wide adverse events, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB.

Privacy and Confidentiality

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

Definitions

- **Privacy**: Having control over the extent, timing, and circumstances of sharing oneself (physically, behaviourally, or intellectually) with others. It is the state or condition of being free from unauthorized intrusion, being observed or disturbed by other people.
- **Confidentiality**: Methods used to ensure that information obtained by investigators about subjects is not improperly divulged.

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

Privacy

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

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

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

Confidentiality

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

anonymity are not the same. If the identity of the subjects of the data can be readily ascertained, then the research is not anonymous and the researchers must minimize the likelihood of disclosure.

At the time of initial review, continuing review, and with any requests for modification that may affect confidentiality, the IRB assesses whether there are adequate provisions to protect data confidentiality. The IRB does this through the evaluation of the methods used to obtain, record, share, and store information about individuals who may be recruited to participate in studies and about subjects. The Principal Investigator provides the IRB with a plan regarding the procedures to be taken to protect the confidentiality of research data and sensitive information. Additionally, the investigator provides information regarding information security procedures and plans to address the protection of paper documents, other physical media (e.g., audio or videotapes), and electronic data and information including the use, maintenance, storage, and transmission of information. The IRB reviews all information received from the investigator and determine whether or not the confidentiality of research data is sufficiently protected. In some cases, the IRB may also require that a Certificate of Confidentiality be obtained to additionally protect research data, see Section 26, Certificates of Confidentiality.

In reviewing confidentiality protections, the IRB shall consider whether or not the data or other information accessed or gathered for research purposes is sensitive and the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research. It shall evaluate the effectiveness of proposed de-identification techniques, coding systems, encryption methods, methods of transmission, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections. In reviewing confidentiality protections, the IRB shall also consider regulations and institutional requirements and policies regarding the use of information and information security.

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

As necessary, the IRB will draw on the expertise of the Office of Information Technology to assess plans for data security.

Vulnerable Populations

When research that includes vulnerable populations is proposed, the IRB must consider the scientific and ethical reasons for including vulnerable subjects in the research. 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. The IRB may determine and require that, when appropriate, additional safeguards be put into place for vulnerable subjects. *Section 12, Vulnerable Subjects in Research*

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

Additional Considerations

Determination of Risk

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

Approval Period

At the time of initial review and at continuing review, the IRB will determine the frequency of review of the research protocol. 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 (e.g., 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 during their review.

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. The expiration date is the date by which the continuing review must occur, may be as late as one year after the effective date of IRB approval.

The effective date of IRB approval will be used to determine the latest permissible date for continuing review. The date the convened IRB or the date that the expedited reviewer conducts continuing review and approves the study, *without conditions*, determines date of the next continuing review. If the IRB determination is "*Conditions Required for Approval*", the effective date of IRB approval will be the date the conditions of the IRB have been verified and satisfied by the convened board designees or the expedited reviewer.

The IRB determination letters clearly note the approval and approval expirations date and must be strictly adhered to. Investigators are notified periodically prior to expirations date to allow sufficient time for submission of continuing review application.

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

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

Review More Often than Annually

The following factors will also be considered when determining which studies require review more frequently than annually:

- 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 other research staff.
- The experience of the Principal Investigator, other investigators, and other research staff in conducting similar research.
- The nature and frequency of adverse events observed in similar research at this and other institutions.
- The novelty of the research making unanticipated adverse events more likely.
- The involvement of especially vulnerable populations likely to be subject to undue influence or coercion (e.g., 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.

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 require on initial review that such verification take place at predetermined intervals during the approval period or may require such verification at the time of continuing review and review of amendments and/or unanticipated problems.

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

Consent Monitoring

In reviewing the adequacy of informed consent procedures for proposed research, the IRB may on occasion determine that special monitoring of the consent process by an impartial observer (e.g., 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 (e.g., persons with impaired decision-making capacity, children who are wards, ICU patients).
- 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 (e.g., prior investigator non-compliance).

Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project. the IRB will develop a monitoring plan. The consent monitoring may be conducted by an individual designated by the IRB, either affiliated or not with the CMU. Arrangements are made with the Principal Investigator for the monitoring of the consent process, typically for a specified number of subjects. When observing the consent process, the monitor evaluates:

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

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

Investigator Qualifications

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

Conflicts of Interest (COI)

The IRB research application asks specific questions regarding conflict of interest for the investigators and research staff compliance with disclosure requirements and whether or not any conflict of interest management plans are in place. As part of the review process, the IRB makes a determination as to whether any conflict of interest is adequately addressed and protects the human subjects in the research. *Section 20, Conflicts of Interest and Commitment in Research*, provides additional discussion of conflicts of interest.

Significant New Findings

During the course of research, significant new knowledge or findings about the research, the test article, and/or the condition under study may develop. The Principal Investigator must report any significant new findings to the IRB. The IRB reviews the findings with regard to the impact on the subjects' rights and welfare. Because the new knowledge and findings may affect the risks or benefits to subjects or subjects' willingness to continue in the research, the IRB may require, during the ongoing review

process, that the Principal Investigator or research staff contact the currently enrolled subjects to inform them of the new information. The IRB communicates this requirement to the Principal Investigator. If the study is still enrolling subjects, the consent document should be updated. The IRB may require that the currently enrolled subjects be re-consented or otherwise provided with the new information. The IRB may also require that former subjects be provided with the new information, such as when it affects their rights or welfare.

Advertisements and Recruitment Materials

The IRB must review and approve any and all advertisements prior to posting or distribution for studies that are conducted under the purview of the CMU IRB. 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 they are clear, ethical and compliant with regulatory requirements. The material needs to be accurate and is not coercive or unduly optimistic to influence 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.
- Emphasis on payment or the amount to be paid, such as bold type or larger font on printed media.
- The inclusion of exculpatory language.
- Claims, either explicitly or implicitly, that the test article (drug, biologic, or device) or procedure is safe or effective for the purposes under investigation.
- Claims, either explicitly or implicitly, that the test article or procedure is known to be equivalent or superior to any other drug, biologic, device or procedure.
- Using terms like “new treatment,” “new medication,” or “new drug” without explaining that the test article or procedure is investigational.
- Promising “free medical treatment” when the intent is only to say participants will not be charged specifically for participating in the research.
- 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 clear and transparent communication limited to the information the prospective subjects need to determine their eligibility and interest. The following items may be included when appropriately worded:

- The name and address of the Principal Investigator and/or research facility.
- The purpose of the research condition being studied and/or the condition being studied.
- In summary form, the criteria that are used to determine eligibility of subjects for the study.
- The time or other commitment required of the subjects.
- The location of the research and the person or office to contact for further information.
- A clear statement that this is research and not treatment.
- A brief list of potential benefits (e.g., no-cost health exam).

An approved advertisement cannot be altered or manipulated in any way without prior IRB approval.

Directory listings of research such as ClinicalTrials.Gov are not considered advertisements and therefore do not require IRB review and approval if the listing is limited to the following basic 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.

Payment 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:

- Demonstrate that proposed payments are *reasonable and commensurate* with the expected contributions of the subject.
- State the terms of the subject participation agreement and the amount of payment in the informed consent form.
- Demonstrate that subject payments are fair and appropriate and that they do not constitute (or appear to constitute) undue pressure on the participant to volunteer for the research study.

The IRB must review both the amount of payment and the proposed method of disbursement to ensure that neither entails a problem 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 (e.g., if they withdraw from the study before their participation is completed) or no payment.

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

Non-Monetary Gifts and Incentives

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

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

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

Lotteries

Incentives in the form of a lottery are permitted and must conform to the terms of Michigan Lottery Law [SOM Act 382, Section 432.105d]. CMU is likely exempt from the licensing requirements for conducting a raffle or lottery if they meet the following conditions:

- Total amount to be awarded in *a single day* cannot exceed $100 The prizes can be in the form of cash, gift certificates/cards, or merchandise.
- There are no second chance drawings, meaning that individuals cannot be entered into a pool for a prize more than one time. This limit meets the State of Michigan's "single gathering" criteria.
- There is no pre-sale of raffle/lottery tickets

The raffle should have a single, defined beginning and end time during which the relevant research participation is conducted (submitting to the raffle) and the prizes are awarded. The informed consent document must include a description of the lottery/raffle process.

All raffle or lottery payments made to research participants conform to the requirements of Payment to Research Participants (Policy 6-5).

CMU Business Practices

It is the investigator's responsibility to comply with the policy of the appropriate CMU business office for processing of payments to research subjects. Investigators are encouraged to seek guidance on internal procedures from the appropriate CMU business office during the initial planning stages of the research project.

State and Local Laws and Laws of Foreign Countries

The HRPP and the IRB rely on CMU's Office of General Counsel for the interpretation and application of Michigan State law and the laws of any other jurisdiction where research is conducted as they apply to human subjects research.

All research practices and consent forms must be consistent with applicable state and local laws. International research must observe the laws of the country in which the research takes place.

Possible IRB Actions

There are several actions that the IRB may take when conducting its review of research. The actions listed below may be used for either expedited or convened board review. Disapproval of a study can only be decided at a convened IRB meeting. An expedited reviewer cannot disapprove a study.

Approval

The research, proposed modification to previously approved research, or other item is approved as submitted. All determinations required for approval, having meet the approval criteria and any applicable special determinations such as accommodations for

vulnerable populations, required waivers, or alternations have been made by the IRB. No further action is needed.

Conditions Required for Approval

The research, proposed modification to the previously approved research, or other item is approved but conditions (required minor revisions) need to be addressed and accepted before the approval can become effective.

Given the scope and nature of the conditions, the IRB may approve research as long as all determinations required for approval, having meet the approval criteria and any applicable special determinations such as accommodations for vulnerable populations, required waivers, or alternations have been made. Any time the IRB cannot meet one or more of the approval criteria 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 (e.g., confirmation that research excludes children).
- Submission of additional documentation (e.g., 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.

The IRB minutes must document the conditions agreed upon by the board, if the determination was “approved with conditions”.

For protocols reviewed at a convened IRB meeting, the needed revisions are agreed upon by the board. The board votes to approve the protocol subject to satisfactorily responding to the conditions. The convened board will designate the person (study reviewers, IRB chair and/or IRB coordinator) to review responsive material from the investigator and determine that the conditions have been satisfied. If the conditions have not been satisfied, or partially satisfied, the responsive materials must be referred to the convened board for review.

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

- The date the conditions were accepted by the board designee will be the recorded as the approval date of the study.
- For initial approval and continuing review, the date by which continuing review must occur.

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 (e.g., the risks and benefits cannot be assessed with the information provided).

The IRB's determination concerning the subsequent revised submission will be documented in the minutes of the IRB meeting or reviewer document for expedited review.

To receive approval for a protocol deferred for substantive issues the following will occur:

- At a subsequent convened meeting, IRB members will have access to the investigator's response material to review for a determination.
- For expedited, the investigator's response material is assigned to the same reviewer(s) for re-evaluation and a determination.
- 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.
- The outcome of the IRB's deliberations is communicated to the investigator in writing.

Failure to submit a response to IRB-stipulated changes or inquiries related to deferred protocols within 60 days of the IRB date of determination will result in administrative closure of the IRB file. The PI will receive notification of the closure of the IRB file, including an explanation for this action. An extension beyond 60 days may be granted by the IRB Chair if the PI provides an adequate justification.

Disapproved

The IRB may determine that the proposed research cannot be conducted at the CMU or by employees or agents of CMU or otherwise under the auspices of CMU. Disapproval can only be decided at the convened IRB meeting. An expedited reviewer cannot disapprove a study.

Approval in Principle

As per federal regulations [45 CFR 46.118], there are circumstances in which a sponsoring agency may require certification of IRB approval as a condition of submitting for or releasing funds but before definitive plans for the involvement of human subjects have been developed (e.g., 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 (i.e., the grant or proposal and any supplemental information provided by the investigator) and, if appropriate, provides certification of IRB approval in principle. If the proposal is funded, the investigator must submit the materials required for initial submissions for review and approval before beginning any human subject activities, including recruitment or collection of pilot data.

Continuing Review and Status Reports

The IRB conducts a continuing review of ongoing research at intervals that are appropriate to the level of risk for each protocol/research plan. Unless the IRB determines otherwise during the initial review, continuing review is not required for research in the following circumstances:

- Research eligible for expedited review in accordance with §46.110.
- Research eligible for expedited review under CMU flexibility criteria.
- Exempt research reviewed by the IRB.
- Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
    - Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
    - Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

The IRB Member must provide a justification on why the non-exempt, minimal research qualifies for continuing review. Research requiring review by a convened IRB conducts a continuing review not less than once per year. The approval period is recorded in the IRB minutes or other IRB electronic records. Via the IRB electronic system the IRB communicates the date by which continuing review must occur to the Principal Investigator and research team. Continuing review must occur as long as the research remains active.

The IRB may determine that continuing review is required for any research protocol that is eligible for expedited review. Justification for requiring continuing review must be documented and may include, but is not limited to any of the following:

- Required by other applicable regulations (e.g., FDA).
- The research involves topics, procedures, or data that may be considered sensitive or controversial.
- The research involves particularly vulnerable subjects or circumstances that increase subjects' vulnerability.
- An investigator has minimal experience in research or the research type, topic, or procedure.
- An investigator has a history of noncompliance.

When the IRB determines that continuing review is required for such research, the rationale is in the IRB record and communicate the requirement to the investigator in the IRB determination letter.

Status Reports

For research that does not require continuing review which meets the criteria listed above, the CMU IRB requires a yearly Status Report indicating the project is still active and affirming that there have been no changes in procedures that have not been approved by the IRB. For research projects involving vulnerable subjects or supported by internal or external grants or contracts, the Status Report will collect information about the number of research participants. The status report will be due by the anniversary of the original approval/determination. If a status report is not submitted within 90 days of the anniversary of the approval/determination date, the protocol will be administratively closed.

For Legacy protocols approved by expedited review before effective date of the revised Common Rule (18-January 2018) will undergo customary continuing review on the next due date. The IRB reviewer may determine that either continuing review should continue (and provide an explanation why) or may be discontinued. The determination will be documented in the protocol file, and the study will be changed to an annual status report.

Limited IRB Review

Continuing review is not required for studies that qualify for a limited IRB review. Research eligible for limited IRB review must:

- Be deemed to be no more than minimal risk.
- Meet one or more of the exempt categories 2, 3, 7, or 8.

If an IRB member reviewing the research finds that research is greater than minimal risk, the reviewer must document the rationale for this determination and the rationale for review by the convened IRB.

The information that researchers must submit for limited IRB review is as follows:

- An application, or a protocol summary containing the relevant information to determine whether the proposed research fulfils the criteria for approval.
- Proposed consent document.
- Recruitment materials.

IRB members conducting limited IRB review may not disapprove research. CMU retains the authority to suspend or terminate IRB approval of research approved with a limited review.

Continuing Review Process

As a courtesy to investigators, the 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.

Approval Considerations

The IRB must determine that the regulatory criteria for approval continue to be satisfied in order to re-approve research. The IRB focuses its considerations at time of continuing review on whether any new information is available that would affect the IRB's prior determination. The following aspects of research the IRB needs to pay attention to during the review process:

- Risk assessment and monitoring.
- Adequacy of the informed consent process.
- Local investigator and institutional issues.
- Research progress.
- Whether the protocol needs verification from sources other than the researchers that no material changes had occurred since previous IRB review.
- The current consent document is still accurate and complete.

Any significant new findings that arise from the review process and that might relate to participants' willingness to continue participation will be provided to participant.

Convened Board Review

In conducting continuing review of research not eligible for expedited review, all IRB members are provided with access to all of the materials listed in *Section 7, Approval Considerations* and are responsible for reviewing the project summary, the current consent document, and the progress report. The primary and secondary reviewers are 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 while assisting the IRB Chair or IRB coordinator in leading the IRB through the evaluation of the regulatory criteria for approval.

Expedited Review

The material listed in *Section 7, Criteria for IRB Approval* are provided to the reviewer to conduct the continuing review under expedited procedures. The reviewer checklist is completed to determine whether the research continues to meet the regulatory criteria for approval using the expedite procedure.

Generally, if at time of initial review the research did not qualify for expedited review then the continuing review does not qualify for expedited review. There are limited circumstances relating to expedited review category (8) and (9) described in *Expedited Review Categories in Section 7* where this may not be true. Previously research activities given a continuing review determination may have changed or will change, where the expedited continuing review requirement may no longer be applicable.

Possible IRB Actions after Continuing Review

The convened IRB or an expedited review done by an IRB member may take any of the following actions, as done at Initial Review. The detailed description of the IRB actions is in *Section 7, Possible IRB Actions*.

- Approval
- Conditions Required for Approval
- Deferred

The convened IRB may also vote to disapprove the study. If the IRB member conducting an expedited review thinks the study should be disapproved, it is referred to the convened board for review. If there are significant concerns by the IRB, suspension or termination of study is a motion the IRB can vote on. See *Section 8*, *Study Suspension, Termination* for a detail discussion of suspensions and terminations.

If at time of continuing review the research study receives "Conditions Required for Approval", the IRB specifies whether any conditions need to be satisfied before an investigator can continue particular research activities related to those conditions or requirements that must be adhered to until the conditions of approval have been satisfied. An example, the IRB continuing review determination requires the investigator to include a new or revised procedure in the research protocol for prospective subject screening. The following condition could be approved by the IRB: *"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."*

A specific time period, such as 1,2, or 3 months, can be specified by the IRB for the condition(s) to be satisfied as long as the restricted activity is not begun or restarted until approval is granted.

Lapse 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 the continuing review does not occur within the timeframe set by the IRB, all research activities must stop, including recruitment (media advertisements must be pulled), enrollment, consent, interventions, interactions, and data collection, unless the IRB finds that it is in the best interests of individual subjects

to continue participating in the research interventions or interactions. *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.*

If failure to complete continuing review and obtain approval prior to the current study expiration date does not generally cause a suspension or termination of IRB approval, for federal reporting purposes; however failing to meet the obligations of continuing review timeframe may cause the IRB to consider suspending or terminating the study. The IRB may look to see if there is a pattern of non-compliance with the requirements for continuing review and should determine why the non-compliance is occurring and take appropriate corrective actions. Examples would be where an investigator repeatedly or deliberately forgets to submit continuing review materials, in a timely manner or the IRB itself is not meeting the expiration date. The IRB must report to FDA/OHRP any instance of serious or continuing non-compliance with FDA regulations or IRB requirements or determinations.

If a research protocol is given a "conditions for approval" determination at the time of the continuing review and the approval expires before the PI responds to the conditions, the PI cannot enroll any new subjects or access medical records after the approval expiration date. Once the PI responds, the designated reviewer will verify conditions have been meet and the study approval will be granted. However, the investigator and the IRB should make every effort to resolve any conditions and finalize approval in as timely a manner as possible.

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

Enrollment of new subjects cannot occur and continuation of research interventions or interactions for already enrolled subjects should be suspended until approval. When the IRB or IRB Chair finds 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, then investigator should submit a request to continue research activities that are in the best interest of subjects. A list of research activities and justification on why they should continue along with indicating if the request applies to all or only certain should be specified in the request. The IRB chair or designee reviews the request and provides a determination regarding what activities, if any, may continue during the lapse. There could be a time limit, other conditions or restrictions included in the IRB determination. Data collection (especially safety information) should continue to occur when the IRB allows currently enrolled subjects to continue to receive the interventions that were being administered to them under the research protocol.

The investigator may make an initial determination, in consultation with the subjects' treating physician, to continue the intervention if there is insufficient time to obtain an

IRB determination (e.g., intervention includes daily administration of an investigational agent). For these rare occurrences, the investigator must, as soon as possible, contact the IRB staff and request an IRB confirmation that the continuation of the intervention was the appropriate determination. The IRB chair or designee reviews the request and provides a determination. If the IRB does not agree with the investigator's determination or agrees to only part, the Principal Investigator is notified on the IRB requirements. The investigator must comply or request a re-review of the determine by providing additional justification or information for the IRB to reconsider the request.

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.

The modification may fall under two types: 1) a permanent change (protocol modification) where the protocol change will apply to all remaining subjects, or 2) a one-time change where the protocol changes for a specific subject (protocol exception). See *Section 7, Protocol/Research Plan Exceptions* for details on protocol exceptions.

If the proposed modification should not alter the original scope, purpose, or intent of the research in which the IRB originally authorized. A new IRB application is generally required if the modification(s) substantially alters the research itself rather than allow such changes to be made to the originally (existing) protocol/research plan.

Additionally, investigators conducting research determined to be exempt or Non-Human Subject Research are urged to seek a determination from the DRC that proposed changes do not alter the underlying regulatory status of the activity.

When the modification is the addition of investigative sites to an approved protocol, CMU must be provided with the approval document from the site's home/affiliate IRB or has ceded review to CMU IRB.

Addition of an investigative site is considered to be a "minor modification" as long as the proper authorization has been received.

Procedures

- Completed *IRB Protocol Change 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 *reconsent* using the revised consent form, an information sheet, letter, script, or other mechanism is used to provide the information.
- When adding study sites include proper authorization from the site(s).
- Any other relevant documentation such as cover letters provided by the investigator, sponsor or coordinating center.

IRB staff reviews 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. An expedited review may be carried out by the IRB Chair and/or designee(s) among the IRB members. The IRB reviewer(s) are responsible to determine that the proposed changes may be approved through the expedited review procedure, and, if not, must refer the research study for convened board review.

Convened Board Review of Modifications

When a proposed change in a research study is not minor, or when a proposed change to an expedited study renders it no longer eligible for expedited review then the IRB must review and approve the proposed change at a convened meeting before the change can be implemented. The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB should be promptly informed of the change following its implementation and should review the change to determine that it is consistent with ensuring the subjects' continued welfare.

All IRB members have access to 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 and evaluating whether the modification alters any previous determinations (e.g. the risk determination) or necessitates any additional determinations (e.g. for vulnerable populations).

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

Expedited Review of Modification

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

The reviewer(s) completes the *reviewer worksheet/checklist* to determine whether the modifications meet the criteria allowing review using the expedited procedure, and if so,

whether the research with the proposed modifications continues to meet the regulatory criteria for approval. The reviewer also evaluates whether the modification alters any previous determinations (e.g., a Subpart determination), or necessitates any additional determinations (e.g., vulnerable populations).

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

Possible IRB Actions After Modification Review

IRB Member(s) conducting expedited review may take any of the following actions as done with an Initial Review, at the time of Continuing Review or the Convened IRB. See *Section 7, Possible IRB Actions* for a detailed description of IRB actions.

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

If an IRB member conducting expedited review believes that the proposed modifications should be disapproved, the IRB member refers the proposed modification to the convened board for review. A convened board may vote to disapprove the proposed changes. If the proposed changes raise significant concerns on the part of the IRB, the IRB may vote to suspend or terminate the research. See *Section 8, Study Suspension, Termination, and Investigator Hold* for a detailed discussion of suspensions and terminations.

Protocol/Research Plan Exceptions

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

Exceptions are planned, and the investigator must get approval from the sponsor and the IRB ahead of time. For sponsored research, prior approval from the sponsor is generally required in addition to IRB approval. Depending on the nature of the exception, an expedited IRB review may be possible. In order to be approved under expedited review the proposed exception must not adversely affect the risk/benefit analysis, participant's rights, safety, welfare, or the overall integrity of the study data. Review of exceptions that represent more than minor changes are reviewed at a convened meeting of the IRB.

Procedures for exceptions are the same as for a protocol modification. The investigator must submit a *Modification Request Form* along with any revised documentation to be

presented to the subject(s) and documentation of sponsor approval, if applicable.

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

Closure of Research Studies

The completion or early termination of the study, is a change in study activity and as such must be reported to the IRB. Although subjects are longer deemed to be "at risk" under the study, a final report to the IRB allows the IRB to close its files. A final report also provides information that may be used by the IRB in the evaluation and approval of related studies.

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

For multi-center research, the study may be closed once all research activities (as above) are complete at the CMU or affiliated site and any sites for which the CMU IRB is the "IRB of record". If the investigator is serving as the lead investigator or the site reviewed by the CMU 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 an *IRB End of Project Report*. With closure submissions, the investigator must provide a summary of the research activity and any findings available at that time via the *IRB End of Project Report*.

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

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

Reporting IRB Actions

All IRB actions are communicated to the investigator, and/or designated contact person for the research study, using the IRB electronic system within ten (10) working days via a letter prepared by the IRB staff.

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

IRB letters are maintained in the electronic IRB study file.

The IRB reports its findings and actions to the organization in the form of its minutes, which are distributed by IRB staff to the Director of Research Compliance and the Institutional Official, if applicable.

Failure to Respond

Failure to submit a response to IRB requirements within 90 days of the IRB date of determination may result in administrative closure of the IRB file (for new study submissions). When research has IRB approval, and an investigator fails to respond to requirements related to a subsequent submission (e.g., a request for modification), the IRB chair or Director of Research Compliance reviews the circumstances, including any potential impact on human subjects and contacts the investigator to try to secure a response. If the investigator continues to be unresponsive, the failure of the investigator may be considered non-compliance and must be reviewed in accordance with the procedures in *Section 16, Non-Compliance*. Notice, including an explanation, is sent by HRPP/IRB staff to the investigator. An extension beyond 90 days may be granted by the IRB if the investigator provides sufficient cause.

Appeal of IRB Decisions

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

In cases where there is disagreement between the IRB and the investigator regarding the nature and extent of requested changes or the necessity of or basis for a suspension or

termination, the investigator may submit an appeal to the IRB to request reconsideration. The investigator may be invited to attend the IRB meeting to discuss the request and provide information, and is required to leave the meeting prior to the IRB's final deliberations and vote. In the event a disagreement cannot be resolved, the investigator and/or the IRB may make an appeal to the Institutional Official, who 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/require modifications/disapproval remain under the purview of the IRB.

Research Previously Approved by another IRB

When an investigator transfers research oversight to the CMU IRB that was previously approved by another IRB, the investigator must notify both IRBs and submit the research for review using the *IRB Active Study Transfer Application*. The IRB works with the investigator and transferring IRB to avoid a lapse in IRB oversight during the transfer process.

Section 8: Study Suspension, Termination, and Investigator Hold

Suspension and Termination

IRB approval may be suspended or terminated if research is not being conducted in accordance with IRB or regulatory requirements or has been associated with unexpected problems or serious harm to subjects. See *Section 15 Unanticipated Problems Involving Risks to Subjects or Others* and *Section 16 Non-compliance* for further discussion.

The IO along with the President, Provost, and Deans, has the authority to suspend or terminate the organization's approval for research. Such actions will be promptly reported to the IRB so that the IRB can review the circumstances and take any necessary actions relevant to IRB review and oversight. The Director of Research Compliance ensures that all steps of this policy are completed within thirty (30) days of the determination. For actions that are more serious, the Director of Research Compliance expedites reporting. If additional time is needed to gather facts, or determine corrective actions, a preliminary report will be submitted within 30 days, to be followed by a final report.

Suspension of IRB approval is a directive of the convened IRB, the IRB Chair, or the DRC to temporarily stop some or all previously approved research activities. Suspension directives made by the IRB Chair or DRC temporarily suspend IRB approval, in part or in full, when the available information suggests that actions must be taken to protect human subjects or the integrity of the research. At the next scheduled convened IRB meeting, the Chair will report the temporary suspension and the convened IRB will determine if the suspension should continue, be lifted, or be modified. Suspended protocols remain open and require continuing review. Investigator MUST continue to provide reports on adverse events and unanticipated problems to both the IRB and sponsor just as if there had never been a suspension (i.e., all events that need to be reported during a study need to continue to be reported during the suspension period.)

The IRB may consider notifying subjects when approval of some or all research activities is suspended by the IRB. When research activities are suspended, the IRB contemplates if addition actions may be necessary to ensure that the rights, safety and welfare of subjects are appropriately protected.

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

Suspensions of IRB approval must be reported promptly to the Institutional Official, sponsors including federal department or agency heads, and federal oversight agencies according to applicable federal and institutional requirements. See *Section 14, Other Reportable Information* for a detailed discussion of reportable events and reporting requirements.

Termination of IRB approval is a directive of the convened IRB to permanently stop all activities in a previously approved research study. Terminated research studies are closed and no longer require continuing review. Terminations of IRB approval of expedited research studies must be made by the convened IRB.

When study approval is terminated by the IRB, in addition to stopping all research activities, the IRB will consider notification of subjects and any actions necessary to ensure that the rights, safety, and welfare of subjects are appropriately protected.

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

Suspensions of IRB approval must be reported promptly to the Institutional Official, sponsors including federal department or agency heads, and federal oversight agencies according to applicable federal and institutional requirements. See *Section 14, Other Reportable Information* for a detailed discussion of reportable events and reporting requirements.

Investigator Hold

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

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 hold does not apply to interruptions of research related to concerns regarding the safety, rights, or welfare of human research participants, research investigators, research staff, or others. If there is an unanticipated problem involving risks to participants or others the study is not eligible for an administrative hold. Investigator hold must not be used to avoid reporting deficiencies or circumstances that otherwise require reporting by regulatory agencies.

Continuing Review and all organizational policies, such as policies on reporting problems, remain in effect for all activities placed under Investigator hold. The IRB approval expiration date is still valid and the Investigator hold cannot be used extend the IRB approval period. An IRB continuing review approval must be obtain prior to the expiration date.

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

A statement that the investigator is voluntarily placing a study on hold;
a. The reason(s) for the hold (i.e. researcher goes on sabbatical; researcher takes a leave of absence);
b. A description of the research activities that will be stopped;
c. Proposed actions to be taken to protect current participants; and
d. Any actions that will be taken prior to IRB approval of proposed changes in order to eliminate apparent immediate risk of harm.

Upon receipt of written notification from the investigator, the IRB staff places the research on the next available IRB meeting agenda for review.

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

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

Investigators must notify the IRB before removing an Investigator Hold.

Protection of Currently Enrolled Participants

Before a study hold, termination, or suspension, is put into effect the IRB 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: Multi-site & Collaborative Research

When engaged in multi-site research, research involving external collaborators, or research that is otherwise under the jurisdiction of more than one IRB, CMU acknowledges that each organization is responsible for safeguarding the rights and welfare of human subjects and for complying with applicable federal regulations. CMU may choose to review the research in its entirety, only those components of the research CMU is engaged in, rely on the review of another qualified IRB, or make other arrangements for avoiding duplication of effort. When CMU is the prime awardee on an HHS grant, it will ensure that at least one IRB reviews the research in its entirety.

A formal relationship must be established with the outside organization or investigator when CMU relies upon another IRB or when serving as the reviewing IRB for an outside organization or external investigator. An Institutional Authorization Agreement, Independent Investigator Agreement, a Memorandum of Understanding, or other such written agreement is utilized to establish a relationship. The written agreement must be executed before CMU will issue any IRB determination documents to the outside organization or investigator or rely on the review of an external IRB.

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

Requests for CMU to either rely upon an external IRB or to serve as the IRB of record for an external organization or investigator should be submitted as early as possible in the grant/contract process by contacting the IRB Coordinator.

Research Previously Approved by another IRB

When an investigator transfers human subjects research to CMU that was previously approved by another IRB, the investigator must:

- Submit the *IRB Active Study Transfer Application* for review, or
- Submit *IRB application for Reliance on External IRB* if CMU is to rely upon the existing IRB of Record.

The research submission is reviewed by the Director of Research Compliance to determine if CMU will accept oversight of the study. If the research is under the oversight of an external IRB of Record, the DRC will review all required documents for local site approval. Research where CMU will assume IRB oversight, the DRC will

assign the submission for an expedited or convened board review. Research activities under the auspices of CMU cannot commence until all necessary approvals are in place including approval by CMU's IRB or an IRB reliance agreement is executed (and the transferred activities are approved by the IRB of Record).

Where stopping research intervention or procedures might harm subjects, with permission of the prior organization's IRB, CMU may request them to continue oversight until the CMU IRB approval is obtained.

IRB Reliance Arrangements in Multi-Site Research

In multi-site investigator-initiated research where a CMU investigator is involved, the IRB encourages the investigator to discuss with collaborators the possibility of designating an IRB of record for the research.

If the research is part of a multicenter grant awarded from NIH, single IRB (sIRB) review is required under most circumstances (https://grants.nih.gov/grants/guide/notice-files/NOTOD-16-094.html). Refer to *Section 9 NIH Single IRB (sIRB) for Multi-Site Research* for details specific to compliance with the NIH sIRB policy.

Reliance Agreements

Before CMU cedes IRB Reviews, reliance agreements must be in place. The Office of Research Compliance works with Grants and Contract Director, if necessary, to ensure reliance agreements are negotiated to reflect study-specific, respective responsibilities of the reviewing IRB and the relying institutions. The reliance agreement:

- Documents the respective authorities, roles, responsibilities, and communication between an organization providing the ethical review and a participating organization relying on a reviewing IRB.
- Describes the responsibilities of all parties and how communication between parties will occur, for example, notifications of the outcome of regulatory review and management of federally mandated reports such as reports of unanticipated problems, serious or continuing noncompliance, and suspensions or terminations of IRB approval.
- When IRB certification requirements apply (e.g., for NIH Genomic Data Sharing etc.), the agreement or written procedures will indicate who is responsible for meeting the certification requirements. Specifies contact information and personnel for both the sIRB and relying institution(s).
- Address whether the replying organization applies its FWA to some or all research, and ensure that the IRB review is consistent with requirements in the relying organization's FWA.
- Address which organization is responsible for obtaining any additional approvals from DHHS when the research involves Subpart B, C, or D determinations, or any applicable federal agency or department (e.g., DOD, etc.)

Participating sites are responsible for maintaining copies of the site agreement in accordance with the terms of their FWA. The sIRB and participating sites establish adequate and appropriate communication plans during the conduct of the study.

Serving as Reviewing IRB

Generally, CMU's IRB does not serve as the IRB of record for an external organization unless CMU is also engaged in the research or has a master agreement in place with the external organization. The DRC evaluates the following factors, and others as appropriate, when considering a request for the CMU IRB to serve as the IRB of record for a particular study or studies:

- The terms of the external organization's FWA.
- Prior experience with the organization and investigators.
- The accreditation status of the external organization's HRPP.
- The compliance history of the organization and investigators (e.g., outcomes of prior audits or inspections, corrective actions).
- The research activities conducted by or at the external organization.
- The willingness of the external organization to accept CMU's reliance terms and procedures; and/or
- The ability of the organizations to collaboratively provide meaningful oversight of the proposed research, taking into account factors such as:
    - The risks and procedures of the research.
    - The resources available at each organization and ability to accommodate or collaborate with each other in observing the consent process, performing compliance reviews, investigations of potential noncompliance, and similar matters.
    - The expertise and experience of the CMU IRB with the proposed research, subject population, and applicable regulations.
    - The familiarity of the CMU IRB with the relevant local context considerations of the external organization.
    - The willingness or ability of the external organization to provide information and respond to questions regarding investigator qualifications, conflicts of interest, organizational requirements, local context, and other matters that may inform the IRB review.

The DRC considers the relevant factors for consideration and in consultation with the IO, will make the final decision regarding whether or not the CMU IRB will serve as the reviewing IRB. The PI will be notified of the decision.

Responsibilities when CMU is the Reviewing IRB

When the CMU IRB serves as the reviewing IRB for another organization, the requirements and procedures outlined throughout this manual apply unless an alternative procedure has been agreed to in the reliance agreement or outlined in a

companion document. Additionally, the following IRB responsibilities are to be applicable for all sites:

- Have the final authority to decide whether CMU or external researcher or research staffs' COI and its management, if any, allows the research to be approved
- Have the authority to request or conduct an audit of research being reviewed.
- Make relevant IRB policies readily available to relying external sites, including their HRPP staff, researchers, and research staff, and ensure that changes to those policies are communicated as well.
- Ensure that a CMU IRB contact person along with contact information is specified for researchers and research staff to obtain answers to questions, express concerns, and convey suggestions regarding the CMU IRB.

When a study has IRB approval and additional sites are to be added, a modification request will be submitted and conducted by the expedited or full board process. To use the expedited process criteria, a site addition usually is considered a "*minor change to previously approved research*". A full board review may be indicated due to following factors: involvement of investigators with a financial conflict of interest, FDA 483 issues that have not been resolved adequately, or any other site-specific issues that are deemed questionable. Additional site amendments (regardless of type of review) do not change the expiration date of the IRB approval for the 'main' protocol.

Responsibilities of the CMU Principal Investigator

Submission of a plan for review to the IRB to ensure that the PI's at collaborating sites have access to current information regarding study status and current protocols, consent documents, etc. regarding the study. (Alternatively, the IRB can review the plan provided by the CMU PI to ensure open communication with the collaborating site(s)). Coordinate with the CMU IRB to ensure submission to the IRB information pertaining to the particular characteristics of each site's local research context to be considered either

(a) through knowledge of its local research context by the IRB,
(b) through consultants, or
(c) through review by appropriate designated institutional officials at external site(s).

Additionally, the submission will also include details for the IRB's evaluation regarding the management plan for information that is relevant to the protection of participants (e.g., unanticipated problems involving risks to participants or others, Interim results, protocol modifications). When CMU researcher is the lead researcher of a multi-site study, this information will also be made known to the IRB of record (e.g. Independent IRB, IRB, etc.).

Ceding IRB Review to an External IRB

Standing Reliance Agreements

CMU has standing agreements in place to engage the service of external IRBs for the review of clinical trials conducted by the University Pediatric/CMU Clinical Research Institute including:

- WCG (Western IRB)
- Public Health Institute (PHI) for COG protocols
- SMART IRB Master Agreement sites
- Advarra

Other investigator-initiated studies, typically unfunded, must be reviewed by the DRC to determine if the service of an external IRB is warranted.

Factors Considered to allow CMU to Cede to an External IRB

CMU may also choose to enter into an agreement to rely upon other external IRBs, most commonly when required as a condition of a grant or contract. Investigators should submit reliance requests as early in the grant/contract process as possible contacting the IRB coordinator.

The DRC evaluates the following factors, and others as appropriate, when considering a request to rely upon an external IRB:

- The accreditation status of the proposed IRB.
- The compliance history of the IRB (e.g., outcomes of prior audits or inspections, corrective actions).
- Prior experience with the IRB.
- The federal IRB registration and organizational FWA, as applicable. The expertise and experience of the proposed IRB (e.g., with reviewing the type of research, research procedures, and subject population(s)).
- The research activities that will be conducted at or by CMU.
- The risks and complexities of the proposed research.
- The proposed reliance terms and procedures including the procedures for collaborative management of matters such as conflicts of interest, noncompliance, unanticipated problems, and federal reports.
- The plan for review and allowance of the incorporation of site-specific consent language.
- The plan for incorporation of other relevant local requirements or context information in the review process.

When reliance on a non-accredited IRB is proposed, the evaluation may also take into consideration one or more of the following based upon the risks of the research, the research activities that CMU will be involved in, and CMU's familiarity with the IRB:

- When the research is minimal risk (or the activities that CMU is involved with are minimal risk), a statement of assurance from the proposed IRB that its review will be consistent with applicable ethical and regulatory standards, and that it will report any regulatory investigations, citations, or actions taken regarding the reviewing IRB, and, when applicable, to the organization's FWA.
- An attestation about, or summary of, any quality assessment of the reviewing IRB such as evaluation by an external consultant or internal evaluation of compliance using the FDA's self-evaluation checklist or AAHRPP's self-evaluation instrument.
- The willingness of the external IRB to accommodate requests for relevant minutes and other records of the proposed study and/or to copy the medical school's HRPP office on correspondence such as determination letters and notices of suspensions or terminations of IRB approval.
- The willingness of the external IRB to accommodate a request for someone from the relying organization to serve as a consultant to the IRB or to observe the review of the proposed study.
- An assessment of the external IRB's policies and procedures.

The DRC considers the relevant factors for consideration and in consultation with the IO, will make the final decision regarding whether or not the CMU IRB will serve as the reviewing IRB. The PI will be notified of the decision.

CMU, External IRB, and CMU Investigator Responsibilities when CMU Cedes Review

The external IRBs that serve as the IRB of Record for CMU research have the same authority as CMU IRB and all determinations and requirements of the external IRBs are equally binding.

CMU remains responsible for the conduct of the research in which it engages. Research reviewed by external IRBs remains subject to review, approval, oversight, and monitoring by CMU (in cooperation with the reviewing IRB when appropriate) and must adhere to all applicable policies, procedures, and requirements of CMU HRPP. As with CMU IRB-reviewed research, officials of CMU may not approve research that is subject to a reliance agreement if it has not been approved by the reviewing IRB. DRC is responsible for notifying the reviewing IRB when CMU policies that may impact IRB review are updated.

Responsibilities of CMU Investigator when Using an External IRB

Investigators must be familiar with and comply with the external IRB's policies and procedures and any additional requirements or procedures outlined in the IRB reliance agreement or companion materials (e.g., reliance SOPs). CMU will support compliance with the terms of reliance agreements by making available to investigators information

relevant to their responsibilities, such as a copy or summary of the agreement, an information sheet, or reliance SOPs.

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

Even though the External IRB may be reviewing the study, it must not commence at CMU or affiliates until all HSR training, COI disclosure, local ICF content review and other required ancillary reviews and certifications have been satisfied.

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

Registration of Studies Reviewed by External IRBs

Investigators must register studies that will be reviewed by an external IRB by submitting an electronic application, *IRB application for Reliance on External IRB*. The IRB and DRC will review the information and verify that CITI training, COI review, and any other applicable approvals or requirements have been completed and determine the need for relaying local context information to the external IRB in accordance with the reliance agreement. The IRB staff will notify the investigators once the proposed research has been cleared for submission to the external IRB via an electronic system notification. Once approved by the external IRB, investigators must submit a copy of the approval letter and any approved consent document(s) including the HIPAA authorization, if applicable. If the protocol was modified during the external IRB review process, the approved version of the protocol should be provided as well.

Post-Approval Requirements

Investigators approved through external IRB review must still report local unanticipated problems, complaints, and any noncompliance to the CMU IRB using an Adverse/Reportable Event Form in addition to reporting to the external IRB. Copies of the report submitted to the external IRB are generally acceptable, but additional information may be requested on an as needed basis.

Investigators must also submit copies of continuing review reports, updated protocols, updated consent forms, study closures and corresponding IRB approval or acknowledgment.

Changes in PI must be submitted to the IRB prior to the new PI or research team member assuming any study responsibilities. CITI trainings, COI review, and any other applicable requirements will be verified.
Notices about, and reports from, DSMB's, external monitors, auditors, or inspectors

must be provided to the IRB as well.

Any of the following issues must be reported immediately (or when research team is made aware of issue) to the CMU IRB office by phone or email:

- Any negative actions by a government oversight office, including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action, FDA Restrictions Placed on IRBs or Investigators, and corresponding compliance actions taken under non-US authorities related to human research protections.
- Any litigation, arbitration, or settlements initiated related to human research protections.
- Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding CMU's HRPP.

In general, Investigators are reminded that all other Institutional reporting requirements remain applicable in addition to HRPP reporting requirements including study closure.

Exceptions to IRB vs. Local Site Responsibilities

The reliance agreement may outline areas of responsibilities that can be handled either by the reviewing IRB or CMU. These may pertain on how scientific review is conducted and managed, documentation of ancillary reviews and institutional permissions for research. Other examples are:

1. Training requirements and verification of qualifications and credentials for external investigators and staff.
2. For-cause and not-for-cause compliance reviews.
3. Site-specific consent language.
4. HIPAA compliance.
5. Handling of matters concerning noncompliance, including which institution is responsible for deciding whether each allegation of non-compliance has a basis in fact, whether an incident of noncompliance constitutes serious or continuing noncompliance, and who will handle reporting to federal agencies.
6. Handling of unanticipated problems, and responsibility of reporting to federal agencies when required.
7. Review of grant and IRB protocol for congruence.
8. Review of investigator financial disclosures for COI (note: the reviewing IRB must provide final approval of any management plans generated to mitigate investigator FCOI).
9. Managing organizational conflict of interest relating to the research.

In the case of the termination of a reliance agreement, identification of the party responsible for continued oversight of active studies until closure or a mutually agreed upon transfer of the study.

NIH Single IRB (sIRB) for Multi-Site Research

In June 2016, the National Institutes of Health (NIH) released a final policy requiring domestic awardees and domestic sites of NIH-funded multi-site research to use a single IRB (sIRB) for review of non-exempt human subject research unless there is justification for an exception. This policy is intended to streamline the IRB review process and reduce inefficiencies and redundancies while maintaining and enhancing subject protections. The policy *does not apply* to career development, research training, or fellowship awards, nor to sites that are not conducting the same protocol as the other sites (e.g., sites providing statistical support or laboratory analysis only) or to foreign sites.

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

Selection and Designation of a sIRB

Due to a lack of sufficient numbers of staff, CMU generally will not serve as a sIRB on multi-site studies.

CMU's investigators submitting applications for NIH-funded multi-site research must describe the sIRB plan in the funding proposal (grant application or contract proposal), and, if applicable, may request direct cost funding to cover additional costs related to the requirements of the NIH policy. The sIRB can be the IRB at one of the participating sites or an independent, fee-based IRB. When the sIRB is named in the proposal, the IRB must have agreed to take on this responsibility in advance. Requests for the CMU's IRB to serve as the sIRB should be directed to the IRB office and the Director of Research Compliance will make a determination in consultation with the IO, if necessary. Requests for CMU to rely upon an external IRB as the sIRB should be submitted as early in the process as possible by an *IRB application for Reliance on External IRB*.

Reliance Agreements for sIRB Studies

A Reliance Agreement (or "Authorization Agreement") between the sIRB and the participating sites is required. The Reliance Agreement documents the respective authorities, roles, responsibilities, and communication between an organization providing the ethical review and a participating organization relying on a reviewing IRB.

Reliance Agreements should describe the responsibilities of all parties and how

communication between parties will occur, for example, notifications of the outcome of regulatory review and management of federally mandated reports such as reports of unanticipated problems, serious or continuing noncompliance, and suspensions or terminations of IRB approval. When IRB certification requirements apply (e.g., for NIH Genomic Data Sharing), the agreement or written procedures should indicate who is responsible for meeting the certification requirements.

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

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

Responsibilities

The sIRB will be responsible for compliance with the regulatory requirements for IRBs specified in the federal regulations (i.e., 45 CFR 46 and other applicable regulations) and for any other responsibilities outlined in the reliance agreement and/or procedures. Participating sites (relying institutions) are responsible for providing relevant local context information to the sIRB, ensuring that the research is conducted in accordance with applicable regulations and the determinations and requirements of the sIRB, and for other responsibilities, as outlined in the reliance agreement and/or procedures.

When an external IRB serves as the sIRB for a study CMU is engaged in, investigators must register the study with CMU's IRB following the procedures outlined in *Section* 9, *Use of External IRB*. Post-approval requirements are summarized in *Section 9, CMU: Post External IRB Approval.*

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

CMU: Post External IRB Approval

CMU 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 CMU 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 IRB coordinator/DRC 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 CMU IRB.

Investigators approved through an external IRB review must still report local unanticipated problems, complaints, non-compliance, CMU IRB in compliance with CMU policy, in addition to any external IRB reporting requirements. Changes in investigators or study personnel must be submitted to the CMU 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 CMU IRB.

Section 10: Documentation and Records

CMU shall prepare and maintain adequate documentation of the IRB's activities. All records must be 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.

CMU IRB Records

CMU 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 CMU'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.
- Verification of Research Conflict of Interest Form completion by investigators, IRB members, and IRB staff.

IRB Study Files

The IRB maintains a separate IRB electronic 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 in accordance with the DHHS regulations. Copies are filed in the electronic study file. CMU IRB maintains a separate electronic file for each research study that includes, but is not limited to:

- The application and all other documents submitted as part of a new study application.
- Documents submitted for continuing review or closure.
- Documents submitted and reviewed after the study has been approved, including modification requests, protocol exception requests, proposed advertisements, data and safety monitoring reports, and reports of protocol deviations,

complaints, non-compliance, significant new findings, unanticipated adverse
- Adverse events and unanticipated problems involving risks to subjects or others.
- Copy of IRB-approved Consent/Assent/Permission Forms.
- DHHS-approved sample consent form document and protocol/research plan, when applicable.
- IRB reviewer determinations.
- Documentation of scientific or scholarly review (if available).
- Documentation of type of IRB review. For exempt and expedited review, this includes the category(ies) under which the review is allowed.
- 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/nonsignificant risk.
- Documentation of audits, inspections, or other similar reports.
- Records include documentation specifying the responsibilities that a relying organization and an organization operating an IRB each will undertake to ensure compliance with the requirements of the Common Rule.
- 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, rationale for conducting continuing review on research that otherwise would not require continuing review, 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 including rationale for an expedited reviewer's determination that research appearing on the expedited review list is more than minimal risk as applicable. For research reviewed by the convened board, these determinations are recorded in the minutes.

In order to allow a reconstruction of a complete history of IRB actions related to the review and approval of the protocol, the IRB electronic records include copies of:

- Investigator brochure, if any.
- Scientific evaluations, when provided by an entity other than the IRB.
- Recruitment materials.
- Progress reports submitted by researchers.
- Reports of injuries to participants.
- Records of continuing review activities.

- Significant new findings.

IRB Minutes

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

When documentation involves minutes and supplemental materials such as checklists or worksheets completed by the IRB members for the convened meeting, the IRB does not collect or retain materials therefore does not utilize these for documenting meeting proceedings including controverted issues. Members are to bring any issues identified on their individual materials forward during discussion and in turn these are documented in the meeting minutes accordingly.

A copy of IRB-approved minutes for each IRB meeting will be made available to the IO.

Minutes of IRB meetings must contain sufficient detail to show:

- Attendance.
    - Names of members or alternates present.
    - Names of members or alternate members who are participating through videoconference or teleconference and documentation that those attending through videoconferencing or teleconferencing received all pertinent materials prior to the meeting and were able to actively and equally participate in all discussions.
    - Names of alternates attending in lieu of specified (named) absent members. (Alternates may substitute for specific absent members or categories of members only as designated on the official IRB membership roster).
    - Names of consultants, investigators, and other guests present.
    - The attendance list shall include those members who attended the meeting, in person or remotely. The minutes must indicate when members enter or leave the meeting. The vote on each action must reflect the numbers of members present for the vote on that item. Members who recuse themselves because of conflict of interest or commitment are listed by name along with the fact that the recusal is due to conflict of interest or
    - commitment.
- The presence of a quorum throughout the meeting, including the presence of one member whose primary concern is in a non-scientific area.
- Business items discussed and any education provided.
- Actions taken, including separate deliberations, actions, and votes for each agenda item undergoing review by the convened IRB.
- Vote counts on these actions (Total number voting; number voting for; number voting against; number abstaining; number recused).
- Basis or justification for actions disapproving or requiring changes in research.

- Summary of any controverted issues and their resolution.
- Approval period for initial and continuing reviews, including identification of research that warrants review more often than annually and the basis for that determination.
- Risk determination for initial and continuing reviews, and modifications when the modification alters the prior risk determination.
- Justification for deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document.
- Study-specific findings supporting that the research meets each of the required criteria when approving a consent procedure that does not include or that alters some or all of the required elements of informed consent, or when waiving the requirement to obtain informed consent altogether.
- Study-specific findings supporting that the research meets each of the required criteria when the requirements for documentation of consent are waived.
- Documenting the criteria for approval are met.
- Study-specific findings supporting that the research meets each of the criteria for approval for vulnerable populations under any applicable Subparts. Significant risk/non-significant risk/ 21 CFR 812 exempt device determinations and the basis for those determinations.
- Determinations of conflict of interest and commitment, and acceptance or modification of conflict management plans.
- Identification of any research for which there is need for verification from sources other than the investigator that no material changes are made in the research. Review of interim reports, e.g., unanticipated problems or safety reports; modification requests; report of violations/deviations; serious or continuing noncompliance; suspensions/terminations; etc.
- A list of research approved under expedited review procedures since the time of the last such report.
- Key information provided by consultants will be documented in the minutes or in a report provided by the consultant.

IRB Membership Roster

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

- Name.
- Earned degrees.
- Employment or other relationship between each member and CMU (i.e., affiliated or non-affiliated). To be categorized as non-affiliated, neither the member nor an immediate family member of the member may be affiliated with CMU.
- 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, in the areas of their practice, sufficient to describe each member's chief anticipated contributions to IRB deliberations.
- Representative capacities of each IRB member. The list should identify the IRB members who are experienced or have knowledge concerning working with children, pregnant women, cognitively impaired individuals, and other vulnerable populations commonly encountered in CMU research along with a member who is the prisoner representative, if necessary.
- Role on the IRB (chair, vice chair, etc.).
- IRB voting status.
- For alternate members, class of members for whom the member could substitute.

The HRPP director keeps the IRB membership list current. When there are additions and/or deletions of board members to a roster, the IORG registration will be updated within 90 days of such changes. For each convened meeting, the designated voting member will be listed on the agenda allowing for the expertise needed for the studies being reviewed.

Documentation of Exemptions

Documentation of verified exemptions consists of the reviewer's citation of a specific exemption category and written concurrence that the activity described in the investigator's application satisfies the conditions of the cited exemption category as detailed in *Section 6*, *Exempt Studies*.

Documentation of Expedited Reviews

IRB electronic records for initial and continuing review by the expedited procedure must include: the specific permissible category; evidence that the activity described by the investigator satisfies all of the criteria for approval; the approval period and any determinations required by the regulations including study-specific findings justifying the following determinations:

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

Access to IRB Records

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

- Electronic records are kept on secure servers maintained by contractors with whom CMU has entered into licensing agreements.
- Doors to the IRB Offices are closed and locked when the rooms are unattended.
- Ordinarily, access to all IRB records is limited to the DRC, IRB Chair, IRB members, IRB staff, authorized institutional officials, and officials of federal and state regulatory agencies (e.g., OHRP, FDA). Research investigators are provided reasonable access to files related to their research. Appropriate accreditation bodies are provided access and may recommend additional procedures for maintaining security of IRB records. All other access to IRB records is limited to those who have legitimate need for them, as determined by the IO and DRC.
- Records are accessible for inspection and copying by authorized representatives of regulatory agencies during regular business hours.
- Records may not be removed from the IRB Office; however, the IRB staff will provide copies of records for authorized personnel if requested.
- All other access to IRB study files is prohibited.

Record Retention

In order to comply with the requirements of OHRP and FDA, IRB records are retained for at least three (3) years following closure, termination, or expiration of IRB approval. For HIPPA requirements, IRB records are retained for at least six (6) years following closure, termination, or expiration of IRB approval.

For research with waivers of authorization, the IRB study file is retained for a period of six (6) years following closure, termination, or expiration of IRB approval.

The records may be maintained in printed form or electronically. Until destruction of IRB records has occurred, they are accessible for inspection and copying by interested parties, including but not limited to representatives of federal agencies and departments, sponsors, and institutional officials, at reasonable times and in a reasonable manner.

Section 11: Obtaining Informed Consent from Research Subjects

No investigator conducting research at, or under the auspices of CMU may involve a human being as a subject in research without obtaining the legally effective informed consent of the subject or the subject's legally authorized representative unless a waiver of consent has been approved by the IRB in accordance with *Section 11, Waiver of Informed Consent* of these procedures. Except as provided in *Section 11, Waiver of Documentation of Informed Consent* and *Waiver of Informed Consent for Planned Emergency Research* of these procedures, informed consent must be documented by the use of a written consent form approved by the IRB.

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

The following procedures describe the requirements for obtaining consent from participants in research conducted at, under the auspices of, or using the services or resources of CMU.

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

Definitions

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

  Michigan law currently does not define who may serve as a LAR for research purposes. However, when an individual has authority under Michigan law to serve as a subject's LAR for healthcare and medical decision-making purposes, it may be reasonable and appropriate – under the circumstances for that person to also make decisions related to the subject's participation in research.

  If an adult is unable to make medical decision due to being declared legally incompetent, a legal representative (court appointed guardian) or durable power of attorney for health care must provide informed consent for non-emergent medical treatment. The court must authorize a legal guardian to make decisions regarding the types of activities, procedures, or treatments call for in the research to serve as LAR. If a court appointed guardian or durable power of attorney for health care are not in place, the investigator should refer to clinical setting guidelines to determine who may serve as LAR for research involving clinical procedures or treatments.

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

The obligation of an LAR is to understand what the potential subject would do if able to provide consent or what they think is in the person's best interest. The LAR therefore should be informed regarding their roles and responsibilities when asked to provide surrogate consent.

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

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

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

Basic Requirements

The requirement to obtain the legally effective informed consent of individuals before involving them in research is one of the central protections provided for by the Federal regulations and CMU IRB. Investigators are required to obtain legally effective informed consent from a subject or the subject's LAR unless the requirement has been waived by the IRB. When informed consent is required, it must be sought prospectively, and properly documented.

The informed consent process involves three key features:

(1) Disclosing to the prospective human subject information needed to make an informed decision.
(2) Facilitating the understanding of what has been disclosed.
(3) Promoting the voluntariness of the decision about whether or not to participate in the Research.

Informed consent is more than just a signature on a form. It is a process of information exchange to include reading, discussing, providing answers to any questions, and obtaining signature on the consent document. The informed consent process is the critical communication link between the prospective human subject and an Investigator, beginning with the initial approach of an Investigator and continuing through the completion of the research. Those obtaining informed consent must have received the

appropriate training and be knowledgeable about the study in order that they may answer questions to help provide understanding to the study participant or potential study participant. The exchange of information between those obtaining informed

consent and study participant can occur via one or more of the following modes of communication, among others: face-to-face dialogue, mail, telephone, video or fax. The process must be conducted in a location that ensures privacy and allows the prospective subject sufficient time to consider the information and ask questions and seek clarification from the investigator. Consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's LAR at the time of consent. Those obtaining informed consent must have a signed and dated written consent form before entering a subject into a study, gathering study data about a subject, and/or conducting any procedures required by the protocol/research plan, unless consent is waived by the IRB.

If someone other than the investigator conducts the interview and obtains consent, the investigator needs to formally delegate this responsibility, and the person so delegated must have received appropriate training to perform this activity. The person so delegated must be knowledgeable about the research to be conducted and the consenting process, and must have the expertise 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 approving 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.

Posting of Clinical Trial Consent Forms

Per the 2018 Common Rule requirements effective January 21, 2019, for each clinical trial conducted or supported by a Federal department or agency, one IRB-approved informed consent form used to enroll subjects must be posted by the awardee or the Federal department or agency component conducting the trial on a publicly available Federal Web site that will be established as a repository for such informed consent forms.

If the Federal department or agency supporting or conducting the clinical trial determines that certain information should not be made publicly available on a Federal Web site (e.g. confidential commercial information), such Federal department or agency may permit or require redactions to the information posted.

The informed consent form must be posted on the Federal Web site after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.
At CMU, informed consent form postings and redactions will be facilitated by the Director of Research Compliance.

These informed consent requirements are not intended to preempt any applicable

federal, state, or local laws that require additional information to be disclosed for the informed consent to be legally effective.

Informed Consent Process

Informed consent must be obtained under the following circumstances:

- Informed consent may only be obtained from subjects who have the legal and mental capacity to give consent. For subjects without that capacity, permission must be obtained from a legal guardian with appropriate authority to make decisions regarding the activities called for in the research or a LAR.
- The informed consent process provides the prospective subject LAR/guardian with sufficient opportunity to read the consent document, if applicable.
- The informed consent process shall be sought under circumstances that provide the subject (or LAR) with sufficient opportunity to consider whether or not to participate.
- The informed consent process shall be sought under circumstances that minimize the possibility of coercion or undue influence.
- The informed consent information must be presented in language that is understandable to the subject or LAR. To the extent possible, the language should be understandable by a person who is educated at an eighth-grade level and layman's terms shall be used in the description of the research. The IRB may require or allow different readability standards based upon the characteristics of the target subject population.
- Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or LAR in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension.
- For subjects whose native language is not English or has limited fluency in the English language, informed consent must be obtained in a language that is understandable to the subject or the subject's LAR. The IRB requires that informed consent discussions include a reliable interpreter when the prospective subject does not understand the language of the person who is obtaining consent.
- The informed consent process may not include any exculpatory language through which the subject is made to waive, or appear to waive any of the subject's legal rights or through which the investigators, the sponsor, the organization where research activities take place, or CMU employees or agents are released from liability for negligence or appear to be so released.
- The investigator is responsible for ensuring that each prospective subject is adequately informed about all aspects of the research and understands the information provided.

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

If a subject can show an understanding of the research activity, then he or she has the capacity to consent to participate in such research activity, as described in this section. The subject needs to appreciate the following:

- 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.

Subjects must show they understand the aspects of the risks, benefits, and available alternative when reaching a decision about participation in the research activity. It is essential this information is processed in a rational manner and the potential subject show they understand them since some aspects may be unique to them as individuals.

The decision-making capacity of a potential research subject should be evaluated when there are reasons to believe that the subject may not be capable of making voluntary and informed decisions about research participation.

The investigator and research staff must have adequate procedures in place for assessing and ensuring subjects' capacity, understanding, and informed consent or assent. The IRB will evaluate whether the proposed plan to assess capacity to consent is adequate including consideration of state and local law and institutional policy.

Persons with some decisional impairments may be able to make voluntary and informed decisions to consent, assent or refuse to participate in research if measures can be put into place to evaluate their understanding. 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, interpreter for hearing-impaired subjects, allowing a waiting period before enrollment, or involvement of a trusted family member or friend in the disclosure and decision making process.

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

In the event that research participants lose or become impaired in decision-making capacity after enrollment, and this is not anticipated in the protocol/research plan, the

investigator is responsible for notifying the IRB. The investigator is responsible for developing a plan for the IRB's consideration which follows the guidelines outlined above for persons with fluctuating or diminishing capacity.

Decisional capacity in the research context has been interpreted by the American Psychiatric Association as requiring:

- Ability to communicate a choice.
- Ability to understand relevant information.
- Ability to appreciate the situation and its likely consequences.
- Ability to manipulate information rationally.

Whenever the participants have the capacity to give consent (as determined by qualified professionals), informed consent should be obtained and documented in accordance with *Section 11, Documentation of Informed Consent*. When participants lack the capacity to give consent, investigators may obtain consent from the LAR of a subject as described in *Section 12, Adults with Impaired Decision-making Capacity*.

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

If the investigator plans to use audio or videotapes, computer video presentations, or written materials, to promote understanding, these materials must be provided to the IRB for review. If the investigator intends to use audio or video recordings to document assent, provisions to ensure the security of the recordings should be described to the IRB. If the investigator will use an assent form to document assent, this must be submitted to the IRB for review. All materials must be approved by the IRB prior to use.

Basic Elements of Informed Consent

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

- A statement that the study involves research, an explanation of the purposes of the research, the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others which may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject must be maintained.
- For research involving more than minimal risk, an explanation as to whether any

compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- For FDA-regulated studies, a statement that notes the possibility that the Food and Drug Administration may inspect the records.
- For applicable FDA-regulated clinical trials, the following statement must be included verbatim:
  "*A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.*"
- For research that involves the collection of identifiable private information or identifiable biospecimens:

  (1) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility, or
  (2) The subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

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

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

- A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit.
- A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions.
- For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

Informed Consent Templates that include the New Common Rule requirements are available and posted to the CMU Office of Research Compliance Website. Investigators are strongly urged to use the updated ICF templates to ensure compliance.

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

Documentation of Informed Consent

Unless the requirement for documentation of consent is waived by the IRB in accordance with *Section 11, Waiver of Informed Consent*, informed consent must be documented by the use of an IRB approved written informed consent document (ICD).

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

informed consent has been presented orally to the subject or the subject's LAR.

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

- The IRB must approve a written summary of what is to be said to the subject (the approved full consent document may serve as this summary).
- The oral presentation and the short form written document should be in a language understandable to the subject.
- There must be a witness to the oral presentation.
- The short form document is signed by the subject.
- The witness must sign both the short form and a copy of the summary.
- The person actually obtaining consent must sign a copy of the summary.
- A copy of the summary must be given to the subject or representative, in addition to a copy of the short form.

Broad Consent

Broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens (collected for either research studies other than the proposed research or non-research purposes) is permitted under the revised Common Rule. The following elements of broad consent shall be provided to each subject or the subject's LAR:

- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others which may reasonably be expected from the research.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject must be maintained.
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- For research involving biospecimens, a statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit.
- For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).
- A general description of the types of research that may be conducted with the identifiable private information or identifiable biospecimens. This description

must include sufficient information such that a reasonable person would expect that the broad consent would permit the types of research conducted.
- A description of the identifiable private information or identifiable biospecimens that might be used in research, whether sharing of identifiable private information or identifiable biospecimens might occur, and the types of institutions or researchers that might conduct research with the identifiable private information or identifiable biospecimens.
- A description of the period of time that the identifiable private information or identifiable biospecimens may be stored and maintained (which period of time could be indefinite), and a description of the period of time that the identifiable private information or identifiable biospecimens may be used for research purposes (which period of time could be indefinite).
- Unless the subject or legally authorized representative will be provided details about specific research studies, a statement that they will not be informed of the details of any specific research studies that might be conducted using the subject's identifiable private information or identifiable biospecimens, including the purposes of the research, and that they might have chosen not to consent to some of those specific research studies.
- Unless it is known that clinically relevant research results, including individual research results, will be disclosed to the subject in all circumstances, a statement that such results may not be disclosed to the subject.
- An explanation of whom to contact for answers to questions about the subject's rights and about storage and use of the subject's identifiable private information or identifiable biospecimens, and whom to contact in the event of a research-related harm.

FDA does not propose to adopt any of the Common Rule provisions pertaining to "broad consent." The Common Rule's version of broad consent has not been adopted by many institutions given the difficulties created by the need to track subjects who are offered and refuse to provide such broad consent, to ensure that their information and specimens are never the subject of an IRB waiver of informed consent. This may be the reason for FDA's determination not to adopt this provision of the Common Rule in the HSR NPRM. (September 29, 2022)

Special Consent Circumstances

Enrollment of Persons with Limited English-language Proficiency

Expected Enrollment

In some studies, the investigator may be able to anticipate enrollment of persons who do not speak or read or have limited proficiency in oral English. When the target subject population includes such persons or the investigator and/or the IRB otherwise anticipates that consent will be conducted in a language other than English, the IRB requires a translated consent document, and other subject materials, to be prepared. In

order to ensure that translated documents are accurate, the IRB may choose to require a certified translation, to have an independent back-translation, or to have a review of the translated documents by an IRB member or other person who is fluent in that language. When non-English speaking subjects enroll, they and a witness sign the translated consent document. The subjects are given a copy of the signed translated consent document.

Unexpected Enrollment

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

If an investigator decides to enroll a subject into a study for which there is not an existing IRB-approved consent document in the prospective subject's language, the *investigator must verify* that specific language "short form" has been used **3 times or less** on that study. For studies where there are multiple consents (e.g., initial, consolidation, maintenance) submitted for review, the initial consenting can be done utilizing the prospective subject's language "short form". The other consent forms will need to be translated into the subject's language since the use of the them is not unexpected and there is a specific time frame for their future use on the study.

Use of Interpreters in the Consent Process

An interpreter will be necessary to facilitate the consent discussion. Preferably someone with an understanding of the clinical setting. This person is independent of the subject (i.e., not a family member) assists in presenting the information and obtaining consent. Whenever possible, interpreters should be provided copies of the translated consent, or short form and the IRB-approved consent script (typically the English-language version of the consent document) generally 24-48 hours, if possible, before the consent discussion with the subject. If the interpreter also serves as the witness, the interpreter may sign the translated consent, or short form consent document and script, as the witness and should note "Interpreter" under the signature line. The person obtaining consent must document if the "short form" process was used in the subject's research record, including the name of the interpreter.

Braille Consent

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

Section 11, Oral Consent.

Consenting in American Sign Language (ASL)

The IRB may approve a consent process using ASL and the IRB-approved written consent form for deaf subjects who are fluent in ASL. When this process is approved, the individual authorized to consent prospective subjects must use a certified interpreter fluent in ASL to conduct the consent process and the documentation of the consent process must conform to the requirements set forth in *Section 11, Informed Consent*.

Oral Consent

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

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

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

Telephone Consent

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

Phone scripts for minimal risk research typically include the following:

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

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

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

General Data Protection Regulation (GDBP)

CMU investigators conducting research in one of the 27 member countries of the European Union, or Iceland, Liechtenstein, and Norway, must be aware that research subjects within those countries of have additional rights under the General Data Protection Regulations (GDPR) including the right to withdraw their consent to participate as easily as they gave their consent initially. They may request that data about them collected in the course of research be erased and the investigators must honor the request or explain why the request cannot be honored.

Physically Challenged Subjects

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

For a variety of reasons, a subject enrolled in a research study may decide to withdraw

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

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

- For FDA-regulated clinical trials, when a subject withdraws from a study, the data collected on the subject to the point of withdrawal remain part of the study database and may not be removed. The consent document cannot give the subject the option of having data removed.
- For research not subject to FDA regulations, the investigator should inform subjects whether the investigator intends to either:
    (1) retain and analyse 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 (e.g., limited to discontinuation of the primary interventional component of a research study), research activities involving other types of participation for which the subject previously gave consent may continue. Investigators should ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and procedures and continued follow-up in person, by phone, or via records review, of data and address the maintenance of privacy and confidentiality of the subject's information.

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

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

Waiver or Alteration 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 research could not practicably be carried out without the waiver or alteration.
- The research involves identifiable private information or identifiable biospecimens, the research could not be carried out practicably without using the information/specimen in an identifiable format.
- The waiver or alteration will not adversely affect the rights and welfare of the subjects.
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation. The intent of this waiver criterion is to require debriefing for participants in deception research.
- Investigators may be asked to provide justification, or additional information or documentation, to support that the above criteria are satisfied.

This option applies to both FDA-regulated and DHHS-conducted or supported research.

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

- The research or demonstration project is to be conducted by or subject to the approval of state or local government officials; and
- The project 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; and
- The project could not practicably be carried out without the waiver or alteration.

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

If an individual was asked to provide broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens and refused to consent, an IRB *cannot waive* consent for secondary research use of the identifiable private information or identifiable biospecimens.

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

Screening, Recruiting, or Determining Eligibility

An IRB may approve a research proposal in which an investigator will obtain

information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects (46.116(G)) without the informed consent of the prospective
subject or the subject's legally authorized representative, if either of the following conditions are met:

- The investigator will obtain information through oral or written communication with the prospective subject or legally authorized representative; or
- The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

Investigators do not have to request waivers of consent for the purposes of screening, recruiting, or determining eligibility but do have to describe the activities in the application or protocol submitted to the IRB. The above does not negate the requirements of other rules, such as HIPAA, when applicable. It also does not negate the requirement to obtain consent, or a waiver of consent, before involving a subject (including the use of their identifiable private information or biospecimens) in other research activities.

Waiver of Documentation of Informed Consent

The IRB may waive the requirement for documentation of informed consent if it finds and documents either of the following:

- The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Subjects must be asked whether they want documentation linking them with the research, and their wishes must govern. (Example: domestic violence research where the primary risk is discovery by the abuser that the subject is talking to investigators); **OR**
- The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Procedures such as non-sensitive surveys, questionnaires and interviews generally do not require written consent when conducted by non-investigators (e.g., marketing surveys, telemarketing); **OR**
- If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk or harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained. The oral or written information provided to participants includes all required and appropriate additional elements of consent disclosure. The IRB will determine whether the researcher should provide participants with a written statement regarding the research.

Investigators who seek and receive approval for a waiver of documentation of consent still must be perform an adequate consent process unless the IRB has granted a *full* waiver of the requirement.

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

Waiver of Signature Requirement

The IRB has implemented equivalent protections to waive the requirement for a signature on a consent document for research involving surveys or interviews conducted telephonically or by internet if all the following conditions are met:

- There is an explicit statement, either in writing or verbally, of consent to participate.
- The research presents no more than minimal risk to participants.
- The research is not supported by a Common Rule agency.

Waiver of Informed Consent for Planned Emergency Research

Note: *CMU IRB will not be the IRB of Record for a study that plans to utilize a waiver of informed consent for planned emergency research (EFIC). If the study is multi-site project, CMU will evaluate if they will participate as a site under a reliance agreement.*

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

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

The Secretary of Health and Human Services (DHHS) has implemented an Emergency Research Consent Waiver under 45 CFR 46.101(i) with provisions equivalent to those of the FDA with the exception of the requirements specified in *Section 11, FDA-regulated Planned Emergency Research and Planned Emergency Research Not Subject to FDA Regulations* below. The DHHS waiver is not applicable to research involving prisoners, pregnant women, fetuses, or in vitro fertilization.

Definitions

- **Planned Emergency Research**: It is research that involves subjects who, are in a life-threatening situation for which available therapies or diagnostics are unproven or unsatisfactory, and because of the subjects' medical condition and the unavailability of LARs of the subjects, it is generally not possible to obtain

legally effective informed consent.

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

Procedures

The IRB may approve the planned emergency research without requiring informed consent of all research subjects prior to initiating the research intervention if the IRB finds and documents that the following conditions have been met:

- The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
- Obtaining informed consent is not feasible because of all of the following:
    - The subjects will not be able to give their informed consent as a result of their medical condition.
    - The intervention under investigation must be administered before consent from the subjects' LARs is feasible.
    - There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.
- Participation in the research holds out the prospect of direct benefit to the subjects because of all of the following:
    - Subjects are facing a life-threatening situation that necessitates intervention.
    - Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects.
    - Risks associated with the research are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
- The research could not practicably be carried out without the waiver.
- The proposed protocol/research plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a LAR for each subject within that window of time and, if feasible, to asking the LAR contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact LARs and make this information available to the IRB at the time of continuing review.
- The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sections 46.116 and 46.117 of 45 CFR

46 and Sections 50.20, 50.25 and 50.27 of 21 CFR 50. These procedures and the informed consent document are to be used with subjects or their LARs in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the research consistent with paragraph 7 e) of this section.

- Additional protections of the rights and welfare of the subjects will be provided, including, at least:
    - Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the research will be conducted and from which the subjects will be drawn.
    - Public disclosure to the communities in which the research will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits.
    - Public disclosure of sufficient information following completion of the research to apprise the community and investigators of the study, including the demographic characteristics of the research population, and its results.
    - Establishment of an independent data monitoring committee to exercise oversight of the research.
    - If obtaining informed consent is not feasible and a LAR is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a LAR, and asking whether he or she objects to the subject's participation in the research. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

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

FDA-regulated Planned Emergency Research

A licensed physician who is a member of, or consultant to, the IRB and who is not otherwise participating in the clinical investigation must concur that the conditions described in *Section 11, Procedures* are satisfied.

Studies involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies that such studies may include subjects who are unable to consent. The submission of those studies in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under 312.30 or 812.35.

If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided in the regulations or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

The IRB determinations and documentation required in *Section 11, Procedures* and this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with 56.115(b).

Planned Emergency Research Not Subject to FDA Regulations

The IRB responsible for the review, approval, and continuing review of the research has approved both the research and a waiver of informed consent and has (i) found and documented that the research *is not subject* to regulations codified by the FDA at 21 CFR Part 50, and (ii) found and documented and reported to the OHRP that the conditions required *Section 11*, *Procedures* have been met relative to the research.

Section 12: Vulnerable Subjects in Research

Research with participants conducted at, or under the auspices of, or using the services or resources of CMU who are vulnerable to coercion or undue influence or have impaired decision-making capacity must include additional safeguards to protect the rights and welfare of these participants. The IRB must ensure that all the regulatory requirements for the protection of vulnerable subjects are met and that appropriate additional protections for vulnerable subjects are in place.

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

Definitions

- **Children**: Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

  Michigan law defines the "age of majority" in MCL 722.51. An individual who is eighteen or older is an "adult" and can consent to undergo most medical procedures. Parents or legal guardians generally must consent on behalf of children younger than eighteen, with the following exceptions:
  - Emancipated minors (generally those who are married or are on active duty in the U.S. armed forces) (MCL 722.4e(1)(g)).
  - Children seeking prenatal and pregnancy-related care (excluding abortions) (MCL 333.9132; MCL 722 .903).
  - Children age 14 and above seeking limited outpatient mental health services (MCL 330.1707).
  - Children receiving substance abuse treatment (MCL 330.1264); and Children seeking treatment for sexually transmitted diseases, including HIV/AIDS (MCL 333.5127).

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

  For research conducted in jurisdictions other than Michigan, the research must comply with the laws regarding the legal age of consent in the relevant jurisdictions. Legal counsel will be consulted about the laws in other

jurisdictions or such "local context" information will be sought through other means (e.g., according to the terms of a reliance agreement).

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

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

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

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

- **Fetus**: A fetus means the product of conception from implantation until delivery.

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

- **Delivery**: A delivery is a complete separation of the fetus from the woman by expulsion or extraction or any other means.

- **Neonate**: A neonate is a newborn.
  - **Viable neonate**: A viable neonate means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration.
  - **Nonviable neonate**: A nonviable neonate means a neonate after delivery that, although living, is not viable.

- **Pregnancy**: Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

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

Involvement of Persons Vulnerable to Coercion or Undue Influence

When the IRB reviews research that involves categories of participants vulnerable to coercion or undue influence, the review process should include one or more individuals who are knowledgeable about or experienced in working with these participants. The IRB may include one or more individuals who are knowledgeable about or experienced in working with individuals from these populations or it may seek such expertise through the use of consultants.

45 CFR 46 has additional subparts designed to provide extra protections for special populations, which also state additional requirements for IRBs.

- Subpart B - Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research.
- Subpart C - Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects.
- Subpart D - Additional Protections for Children Involved as Subjects in Research

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

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

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

Responsibilities

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

The IRB shall include representation, either as members or using consultants, of

individual(s) who are knowledgeable about or experienced working with the vulnerable populations involved in the research proposal under review.

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

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

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

Procedures

Initial Review of Research Proposal

- The investigator identifies the potential to enroll vulnerable subjects in the proposed research at initial review and provides justification for their inclusion in the study.
- The investigator describes safeguards to protect the subject's rights and welfare in the research proposal.
- The IRB staff, in collaboration with the IRB chair as needed, ensure that the IRB has the relevant expertise with the vulnerable population, and, if necessary, arrange for consultation. When the research involves no more than minimal risk and is eligible for expedited review, the designated reviewer may determine the need for additional expertise to ensure the protection of the vulnerable population(s).
- The IRB evaluates the proposed safeguards for subjects, including, if applicable, the proposed plan for identifying, recruiting, and obtaining consent from subjects and or their LARs and the plans for assent of children and adults unable to provide consent. When applicable, the IRB considers any costs associated with participation in the proposed research and any plans for reimbursement of expenses or provision of compensation, and the potential impact of such on the vulnerable population(s).
- The IRB evaluates the research to determine whether the proposed plan is adequate or if additional protections are needed such as interim monitoring, review more than annually, or the use of a data and safety monitoring board, consent monitor, or research subject advocate.
- The IRB considers each of the specific findings discussed in the IRB application forms for research involving vulnerable subjects, as documented by IRB approval.

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

Continuing Review and Modifications to Research

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

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

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

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

Research Involving Pregnant Women, Human Fetuses and Neonates

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

Research Involving Pregnant Women or Fetuses

Conducted or Supported by DHHS

For DHHS-conducted or supported research, 45 CFR 46 Subpart B applies to all nonexempt human subject research involving pregnant women, fetuses, and neonates.

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

- Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.

- The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important *biomedical* knowledge which cannot be obtained by any other means.
- Any risk is the least possible for achieving the objectives of the research.
- If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent.
- If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
- Each individual providing consent under paragraph four (4) or five (5) of this section is fully informed regarding the reasonably foreseeable impact of the
- Research on the fetus or neonate.
- For children see *Section 12 Definitions,* who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in Section 12. No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
- Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
- Individuals engaged in the research will have no part in determining the viability of a neonate.

Not Conducted or Supported by DHHS

For non DHHS-conducted or supported research, no additional safeguards are required and there are no restrictions on the involvement of pregnant women in research where the risk to the fetus is no more than minimal.

Research involving Neonates of Uncertain Viability or Nonviable Neonates

Not Conducted or Supported by DHHS

Neonates of uncertain viability and nonviable neonates may be involved in research involving more than minimal risk if all the following conditions listed below are met.

The IRB will determine on a case-by-case basis whether safeguards or restrictions should be required for more than minimal risk research.

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

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

- The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective.

OR

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

AND

- The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's LAR is obtained in accord with the provisions of permission and assent, except at the consent of the father or his LAR need not be obtained if the pregnancy resulted from rape or incest.

Nonviable neonates after delivery may not be involved in research unless all the following additional conditions are met:

- Vital functions of the neonate will not be artificially maintained.

- The research will not terminate the heartbeat or respiration of the neonate.
- There will be no added risk to the neonate resulting from the research.
- The purpose of the research is the development of important knowledge that cannot be obtained by other means.
- The legally effective informed consent of both parents of the neonate is obtained in accord with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission and assent do not apply.

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

Conducted or Supported by DHHS

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

Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
Individuals engaged in the research will have no part in determining the viability of a neonate.
The requirements of Neonates of Uncertain Viability or Nonviable Neonates (see below in this section) have been met as applicable.
Until it has been ascertained whether a neonate is viable, the neonate may not be involved in research unless both of the following additional conditions are met. The IRB must determine that:
Either the research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective.

OR

The purpose of the research is the development of important *biomedical* knowledge that cannot be obtained by other means and there will be no added risk to the neonate resulting from the research.

AND

The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's LAR is obtained in accord with the provisions of permission and assent, except that the consent of the father or his LAR need not be obtained if the pregnancy resulted from rape or incest.

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

- Vital functions of the neonate will not be artificially maintained.
- The research will not terminate the heartbeat or respiration of the neonate.
- There will be no added risk to the neonate resulting from the research.
- The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.
- The legally effective informed consent of both parents of the neonate is obtained in accord with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission and assent do not apply.

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

Viable Neonates

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

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

Research involving, after delivery the: placenta; dead fetus; macerated fetal material; or cells, tissues, or organs excised from a dead fetus, must be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities. If information associated with material described above in this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent sections of these policies and procedures are applicable.

Research Not Otherwise Approvable

Research Not Conducted or Supported by DHHS

If the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates, and the research is not approvable under the above provisions, then the IRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). Based on the

recommendation of the panel, the IRB may approve the research based on either:

- That the research in fact satisfies the conditions detailed above, as applicable.
- *All the following*:
    - The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates.
    - The research will be conducted in accord with sound ethical principles.
    - Informed consent will be obtained in accord with the provisions for informed consent and other applicable sections of the *Human Research Protection Program (HRPP) Policy Manual.*

Research Conducted or Supported by DHHS

DHHS conducted or supported research that falls in this category must be approved by the Secretary of Health and Human Services. If the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and the research is not approvable under the above provisions, then the research will be sent to OHRP for DHHS review.

Research Involving Prisoners

Applicability

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

The requirements apply to all biomedical and behavioral research conducted at, under the auspices of, or using the services or resources of CMU involving prisoners as subjects. Even though the IRB may approve a research study involving prisoners as

subjects according to this policy, investigators are still subject to the Administrative Regulations of the Michigan Department of Corrections and any other applicable State or local laws. [45 CFR 46.301]

Minimal Risk

Minimal risk, in studies involving prisoners, means the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of *healthy persons*.

Composition of the IRB

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

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

Review of Research Involving Prisoners

Initial Review

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

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

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

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

Modifications and Continuing Review

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

Incarceration of Enrolled Subjects

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

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

- Confirm that the participant meets the definition of a prisoner.
- Consult with the investigator to determine if it is in the best interests of the participant to continue participation in the study, in part or in full, and if so, if there are specific study activities which are in the best interests of the subject and should continue until the IRB is able to review the research applying the standards and requirements for research involving prisoners.
- If the participant should continue, one of two options are available:
    - Keep the participant enrolled in the study and review the research applying the standards and requirements for research involving prisoners. If some of the requirements cannot be met or are not applicable (e.g., procedures for the selection of subjects within the prison), but it is in the best interests of the participant to remain in the study, keep the

participant enrolled and inform OHRP of the decision along with the justification.
    - Remove the participant from the study and keep the participant on the study intervention under an alternate mechanism such as compassionate use, off label use, etc.

Additional Duties of the IRB

In addition to all other responsibilities prescribed for IRB in other sections of the *Human Research Protection Program (HRPP) and Institutional Review Board (IRB) Policy Manual*, the IRB reviews research involving prisoners and approves such research only if it finds that:

- The research falls into one of the following permitted categories [45 CFR 46.306(a)(2)]:
    - Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.
    - Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.
    - Research on conditions particularly affecting prisoners as a class (for example, research on diseases or social and psychological problems much more prevalent in prisons) provided that the study may proceed only after the DHHS Secretary has consulted with appropriate experts in penology, medicine, and ethics, and published notice in the Federal Register of intent to approve the research.
    - Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols/research plans approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the DHHS Secretary has consulted with appropriate experts in penology, medicine, and ethics, and published notice in the Federal Register of intent to approve the research.
    - The research qualifies under the HHS Secretarial waiver that applies to certain epidemiological research (68 FR 36929, June 20, 2003). The criteria for this category are that the research must have as its sole purpose to describe the prevalence or incidence of a disease by identifying all cases, or (ii) to study potential risk factor associations for a disease.
- Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired.
- The risks involved in the research are commensurate with risks that would be

accepted by non-prisoner volunteers.
- Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the investigator provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that research project.
- The information is presented in language which is understandable to the subject population.
- Adequate assurance exists that parole boards will not consider a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole.
- Where the IRB finds there may be a need for follow-up examination or care of subjects after the end of their participation, adequate provision has been made for such examination or care, considering the varying lengths of individual prisoners' sentences, and for informing subjects of this fact.

Certification to DHHS

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

For all DHHS conducted or supported research, CMU 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 CMU 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.

Waiver for Epidemiology Research

The Secretary of DHHS has waived the applicability of 45 CFR 46.305(a)(l) and 46.306(a)(2) for certain research conducted or supported by DHHS that involves epidemiological studies that meet the following criteria:

- The sole purposes are:
    - to describe the prevalence or incidence of a disease by identifying all cases, or
    - to study risk factor associations for a disease.
- The IRB 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 HHS 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 the research.

Research Involving Children

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

Allowable Categories

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

- 45 CFR 46.404/21 CFR 50.51: Research/Clinical Investigations not involving greater than minimal risk. Research determined to not involve greater than minimal risk to child subjects may be approved by the IRB only if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in *Section 12, Parental Permission and Assent*.
- 45 CFR 46.405/21 CFR 50.52: Research/Clinical Investigations involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may be approved by the IRB only if the IRB finds and documents all the following:
    - The risk is justified by the anticipated benefit to the subjects.
    - The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative options.
    - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in *Section 12, Parental Permission and Assent*.
- 45 CFR 46.406/21 CFR 50.53: Research/Clinical Investigations involving greater than minimal risk and no prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition. Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, may be approved by the IRB only if the IRB finds and documents all of the following:
    - The risk represents a minor increase over minimal risk.
    - The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations.
    - The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition.
    - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in *Section 12, Parental Permission and Assent*.
- 45 CFR 46.407/21 CFR 50.54: Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children. When the IRB does not believe that the research meets the requirements of any of the above categories, and the IRB finds and documents that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, the IRB shall refer the research for further review as follows:

- DHHS -conducted or supported research in this category is referred for review by the Secretary of Health and Human Services. However, before doing so the IRB must determine that the proposed research also meets all the requirements of the Common Rule.
- FDA-regulated research in this category is referred for review by the Commissioner of Food and Drugs.
- For research that is not DHHS conducted or supported and not FDA regulated, the IRB consults with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, and law). Based on the recommendation of the panel, the IRB may approve the research because it satisfies the conditions of the previous categories, as applicable; or all the following:

    - The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.
    - The research will be conducted in accord with sound ethical principles.
    - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in *Section 12, Parent Permission and Assent*.

Parental Permission and Assent

Parental Permission

The IRB must determine that adequate provisions have been made for soliciting the permission of each child's parent or guardian.

Parents or guardians must be provided with the basic elements of consent and any additional elements the IRB deems necessary, as described in *Section 11, Basic Elements of Informed Consent*.

The IRB may find that the permission of one parent is sufficient for research to be conducted under 45 CFR 46.404/21 CFR 50.51 and 45 CFR 46.405/21 CFR 50.52 in S*ection 12, Allowable Categories*. The IRB's determination of whether permission must be obtained from one or both parents will be documented in the reviewer's notes when a study receives expedited review, and in meeting minutes when reviewed by the convened committee.

Permission from both parents is required for research to be conducted under 45 CFR 46.406/21 CFR 50.53 and 45 CFR 46.407/21 CFR 50.54 of *Section 12, Allowable Categories* unless one of the following apply:

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

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

- The research meets the provisions for waiver in *Section 11, Waiver of Informed Consent*.
- If the IRB determines that the research is designed to study conditions in children or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children) provided that an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and that the waiver is not inconsistent with Federal, State, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol/research plan, the risk and anticipated benefit to the research subjects, and the child's age, maturity, status, and condition.

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

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

Assent from Children

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

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

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

Because "assent" means a child's affirmative agreement to participate in research, the child must actively show his or her willingness to participate in the research, rather than

just complying with directions to participate and not resisting in any way.

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

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

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

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

- Tell why the research is being conducted.
- Describe what will happen and for how long or how often.
- Say it's up to the child to participate and that it's okay to say “No.”
- Explain if it will hurt and if so for how long and how often.
- Say what the child's other choices are.
- Describe any good things that might happen.
- Say whether there is any compensation for participating.
- Ask for questions.

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

Children Who are Wards

Children who are wards of the State or any other agency, institution, or entity can be included in research approved under 45 CFR 46.406/21 CFR 50.53 or 45 CFR 46.407/21 CFR 50.54 in *Section 12 Allowable Categories*, only if such research is at least one of the following:

- Related to their status as wards.
- Conducted in schools, camps, hospitals, institutions, or similar settings in which most children involved as subjects are not wards.

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

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

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

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

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

Decision-Making Capacity

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

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

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

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

Inclusion of Adults with Impaired Decision-Making Capacity in Research

Research involving adult subjects without the ability to provide consent or with impaired decision-making capacity should only be conducted when the aims of the research cannot reasonably be achieved without their participation.

Investigators must disclose to the IRB both plans and justification for including adults with impaired decision-making capacity in a given research proposal. If adults with questionable or fluctuating capacity will be included, investigators must specify procedures for assessing capacity prior to providing informed consent and, if appropriate, for re-evaluating capacity during study participation. If a prospective subject's capacity to consent is expected to diminish, the investigator should consider requesting that the subject designate a future LAR prior to enrollment in the research, including the future LAR in the initial consent process, and obtaining written

documentation of the subject's wishes regarding participation in the research. When the study includes subjects likely to regain capacity to consent while the research is ongoing, the investigator should include provisions to inform them of their participation and seek consent for ongoing participation.

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

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

When a prospective subject is deemed to lack capacity to consent to participate in research, investigators may obtain informed consent from the individuals' surrogate or LAR see *Section 11, Obtaining Consent from Research Subjects*. Under these circumstances, the prospective subject should still be informed about the research in a manner compatible with the subjects' likely understanding and, if possible, be asked to assent to participate. Potential subjects who express resistance or dissent (by word, gesture, or action) to either participation or use of surrogate consent, should be excluded from the study. Some subjects may initially assent but later resist participation. Under no circumstances may an investigator or caregiver override a subject's dissent or resistance. When assent is possible for some or all subjects, the investigator should provide the IRB with an assent plan that describes when and how assent will be obtained, provisions that will be taken to promote understanding and voluntariness, how assent will be documented, and a copy of the assent form. If the investigator intends to use audio or video recordings to document assent, provisions to ensure the security of the recordings should be described to the IRB.

When inclusion of adults with impaired decision-making capacity is not anticipated and a plan for inclusion of such subjects has not been reviewed and approved by the IRB, and an enrolled subject becomes unable to provide consent or impaired in decision-making capacity, the investigator is responsible for promptly notifying the IRB. The

investigator should consider whether continuing participation is appropriate and, if so, present a plan for surrogate consent from a LAR and, if appropriate, a plan to periodically evaluate capacity and re-obtain consent if possible.

Informed Consent

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

As discussed previously, the informed consent process involves three key features:

> (1) providing the prospective subject the information needed to make an informed decision (in language understandable to him or her);
> (2) facilitating the understanding of what has been disclosed; and
> (3) promoting the voluntariness of the decision about whether to participate in the research.

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

IRB Review

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

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

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

- Whether the aims of the research cannot reasonably be achieved without inclusion of the population.
- Whether the research is likely to improve the understanding of the condition, disease, or issue affecting the subject population.

- Whether any experimental procedure or interventions have undergone preclinical testing or human testing on other populations and whether the data from that testing supports its use in the proposed research.
- Whether the procedures or interventions that the subject will undergo in the research place them at increased risk and if appropriate mechanisms are in place to minimize risks, when possible.
- Whether the data and safety monitoring plan, including any stopping rules, is appropriate given the risks of the research and the vulnerability of the population.
- Whether the procedures for withdrawing individual subjects from the research are appropriate.
- Whether the recruitment procedures, consent process, and any plans for financial compensation support voluntariness and minimize the likelihood of undue influence or coercion.
- Whether the subjects will be exposed to financial or other risks that they might not consider acceptable if they had the capacity to provide consent, and whether appropriate mechanisms have been put into place to minimize these risks.
- Whether the procedures for determining capacity to provide consent, and for evaluating capacity on an ongoing basis, if applicable, are appropriate.
- Whether the procedures for informing subjects who regain capacity about their involvement in the research, and for obtaining consent for on-going participation, if applicable, are appropriate.
- Whether assent should be required when possible, and, if so, if the proposed procedures to obtain and document assent are appropriate.
- Whether periodic re-evaluation of capacity and/or periodic re-consent should be required.
- Whether a research subject advocate or consent monitor should be required, for some or all subjects.

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

Research Involving Students, Residents or Employees

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

- Recruitment should not be conducted in ways that students, residents and employees may reasonably perceive to be coercive.
- Ensure that students, residents and employees understand that they may choose

not to participate in the research.

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

An "honest broker" is a neutral third party who is not part of the research team. This person acts on the behalf of the researcher or institution to provide information in such a manner whereby it would not be reasonably possible for the investigators or others to identify the student, resident, or employee directly or indirectly. The honest broker collects and collates pertinent information from the protocol measurements, removes identifiers, and releases only coded information to the researcher. An honest broker may not provide researchers with the code or any other means to re-identify participants.

Section 13: FDA-Regulated Research

FDA regulations apply to research that involves an FDA-regulated test article in a clinical investigation involving human subjects as defined by the FDA regulations. For FDA-regulated research, the IRB must apply the FDA regulations at 21 CFR 50 and 21 CFR 56. If the research is conducted or supported by a Common Rule agency or department, or if compliance with the Common Rule is required by state law, or the terms of an FWA, IAA, or an award or contract, then the Common Rule 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 CMU.

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.
- **Clinical Investigation**: Clinical investigation means any experiment that involves a test article and on or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 506(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies. [21 CFR 50.3(c)]
- **Dietary Supplement**: A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains a dietary ingredient. The dietary ingredients in these products can include vitamins, minerals, herbs and other botanicals, amino acids, other dietary substances intended to supplement the diet, and concentrates, metabolites, constituents, extracts, or combinations of the preceding types of ingredients. See section 201(ff) of the FD&C Act [21 U.S.C. 321(ff)].

- **Emergency Use**: Emergency use is defined as the use of an investigational product with a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval. [21 CFR 56.102 (d)]
- **Human Cells, Tissues, or Cellular or Tissue-based Products:** HCT/P's means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are 91 not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue.

  HCT/P's may be regulated as drugs, devices, and/or biologics when the use does not qualify for an establishment exception or regulation solely under section 361 of the PHS Act and 21 CFR 1271.
- **Humanitarian Use Device (HUD)**: A Humanitarian Use Device is a device intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year.
- **Investigational Drug**: Investigational or experimental drugs are new drugs that have not yet been approved by the FDA or approved drugs that are being studied in a clinical investigation for a new indication or use.
- **Investigational Device**: Investigational device means a device (including a transitional device) that is the object of an investigation. Investigation, as it pertains to devices, means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.
- **IND**: IND means an investigational new drug application in accordance with 21 CFR Part 312.
- **IDE**: IDE means an investigational device exemption in accordance with 21 CFR 812.
- **In Vitro Diagnostic Product (IVD)**: In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. [21 CFR 809.3(a)]
- **Non-Significant Risk (NSR) Device**: A non-significant risk device is an investigational device that does not meet the definition of a significant risk device.
- **Significant Risk (SR) Device:** Significant risk device means an investigational device that:
    - Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject.

    - Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or

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

FDA Exemptions

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

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

Procedures

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

During the pre-review process, IRB coordinator will assess whether FDA regulations are applicable using the IDE/IND Decision Worksheet. If FDA regulations apply and the research is not exempt; IRB coordinator 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, CMU 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, IRB coordinator reviews the study to determine if ICH-GCP E6 applies and obtain investigator affirmation of compliance, if needed.

Investigator Responsibilities

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

- The investigator is responsible for indicating on the IRB application that the proposed research is FDA-regulated and for providing relevant information regarding the test article.
- The investigator is responsible for ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs (including biological products) or agreement for clinical investigations of medical devices, the investigational plan and other applicable regulations, and any requirements imposed by the FDA or IRB.
- The investigator is responsible for personally conducting or supervising the investigation. When certain study-related tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.
- The investigator must maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks (e.g., it can refer to an individual's CV on file and/or training conducted by the investigator/sponsor), and identify the dates of involvement in the study. A separate list should be maintained for each study conducted by the investigator.
- The investigator is responsible for protecting the rights, safety, and welfare of subjects under their care during a clinical trial. This responsibility includes:
    - Informing subjects about the test articles being used for investigational purposes and ensuring that the requirements relating to obtaining informed consent are met.
    - Providing or arranging for reasonable medical care for study subjects for medical problems arising during participation in the trial that are, or could be, related to the study intervention.
    - Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable, or when specialized care is needed).
    - Adhering to the protocol/investigational plan so that study subjects are not exposed to unreasonable risks.
    - As appropriate, informing the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and the subject agrees to the primary physician being informed.
- The investigator is responsible for reading and understanding the information in the investigator brochure or device brochure, including the potential risks and side effects of the drug or device.
- The investigator is responsible for maintaining adequate and accurate records in

accordance with FDA regulations and to making those records available for inspection by the FDA. These records include: correspondence with other investigators, the IRB, the sponsor, monitors, or the FDA; drug and device accountability records; case histories; consent forms; and documentation that consent was obtained prior to any participation in the study. Records must be retained for a minimum of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such. Other regulations, such as HIPAA, institutional policies, or contractual agreements with sponsors may necessitate retention for a longer period of time.

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

Digital Health

Certain medical and decision support software have been excluded from the definition of medical device under the 21st Century Cures Act and thus are not subject to FDA's regulations. These include exclusions for software functions:

- Intended for administrative support of a health care facility, including the processing and maintenance of financial records, claims or billing information, appointment schedules, business analytics, information about patient

populations, admissions, practice and inventory management, analysis of historical claims data to predict future utilization or cost-effectiveness, determination of health benefit eligibility, population health management, and laboratory workflow.

- Intended for maintaining or encouraging a healthy lifestyle and *unrelated to the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition.*
- Intended to serve as electronic patient records, including patient-provided information, to the extent that such records are intended to transfer, store, convert formats, or display the equivalent of a paper medical chart, so long as-
    - such records were created, stored, transferred, or reviewed by health care professionals, or by individuals working under supervision of such professionals;
    - such records are part of health information technology that is certified under section 300jj–11(c)(5) of title 42; and
    - such function is *not intended to interpret or analyse patient records, including medical image data, for the purpose of the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition.*
- Intended for transferring, storing, converting formats, or displaying clinical laboratory test or other device data and results, findings by a health care professional with respect to such data and results, general information about such findings, and general background information about such laboratory test or other device, *unless such function is intended to interpret or analyse clinical laboratory test or other device data, results, and findings.*
- Not intended to acquire, process, or analyse a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system.
    - Is intended for the purpose of displaying, analysing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines).
    - Is intended for the purpose of supporting or providing recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition; and
    - Is intended for the purpose of enabling such health care professional to independently review the basis for such recommendations that such software presents so that it is not the intent that such health care professional rely primarily on any of such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient.

Additional information regarding the application of these exclusions is available on the FDA website referenced below.

Research involving software excluded from the definition of medical device will be evaluated by the CMU IRB in accordance with any other applicable regulations (e.g., the Common Rule, HIPAA) and the criteria outlined in this manual.

Other digital health products may be subject to FDA regulations and will be evaluated accordingly. FDA has provided a website listing of "*Guidances with Digital Health Content*" to help the regulated community understand FDA's interpretation and

application of the regulations and to describe when FDA will practice enforcement discretion in regards to certain requirements such as those for pre-market review and for device reports. Investigators are encouraged to consult these guidances in advance of their submission to the IRB and to consult directly with the FDA as needed.

Human Cells, Tissues, or Cellular or Tissue-based Products

Generally, research involving HCT/P's regulated as drugs, devices, and/or biologics will require an IND or IDE depending on how the HCT/P is categorized. Because the regulatory and policy framework for HCT/P's is complex, consultation with the FDA prior to submission to the IRB is encouraged to appropriately categorize the HCT/P, understand which regulations and requirements apply, and to obtain an IND or IDE if necessary (or FDA determination that such is not required).

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 (i.e., not intended to be used for a therapeutic purpose). Whether a study falls under FDA oversight is determined by the intent of the clinical investigation. If the clinical investigation is intended only to evaluate the dietary supplement's effect on the structure or function of the body, FDA research regulations do not apply. However, if the study is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, then FDA regulations do apply. Studies involving the ingestion of dietary supplements that are not subject to FDA oversight are still research, and therefore must be reviewed by the IRB.

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

As with any research involving a test article, the investigator must supply the IRB with sufficient information to determine that the criteria for approval are satisfied and to determine or verify whether or not the research requires an IND. Applications should provide detail consistent with that expected on a drug protocol/research plan and consistent with the level of risk associated or anticipated with the research. At a minimum, the protocol/research plan should provide the following information regarding the supplement: Name, Manufacturer, Formulation, Dosage, Method/Route of Administration, Mechanism of Action, Known Drug Interactions, Risk Profile, IND number (or justification for why an IND is unnecessary), documentation of approval for use in humans, documentation or certification of Quality or Purity. As with drugs and devices there should be an accountability plan for the product describing where and how

the product will be stored, how it will be dispensed, how usage is tracked, and how it will be disposed of or returned. If the study entails greater than minimal risk, a plan for Data and Safety Monitoring must be included.

Clinical Investigations of Drugs and Devices

IND/IDE Requirements

For studies submitted to CMU IRB evaluating the safety or effectiveness of medical devices or experiments using drugs, biologics, dietary supplements, and other compounds that may be considered a drug or device under FDA regulations, the investigator must indicate on the *electronic application form* whether or not an IDE or IND is in place, and, if not, the basis for why an IDE or IND is not needed.

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

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

For investigational devices, the study may be exempt from IDE requirements (IDE exempt) or, in the case of Non-Significant Risk (NSR) device studies, follow abbreviated IDE requirements which do not require formal approval by the FDA. If a sponsor has identified a device study as IDE-exempt or NSR, then the investigator should include documentation with the submission providing the basis for exempt or NSR categorization for the IRB's consideration. If the FDA has determined that the study is IDE-exempt or NSR, documentation of that determination must be provided.

The IRB will review the application and, based upon the documentation provided, determine:

(1) That there is an approved IND/IDE in place;
(2) That the FDA has determined that an IND is not required or that a device study is exempt or NSR; or,
(3) If neither of the above, whether or not an IND is necessary, or that a device study is exempt or NSR, using the criteria below.

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

IND Exemptions

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

- **Category One:** *21 CFR 321.2(b)(1)* The drug being used in the research is lawfully marketed in the United States and all of the following conditions are met:
    - The research is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
    - In the case of a prescription drug, the research is not intended to support a significant change in the advertising for the product.
    - The research does not involve a route of administration, dose, subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
    - The research is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively].
      The research is conducted in compliance with the requirements of 21 CFR 312.7 (i.e., the research is not intended to promote or commercialize the drug product).
    - The research does not intend to invoke FDA regulations for planned emergency research [21 CFR 50.24].

- **Category Two:** 21 CFR 312.2(b)(2) The research involves an *in vitro* diagnostic biological product (blood grouping serum, reagent red blood cells, or anti-human globulin) if both the following conditions are met:
    - The product is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and
    - The product is shipped in compliance with 21 CFR 321.160.

- **Category Three**: 21 CFR 320.31(b)and(d) The research involves Bioavailability or Bioequivalence (BA/BE) studies if all of the following conditions are met:
    - The drug product does not contain a new chemical entity [21 CFR 314.108], is not radioactively labeled, and is not cytotoxic.
    - The dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product.
    - The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively].
    - The sponsor meets the requirements for retention of test article samples [21 CFR 320.31(d)(1)] and safety reporting [21 CFR 320.31(d)(3)].

- **Category Four:** 21 CFR 361.1 The research involves using a radioactive drug or biological product if all of the following conditions are met:
    - It involves basic research not intended for immediate therapeutic, diagnostic, or similar purposes, or otherwise to determine the safety and efficacy of the product.

- The use in humans is approved by a Radioactive Drug Research Committee (RDRC) that is composed and approved by the FDA.
- The dose to be administered is known not to cause any clinically detectable pharmacological effect in humans.
- The total amount of radiation to be administered as part of the study is the smallest radiation dose practical to perform the study without jeopardizing the benefits of the study and is within specified limits.

- **Category Five:** (FDA Guidance) FDA practices enforcement discretion for research using cold isotopes of unapproved drugs if all of the following conditions are met:
  - The research is intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a drug labeled with a cold isotope or regarding human physiology, pathophysiology, or biochemistry.
  - The research is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject.
  - The dose to be administered is known not to cause any clinically detectable pharmacologic effect in humans based on clinical data from published literature or other valid human studies.
  - The quality of the cold isotope meets relevant quality standards.
  - The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively].

- **Category Six:** (FDA Guidance) The research involves studies of marketed drugs to treat cancers if all of the following conditions are met:
  - The study is not intended to support FDA approval of a new indication or a significant change in the product labeling.
  - The study is not intended to support a significant change in the advertising for the product.
  - Based on the scientific literature and generally known clinical experience, there is no significant increase in the risk associated with the used of the drug product.
  - The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively].
  - The studies will not be used to promote unapproved indications, in compliance with 21 CFR 312.7.

- **Category Seven:** A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.

IDE Exemptions

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

- The research involves a device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
- The research involves a device other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR 807 in determining substantial equivalence (a "510k" device).
- The research involves a diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
    - Is noninvasive.
    - Does not require an invasive sampling procedure that presents significant risk.
    - Does not by design or intention introduce energy into a subject.
    - Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- The research involves a device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
- The research involves a device intended solely for veterinary use.
- The research involves a device shipped solely for research on or with laboratory animals and is labeled in accordance with 21 CFR 812.5(c).
- The research involves a custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

Significant and Non-Significant Risk Device Studies

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

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

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject.
- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject.
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject.
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

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

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

The sponsor or sponsor-investigator is responsible for providing the IRB with an explanation describing the basis for their initial determination of NSR and any other information that may help the IRB in evaluating the risk of the study (e.g., 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 (e.g., 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)). Non-significant risk device studies do not require submission of an IDE application to the FDA but must be conducted in accordance with the abbreviated requirements of IDE regulations (21 CFR 812.2(b)). Under the abbreviated requirements, the following categories of investigations are considered to have approved applications for IDE's, unless the FDA has notified a sponsor under 812.20(a) that approval of an application is required: Labels the device in accordance with 812.5.

An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor (or sponsor-investigator):

- Obtains IRB approval of the investigation after presenting the reviewing IRB with an explanation of why the device is not a SR device, and maintains such approval.

- Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under 56.109(c).
- Complies with the requirements of 812.46 with respect to monitoring investigations.
- Maintains the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10).
- Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7).
- Complies with the prohibitions in 812.7 against promotion and other practices.

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

Humanitarian Use Devices

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

Definitions

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

IRB Review Requirements

A Humanitarian Use Device (HUD) may only be used in a facility after an IRB has approved its use, except in certain emergencies. The HDE holder is responsible for ensuring that an HUD is provided only to facilities having an IRB constituted and acting

in accordance with FDA regulations governing IRBs (21 CFR Part 56), including continuing review of use of the device.

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

Procedures

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

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

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

- Humanitarian Use Devices (non-research uses) application form.
- 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 (e.g., 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 CMU or affiliated institutions. The IRB evaluates the patient information packet and proposed consent process and will determine if the materials are adequate and

appropriate for the patient population. The IRB may require the use of a consent form to document consent for the use of the HUD.

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

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

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

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

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

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

Uses of HUDs

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

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

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

Expanded Access to Investigational Drugs, Biologics, and Devices

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

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

Expanded Access to Investigational Drugs and Biologics

The FDA's expanded access rule for investigational drugs, including biologics classified as drugs, is intended to improve access to investigational drugs, and approved drugs

with limited availability under a risk evaluation and mitigation strategy (REMS), for patients with serious or immediately life-threatening diseases or conditions who lack other therapeutic options and may benefit from the investigational diagnostic or therapy. Expanded access is sometimes referred to as compassionate use, or treatment use.

For the purpose of expanded access to investigational drugs, immediately life-threatening disease or condition means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. Serious disease or condition means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. [21 CFR 312.300(b)]

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

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

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

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

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

- Provide general criteria for authorizing charging for an investigational drug [(a)].
- Provide criteria for charging for an investigational drug in a clinical trial [(b)].

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

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

Expanded Access for Individual Patients

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

Sponsor or Manufacturer Approval

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

FDA Approval

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

If the sponsor or manufacturer declines treatment of the patient under an existing IND study or Access Protocol but agrees to make the investigational drug available for the patient, physicians may apply to the FDA for an individual patient Access IND using Form *FDA 3926*, a streamlined IND application specifically designed for such requests. Form *FDA 3926*, and *related guidance*, is available on an FDA *website*. Form *FDA 3926* includes a section where an investigator can request approval from the FDA for alternative IRB review procedures; these alternative procedures enable review by the IRB Chair (or a Chair-designated IRB member) in lieu of review by the convened IRB. This alternative review procedure is referred to as a "concurrence review" in FDA

guidance; however, the IRB Chair must review the same materials and make the same determinations as the convened board would. IRB Chair review can also be used for any post-approval reviews (e.g., unanticipated problems, continuing review, closure, etc.).

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

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

IRB Review

Unless the conditions that permit an emergency use exemption, *Section 13, Emergency Use of Investigational Drugs and Devices,* are satisfied, prospective IRB review and approval is required for all expanded access uses, including clinical patient use. This requires, among other things, that the IRB review the expanded access use at a convened meeting at which a majority of IRB members are present. IRB approval must be obtained prior to initiating treatment with the investigational drug. When the FDA has authorized the use of alternative IRB review procedures (which can be presumed when the request is made on Form *FDA 3926* unless the FDA specifically states that the request is denied), the review may be conducted by the IRB Chair (or designee). Otherwise, the review must be conducted by the convened IRB.

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

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

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

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

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

Post-Approval Requirements

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

Expanded Access to Investigational and Unapproved Medical Devices

As with investigational drugs, unapproved medical devices may normally only be used in humans in an approved clinical trial under the supervision of a participating clinical investigator. However, there are circumstances under which a health care provider may use an unapproved device outside of a clinical study when it is not possible to enroll a patient in a clinical study and the patient is facing life-threatening circumstances or suffering from a serious disease or condition for which no other alternative therapy or diagnostic exists or is a satisfactory option for the patient.

FDA has made the following mechanisms available for these circumstances:

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

Investigators seeking access to investigational or unapproved devices under one of the above provisions should work closely with the sponsor or manufacturer, the FDA, and CMU HRPP, to ensure that proper regulatory procedures are followed. FDA has made information about expanded access to medical devices available on a *website*.

Compassionate Use of Investigational/Unapproved Medical Devices

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

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

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

FDA Approval

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

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

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

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

When the compassionate use is conducted under an IDE, a licensed provider who receives an investigational device is an "investigator" under FDA regulations and is

responsible and accountable for all applicable investigator responsibilities under 21 CFR 812 (IDE regulations), 21 CFR 50 (Informed Consent), and 21 CFR 56 (IRB).
When the provider obtains an IDE for compassionate use, the provider is considered a "sponsor-investigator" and is responsible for the responsibilities of both sponsors and investigators under 21 CFR 812, as applicable, including medical device reports and progress reports.

IRB Review

Unless the conditions that permit an emergency use exemption are satisfied as outlined in *Section 13, Emergency Use of Investigational Drugs and Devices,* IRB approval must be obtained prior to initiating treatment with the investigational device. When the request is for single-patient compassionate use, the review may be conducted by the IRB Chair (or designee). Otherwise, the review must be conducted by the convened IRB.

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

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

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

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

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

Post-Approval Requirements

Investigators are responsible for complying with any sponsor or FDA reporting requirements. The post-approval requirements for research described throughout this

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

Treatment Use of Investigational/Unapproved Devices

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

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

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

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

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

IRB Review

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

- A summary of the request and any associated documents for a treatment use access use.
- A copy of the Letter of Authorization (LOA) from the Commercial Sponsor or

- Manufacturer or other documentation supporting sponsor/manufacturer approval.
- A copy of the information submitted to the FDA (and FDA approval, if available).
- A copy of the Investigator's Brochure or similar documentation that provides information regarding the potential risks and benefits of the investigational device/diagnostic.
- A copy of the plan for treating and monitoring the patient.
- A copy of the draft informed consent document.

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

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

Post-Approval Requirements

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

Emergency Use of Investigational Drugs and Devices

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

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

For emergency use of drugs, FDA approval must be obtained prior to initiating treatment (see Section above). For emergency use of devices, prior FDA approval is not required if the provider determines and documents that:

(1) the patient has a life threatening or serious disease or condition that needs immediate treatment;
(2) no generally acceptable alternative treatment for the condition exists; and
(3) because of the immediate need to use the device, there is no time to use existing procedures to obtain FDA approval for the use.

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

Note: DHHS regulations do not permit research activities to be started, even in an emergency, without prior IRB approval. When emergency medical care is initiated without prior IRB review and approval, the patient *may not be considered a research subject under 45 CFR Part 46*. However, nothing in the DHHS regulations at 45 CFR Part 46 is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state or local law.

Emergency Use Exemption from Prospective IRB Approval

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

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

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

Unless the provisions for an emergency exception from the informed consent requirement are satisfied (see *Emergency Exception from the Informed Consent Requirement*) below, informed consent must be obtained in accordance with 21 CFR 50 and documented in writing in accordance with 21 CFR 50.27.

The IRB must be notified within five (5) business days when an emergency exemption is invoked via the submission of an *Emergency Use Report*. The IRB chair or their designee will review the report to verify that circumstances of the emergency exception conformed to FDA regulations. This must not be construed as IRB approval, as an exemption from the requirement for prospective IRB approval has been invoked. When appropriate, in the event a manufacturer requires documentation from the IRB prior to the emergency use, the IRB Chair or designee will review the proposed use, and, if appropriate, provide a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c).

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

Emergency Exception from the Informed Consent Requirement

An exception under FDA regulations at 21 CFR 50.23(a-c) permits the emergency use of an investigational drug or device without informed consent when the *investigator and an independent physician* who is not otherwise participating in the clinical investigation (the emergency use) certify in writing all four (4) of the following conditions:

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

If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent physician determination in advance of using the test article, the determinations of the clinical investigator shall be made and, within five (5) business days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

The IRB must be notified within five (5) business days when an emergency exception is invoked via the submission of an *Emergency Use Report* and documentation of the independent physician evaluation. The IRB Chair or designated IRB member will review the report to verify that circumstances of the emergency exception conformed to FDA regulations.

Waiver of Informed Consent for Planned Emergency Research

CMU IRB follows FDA regulations, 21 CFR 50.24, and any applicable state requirements which permit waiver of informed consent requirements for

emergency research when human subjects in need of emergency medical intervention cannot provide legally effective informed consent and their legally-authorized representatives are also unable or unavailable to give informed consent on their behalf.

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

Charging Subjects for Investigational Products

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

Charging for Investigational Medical Devices and Radiological Health Products

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

Charging for Investigational Drugs and Biologics

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

- Provide general criteria for authorizing charging for an investigational drug [21 CFR 312.8(a)].
- Provide criteria for charging for an investigational drug in a clinical trial [21 CFR 312.8(b)].
- Set forth criteria for charging for an investigational drug for an expanded access for treatment use [21 CFR 312.8(c)].
- Establish criteria for determining what costs can be recovered when charging for an investigational drug 21 CFR 312.8(d)].

Additional information is available in FDA guidance: Charging for Investigational Drugs Under an IND — Questions and Answers.

Section 14: Other Reportable Information

When research is under the oversight of CMU IRB, in addition to UAPs, noncompliance, and complaints, any change to the research implemented without IRB approval and any information that may impact the rights, safety, or welfare of subjects or inform the IRB's oversight of the research must be reported to the IRB within seven (7) business days of discovery using the *New Information Form*, as applicable.

Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in *Section 9, External IRB Review of CMU Research*.

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

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

Review Procedures

- Upon receipt of the report, the IRB coordinator pre-reviews the submission and, if needed, contacts the investigator for corrections or additional information. If the information provided suggests that subjects may be at risk of harm without immediate intervention or that research misconduct may have occurred, the

Director of Research Compliance, IRB Chair, and, when appropriate, the IO, will be notified so that they can take any necessary steps to ensure the safety of subjects or investigate the matter.

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

Section 15: Unanticipated Problems Involving Risks to Subjects or Others

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

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

The IRB will consider when reviewing protocol deviations, noncompliance, subject complaints, and other reportable events whether the event or issue was caused by, contributed to, or otherwise related to an UAP.

Definitions

Unanticipated problems involving risk to participants or others:

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

- Is unexpected.
- Is at least possibly related to participation in the research.
- Indicates that subjects or others are at a greater risk of harm (including physical, psychological, economic, legal or social harm) than was previously known or recognized.

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

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

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

Adverse Event: For the purposes of these policies and procedures, an adverse event (AE) is any untoward or unfavorable occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Adverse events encompass both physical and psychological harms. They occur most commonly

in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

Note: Only a fraction of Adverse Events are UPIRSOs and not all UPIRSOs are Adverse Events.

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

Procedures

Reporting

Adverse events in clinical trials must be reported to the sponsor in compliance with FDA regulations and sponsor requirements. Unless specifically required by the IRB for a given protocol, CMU IRB does not accept reports of adverse events that are not UAPs.

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

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

Examples of UAPs include:

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).
- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). A summary and analyses supporting the determination should accompany the report.
- An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is

listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects. A discussion of the divergence from the expected specificity or severity should accompany the report.

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

Review Procedures

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

If, after reviewing a report, the IRB finds that the event is an unanticipated problem involving risks to participants or others or that suspension or termination of approval is warranted, the IRB will

a. notify the investigator in writing of its findings, with copies to the Chair of the investigator's department and/or research unit, other affected units, and the investigator's supervisor; and
b. report its findings and recommendations to the IO for further reporting to the appropriate federal officials (e.g., NSF, OHRP, and FDA).

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

Reporting Other Events

All events, problems, and new information that do not meet the above reporting requirements should be reported to the IRB in summary form at the time of the next continuing review, status report, or protocol closure report.

The IRB recognizes that sponsors may require that the PI report all serious adverse events and safety reports to the IRB. To comply with sponsor requirements, PIs should report adverse events and safety reports that do not meet the above reporting requirements. IRB Administrative Staff will acknowledge receipt of these reports by returning a dated acknowledgement to the PI.

Section 16: Non-Compliance

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

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

All complaints, concerns and allegations of non-compliance are centrally reported to the Office of Research Compliance (ORC) through a variety of mechanisms including an on-line confidential reporting tool, a telephone hotline and e-mail. All IRB related reports are relayed to the IRB Chair by the Office of Research Compliance.

Definitions

- **Non-compliance**: Non-compliance is defined as failure to adhere to federal, state, or local regulations governing human subject research, institutional policies related to human subject research, or the requirements or determinations of the IRB. Non-compliance may be minor or sporadic or it may be serious or continuing.
- **Serious non-compliance**: Serious non-compliance is defined as non-compliance that, in the judgment of either the IRB Chair or the convened IRB, creates an increase in risks to subjects, adversely affects the rights, welfare or safety of subjects, adversely affects the scientific integrity of the study or compromises the integrity of the HRPP. Wilful violation of regulations, policies, or procedures may also constitute serious non-compliance. For example, research being conducted without prior IRB approval or participation of subjects in research activities without their prior consent.
- **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.

- **Concern:** An inquiry, question or request for clarification regarding conduct of research that is not specifically an allegation of non-compliance. Concerns are handled similarly to complaints unless it becomes apparent that the concern should be handled as an allegation of non-compliance.

Reporting

Investigators and research staff are required to report instances of possible non-compliance within ten (10) business days of discovery using the A*dverse/Reportable Event Form*. 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 CMU IRB. In such cases, the reporting party is responsible for making these reports in good faith, maintaining confidentiality and cooperating with any IRB and/or institutional review of these reports.

If an individual, whether investigator, study staff, or other, is uncertain whether there is cause to report noncompliance, he/she may contact the IRB Chair, Vice Chair(s), IRB Coordinator, DRC or Assistant DRC directly to discuss the situation informally.

Reports of noncompliance must be submitted to the IRB Office within ten (10) working days of discovery of this noncompliance. The report must include a complete description of the noncompliance, the personnel involved.

Complainants may choose to remain anonymous.

Review of Allegations of Non-compliance

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

- All documents relevant to the allegation.
- The last approval letter from the IRB
- The last approved IRB application and protocol
- The last approved consent document
- The grant, if applicable
- Any other pertinent information (e.g., questionnaires, DSMB reports, etc.).

When the review is conducted by a designee, the designee will summarize the allegation review in a report and submit the report to the IRB Chair.

When the IRB chair 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, the report or allegation does represent non-compliance, the non-compliance is processed according to *Section 16, Review of Findings of Non-compliance*.

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

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

Review of Findings of Non-compliance

Non-compliance that is Not Serious or Continuing

If the IRB Chair 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 with notification to the IO.

Serious or Continuing Non-compliance

If the Chair determines that non-compliance has occurred and that the non-compliance may meet the definition of serious or continuing non-compliance, the report of non-compliance is referred for review by the IRB at the next available convened meeting. However, the IRB chair or designee may use discretion and call an emergency IRB meeting should the circumstances warrant an urgent meeting.
All initial findings of potential serious or continuing non-compliance referred to the IRB is reviewed at a convened meeting.
At this stage, the IRB may:

- Find that there is no issue of non-compliance.
- Find that there is non-compliance that is neither serious nor continuing and that an adequate corrective and/or preventive action plan is in place.
- Find that there is serious or continuing non-compliance and modify or require a corrective and/or preventive action plan.
- Find that additional information is required to make a final determination. In this instance, the IRB will request additional information, and indicate whether such information will be reviewed by the full committee or a subcommittee. If by a subcommittee, a report is written by the subcommittee for review by the convened IRB for final determination.

Final Review

The IRB makes a final determination as to whether the non-compliance is serious or continuing. Upon a finding of serious or continuing non-compliance, possible actions by the IRB include, but are not limited to:

- Request a corrective and/or preventive action plan from the investigator.
- Verification that subject selection is appropriate.
- Observation of informed consent.
- Require an increase in data and safety monitoring of the research activity.
- Request a directed assessment/audit of areas of concern.
- Request a status report after each participant receives intervention.
- Modify the continuing review cycle.
- Require additional investigator and staff education.
- Notify current subjects (e.g., if the information about the non-compliance might affect their willingness to continue participation).
- Require modification of the protocol/research plan.
- Require modification of the information disclosed during the consent process.
- Require current subjects to re-consent to participation.
- Suspend the study.
- Terminate the study.

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

The investigator is informed of the IRB determination and the basis for the determination in writing. If the IRB determines that the non-compliance was serious or continuing, the results of the final review will be reported as described below in *Section 17, Reporting to Regulatory Agencies and Institutional Officials*.

Section 17: Subject Complaints

The Office of Research Compliance is concerned about the safety, rights and welfare of all individuals participating in research projects at CMU and its affiliated sites. We take all research concerns or complaints very seriously.

Concerns or complaints can be reported by:

- Calling the ORC at 989-774-3477,
- Contact us by email at *ComplianceQuestions@cmich.edu*
- Contact us by email at *researchconcern@cmich.edu*
- Visit *https://www.cmich.edu/offices-departments/office-research-graduate-studies/office-of-research-compliance* for more information about reporting research concerns and complaints.

The Office of Research Compliance will handle complaints or concerns expressed by subjects or others in a prompt and confidential manner. The PI and all other research team members are responsible for the safety and welfare of all subjects enrolled in their studies. When investigators or team members hear complaints or concerns from subjects, he or she will try to resolve them.

Regardless of who serves as the IRB of record, investigators conducting the research under the auspices of CMU must report complaints to CMU Office of Research Compliance. Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in *Section 9, NIH Single IRB (sIRB) for Multi-Site Research*. Investigators conducting research under the oversight of CMU IRB report complaints using the *Adverse/Reportable Event form*. Investigators are encouraged to contact the IRB Chair or DRC when they are having difficulty resolving a complaint or concern, and whenever circumstances warrant (e.g., immediate attention is needed).

When the Office of Research Compliance is the direct recipient of complaints or concerns, the staff will do the following:

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

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

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

Within three (3) business days of receipt of the complaint, IRB staff generates a letter to acknowledge that the complaint has been received and is being investigated, if the person making the complaint provided contact information.

Section 18: Reporting to Regulatory Agencies & Institutional Officials

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

Procedures

The DRC or designee 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 Director and Assistant Director of Research Compliance 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 (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.).
- Plans, if any, to send a follow-up or final report by the earlier of:
    - A specific date.
    - When an investigation has been completed or a corrective action plan has been implemented.

- The IRB chair and Institutional Official review the letter and make modifications as needed.
- The affiliated institution's designee reviews and makes comments if applicable.
- The IO is the signatory.

The Director or Assistant Director of Research Compliance sends a copy of the report to:

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

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

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

CMU will report to AAHRPP when they or the any researcher (if the Researcher is notified rather than the CMU) become aware:

- Any negative actions by a government oversight office, including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated, FDA Restrictions Placed on IRBs or

Investigators, and corresponding compliance actions taken under non-US authorities related to human research protections
- Any litigation, arbitration, or settlements initiated related to human research protections, subject to approval be university counsel.
- Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding the Organization's HRPP.

The report will be developed by the DRC and signed by the IO as soon as possible but generally with 48 hours after the organization becomes aware of any of the triggering events listed above.

Section 19: Investigator Responsibilities

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

Investigators

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

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

- Designing the research.
- Obtaining information about living individuals by intervening or interacting with them for research purposes.
- Obtaining identifiable private information about living individuals for research purposes.
- Obtaining the voluntary informed consent of individuals to be subjects in research.
- Studying, interpreting, or analysing identifiable private information or data for research purposes.

Principal Investigators

At CMU only a paid faculty member may serve as the Principal Investigator (PI) or as the sponsor on a research project involving human subjects. Other individuals, such as research scientists or post-doctoral fellows may be allowed to be the PI at the discretion of the Director of Research Compliance, in consultation, with the IO and Director of Graduate Studies. CMU may establish more stringent qualifications for individuals to serve as the PI, regardless of a finding by the IRB, whether it is the CMU IRB or an external IRB. The Director of Research Compliance or the IRB (either CMU 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 CMU policy.

Office of Research Compliance follows the Office of Sponsor Project's policy "*Eligibility to serve as CMU Principal Investigator/Project Director on Sponsored Projects*" which has designated individuals in the following categories as being eligible to serve as PI:

- All CMU tenure or tenure-track faculty
- All non-tenure College of Medicine faculty with a CMU paid appointments

- All professional staff with CMU permanent appointments
- CMU Medical Education Partners (CMEP) employees: submissions must also include a project Lead who is a paid CMU employee or faculty member, who meets the PI eligibility criteria. See the first three bullet point above.

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

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

Studies that require expertise or skills beyond those held by the PI must either be modified or have expertise and skills supplemented by the inclusion of one or more additional qualified sub-investigators.

Student Investigators

Students may not serve as PI. They must have a faculty sponsor who fulfills the PI eligibility criteria and who will serve as PI and faculty advisor on the study.

Sub-Investigators/Co-Investigators

A sub-investigator is any investigator other than the PI who is involved in the conduct of a research study.

Research Team

Also known as "Key Personnel", they can be the PI or other individuals who contribute to the scientific development or execution of a project in a substantive, measurable way, regardless of whether they receive salaries or compensation under the protocol.

The research team also consists of individuals who intervene or interact directly with human subjects (including the recruitment or consenting process), or who analyze data and/or tissue samples derived from humans.

Responsibilities

In order to satisfy the requirements of CMU 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 (e.g., children, prisoners, 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.
- 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.
- Ensure that when protected health information is used, legally effective HIPAA authorization is obtained for each subject unless the Privacy Board or IRB has approved a waiver of the requirement.
- Ensure that the language in the consent form is consistent with that in the protocol/research plan, any associated grant or contract, and, if applicable, in the HIPAA authorization.
- Obtain and document informed consent and ensure that no human subject is involved in the research prior to obtaining consent or consent/permission from their legally authorized representative (LAR), unless a waiver of the requirement

has been approved by the IRB.
- Have a procedure to receive questions, complaints, or requests for additional information from subjects and respond appropriately.
- Ensure that pertinent laws, regulations, and institution procedures and guidelines are observed by investigators and research staff.
- Ensure that all information provided to the IRB is accurate and complete so that the IRB may fulfil 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 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, , and any other reportable events to the IRB.
- Notify the IRB if information becomes available that indicates a change to the potential risks or benefits, merit, or feasibility of the research.
- Obtain IRB review and approval before changes are made to the research unless a change is necessary to eliminate apparent immediate hazards to the subject(s).
- Seek HRPP or IRB assistance when in doubt about whether proposed research requires IRB review.
- Retain records for the time period and in the manner described to and approved by the IRB and as required by applicable regulations, agreements, and CMU policies.

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

Investigator Records

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

- Study Records
    - Individual subject records or case histories.
    - Materials provided to or completed by subjects.
    - Documentation of the consent process (addressing who, what, when, and how), if applicable.
    - Signed consent forms and HIPAA authorizations, if applicable.
    - Adverse events.
    - Subject complaint reports.
    - Results of all research exams, procedures, and visits.
    - Test article records.

    - Records of payment or reimbursement.
    - Records related to the withdrawal of subjects, in part or in full.
- Regulatory Records
    - All versions of the IRB-approved protocol/research plan.
    - All versions of IRB-approved consents, parental permission, and assent forms, scripts, or information sheets, if applicable.
    - All versions of the HIPAA authorization form, if applicable.
    - All submissions to and correspondence (i.e., approvals, reporting forms and responses) with the IRB.
    - All correspondence with the sponsor and others regarding the study.
    - Investigational product accountability records, if applicable.

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

As needed, the Director of Research Compliance, and IRB chair are available to address investigators' questions, concerns, and suggestions.

Investigators who have concerns or suggestions regarding the CMU HRPP or IRB(s) that require greater attention should also convey them 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 Office of Research compliance website for investigators and research staff, investigators are also made aware of the process for expressing their concerns via statement on approval letters.

Section 20: Conflicts of Interest and Commitment in Research

It is CMU 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.

Characteristics of quality research environment is openness and honesty which are indicators of integrity and responsibility that promotes quality research and strengthens the research process. Therefore, conflicts of interest and commitment should be eliminated when possible and effectively managed and disclosed when they cannot be eliminated.

Disclosure of Researcher Conflicts of Interest and Commitment Definitions

CMU Policy 3-9: A conflict of interest may occur when a university faculty/staff member meets any one of the following criteria:

1. The faculty/staff member is:
    a. an officer, director, trustee, sole proprietor, partner, employee, sales representative or agent of, or
    b. a consultant, independent contractor or advisory board member to an external organization or corporation either seeking to do or doing business with the University, funding a sponsored project, or providing goods or services under a sponsored project in which the faculty/staff member is participating in any capacity; or
2. The faculty/staff member is the actual or beneficial owner of more than five percent (5%) of the voting stock or controlling interest of such organization or corporation, or the market value of her/his stock exceeds $10,000; or
3. The faculty/staff member has dealings with such organization or corporation from which he/she derives income (e.g., royalties, stipends, salary) of more than $10,000 per year, exclusive of dividends and interest; or
4. The assets of the faculty/staff member's Family/Household, alone or in combination with the assets of the faculty/staff member, meet any of the criteria stated in paragraphs 1, 2 and 3 above. Family/Household is defined to include a) immediate family (spouse, parents and children) and b) persons living at the same residence as the faculty/staff member, except their tenants or employees.

CMU Policy 3-34: Participating faculty/staff members in a sponsored project includes:

- The project director/principal investigator.
- Co-project director/co-principal investigator.
- Any other person at the University who is responsible for the design, conduct, or reporting of research or educational activities funded or proposed for funding through a sponsored project.

NSF: Significant financial interests of the investigator (including those of the investigator's spouse and dependent children) (i) that would reasonably appear to be affected by the research or educational activities funded or proposed for funding by NSF; or (ii) in entities whose financial interests would reasonably appear to be affected by such activities.

PHS: A significant financial interest that could directly and significantly affect the design, conduct, or reporting of PHS-funded research. This applies to Project Director or Principle Investigator and any other person identified as senior/key personnel in CMU's grant application, progress report, or any other report submitted to the PHS by CMU.

FDA: For clinical studies involving the use of new human drugs and biological products or medical devices, certifications and disclosure requirements are defined in FDA regulations, 21 CFR Part 54.

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

reclassification petition. The applicant is responsible for submitting the required certification and disclosure statements. (See 21 CFR 54.2(g)). Note that for the purposes of financial disclosure, the term "applicant" includes "submitter" and the term "application" includes "510(k) submission."

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

Pursuant to CMU Policy 3-9, *Conflicts of Interest and Commitment*, which serves as the IRB research conflict of interest policy, the CMU IRB collaborates with Executive Director of the Research and Innovation to ensure that conflicts of interest for any study team member listed on the IRB application are identified and managed before the IRB completes its review of any research application. The IRB prohibits participation by the researcher with a potential conflict until the review process is completed and the results are made available to the IRB.

Evaluation of Conflicts of Interest and Commitment

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

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

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

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

Management of Conflicts of Interest and Commitment

The convened IRB has final authority to determine whether the research, the conflicts of interest and commitment, and the conflict management plan, if any, allow the research to be approved. With regard to the conflict management plan issued by CMU or another organization, the convened IRB may either affirm or add additional stipulations. The convened IRB can require additional measures to manage a conflict of interest so that the research may be approved. However, the IRB must adhere to, at a minimum, the conflict management plan approved by CMU or a relying organization. If additional conflict management is required by the IRB, the convened IRB shall provide the modified management plan to the Executive Director of the Research and Innovation to review and communicate to the study team member. If the significant financial interest or commitment changes, the Executive Director of the Research and Innovation and IRB adjusts the management plan accordingly.

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

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

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

IRB Member Conflict of Interest (COI)

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

IRB members and alternate members of the IRB complete a *Conflict of Interest Form* when first appointed and annually thereafter, or when there is a change in the conflict status to disclose. If a conflict of interest exists the IRB coordinator will not assign members or alternates to review studies for which the member or alternate has a conflict. IRB staff may consult with the IRB chair to clarify whether a specific study poses a member conflict.

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

- Involvement in the design, conduct, and reporting of the research.
- Significant financial interests. CMU Policy 3-9, *Conflicts of Interest and Commitment*, defines significant financial interests related to research, including research being reviewed by the IRB.
- Any other situation where an IRB member believes that another interest conflicts with his or her ability to deliberate objectively on a study.

The IRB chair must ask IRB members at the beginning of each convened meeting if any members have a conflict of interest regarding any of the items to be reviewed and reminds members that they must recuse themselves by leaving the room during the discussion and vote of the specific research study. If a conflicted member is participating by conference call, videoconference or web meeting, the member's participation concludes and the call disconnected for both the discussion and vote. If the IRB requests, the conflicted member may remain or return in order to provide information or answer questions but will leave or disconnect before final IRB deliberations and vote.

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

Institutional Conflicts of Interest

As an organization that conducts and reviews research involving human subjects, CMU recognizes its obligation to protect the rights and welfare of those subjects and ensure the integrity of the research and the human research protection program. Toward this end, the financial interests of CMU and institutional officials must be identified, evaluated, managed, and minimized or eliminated in order to ensure that meeting that obligation is not jeopardized.

The Conflict Review Committee (CRC) will be responsible for evaluating potential institutional conflict of interest and will take actions as required to avoid, or to appropriately manage, apparent institutional COI. These actions may involve referral to appropriate advisors outside the facility or obtaining advisement from CMU General Counsel. If used, outside advisors will be individuals who have sufficient seniority, expertise, and independence to evaluate the competing interests at stake and to make credible and effective recommendations. All outside advisors will be independent of the management of oversight for the HRPP within the institution. The use of outside advisors will increase the transparency of the deliberations and enhance the credibility of determinations. After reviewing a significant financial interest in research, the CRC will communicate its conclusions, along with any management arrangements to be imposed, to the IRB. All relevant conflicts will be disclosed to research participants in a form to be determined by the IRB. The CRC also will communicate conclusions and COI management strategies to the IO and the PI.

Recruitment Incentives

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

Section 21: Participant Outreach

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

Outreach Resources and Educational Materials

The HRPP office dedicates a section of the website to research participants entitled "Information for Research Participants." This website includes resources, such as Frequently Asked Questions (FAQs), and a listing of relevant research-related links to the Office for Human Research Protections (OHRP) campaign to inform the general public about participating in research.

Various colleges and departments offer annual programs that enhance understanding of research among the university and Mt. Pleasant communities.

The Office of Research and Graduate Studies, the College of Medicine and Medical Education Partners, and the College of Health Professions sponsor annual research exhibitions and symposia in the spring.

The Department of Psychology operates the SONA Student Pool, which encourages students enrolled in psychology courses to participate in ongoing research projects.

The College of Education and Human Services supports ongoing outreach programs as part of its mission.

Additionally, various academic units offer events designed to inform the university and Mt. Pleasant communities about current research on issues of concern to the community.

Evaluation

CMU is committed to ensuring that educational opportunities are offered to research participants, prospective research participants, and community members that will enhance their understanding of research involving human participants at CMU. The academic and administrative entities that sponsor outreach programs are responsible for periodically evaluating their programs.

Section 22: Health Insurance Portability and Accountability Act (HIPAA)

The *Health Insurance Portability and Accountability Act of 1996* (HIPAA) is a federal law that defines national standards related to its three major components, the HIPAA Privacy Rule, Security Rule, and Breach Notification Rule. While the primary impact of HIPAA is on the routine provision of and billing for health care, HIPAA also affects the conduct and oversight of research.

The Privacy Rule (45 CFR 160) defines individually identifiable health information transmitted or maintained by a covered entity in any form or media (electronic, written, or oral) as *Protected Health Information* (PHI) and establishes the conditions under which investigators may access and use this information in the conduct of research. Except as otherwise permitted, the Privacy Rule requires that a research subject "authorize" the use or disclosure of his/her PHI to be used in research. This authorization is distinct from the subject's consent to participate in research, which is required if the research is subject to the Common Rule, FDA regulations, and/or state laws that provide additional protection for research involving certain categories of health information (such as information derived from HIV/AIDS testing, genetic testing, and mental health records). When research consent is not required by regulation or law (e.g., for exempt research) or the requirement for research consent has been waived by an IRB, the requirements for authorization still apply unless an IRB or Privacy Board has determined that the criteria for a waiver of the authorization requirement is satisfied.

At CMU, for exempt projects and other research that does not require IRB review, the IRB chair or designee may act on requests for waivers and alterations of the HIPAA Authorization requirement for research purposes.

Definitions

These definitions are adapted from "*Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule"*, published by DHHS.

- **Access**: The mechanism of obtaining or using information electronically, on paper, or other medium for the purpose of performing an official function.
- **Accounting of Disclosures**: Information that describes a covered entity's disclosures of PHI other than for treatment, payment, and health care operations; disclosures made with Authorization; and certain other limited disclosures. For those categories of disclosures that need to be in the accounting, the accounting must include disclosures that have occurred during the 6 years (or a shorter time period at the request of the individual) prior to the date of the request for an accounting.
- **Authorization**: An individual's written permission to allow a covered entity to use or disclose specified PHI for a particular purpose. Except as otherwise

permitted by the Privacy Rule, a covered entity may not use or disclose PHI for research purposes without a valid Authorization that includes all of the required elements under the Privacy Rule.

- **Covered entity**: A health plan, a health care clearinghouse, or a health care provider who transmits health information in electronic form in connection with a transaction for which DHHS has adopted a standard.
- **Data Use Agreement**: An agreement into which the covered entity enters with the intended recipient of a limited data set that establishes the ways in which the information in the limited data set may be used and how it will be protected.
- **De-identified.** Data is considered de-identified under HIPAA when they do not identify an individual, and there is no reasonable basis to believe that the data can be used to identify an individual.
  The Privacy Rule defines two methods for de-identifying PHI:
  (1) when the PHI is stripped of all 18 HIPAA-defined identifying elements and the covered entity does not have actual knowledge that the remaining information could be used alone or in combination with other information to identify an individual who is a subject of the information (Safe Harbor method); or
  (2) when an appropriate expert determines that the risk is very small that the information could be used, alone or in combination with other reasonably available information, by an anticipated recipient to identify an individual who is a subject of the information (Expert Determination method).
- **Designated Record Set**: A group of records maintained by or for a covered entity that includes: (1) medical and billing records about individuals maintained by or for a covered health care provider; (2) enrollment, payment, claims adjudication, and case or medical management record systems maintained by or for a health plan; or (3) used, in whole or in part, by or for the covered entity to make decisions about individuals. A record is any item, collection, or grouping of information that includes PHI and is maintained, collected, used, or disseminated by or for a covered entity.
- **Disclosure**: The release, transfer, provision of access to, or divulging in any manner, of information outside the entity holding the information.
- **Genetic Information:** Genetic information means, with respect to an individual, information about: (i) The individual's genetic tests; (ii) The genetic tests of family members of the individual; (iii)The manifestation of a disease or disorder in family members of such individual; or (iv) Any request for, or receipt of, genetic services, or participation in clinical research which includes genetic services, by the individual or any family member of the individual.

  Genetic information concerning an individual or family member of an individual includes the genetic information of: (i) A fetus carried by the individual or family member who is a pregnant woman; and (ii) Any embryo legally held by an individual or family member utilizing an assisted reproductive technology. Genetic information excludes information about the sex or age of any individual.

- **Genetic services:** A genetic test; genetic counseling (including obtaining,

interpreting, or assessing genetic information); or genetic education.

- **Genetic test:** Means an analysis of human DNA, RNA, chromosomes, proteins, or metabolites, if the analysis detects genotypes, mutations, or chromosomal changes. Genetic test does not include an analysis of proteins or metabolites that is directly related to a manifested disease, disorder, or pathological condition.
- **Health Information**: Health Information means any information, including genetic information, whether oral or recorded in any form or medium, that: (1) is created or received by a health care provider, health plan, public health authority, employer, life insurer, school or university, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual.
- **Individually Identifiable Health Information**: Information that is a subset of health information, including demographic information collected from an individual, and

  (1) is created or received by a health care provider, health plan, employer, or health care clearinghouse; and
  (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual; and
  (a) that identifies the individual; or
  (b) with respect to which there is a reasonable basis to believe the information can be used to identify the individual.
- **Limited Data Set**: Refers to data sets that exclude 16 categories of direct identifiers that are specified in the Privacy Rule. Limited Data Sets may be used or disclosed, for purposes of research, public health, or health care operations, without obtaining either an individual's Authorization or a waiver or an alteration of Authorization for its use and disclosure, only if the covered entity *obtains satisfactory assurances in the form of a Data Use Agreement*. Limited Data Sets are not de-identified information under the Privacy Rule.
- **Minimum Necessary**: The least PHI reasonably necessary to accomplish the intended purpose of the use, disclosure, or request. Unless an exception applies, this standard applies to a covered entity when using or disclosing PHI or when requesting PHI from another covered entity. A covered entity that is using or disclosing PHI for research without Authorization must make reasonable efforts to limit PHI to the minimum necessary. A covered entity may rely, if reasonable under the circumstances, on documentation of IRB or Privacy Board approval or other appropriate representations and documentation under section 164.512(i) as establishing that the request for PHI for the research meets the minimum necessary requirements.
- **Privacy Board**: A board that is established to review and approve requests for waivers or alterations of Authorization in connection with a use or disclosure of PHI as an alternative to obtaining such waivers or alterations from an IRB. A Privacy Board consists of members with varying backgrounds and appropriate professional competencies as necessary to review the effect of the research protocol/research plan on an individual's privacy rights and related interests. The

board must include at least one member who is not affiliated with the covered entity, is not affiliated with any entity conducting or sponsoring the research, and is not related to any person who is affiliated with any such entities. A Privacy Board cannot have any member participating in a review of any project in which the member has a conflict of interest or commitment.

- **Protected Health Information**: Protected Health Information (PHI) means individually identifiable health information that is transmitted by electronic media; maintained in electronic media; or transmitted or maintained in any other form or medium. PHI excludes individually identifiable health information in education records covered by the Family Educational Rights and Privacy Act (FERPA), as amended, 20 U.S.C. 1232g; in records described at 20 U.S.C. 1232g(a)(4)(B)(iv); in employment records held by a covered entity in its role as employer; and regarding a person who has been deceased for more than 50 years.
- **Psychotherapy Notes:** Psychotherapy notes means notes recorded (in any medium) by a health care provider who is a mental health professional documenting or analysing the contents of conversation during a private counseling session or a group, joint, or family counseling session and that are separated from the rest of the individual's medical record. Psychotherapy notes excludes medication prescription and monitoring, counseling session start and stop times, the modalities and frequencies of treatment furnished, results of clinical tests, and any summary of the following items: Diagnosis, functional status, the treatment plan, symptoms, prognosis, and progress to date.
- **Research**: A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. This includes the development of research repositories and databases for research.
- **Use**: With respect to individually identifiable health information, the sharing, employment, application, utilization, examination, or analysis of such information within the covered entity or health care component (for hybrid entities) that maintains such information.
- **Waiver or Alteration of Authorization**: The documentation that the covered entity obtains from an investigator or an IRB or a Privacy Board that states that the IRB or Privacy Board has waived or altered the Privacy Rule's requirement that an individual must authorize a covered entity to use or disclose the individual's PHI for research purposes.
- **Workforce**: Employees, volunteers, trainees, and other persons whose conduct, in the performance of work for a covered entity, is under the direct control of the covered entity, whether or not they are paid by the covered entity.

The Role of the IRB under the Privacy Rule

Under the Privacy Rule, IRBs have authority to consider, and act upon, requests for a partial or complete waiver or alteration of the Privacy Rule's Authorization requirement for uses and disclosures of PHI for research. Although the Common Rule and FDA regulations include protections to help ensure the privacy of subjects and the

confidentiality of information (as applicable, to research activities that are regulated under those sets of regulations), the Privacy Rule supplements these protections where HIPAA is applicable, by requiring covered entities to implement specific measures to safeguard the privacy of PHI. If certain conditions are met, an IRB may grant a waiver or an alteration of the Authorization requirement for research uses or disclosures of PHI.

CMU IRB and, when mutually agreed, the external IRBs it relies upon, fulfill the functions of a Privacy Board for human subject research.

The Privacy Rule does not alter IRB membership requirements, jurisdiction on matters concerning the protection of human subjects, or other procedural IRB matters. An IRB must follow the procedural requirements of the Common Rule and, if applicable, FDA regulations, including using either the normal review procedures (review by the convened IRB) or, as appropriate, the expedited review procedures when considering a request to waive or alter the Authorization requirement.

When a request for a waiver or an alteration of the Authorization requirement is considered by the convened IRB, a majority of the IRB members must be present at the meeting, including at least one member whose primary concerns are in nonscientific areas. In order for an approval of a waiver or an alteration of the Privacy Rule's Authorization requirement to be effective, it must be approved by a majority of the IRB members present at the convened meeting. If a member of the IRB has a conflict of interest or commitment with respect to the PHI use and disclosure for which a waiver or an alteration approval is being sought, that member may not participate in the IRB review or approval.

DHHS has established categories of research that may be reviewed by an IRB through an expedited review procedure. Expedited review of a request for a waiver or an alteration of the Authorization requirement is permitted if the research study qualifies for expedited review under DHHS requirements. A modification to a previously approved protocol/research plan, which only involves the addition of an Authorization for the use or disclosure of PHI to the IRB-approved informed consent, may be reviewed by the IRB through an expedited review procedure, because this type of modification may be considered to be no more than a minor change to research. If expedited review procedures are appropriate for acting on the request, the review may be carried out by the IRB chair or by one or more experienced reviewers designated by the Chair from among the IRB members. A member with a conflict of interest or commitment may not participate in an expedited review. If an IRB uses expedited review procedures, it must adopt methods for keeping all of its members advised of requests for waivers or alterations of the Authorization requirement as well as those requests that have been granted under an expedited review procedure.

IRB documentation of approval of a waiver or alteration of the authorization requirement includes:

- The identity of the approving IRB.

- The date on which the waiver or alteration was approved.
- A statement that the IRB has determined that the alteration or waiver or authorization, in whole or in part, satisfies the three criteria in the Rule.
- A brief description of the PHI for which use or access has been determined by the IRB to be necessary in connection with the specific research activity.
- A statement that the waiver or alteration was reviewed and approved under either normal or expedited review procedures.
- The required signature of the IRB chair or designee.

CMU or an affiliated institution does not release PHI to investigators or other third parties without individual authorization or proper documentation of an IRB or Privacy Board approval of a waiver or alteration of the requirement.

Authorization

Except as otherwise permitted, the Privacy Rule requires that a research subject "authorize" the use or disclosure of his/her PHI to be used in research. This authorization is distinct from the subject's consent to participate in research, which is required for research to which the Common Rule, FDA regulations, and/or state laws regarding certain categories of health information apply (although certain research that is subject to the Privacy Rule may be exempt from Common Rule requirements). Just as a valid consent under Common Rule and FDA regulations must meet certain requirements, a valid authorization must be written in plain language and contain certain statements and core elements (45 CFR 164.508.6(c)).

Once executed, a signed copy must be provided to the individual providing authorization. Signed authorizations must be retained by the covered entity for six (6) years from the date of creation or the date it was last in effect, whichever is later.
A research subject has the right to revoke their authorization at any time. See Section Accounting of Disclosures for more information regarding an individual's right to revoke, procedures, and exceptions.

When an authorization permits disclosure of PHI to a person or organization that is not a covered entity (such as a sponsor or funding source), the Privacy Rule does not continue to protect the PHI disclosed to such entity. However, other federal and state laws and agreements between the covered entity and recipient such as a Business Associate Agreement (BAA) or Confidentiality Agreement may establish continuing protections for the disclosed information. Under the Common Rule or the FDA regulations, an IRB may impose further restrictions on the use or disclosure of research information to protect subjects.

Authorization core elements include:

- A description of the PHI to be used or disclosed, identifying the information in a specific and meaningful manner.
- The names or other specific identification of the person or persons (or class of persons) authorized to make the requested use or disclosure.

- The names or other specific identification of the person or persons (or class of persons) to whom the covered entity may make the requested use or disclosure.
- A description of each purpose of the requested use or disclosure.
- Authorization expiration date or expiration event that relates to the individual or to the purpose of the use or disclosure (A statement that there is "no expiration date or event" or that authorization expires at the "end of the research study" or "unless and until revoked" by the individual are permissible for research, including authorizations for future research).
- Signature of the individual and date. If the individual's LAR signs the Authorization, a description of the representative's authority to act for the individual must also be provided.

Authorization required statements:

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

Waiver or Alteration of the Authorization Requirement

Obtaining signed authorization to access and use of PHI for research is not always feasible. The Privacy Rule contains criteria for waiver or alterations of authorization. If a covered entity has used or disclosed PHI for research pursuant to a waiver or alteration of authorization, documentation of the approval of the waiver or authorization must be retained for six (6) years from the date of its creation or the date it was last in effect, whichever is later. This is in addition to any other documentation requirements that might apply.

For research uses and disclosures of PHI, an IRB or Privacy Board may approve a waiver or an alteration of the authorization requirement in whole or in part. A complete waiver occurs when the IRB or Privacy Board determines that no authorization will be required for a covered entity to use and disclose PHI contemplated to be used or disclosed for that particular research project. A partial waiver of authorization occurs when the IRB or Privacy Board determines that a covered entity does not need authorization for all PHI uses and disclosures for research purposes for some defined group of research purposes, such as accessing PHI for research recruitment purposes. An IRB or Privacy Board may also approve a request that removes some, but not all, required elements or statements of an authorization (an alteration).

In order for an IRB or Privacy Board to waive or alter authorization, the Privacy Rule (45 CFR 164.512(i)(2)(ii)) requires the IRB or Privacy Board to determine the following:

- The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
    - An adequate plan to protect health information identifiers from improper use and disclosure.
    - An adequate plan to destroy identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
    - Adequate written assurances that the PHI will not be reused or disclosed to (or shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.
- The research could not practicably be conducted without the waiver or alteration.
- The research could not practicably be conducted without access to and use of the PHI.

The Privacy Rule allows institutions to rely on a waiver or an alteration of Authorization obtained from a single Privacy Board to be used to obtain or release PHI in connection with a multi-site project.

Activities Preparatory to Research

Under the preparatory to research provision of the Privacy Rule, a covered entity may permit an investigator who works for that covered entity to use PHI for purposes preparatory to research such as assessing the feasibility of conducting a research project, developing a grant application or protocol or identifying potential subjects.

The covered entity must obtain from an investigator representation, either in writing or orally, that

(1) the use or disclosure is requested solely to review PHI as necessary to prepare a protocol/research plan or for similar purposes preparatory to research,
(2) that the investigator will not remove any PHI from the covered entity (e.g., physically taken out of a facility, or downloaded and retained on the investigator's device) in the course of review, and
(3) the PHI for which access is sought is necessary for the research purpose. [45 CFR 164.512(i)(1)(ii)]

At CMU, this is accomplished by the investigator submitting a request for waiver of consent and authorization for screening purposes to the IRB.

Federal guidance has drawn a distinction between activities that may be undertaken by

a researcher who is a member of the covered entity's workforce, e.g., an employee of the covered entity, and a researcher who is not part of the covered entity's workforce. This guidance indicates that researchers may use PHI under the preparatory to research provision to *identify* potential study subjects, so long as no PHI is removed from the covered entity and the remaining two representations set forth above can be made. However, the guidance also indicates that researchers may not use PHI obtained pursuant to the "preparatory to research" provision to *contact* potential study subjects unless

(i) the researcher is a member of the covered entity's workforce, or
(ii) the researcher enters into a BAA with the covered entity. Therefore, if the researcher is not a workforce member or business associate of the covered entity, then the researcher may contact potential subjects only pursuant to a partial waiver of authorization from the cognizant IRB or privacy board, or pursuant to the Authorization of the subject.

Research Using Decedent's Information

The HIPAA Privacy Rule protects the individually identifiable health information about a decedent for 50 years following the date of death of the individual. When a researcher seeks to use PHI from decedents for a research protocol, the researcher must

(1) obtain authorization from the personal representative of the decedent (i.e., the person under applicable law with authority to act on behalf of the decedent or the decedent's estate),
(2) obtain a waiver of the requirement to obtain authorization from an IRB or Privacy Board, or
(3) attest to the covered entity holding the PHI that the use or disclosure is solely for research on the PHI of decedents, that the PHI being sought is necessary for the research, and, if requested by the covered entity, provide documentation of the death of the individuals about whom information is being sought.

Storage and Use of PHI for Future Research

The Privacy Rule recognizes the creation of a research database or a specimen repository to be a research activity if the data/specimens to be stored contain PHI. When researchers establish a database or repository containing PHI for the purposes of future research, or intend to maintain PHI following completion of a primary study for potential future research use, individual authorization for the storage of PHI for such future research must be sought unless the IRB has determined that the criteria for a waiver of the authorization requirement are satisfied. See *Section 22, Waiver or Alteration of the Authorization Requirement* of this policy manual for a discussion of waivers of authorization.

An authorization for use and/or disclosure of the stored PHI for future research must describe the future research uses and/or disclosures in sufficient detail to allow the potential subject to make an informed decision. The Rule does not require that an authorization describe each specific future study if the particular studies to be

conducted are not yet determined. Instead, the authorization must adequately describe future purposes such that it would be reasonable for the subject to expect that their PHI could be used or disclosed for such research. When developing the description of potential future research uses, the investigator should be cognizant of uses of information/specimens that the community may consider particularly sensitive, such as genetics, mental health, studies of origin, and use of tissues that may have cultural significance, including whether any stage laws may impose additional consent requirements with respect to any of these sensitive categories of information.

The authorization for future research can be a stand-alone document or may be incorporated into authorization for the establishment of the database or repository or for the primary study, unless the research involves the use or disclosure of psychotherapy notes. Authorizations for the use or disclosure of psychotherapy notes can only be combined with another authorization for a use or disclosure of psychotherapy notes.

If the authorization for future research is combined with consent/authorization for another research activity (e.g., a clinical trial), the consent/authorization must clearly differentiate between the research activities and allow the individual to opt-in to the future research. The use of opt-outs for future research are not permitted under the Privacy Rule because an opt-out process does not provide individuals with a clear ability to authorize the use of their PHI for future research and may be viewed as coercive.

It is important to note that securing a HIPAA authorization for unspecified future research activities may not, by itself, satisfy all applicable legal consent requirements. The Common Rule, FDA regulations, and state laws also must be considered, as applicable, in evaluating whether the information (including PHI) or identifiable biospecimens may be used for future research projects.

Corollary and Sub-studies

Consistent with the discussion above relating to future uses of research databases or repositories, the Privacy Rule mandates that subject participation in corollary or sub studies not essential to the primary aims of the research, such as when PHI from an interventional clinical trial is used to create or to contribute to a central research repository, must be on a voluntary, "opt-in" basis. This is particularly important when the primary research offers a potential direct benefit to the research subject, such as treatment, that might compel the potential subject to agree to an ancillary study, even if the subject would prefer not to do so.
HIPAA reinforces this ethical principle by explicitly stating that authorization for "unconditioned" activities, for which there is no associated treatment, benefit, or other effect on the individual subject associated with participation, cannot be required. The published preamble to HIPAA Omnibus clarifies the basis for this position, and the requirement that authorization for unconditioned activities involves a clear opt-in mechanism, stating:

> *"This limitation on certain compound authorizations was intended to help*

ensure that individuals understand that they may decline the activity described in the unconditioned authorization yet still receive treatment or other benefits or services by agreeing to the conditioned authorization."

AND

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

As with authorization for future research (which is one form of "unconditioned activity"), it is acceptable to combine in a single document the authorization for a conditioned activity, such as a clinical trial, with authorization for other forms of unconditioned activity such as a corollary or sub-study that does not directly benefit or effect the individual participant, provided that:

- The authorization clearly differentiates between the conditioned and unconditioned research activities.
- The authorization clearly allows the individual the option to opt-in to the unconditioned research activities.
- Sufficient information is provided for the individual to be able to make an informed choice about both the conditioned and unconditioned activities.

Separate authorization must be obtained for each research activity that involves the use and disclosure of psychotherapy notes. For example, authorization for the use and disclosure of psychotherapy notes for a clinical trial cannot be combined with an authorization for the use and disclosure of those psychotherapy notes for a corollary research activity.

De-identification of PHI under the Privacy Rule

Covered entities may use or disclose health information that is de-identified without restriction under the Privacy Rule, because information that has been de-identified consistent with the Privacy Rule requirements is not considered individually identifiable health information. The "Safe Harbor" method permits a covered entity to de-identify data by removing all 18 data elements specified in the Privacy Rule that could be used to identify the individual or the individual's relatives, employers, or household members. To satisfy the Safe Harbor method of de-identification, the covered entity also must have no actual knowledge that the remaining information could be used alone or in combination with other information to identify individuals. Under this Safe Harbor method, the identifiers of the individual or his or her relatives, employers, or household members that must be removed are the following:

- Names.
- All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP Code, and their equivalent geographical codes, except for the initial three digits of a ZIP Code if, according to the current publicly available data from the Bureau of the Census:

    - The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people.
    - The initial three digits of a ZIP Code containing 20,000 or fewer people are changed to "000."
- All elements of dates except the year for dates:
    - Directly related to an individual, including birth date, admission date, discharge date, and date of death.
    - All ages over 89 years and all elements of dates (including year) indicative of such ages; such ages and elements may be aggregated into a single category of age 90 years and older.
- Telephone numbers.
- Facsimile numbers.
- Electronic mail addresses.
- Social security numbers.
- Medical record numbers.
- Health plan beneficiary numbers.
- Account numbers.
- Certificate/license numbers.
- Vehicle identifiers and serial numbers, including license plate numbers.
- Device identifiers and serial numbers.
- Web universal resource locators (URLs).
- Internet Protocol (IP) address numbers.
- Biometric identifiers, including fingerprints and voiceprints.
- Full-face photographic images and any comparable images.
- Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification.

Alternatively, a qualified statistician may certify that the risk is very small and that health information could be used, alone or in combination with other available information, to identify individuals. The qualified statistician must document the methods and results of the analysis that justify such a determination. This analysis must be retained by the covered entity for six (6) years from the date of its creation or when it was last acted on, whichever is later.

The Privacy Rule permits a covered entity to assign to, and retain with, the de-identified health information, a code or other means of record re-identification if that code is not derived from or related to the information about the individual and is not otherwise capable of being translated to identify the individual. The covered entity may not use or disclose the code or other means of record identification for any other purpose and may not disclose its method of re-identifying the information.

*NOTE**:** Data that are considered de-identified under HIPAA may still be considered human subject data under the Common Rule and may require IRB review and approval. Removal of HIPAA-identifying elements does not necessarily mean that the identity of the subject is not or may not readily be ascertained by the investigator or associated with the information and thus be considered identifiable private*

information under the Common Rule. The reverse can also be true (and, in practice, is more likely to occur): information may not be "identifiable" under the Common Rule but, because it contains certain HIPAA identifiers, it is considered identifiable under HIPAA.

Limited Data Sets and Data Use Agreements

Limited data sets are data sets stripped of certain direct identifiers. Limited data sets may be used or disclosed only for public health, research, or health care operations purposes. Because limited data sets may contain identifiable information, they are still PHI and as such are not considered de-identified under the Privacy Rule. Unlike de-identified data, PHI in limited data sets may include: addresses other than street name or street address or post office boxes; all elements of dates (such as admission and discharge dates); and unique codes or identifiers not listed as direct identifiers. The following direct identifiers *must be removed* for PHI to qualify as a limited data set:

- Names.
- Postal address information, other than town or city, state, and ZIP code.
- Telephone numbers.
- Fax numbers.
- Email addresses.
- Social Security numbers.
- Medical record numbers.
- Health plan beneficiary numbers.
- Account numbers.
- Certificate and license numbers.
- Vehicle identifiers and license plate numbers.
- Device identifiers and serial numbers.
- Web universal resource locators (URLs).
- Internet protocol (IP) addresses.
- Biometric identifiers.
- Full-face photographs and any comparable images.

Before disclosing a limited data set, a covered entity **must** enter into a *data use agreement* (DUA) with the recipient, even when the recipient is a member of its workforce. The DUA establishes the parameters around the proposed uses and disclosures of the data, who is permitted to have access to the data, and stipulates that no other use or disclosure will be made other than as permitted by the DUA or as otherwise required by law, no attempt will be made to identify or contact individuals whose data are included in the limited data set, that appropriate safeguards are in place to protect the data from unauthorized use or disclosure, that any agents, including subcontractors, to whom the recipient provides the LDS will agree to the same restrictions and conditions that apply to the recipient, and that the recipient will report any uses or disclosures of the information that they become aware of that are not in keeping with the terms of the DUA. Data Use Agreements for the purposes of research are available through CMU. Contact the IRB to determine who must

authorize a DUA for a specific project.

Research Subject Access to PHI

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

Accounting of Disclosures

The Privacy Rule generally grants individuals the right to a written "Accounting of Disclosures" of their PHI made by a covered entity without the individual's authorization in the six (6) years prior to their request for an accounting. A covered entity must therefore keep records of such PHI disclosures for six (6) years.
It is important to understand the difference between a *use* and a *disclosure* of PHI. In general, the *use* of PHI means use of that information within the covered entity. A disclosure of PHI means "the release, transfer, provision of access to, or divulging in any manner of information outside of the entity holding the information." The Privacy Rule restricts both uses and disclosures of PHI, but it requires an accounting only for certain PHI disclosures.

Generally, an Accounting of Disclosures is required for:

- Routinely Permitted Disclosures (e.g., under public health authority, to regulatory agencies, to persons with FDA-related responsibilities) with limited exceptions (e.g., law enforcement, national security).
- Disclosures made pursuant to:
    - Waiver of Authorization.
    - Research on decedents' information.
    - Reviews Preparatory to Research.

An accounting is not needed when the PHI disclosure is made:

- For treatment, payment, or health care operations.
- Under an Authorization for the disclosure.
- To an individual about himself or herself.
- As part of a limited data set under a data use agreement.
-

The Privacy Rule allows three (3) methods for accounting for research-related disclosures that are made without the individual's Authorization or other than a limited data set:

(1) a standard approach;
(2) a multiple-disclosures approach; and

(3) an alternative for disclosures involving 50 or more individuals. Whichever approach is selected, the accounting is made in writing and provided to the requesting individual. Accounting reports to individuals may include results from more than one accounting method.

Section 23: Additional Protections for Information/Records under Michigan Law

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

Michigan Public Health Code defines a "communicable disease" as "an illness due to a specific infectious agent or its toxic products that results from transmission of that infectious agent or its products from a reservoir to a susceptible host, directly as from an infected individual or animal, or indirectly through the agency of an intermediate plant or animal host, vector, or the inanimate environment." MCL 333.5101(1)(b)

A "serious communicable disease or infection" is defined as "a communicable disease or infection that is designated as serious by the department [of Community Health pursuant to PA 368 of 1978].... Serious communicable disease or infection includes, but is not limited to, HIV infection, acquired immunodeficiency syndrome, sexually transmitted infection, and tuberculosis." MCL 333.5101(1)(g).

Any report, record, or data related to HIV/AIDS, or other serious communicable disease, (i.e. testing, care, treatment, reporting, or research, and information related to partner notifications under MCL 333.5114a) are confidential and subject to the physician patient privilege. MCL 333.5131 (referring to MCL 600.2157). However, information on a positive test result MUST be disclosed to the local health department/ Michigan Department of Community Health pursuant to MCL 333.5114 and if assistance with partner notification is required, with the requirements of MCL 333.5114a.
In response to a court order and subpoena, HIV/AIDS information is limited only to cases in which (a) the court is petitioned for an order to disclose, or (b) the court issues an order to disclose. MCL 333.5131(3)(a) and (b).

If the court is petitioned for the records, the court must determine: (1) "that other ways of obtaining the information are not available or would not be effective"; and (2) "the public interest and need for the disclosure outweigh the potential for injury to the patient". MCL 333.5131(3)(a).

If the court issues an order for disclosure, the order must: (1) limit "disclosure to those parts of the patient's record that are determined by the court to be essential to fulfill the objective of the order"; (2) limit "disclosure to those individuals whose need for the information is the basis of the order"; and (3) include "such other measures as considered necessary by the court to limit the disclosure for the protection of the patient." MCL 333.5131(3)(b).

Section 24: Information Security

CMU has established standards and safeguards to protect research participants and patient information and to ensure compliance with federal and state information security regulations. There may be additional requirements of an external research site (e.g., a hospital or other covered entity), and the sponsor, depending on the study and type of data (e.g., 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.

CMU information security standards and requirements must be met if CMU IRB is the IRB of record, or if the research is conducted at, under the auspices of, or using the services or resources of CMU.

The use of personal computers and devices (e.g., laptops, desktops, tablets, smartphones, portable/USB drives) for storing research data is prohibited unless they have been secured by CMU IT.

The use of computers and devices owned and managed by another entity (e.g., DMC-Children's Hospital of Michigan, Ascension St. Mary, Covenant Medical Center) for storing, even temporarily, or transmitting PHI or PII (Personally Identifiable Information) for research requires that CMU Information Technology to be aware of such use.

Any potential or known breach of a device used in the research study, whether the device is owned by CMU or not, or breach of study data must be immediately reported to the IRB and Office of Information Technology (IT) so that appropriate steps can be taken to assess the situation, protect the information, and comply with regulations and reporting requirements. If Protected Health information is involved, the CMU HIPAA Privacy Office or Privacy Office of affiliated hospital system(s) also needs to be notified.

Lost or stolen devices that are used for research, whether owned by CMU 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 CMU 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 CMU IT and the IRB.

Investigators and research staff working with or at DMC- Children's Hospital of Michigan, Ascension St. Mary, Covenant Medical Center, 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 CMU 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 CMU security standards and requirements at all times.

CMU Information Technology staff provide extensive guidance to assist the research community with standards and safeguards to protect research participant/patient information and to ensure compliance with federal and state information security regulations (Policy 3-30; Policy 3-49). The IRB encourages investigators to consult with their department IT staff to verify the programs they will utilize in their research meets the standards accepted and safeguard established by CMU Office of Information Technology (e.g. google forms, survey monkey, Qualtrics, ZOOM).

NIH GRANTS

The NIH has specific requirements about ensuring data security when collecting identifiable research data, as described in NIH Grants Policy Statement as follows:

"Recipients of NIH funds are reminded of their vital responsibility to protect sensitive and confidential data as part of proper stewardship of federally funded research, and take all reasonable and appropriate actions to prevent the inadvertent disclosure, release or loss of sensitive personal information. NIH advises that personally identifiable, sensitive and confidential information about NIH-supported research or research participants are not 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 25: Sponsored Projects

Any sponsored research conducted under the auspices of CMU is conducted in accordance with federal or state guidelines and ethical standards.

The oversight of industry sponsored clinical trials was recently transitioned to the College of Medicine (CMED), while the Office of Sponsored Programs (OSP) continues to oversee all other sponsored clinical trial agreements, including industry-sponsored Children's Oncology Group funding (which is primarily federally funded).

If the industry-sponsored research is to be conducted under an Investigational New Drug (IND) or Investigational Device Exemption (IDE) application, then in collaboration with the IRB, OSP and/or CMED will determine if it is appropriate to enter into an industry-sponsored agreement. The sponsored research will be evaluated to see that there are qualified investigators and adequate facilities to conduct such research.

Definitions

Sponsor: The company, institution, individual donor, or organization responsible for the initiation, management or financing of a research study.

Sponsored research: Refers to scholarly, professional, and creative activities that CMU personnel conduct as documented in external restricted funding instruments such as grants, contracts, cooperative agreements, or other agreement types. This includes including clinical trials involving investigational drugs, devices, or biologics.

Responsibility

The Office of Sponsor Projects will review sponsor grants, contracts and other written agreements utilizing OSP Policy 11,019. OSP and CMED negotiate contracts for research involving human subjects. The OSP and/or CMED will collaborate with the of Research Compliance (ORC), if necessary, to ensure that consent and contract language are consistent.

OSP and CMED will ensure that agreements involving research involving human subjects will be reviewed for the following provisions:

- All sponsor agreements will indicate that the CMU investigator will follow the protocol, applicable regulations, and applicable ethical standards.
- If there is potential for research-related injuries, sponsor agreements will define who will provide care for research-related injuries and who will cover the costs for such care.
- If the sponsor will monitor the conduct of the research, or conduct monitoring activities remotely, the contract will be required to state that if the study monitor

uncovers information that could affect the safety of participants or their willingness to continue participation, influence the conduct of the study, or alter the IRB's approval to continue the study, the sponsor will make sure that the information is promptly (no longer than 30 days) communicated to the IRB.

- Contracts or other funding agreements require the sponsor to send data and safety monitoring plans and reports to the organization. Contracts or other funding agreements specify the time frame for providing routine and urgent data and safety monitoring reports to the organization as indicated in the data and safety monitoring plan approved by the IRB. At a minimum, data and safety monitoring reports should be sent annually, so they can be considered by the IRB at the time of continuing review.
- If the sponsor discovers results that could affect the safety or medical care of subjects or others involved in the study; the sponsor will make sure the IRB is notified. This requirement survives for a period following closure of a study to be determined on a case-by-case basis (e.g., two years).
- Payment arrangements among sponsors, organizations, investigators, and those referring research participants may place participants at risk of coercion or undue influence or cause inequitable selection. Payment (i.e., "finder's fees") in exchange for referrals of prospective participants from researchers (e.g., physicians) is not permitted.
- Similarly, payments designed to accelerate recruitment that is tied to the rate or timing of enrollment ("bonus payments") are also not permitted.

Section 26: Special Topics

Mandatory Reporting

While any person may make a report if they have reasonable cause to believe that a child or elder was abused or neglected, Michigan law mandates that certain persons who suspect child or elder abuse or neglect report this to Children's Protective Services, at 855-444-3911.

CMU policy requires the solicitation of informed consent from all adult research subjects and, where appropriate, assent from children involved as research subjects, in addition to the permission of their parents. In situations where conditions of abuse or neglect might be revealed, mandated reporters should make themselves known as such to parents of children under age 18, to subjects who are children, and to subjects who are potential victims of abuse or neglect. See Act No. 238, Public Acts of 1975, as amended, being Sections 722.621 –722.638, Michigan Compiled Laws.

Mandated reporter guides may be found at:
http://chanceatchildhood.msu.edu/pub.html

Certificates of Confidentiality

Certificates of Confidentiality (CoC) protect research information by prohibiting certain disclosures and conditioning others upon consent from the subject. The protections and requirements of CoCs are outlined in 42 U.S.C. 241(d) and NIH policy (when applicable) and summarized below.

CoC's are obtained as follows:

- CoCs are issued automatically when research is conducted or supported by NIH and falls within the scope of the NIH policy.
- Research that is not funded by NIH (non-NIH research) may still have the protections afforded by CoCs through successful application to the NIH, FDA, or other authorized Federal agencies or departments.

Additional information about CoCs and the application process for non-NIH research is available on the NIH CoC Website.

Definitions

Identifiable, sensitive information means information that is about an individual and that is gathered or used during the course of biomedical, behavioral, clinical, or other research and:

- Through which an individual is identified.
- For which there is at least a very small risk, as determined by current

scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual.

Sensitive Information may be the collection of, for example:

- Information about sexual attitudes, preferences, practices.
- information about personal use of alcohol, drugs, or 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.

Protections and Requirements

When a CoC is issued, whether automatically or under an approved application, the person(s) engaged in the research must not disclose or provide the name of a subject or any information, document, or biospecimen that contains identifiable, sensitive information about the subject and that was compiled for the purposes of the research:

- In any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, ***unless*** the disclosure is made with the consent of the individual to whom the information, document, or biospecimen pertains.
- To *any other person not connected* with the research, unless:
    - Required by Federal, State, or local laws (e.g., adverse event reporting to the FDA, transmissible disease reporting required under State law), but excluding proceedings as described above.
    - Necessary for the medical treatment of the subject to whom the information, document, or biospecimen pertains and made with the consent of the subject.
    - Made with the consent of the individual to whom the information, document, or biospecimens pertains.
    - Made for the purposes of other scientific research that complies with applicable Federal regulations governing the protection of human subjects in research.

Additional Protections

Identifiable, sensitive information protected under a CoC, and all copies thereof, are immune from the legal process, and shall not, without the consent of the of the individual to whom the information pertains, be admissible as evidence or used in any action, suit, or other judicial, legislative, or administrative proceeding.

Identifiable, sensitive information that has been collected under a CoC, and all copies thereof, are protected for perpetuity.

Nothing in the rule (42 U.S.C. 241(d)) may be construed to limit the access of a subject to information about himself or herself collected during the research.

When consent is obtained, the consent should inform subjects that a CoC is in place and describe the protections and limitations.

Limitations

A Certificate of Confidentiality protects research subjects only from legally compelled disclosure of their identity. It does not restrict voluntary disclosures. The protection offered is not absolute.

It 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 LAR 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.

NIH Policy

The NIH Policy on CoCs applies to *"all biomedical, behavioral, clinical, or other research funded wholly or in part by the NIH, whether supported through grants, cooperative agreements, contracts, other transaction awards, or conducted by the NIH Intramural Research Program, that collects or uses identifiable, sensitive information"* that was commenced or ongoing on or after December 13, 2016.

CoCs are automatically granted, and the requirements of such must be complied with, whenever a NIH-funded activity falls within the scope of the policy. Investigators and institutions are responsible for determining when a NIH-funded activity falls within the scope of the policy.

NIH policy expands upon 42 U.S.C. 241(d) by explaining that NIH considers research in which identifiable, sensitive information is collected or used, to include:

- Human subjects research as defined in 45 CFR 46, including research determined to be exempt (except for exempt research when the information obtained is recorded in such a manner that human subjects cannot be identified or the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects).
- Research involving the collection or use of biospecimens that are identifiable to an individual or for which there is at least a very small risk that some combination of the biospecimen, a request for the biospecimen, and other

available data sources could be used to deduce the identity of an individual.

- Research that involves the generation of individual level, human genomic data from biospecimens, or the use of such data, **regardless of whether the data is recorded in such a manner that human subjects can be identified or the identity of the human subjects can readily be ascertained.**
- Any other research that involves information about an individual for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual, as defined in subsection 301(d) of the Public Health Service Act.

NIH CoC Policy Determination

At CMU, Office of Sponsor Project (OSP) staff will, in consultation with the investigator(s) (or Program or Project Director, if applicable), determine if the NIH policy applies to any NIH-funded activity. The questions outlined in the NIH policy will be used to guide the analysis. When it has been determined that the NIH policy doesn't apply, investigators (or Program or Project Directors, if applicable) are responsible for consulting with OSP whenever they are proposing changes to the NIH-funded activity that may impact or change the analysis. The NIH policy includes additional responsibilities and requirements for internal controls and for ensuring that recipients of identifiable, sensitive information protected by a CoC understand that they are also subject to the requirements of subsection 301(d) of the Public Health Service Act.

Application Procedures for non-NIH Research

Any person engaged in human subjects research that collects or uses identifiable, sensitive information may apply for a CoC. For most research, CoCs are obtained from NIH; an investigator may apply for a CoC through the NIH Institute or Center funding research in a scientific area similar to the project.

If the research is conducting a sensitive research project that is covered by the Agency for Healthcare Research and Quality (AHRQ) confidentiality statute (42 U.S.C. section 299c-3(c)) or the Department of Justice (DoJ) confidentiality statute (42 U.S.C. section 3789g), then a CoC may not be needed.

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

CoCs may also be issued by other Federal agencies and departments, such as CDC, SAMSHA, or HRSA.

For more information, see the NIH CoC Website.

IRB Review

Investigators are responsible for clearly representing in the IRB submission that a CoC is in place, or that an application for CoC has been submitted. When the CoC application is in process or pending, the IRB may condition final approval upon its receipt.

For studies that are already underway, investigators must submit a *IRB Protocol Change Form* to the IRB, along with updated consent language (if applicable), when a CoC is applied for, or when automatically issued under the NIH policy.

When reviewing research under a CoC, CMU IRB will evaluate whether the research plan is consistent with the obligations to protect information and specimens under a CoC and whether the consent language, if applicable, discloses the CoC and appropriately describes the associated protections and limitations. Sample consent language is available on the NIH CoC Website.

When non-NIH research is not under a CoC, the IRB may require an investigator to apply for a CoC if the research includes identifiable, sensitive information and the IRB determines that a CoC is necessary to minimize risks and adequately protect subjects' privacy and the confidentiality of subjects' information or specimens.

Case Reports Requiring IRB Review

Federal regulations at 45 CFR 46.102(d) and 45 CFR 164.501 define research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. A retrospective review and analysis on a series of patients seen in one's own practice is not research and the information used in the report originally was collected solely for non-research purposes as the result of a clinical experience. A report of 1-3 medical cases does not need to be submitted to the IRB for approval.

The reporting on such a small number of patients does not develop or contribute to generalizable knowledge since it is not a systematic investigation, which includes a hypothesis that is then investigated prospectively. CMU regards such limited case report as an educational activity, not research, and thus it is permissible under the Privacy Rule (HIPAA) as a part of health care operations (45 CFR 164.501) when the case report will be used internally, or in other learning environments, for educational purposes.

When four (4) or more patients' commonalities are being evaluated and conclusions are to be drawn (i.e. systematic investigation), this resembles a prospectivity designed study and as such requires IRB review and approval.

An IRB review should be sought if a report of 1-3 patients is intended to develop or contribute to generalizable knowledge. The IRB will determine, using procedures outlined in *Section 5: Human Subject Research Determination*, if the case report fits the definition of research.

Regardless of the number of cases, providers must comply with all applicable laws, hospital, and CMU policies related to the use and release of health information. Permission from the patients who will be included in the report should be sought whenever possible, and journals may require such as a condition of publication.

A copy of this policy can be provided to journal editors or others who request confirmation of IRB determination. If a letter is needed confirming that an approval is not needed, submit a *Does My Project Need IRB Review* form for an IRB determination.

Repositories, Databases and Registries

A research repository is defined as a collection of data/biospecimens that have been collected and stored with the intention of using the materials for future research, either by the investigator who collected them or by sharing the materials with other investigators. A "repository" may be referred to as a bank, registry, data-repository, secondary database, or other term.

There are two types of repositories:

- Non-research repositories are not associated with research when they are created and maintained. Examples are data/samples stored for diagnosis, treatment, billing, marketing, quality control, and public health quality.
- Research repositories are created and maintained for specific research purposes. Such purposes may include databases to identify prospective subjects, patient outcome information to evaluate treatment effectiveness, and tissues samples for future research. If non-research repository has the addition of new fields that are not associated with the core purpose of repository, then a research repository has been created due to altering the repository to facilitate research.

Non-Research Repositories

The non-research repositories may contain information that is useful to researchers' even though they are not created for research purposes.

- IRB oversight is not required if the repository was created and operated without involving human subject research.
- IRB oversight is required if identifiable private information or identifiable human specimens from non-research repository is used for research.
- IRB oversight is required when the safety or effectiveness of a medical device is being evaluated (i.e., *in vitro* testing of a new laboratory instrument).

When use of coded private information or specimens will be used in the research, should have IRB review or be have a not human subject research determination made using "*Does My Project Need IRB Review*" form (See section 5).

Since there is extensive variation in how registries operate, the IRB application should include sufficient information regarding the scientific goals, functions, and operational procedures when using data or specimens from non-research repositories. Also include if there are any terms or conditions or restrictions on use of the data/specimens. If a person declines to have their data/specimens used for research, then the research cannot include the data/specimen in the research. Unless the request to use the data/specimens meets the criteria for a waiver, informed consent and HIPAA authorization (if applicable) must be obtained.

Research Repositories

There are three (3) distinct activities associated with research repositories.

1. Collection of data/specimens.
2. Storage and management of data/specimens.
3. Distribution of data/specimens.

Collection

The IRB submission should include sufficient information regarding the scientific goals, functions, and operational procedures to the collection of data or specimens.

Informed consent and HIPAA authorization (when applicable) must be obtained unless the IRB determines that the criteria for a waiver are satisfied. The following information should be included in the informed consent document:

- A clear description of
    - What data/specimens will be collected.
    - Where the data/specimens will be stored, who will have access, and how the data/specimens will be secured.
    - Whether the data/specimens will be identifiable, coded, or deidentified.
    - The types of research to be conducted and any limitations or restrictions on such.
    - The conditions under which data/specimens will be released to recipient investigators.
- A statement regarding future withdrawal of the data from the study (i.e., state whether subjects may, in the future, request that their data be destroyed or that all personal identifiers be removed from data and how to make such a request).
- When appropriate, the plan for management of incidental findings and sharing of results.

Storage and Management

Repositories should have operational procedures describing:

- The conditions under which data/specimens will be accepted (e.g., inclusion criteria).
- Informed consent.

- IRB review.
- The sources of data/specimens.
- Whether data/specimens will be identifiable, coded, or de-identified, and, if coded, management of the linkage key.
- Physical and procedural mechanisms for the secure receipt, storage, and distribution of data/specimens.

Distribution

Repositories should have operational procedures describing:

- How data/specimens may be requested and by whom.
- Any requirements associated with a request for data/specimens.
- Verification of IRB approval or that approval is not required.
- Any limitations or restrictions on how data/specimens may be used.
- Whether released data/specimens will be identifiable, coded, or de-identified, and, if coded, any circumstances under which recipient investigators will access to or be provided with the key or other means to re-identify.
- Study personnel serving in role of honest-broker in managing codes and de-identification prior to sharing with recipient researchers
- Agreements with recipient investigators specifying the terms of use.
- potential for re-consent of donors who are minors at the time of donation but turn 18 while the biobank is active.
- Length of time a biospecimens will be kept (indefinitely, until depleted).

IRB Oversight

IRB approval is required for each of the following:

- The establishment and operation of a research repository when the data/specimens are accessed, received, stored, or distributed are identifiable.
- For the use of data/specimens from a repository when the recipient investigator(s) know or may readily ascertain the identity of individual subjects, and, regardless of identifiability, when specimens will be used to evaluate the safety or effectiveness of a medical device.
    - The only exception is when the coded private information or specimens are to be obtained from an IRB-approved repository and the rules of that repository forbid the release of identifiable information, the release of the key to the code or other means that would allow re-identification, or the release of sufficient information that investigators could readily ascertain the identity of subjects.

Research Involving or Generating Genetic Information

Genetic research studies present risks that are not always the same as biomedical research. Primary risks of genetic research are risks of social and psychological harm along with legal and economics risks rather than risks of physical harms. These risks may provoke anxiety and confusion about subject's personal health, compromise subject's insurability/employability, damage familial relationships, change immigration status, and limit education options, and may create a social stigma. The IRB may not necessarily consider them to be minimal risk.

Genetic research does not mean only research that involves looking for mutations in DNA. Research that involves looking at the differences between proteins in individuals with or without a certain disease can also qualify as genetic research. Records research involving information that was derived from a previous genetic test can also qualify as genetic research.

Definitions:

- **Genetic research**: Research using human DNA samples, genetic testing or genetic information.
- **Genetic information**: Information about an individual or the individual's blood relatives obtained from a genetic test.
- **Genetic test**: A test for determining the presence or absence of genetic characteristics in a human individual or the individual's blood relatives, including tests of nucleic acids, such as DNA, RNA, and mitochondrial DNA, chromosomes or proteins in order to diagnose or determine a genetic characteristic.
- **Genetic characteristic**: A gene, chromosome or alteration thereof that may be tested to determine the existence of or risk for acquiring a disease, disorder, trait, propensity or syndrome, or to identify an individual or a blood relative. "Genetic characteristic" does not include family history or a genetically transmitted characteristic whose existence or identity is determined by means other than through a genetic test.
- **Genomics**: The study of the entire genome of an organism, where the genome is the entire set of genetic instructions found in a cell.
- **Large-Scale genomic data**: This is data from genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, metagenomic, epigenomic, and gene expression data. Analysing two or more genes can count as "large-scale genomic data" if done in more than 1000 human subjects.
- **Epigenetics:** The study of changes caused by the activation and deactivation of genes without any change in the underlying DNA sequence of the organism. Epigenetics refers to both heritable changes in gene activity and expression (in the progeny of cells or of individuals) and also stable, long-term alterations in the transcriptional potential of a cell that are not necessarily heritable.

The National Human Genome Research Institute (NHGRI) has a *Health FAQs* website to the answer frequently asked questions about genetic disorders, the impact of genomics on subjects' health, and the emerging science of pharmacogenomics. (https://www.genome.gov/For-Patients-and-Families/Health-FAQ)

Return of results to individual participants

1- The investigator will need to determine the following:

- What results will be returned to the participants?
  - General study results
  - Individual study results
  - Incidental findings
  - Secondary findings
- Who will be providing the results to the participants?
- Can the return of results continue after the participant's involvement, or at study ends?
- May participants "opt out" of receiving certain kinds of findings?

2- Explain the basis for returning (or not returning) each type of findings. Factors affecting the decision include:

- Whether individual research result are likely to be of clinical significance
  - The research finding are scientifically valid and confirmed (done in a CLIA approved Lab).
  - Diagnostic test devices may be required to obtain an FDA IDE.
- Potential psychological or emotional ramifications of learning the information.
  - Who will provide any relevant genetic or other counseling (e.g., helping subjects decide whether to seek additional testing and who will cover the costs?
- Ethical considerations of allowing participants to "opt out" of receiving clinically significant, actionable, and lifesaving findings.

3- If research findings are not routinely returned to participants, plan for the case of unanticipated information that could be medically compelling to the participant. Certain incidental and secondary findings are predictably associated with a particular modality or type of research, and researchers have a duty to anticipate such incidental findings—whether common or rare—to the extent possible.

Informed Consent Considerations

Among other regulatory and ethical requirements, the consent document(s) should adequately describe elements that have special significance for genetic information.
Content:

1- Sharing of DNA sample or genetic information for future research. Participants can be invited to choose between different levels of access, but researchers should limit the number of choices to avoid participant confusion.

2- Plans for disclosure or purposeful non-disclosure of research results (45 CFR 46.116(c)(8))
3- Risks (and mitigations thereof) particular to knowledge/sharing of genetic information.
4- The extent to which primary participants' family members may be involved.
5- The options for participant withdrawal from the study. Any time limits for withdrawal must be specified in the consent.
6- Costs associated with participation in the research for the participant or family.
7- As a best practice, the components specific to informed consent for genetic testing under Michigan law (MCL 333.17020 and 333.17520). The laws do not apply to procedures performed as a component of biomedical research subject to FDA and OHRP oversight.

Who provides consent:
If the study continues throughout the time when child participants may have reached the age of majority, the study must seek reconsent from the now-adult participants themselves. This includes ongoing use of data or biospecimens collected for a research repository.

A legally authorized representative must consent to research participation on behalf of adults with cognitive impairment or otherwise impaired decision making ("incapacitated individuals") and on behalf of children.

Risk Assignment

IRBs are responsible for evaluating the risks of a research study, weighing the *probability* of each risk coming to pass, and assessing the *magnitude* of harm that may result. Harm to research participants and their families based on genetic information can be both higher probability and higher magnitude than most other kinds of personally identifiable information, so genetic analysis studies may be considered to pose greater than minimal risk even when physical and/or psychological risks are minimal.

Expedited review is permitted for genetic research studies if the IRB application is otherwise eligible for expedited review. Genetic research alone is usually not a trigger for a convened board review. Annual continuing review for these studies is not required if the IRB application is otherwise eligible for No Continuing Review.

Genomic Data Sharing (GDS)

Sharing genomic research data is essential for translating research results into knowledge, products, and procedures to improve human health. The GDS Policy applies to all NIH-funded research (grants, contracts, intramural research) that generates large-scale human or non-human genomic data and the use of the data for subsequent research.

The GDS Policy applies to all NCI-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. NCI

may choose to apply the GDS Policy to projects generating smaller scale genomic data depending on the

- state of the science.
- needs of the research community.
- programmatic priorities of NCI.

Examples of small-scale projects that NCI would likely mandate data sharing for include, but are not limited to, projects:

- examining rare cancers,
- rare-cancer-related outcomes, or rare-cancer subtypes.
- focusing on under-studied populations. relating to mitochondrial DNA sequencing

The FDA defines a rare disease as a disease or condition affecting less than 200,000 in the United States.

As the GDS Policy applies to a broad range of research, genomic data should be shared via a supported NIH repository. The NCI Cancer Research Data Commons' (CRDC) Genomic Data Commons accepts genomic data sets. Additionally, the repositories included on the NIH Genomic Data Sharing Repository list accept genomic data.

For information on the NIH Genomic Data Sharing Policy (NOT-OD-14-124) see the NIH Scientific Data Sharing website.

Community Based Research

Community based research (CBR) is research that is based in a community and conducted in partnership with members of that community. *Community* is often self-defined, but general categories of community include geographic community, a community of individuals with a common problem or issue, or a community of individuals with a common interest or goal.

Where research is being conducted in communities, investigators are encouraged to involve members of the community in the research process, including the design and implementation of research and the dissemination of results when appropriate.

The most significant community involvement is in a subset of CBR called Community Based Participatory Research (CBPR) where there is an equal partnership between the academic investigators and members of a community, with the latter actively participating in all phases of the research process including the design and implementation of research and the dissemination of results when appropriate.

HRPP Staff are available to assist with education, project-specific questions and submission requirements related to CBPR such as:

- Regulatory considerations related to researcher engagement, performance sites, and involvement of vulnerable populations.
- Institutional and/or investigator collaboration agreements.
- Training requirements.

Questions to be considered as CBPR studies are developed, and issues that the IRB will consider when reviewing CBPR, are as follows:

- How was the community involved or consulted in defining the need for the proposed research (i.e., getting the community's agreement to conduct the research)?
- How was the community involved or consulted in generating the study research plan?
- How will the research procedures, including recruitment strategies and consent processes be assessed to ensure sensitivity and appropriateness to various communities (e.g., literacy issues, language barriers, cultural sensitivities, etc.)?
- How will the community be involved in the conduct of the proposed research?
- How will community members who participate in the implementation of the research be trained and supervised?
- How have "power" relationships between investigators and community members on the research team, and in subject recruitment strategies been considered to minimize coercion and undue influence?
- What are the risks and benefits of the research for the community as a whole?
- How will boundaries between multiple roles (e.g., investigator, counselor, peer) be maintained, i.e., what happens when the investigator/research staff is the friend, peer, service provider, doctor, nurse, social worker, educator, funder, etc.)?
- How will the research outcomes be disseminated to the community?
- Is there a partnership agreement or memorandum of understanding to be signed by the investigator and community partners that describes how they will work together?

When the IRB reviews research involving community members in the research process, importantly the design and implementation of research and the dissemination of results, additional considerations need to be thought out:

- Education of IRB members in community based participatory research.
- Inclusion of IRB members with expertise in community based participatory research.
- Inclusion of consultants to the IRB with expertise in community based participatory research.
- Inclusion of information on IRB applications concerning community based research.
- IRB experience with this type of research.

International Conference on Harmonization Good Clinical Practice

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting clinical research that involves human participants in research. A sponsor may require that the FDA-approved protocol and any investigator SOPs associated with that protocol would assure ICH-GCP compliance in addition to any other regulatory or institutional requirements that apply to the research study.

When CMU commits to comply with ICH-GCP E6 as a term of a grant or contract, investigators and the IRB take on additional responsibilities. Investigators who agree to perform research represented to be ICH-GCP-compliant are required to follow the protocol as written and will be advised by the IRB to review all investigator obligations in the ICH-GCP as well as any aspects of ICH-GCP incompletely or not at all captured in the research protocol and investigator SOPs. CMU will evaluate compliance by consulting the current ICH-GCP E6(R2) guidance posted by the FDA on their website.

IRB Responsibilities

When reviewing research following ICH-GCP, the IRB will review the research plan submitted to identify aspects that may be inconsistent with ICH-GCP. Such review will include evaluation of the adequacy of the available nonclinical and clinical information on an investigational product to support the proposed clinical research study, and a review that proposed clinical research is scientifically sound and answers the proposed questions. ICH-GCP E6(R2) specifically requires in addition to determinations required by institutional policy, the following:

- The IRB obtain and review written information that will be provided to subjects and the investigator's current curriculum vitae and/or other documentation evidencing the investigator's qualifications. (4.1.1)
- The IRBs written determination letter must clearly identify the trial, the documents reviewed, and the dates that actions were taken.

Investigator Responsibilities

Investigators should be fully aware of their obligations and responsibilities required by CMU and applicable regulatory agencies prior to conducting research. This section provides a summary of investigator responsibilities pertinent to data and document management in accordance with the ICH-GCP (E6(R2)4.2) Guideline.

- The investigator should be aware of, and should comply with GCP.
- The investigator should permit monitoring and auditing by the sponsor, and inspection by appropriate regulatory authorities. (4.1.4)
- The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties. (4.1.5)

- The investigator must have adequate resources to conduct the trial, including:
    - Being able to demonstrate (e.g., based on retrospective data) the potential for recruiting the required number of subjects within the agreed upon recruitment period. (4.2.1)
    - Sufficient time to properly conduct and complete the trial within the agreed trial period. (4.2.2)
    - Adequate number of qualified staff and adequate facilities to the foreseen duration of the trial to conduct the trial properly and safely. (4.2.3)
    - Ensuring that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions. (4.2.4)
- The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site. (4.2.5)
- If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated. (4.2.6)
- A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the research study, should be responsible for all research-related medical (or dental) decisions. (4.3.1)
- During and following a participant's participation in a research study, the investigator should ensure that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the research. The investigator should inform a participant when medical care is needed for intercurrent illness(es) of which the investigator becomes aware. (4.3.2)
- It is recommended that the investigator inform the participant's primary physician about the participant's participation in the research study if the participant has a primary physician and if the participant agrees to the primary physician being informed. (4.3.3)
- Although a participant is not obliged to give his/her reason(s) for withdrawing prematurely from a research study, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the participant's rights. (4.3.4)
- The investigator should sign the protocol, or an alternative contract, to confirm their agreement to comply with the approved protocol. (4.5.1)
- The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB of an amendment. (4.5.2)
- The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol. (4.5.3)
- In addition to reporting to the IRB, when the investigator implements a deviation from or change in the protocol to eliminate an immediate hazard(s) to subject(s)

without prior approval, this must be reported as soon as possible to the sponsor. (4.5.4)

- The investigator is ultimately responsible for investigational product accountability and for all of the responsibilities outlined in section 4.6 of ICH-GCP E6(R2)
- The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor (and IRB) any premature unblinding. (Section 4.7 of ICH-GCP E6(R2))
- Additional requirements for Informed Consent (Section 4.8 of ICH-GCP E6(R2))
    - When subjects or LARs are informed on any new information that may be relevant to the subject's willingness to continue participating in the trial, the communication of this information should be documented.
    - In addition to the subject signature and date on the written informed consent form, the form should be personally signed and dated by the person who conducted the informed consent discussion.
    - Prior to participation in the trial, the subject or LAR should receive a copy of the signed and dated consent form and any other written information provided to the subjects. During the trial, the subject or LAR should receive a signed and dated copy of any updated consent forms and any other updated written information.
    - If a subject is unable to read or if a LAR is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects is read and explained to the subject or the subject's LAR, and after the subject or the subject's LAR has orally consented to the subject's participation in the trial, and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's LAR and that informed consent was freely given by the subject or the subject's LAR.
    - The consent discussion and written informed consent form should include the following additional elements:
        - An explanation of the trial treatment(s) and the probability for random assignment to each treatment.
        - An explanation that the monitor(s), auditor(s), the IRB, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or LAR is authorizing such access.
        - An explanation of the anticipated prorated payment, if any, to the subject for participating in the trial.
        - An explanation of the reasonably foreseeable risks or

inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
        - A statement that the trial has the approval of the IR.
- Investigators must comply with the requirements for records and reports outlined in section 4.9 of ICH-GCP E6(R2) including the requirements for accuracy, completeness, legibility, and timeliness.
- Investigators must comply with the requirements for progress reports outlined in section 4.10 of ICH-GCP E6(R2) to the IRB and sponsor.
- Investigators must comply with the requirements for safety reporting outlined in Section 4.11 of ICH-GCP E6(R2) including the redaction of personally identifying information.
- Investigators must comply with the requirements for premature termination or suspension of a trial outlined in section 4.12 ICH-GCP E6(R2) including the requirements for sponsor (and IRB) reporting.
- Upon completion of the research study, the investigator should inform the IRB and provide the IRB with a summary of the research results, and provide any reports required by the regulatory authority(ies) per section 4.13 of ICH-GCP E6(R2).

International Research

For international research where CMU investigators conduct the research in foreign countries, the IRB will review the research to assure adequate provisions are in place to protect the rights and welfare of the participants. All policies and procedures that are applied to research conducted domestically should be applied to research conducted in other countries, as appropriate (45 CFR 46 101(a),(h)). Approval of research is permitted if "*the procedures prescribed by the foreign institution afford protections that are at least equivalent to those provided in 45 CFR 46."*

For federally-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 are obtained.

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

- When the foreign institution or site has an established IRB/EC, the investigator must obtain approval to conduct the research at the "not engaged" site from the site's IRB/IEC or provide documentation that the site is IRB/EC has determined that approval is not necessary for the investigator to conduct the proposed research at the site.
- When the foreign institution or site does not have an established IRB/IEC, a letter of cooperation must be obtained demonstrating that the appropriate institutional or oversight officials permit the research to be conducted at the performance site.

- IRB approval to conduct research at the foreign institution or site is contingent upon receiving documentation of the performance site's IRB/EC determination, or letter of cooperation, as applicable.

CMU IRB seeks sufficient knowledge of the local research context by requesting approval for the project from local IRBs or ethics committees (which may or may not be OHRP-registered) and/or local letters of support. The source of this information will depend on the nature of the study, on the country, and on the resources available to the investigator. Where there is a local IRB/EC, CMU IRB must receive and review the foreign institution or site's IRB/EC review and approval of each study prior to beginning the research at the foreign institution or site.

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

OHRP also publishes *The International Compilation of Human Research Standards*, a listing of over 1,000 laws, regulations, and guidelines on human subject protections in over 100 countries and from several international organizations. This document should be consulted to determine country level guidelines on human subject research. Many of the listings embed hyperlinks to the source document.
http://www.hhs.gov/ohrp/international

IRB Responsibilities

In addition to the IRB review considerations discussed elsewhere in this manual, the IRB will consider the following when reviewing international research:

- The qualifications of the investigator and research staff to conduct research in that country including knowledge of relevant laws, regulations, guidance and custom.
- Whether the consent process and consent documents are appropriate for the language(s) of the subjects and the subject population, and that arrangements are made to be able to communicate with subjects throughout the study (e.g., to ask and answer questions).
- How modifications to the research will be handled.
- How complaints, noncompliance, protocol deviations and unanticipated problems involving risks to subjects or others are handled.
- How post-approval monitoring will be managed.
- Whether the investigator has obtained the appropriate host country permissions to conduct research (e.g., institutional, governmental or ministerial, IRB, local, or

tribal). When appropriate, the IRB communicates and coordinates with the local institutions or ethics committees.
- Mechanisms for communicating with the investigators and research staff when they are conducting the research in other countries.

Investigator Responsibilities

The investigator conducting international research is responsible for:

- Ensuring that the resources and facilities are appropriate for the nature of the research.
- Verifying the qualifications of the investigators and research staff for conducting research in the country(ies).
- Obtaining all appropriate host country permissions to conduct research (e.g., institutional, governmental or ministerial, IRB, local, or tribal).
- Ensuring that the consent process and consent document are appropriate for the language(s) of the subjects and the subject population, and that arrangements are made to be able to communicate with subjects throughout the study (e.g., to ask and answer questions).
- Ensuring that the following activities will occur:
- Initial review, continuing review, and review of modifications.
- Post-approval monitoring of the conduct of the research in accordance with the plan approved by the IRB.
- Handling of complaints, noncompliance and unanticipated problems involving risk to subjects or others.
- Not relying upon an IRB or EC that does not have policies and procedures for the activities listed above.
- Ensuring that reportable information such as complaints, noncompliance, protocol deviations and unanticipated problems involving risks to participants or other are communicated to the IRB.
- Notifying the IRB promptly if a change in research activities alters the performance site's engagement in the research (e.g., performance site "not engaged" begins to obtain consent of research participants, etc.).
- Ensuring that there are mechanisms for communicating with the IRB when they are conducting the research in other countries.

Consent Documents

The informed consent documents must be appropriate for and in a language understandable to the proposed subjects. The IRB will review the proposed document and a back translation of the exact content contained in the foreign language informed consent document, with the credentials of the translator detailed in the *IRB application* or *IRB Protocol Change Form*. All documents, including verification of the back translation, are maintained in the IRB file.

General Data Protection Regulation (GDBP)

CMU investigators conducting research in one of the 27 member countries of the European Union (EU), or Iceland, Liechtenstein, and Norway, must be aware that research subjects within those countries of have additional rights under the General Data Protection Regulations (GDPR) including the right to withdraw their consent to participate as easily as they gave their consent initially. They may request that data about them collected in the course of research be erased and the investigators must honor the request or explain why the request cannot be honored. *Policy 3-55* is to ensure CMU is compliance with EU regulations.

Monitoring of Approved International Research

The IRB is responsible for the ongoing review of international research conducted under its jurisdiction through the continuing review process in accordance with all applicable federal regulations.

When the IRB and a local ethics committee are both involved in the review of research, there is a plan for coordination and communication with the local IRB/ECs.

The IRB requires documentation of regular correspondence between the investigator and the foreign institution or site and may require verification from sources other than the investigator that there have been no changes made to the research since its last review.

Export Control Considerations

Traveling to, collaborating with, or conducting research with entities or individuals in sanctioned countries may be subjected to export control-specific regulations overseen by several federal agencies and may trigger further review. These regulations have identified several countries under heavy embargo or sanctions via the Office of Foreign Assets Control (OFAC). Investigators and their teams should only travel to, collaborate with, conduct research activities with, or export or import any items to or from embargoed countries after consulting with *Export Control staff in the Office of Research Compliance*. Submitting the *Export Control Form* assists the Export Staff in determining if additional action is required or if the activity may proceed.

Note that investigators need to be aware that taking electronic devices such as laptops, tablets and cell phone, and associated software out of the US may be subject to export and re-import regulations of the United States as well as the foreign country. The requirements vary by country being visited.

The Office of Research Compliance recommends that investigators contact the export control staff before submitting their proposal to the IRB if the research activities involve sanctioned countries or those that are under heightened risk.

Pilot Studies

Pilot studies serve various purposes such as determining whether a research project is feasible given available resources, and it is often not clear whether they meet the regulatory definition of research. Investigators should consult the IRB Chair or the DRC to assist in determining if the study is research.

A pilot study is defined as "A small-scale test of the methods and procedures to be used on a larger scale" (Porta, *Dictionary of Epidemiology*, 5th edition, 2008). The goal of pilot work is not to test hypotheses about the effects of an intervention, but rather, to assess the feasibility/acceptability of an approach to be used in a larger scale study. Thus, in a pilot study you are not answering the question "Does this intervention work?" Instead you are gathering information to help you answer "Can I do this?"

The goal of pilot studies is not to test hypotheses; thus, no inferential statistics should be proposed. Therefore, it is not necessary to provide power analyses for the proposed sample size of your pilot study. Instead, the proposed pilot study sample size should be based on practical considerations including participant flow, budgetary constraints, and the number of participants needed to reasonably evaluate feasibility goals.

Rather than focusing on feasibility and acceptability, too often, proposed pilot studies focus on inappropriate outcomes, such as determining "preliminary efficacy." The most *common misuses* of pilot studies include:

- Attempting to assess safety/tolerability of a treatment,
- Seeking to provide a preliminary test of the research hypothesis, and
- Estimating effect sizes for power calculations of the larger scale study.

Response Plan for Emergencies-Disasters Impacting the HRPP

This section establishes the process for initiating a response to an emergency/disaster situation impacting the HRPP or HRPP operations. Challenges to HRPP operations or the conduct of Human research may arise, for example from:

- Extreme weather events.
- Natural disasters.
- Man-made disasters.
- Infectious disease outbreaks.

HRPP leadership defers to designated institutional leadership and institution-wide disaster and emergency response planning and limits HRPP-specific disaster and emergency response planning only to those areas of operations or human research protections not otherwise covered by institution-level plans, *CMU Emergency Management Program, policy 3-60*. For studies being conducted in Detroit at DMC-Children's Hospital of Michigan (DMC-CHM), the Clinical Research Institute will follow the DMC-CHM institution-level plan/University Pediatrics plan and communicate with the Director of Research Compliance for assessment and appropriate response. The

HRPP evaluates its emergency response plans at least annually in accordance with the *Section II: Quality Assurance and Improvement*.

If an emergency/disaster has occurred, or there is an imminent possibility of an upcoming emergency/disaster, the Director of Research Compliance will assess the nature of the event and the appropriate response as follows:

1. Contact the IO and or designated institutional personnel responsible for institutional level emergency preparedness and determine whether there are new or revised institution level emergency preparedness plans relevant to the current or anticipated emergency. If yes, proceed in accordance with those plans and determine whether further contact or notification of the human research community is necessary.
2. Assess whether the emergency/disaster could impact HRPP operations.
    a. If the current or anticipated emergency/disaster will prevent any upcoming IRB meetings from properly convening in-person, and an in-person meeting was planned, determine whether the meeting can be conducted virtually or via teleconference. If yes, work with IRB members and staff to arrange for a virtual meeting as per Section VII: IRB Review Process. If a virtual meeting is also not feasible under the circumstances caused by the emergency/disaster, determine whether to cancel or reschedule the meeting(s). If currently approved Human Research has or will expire prior to IRB review due to the IRB meeting cancelation/rescheduling, treat as expiration of IRB Approval.
    b. If IRB staff will be unable to complete their protocol processing and review responsibilities during the emergency/disaster, or if capacity will be limited for a period of time work with the staff to use any available capacity to prioritize protocol processing, pre-review, and review of continuing review submissions. If currently approved Human Research has or will expire prior to IRB review due to IRB office capacity limitations treat as expiration of IRB Approval. Notify the research community of the IRB Office's limited capacity to process and review submissions. When the emergency/disaster no longer presents a limitation to IRB Office functions, notify the IRB members and staff and research community that normal business operations have resumed.
    c. If impact to local HRPP operations will be extensive or long-lasting, determine whether reliance on an external IRB(s) is required. If reliance on one or more external IRBs is required and the necessary reliance agreements are not currently in place, work with the IO or designee to identify appropriate candidates for external IRB reliance and follow Section IX: Multi-site & Collaborative Research to establishing the appropriate authorization agreements.
    d. If data or records (paper or electronic) are unavailable during the current or anticipated emergency/disaster, consult with local IT support and or electronic system vendors to implement alternative procedures to access data/backup data.

3. Assess whether the emergency/disaster could necessitate additional flexibility in IRB review processes. If yes, review additional considerations with the IRB Chair(s) and staff in advance of upcoming IRB meetings. Communicate to IRB Members (including Designated Reviewers performing non-committee reviews) that the additional considerations may be incorporated into IRB reviews where appropriate to maximize regulatory flexibility while continuing to assure research subject safety during the emergency/disaster. Determine whether additional communications to the research community are necessary to inform investigators of any additional measures the IRB will take to maximize regulatory flexibility during the emergency/disaster and notify the community as appropriate.
4. Assess whether the emergency/disaster could impact some or all investigators' ability to conduct Human Research. If yes, notify the research community of the need for protocol-specific emergency/disaster risk mitigation planning. Provide investigators with guidance as needed. If the emergency/disaster could impact clinical care standards which could in turn impact research, develop guidance for researchers that clarify what does and does not require IRB review (e.g., screening procedures mandated by the health care system in which a clinical trial is being conducted). When the emergency/disaster no longer presents a limitation to Human Research activities, notify the research community that normal business operations have resumed.
5. Evaluate whether the nature of the emergency/disaster may pose additional threats or risk to specific aspects of the institutions research activities or facilities. (For example, man-made disasters, industrial accidents, or terrorist threats could potentially impact some chemical, biological, or radiologic facilities to a greater extent than other facilities.) If yes, and if broader institution-level emergency/disaster preparedness measures do not already address these specific work with the appropriate institutional leadership to escalate and address any additional threats or risks.

Section 27: Special Topics- Federal Agencies

Department of Defense

Research sponsored by the Department of Defense (DOD) involving collaboration with DOD or involving DOD facilities or personnel (military or civilian), is subject to additional requirements including special protections for research participants, as well as additional review and reporting requirements for investigators and IRBs. Investigators should review these requirements when planning a DoD-supported research project as they may add a significant amount of time to the review and approval process of research.

The research needs to be conducted in compliance with part 219 of title 32 CFR, part 980 of title 10 USC, applicable parts of title 21 CFR (50, 56, 312, 600, 812), DoD Instruction 3216.02, DoD Directive 3210.07, and applicable additional requirements from respective DOD component(s). The focus of this guidance document is on requirements outlined in DoD Instruction 3216.02 (DODI 3216.02), *Protection of Human Subjects and Adherence to Ethical Standards in DOD-Supported Research* (April 15, 2020)

Each DOD Component (e.g., Army, Navy, Air Force) may have additional requirements beyond those included in this guidance document. Principal investigators are advised to check with their sponsoring Component program manager about any additional requirements.

It is the responsibility of the PI to ensure compliance with DOD requirements for human subject protection. IRB staff, chairs and members will use these SOPs, DOD 3216.02, and any relevant DOD component-specific instructions or materials to guide the IRB review and oversight of DOD research.

DOD components include, but may not be limited to

Navy	Amy	Air Force
Office of Naval Research	US Army Corps of Engineers	Air Force Academy
Naval Academy	Military Academy (West Point)	Coast Guard
US Naval Observatory	National Guard	Coast Guard Academy
Marines	Missile Defense Agency	National War College
Defense Advanced Research Projects Agency (DARPA)	National Geospatical-Intelligence Agency	Pentagon Force Protection Agency
Defense Intelligence Agency	National Security Agency	Tricare Health System

Key DoD Standards and Requirements

Single IRB Requirement

The DOD requires the use of a single institutional review board (IRB) in accordance with Section 219.114 of Title 32, CFR. If a DOD institution believes that the research is not subject to the provision listed in Section 219.114(b) of Title 32, CFR, the applicable DOD Component Office of Human Research Protections (COHRP) may determine and document, in accordance with Section 219.114(b)(2)(ii) of Title 32, CFR, that use of a single IRB is not appropriate for the particular context of the proposed research.

Human Subject Research DOD Special Requirements

Human research must comply with DOD requirements when:

- The research is funded by a DOD Component, including cases where CMU is the recipient of a subaward from the direct recipient of DOD funds, or
- The research involves cooperation, collaboration or other type of agreement with a DOD Component, or
- The research uses property, facilities, or assets of a DOD Component, or
- The participant population will intentionally include personnel (military and/or civilian) from a DOD Component. (DOD requirements do not apply when DOD personnel incidentally participate in research where they are not the intended research population or where the project is not DoD-supported).

DOD Human Research Protections Office (HRPO) Administrative Review

The HRPO for the sponsoring component must perform an administrative review of the research before activities with research participants may begin. The review involves confirmation that CMU IRB review and approval of the proposed research are in compliance with DOD requirements for the protection of research participants. If research will be conducted in a foreign country, the administrative review will also ensure compliance with any applicable laws and requirements and cultural sensitivities of a foreign country. While the HRPO review is not an IRB review, the HRPO may require changes to the research prior to the start of the research. The Principal Investigator is responsible for submitting the information required by the sponsoring Component.

Minimal Risk

The definition of minimal risk based on the phrase *"ordinarily encountered in daily life or during the performance of routine physical or physiological examination or tests"* may not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life, such as those:

- Encountered by Service members, law enforcement, or first responders while on duty.

- Resulting from or associated with high-risk behaviors or pursuits.
- Experienced by individuals whose medical conditions involve frequent tests or constant pain.

Training Requirements

DOD requires that key personnel complete human research protections training. There might be specific DOD educational requirements or certification required by different DOD components. CMU initial and continuing education requirement for the Human Subjects Protection training as outlined in this manual meets the requirements for many DOD Components. Investigators are responsible for ensuring that all study team members engaged in the conduct of research complete CMU required CITI training.

Scientific Review

The IRB must consider the scientific merit of the research during their review. The IRB may rely on outside experts to provide an evaluation of scientific merit. Scientific review must demonstrate that the research uses procedures consistent with sound research design and is likely to yield the expected results and should include the assessment of the following elements:

- Significance of the research question;
- Scientific approach;
- Research team qualifications; and
- Facilities and resources available.

The name and qualification of the reviewer(s) should be included as part of the review.

Appointment of a Research Monitor

When DOD research involves **more than minimal risk**, the IRB **will** require and approve an independent research monitor by name. When research involves no more than minimal risk, an investigator may identify a research monitor or the IRB or IO may appoint a monitor. There may be more than one research monitor (e.g. if different skills or experience are needed). The monitor may be an ombudsman or a member of the data safety monitoring board.

The IRB must approve a written summary of the monitors' duties, authorities, and responsibilities and the IRB or a HRPP official shall communicate with research monitors to confirm their duties, authorities, and responsibilities.

The duties of the research monitor are determined based on specific risks or concerns about the research. The monitor:

- May perform oversight functions (e.g., observe recruitment, enrollment procedures, and the consent process, oversee study interventions and interactions, review monitoring plans and reports of unanticipated problems

involving risks to participants or others, oversee data matching, data collection and analysis).
- May discuss the research protocol with researchers, interview human subjects, and consult with others outside of the study.
- The research monitor has the authority to stop a research study in progress, remove individual subjects from the study, and to take whatever steps are necessary to protect the safety and well-being of participants until the IRB can assess the monitor's report.
- Research monitors are obligated to promptly report their observations and findings to the IRB or other designated official.

DOD Approval of Surveys/Interviews

Research involving surveys or interviews with DOD personnel (military or civilian) or their families may require DOD approval after the research protocol is reviewed and approved by the IRB. When a survey crosses DOD Components, additional review is required. The DOD Component program manager can confirm any additional review requirements and the timing of the review (before or after IRB review). Documentation of this review must be provided to the IRB.

International Research

In its review of research conducted outside of the United States, the IRB must confirm that all national laws and requirements of the foreign country have been met and consider the cultural sensitivities in the setting where the research will take place. The investigator must:

- Obtain permission to conduct research in that country by certification or local ethics review; and
- Follow all local laws, regulations, customs and practices.

Collaborations

Collaborating institutions in multi-site research must hold a federalwide assurance. When any institution relies upon another institution's IRB for DOD research, there must be a written agreement defining the responsibilities and authorities of each organization in complying with the terms of each institution's Federal assurance and DoDD 3216.02.

When conducting multi-site or collaborative research, a formal agreement between organizations is required to specify the roles and responsibilities of each party.

Civilian researchers attempting to access military subjects should seek collaboration with a military researcher familiar with service-specific requirements.

Prohibited Research

Research with detainees or prisoners of war, except research with investigational new drugs or devices when the purpose is for diagnosis or treatment of a medical condition in a patient, with their informed consent, and where such treatment would also be offered to US military service members at the same location and with the same medical condition consistent with established medical practice.

- DOD Instruction 2310.01E defines a detainee as: "Any individual captured by, or transferred to the custody or control of, DOD personnel pursuant to the law of war. This does not include persons being held solely for law enforcement purposes, except where the United States is the occupying power. Detainees who are U.S. citizens or U.S.
- Classified human subjects research: CMU *does not* conduct classified research.
- Human testing of chemical or biological agents, except for certain prophylactic, protective or peaceful purposes.

Experimental Subjects

10 USC 980 provides a special definition for experimental subjects as those included in "an activity, for research purposes, where there is intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction." Research involving a human being as an experimental subject is a subset of research involving human participants.

Limitations on Waivers of Informed Consent and Consent by LARs

The Common Rule identifies conditions where an IRB may waive consent for DOD-conducted and DOD-supported research involving humans as research participants.

However, the requirement to obtain consent cannot be waived for any research using DOD funds and meeting the definition of research involving a human being as an experimental subject per the 10 USC 980 statute. This places limitations on research involving deception, decisionally-impaired individuals, or research being conducted under emergency conditions where the participant may not be able to provide consent.

10 USC 980 statute only applies to certain intervention studies. It does not apply to retrospective research involving analysis of data or specimens, observational studies, blood draws, or tissue collection, and does NOT apply to screening of records to identify possible research participants. The IRB may grant a waiver of consent for such activities.

The Secretary of Defense may waive the requirements for consent when *all* of the following are met:

- The research is necessarily to advance the development of a medical product for the Military Services.
- The research may directly benefit the individual experimental subject.
- The research is conducted in compliance with all other applicable laws and

regulations.

Vulnerable Populations

DOD requires that the protection of Common Rule Subpart B (Pregnant Women/Fetuses), C (Prisoners), and D (Children) be applied to the research it supports. The DOD (and the IRB) considers the need for similar safeguards for other vulnerable populations such as those with cognitive impairment, mental illness, physical disability or any other circumstance that might require special protections.

- Non-exempt research involving **pregnant women, fetuses, or neonates** as subjects must meet the requirements of Subpart B of the Common Rule, with the following modifications:
    - The applicability of Subpart B is limited to non-exempt research involving: Pregnant women as human subjects involved in research that is more than minimal risk and that includes interventions or invasive procedures to the woman or the fetus.
    - Involving fetuses or neonates as subjects.
    - For purposes of applying Subpart B, the phrase "biomedical knowledge" will be
    - replaced with "generalizable knowledge."
    - Fetal research must comply with the US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g.

- Research involving **prisoners** as subjects must meet the requirements of Subpart C of the Common Rule, with two additional categories permissible:
    - Epidemiological research that meets the waiver criteria in accordance with Pages 36929-36931 of Volume 68, Federal Register, may be approved in accordance with the applicable requirements of Subpart C of Part 46 of Title 45, CFR, DoD requirements, and other applicable requirements.
    - Human subjects research that would otherwise meet exemption criteria may be conducted but must first be approved by an IRB and must meet the requirements in Subpart C of Part 46 of Title 45, CFR, DoD requirements, and other applicable requirements.

- When a previously enrolled **participant becomes a prisoner** and the relevant research protocol was not reviewed and approved by the IRB in accordance with Subpart C of 45 CFR 46, the principal investigator must promptly notify the IRB. For DOD supported research, the non-DOD institution must notify the HRPO and other federal agencies, if required.
    - This type of request for change in the research protocol cannot be reviewed and approved by expedited review. The research does not have to meet one of the six allowable DoD categories for research involving prisoners.

    - A convened IRB must determine if the participant can continue and be concurred by the Director of Research Compliance in consultation with the IO.
- This approval is limited to the individual prisoner-subject and does not allow recruitment of prisoners as participants. Research involving **Children** as subjects must meet the requirements of Subpart D of the Common Rule, including that:
    - The exemption for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

DOD Affiliated Personnel

- DOD Affiliated Personnel means service members, reserve service members, National Guard members, DOD civilians, and DOD contractors. Service members and all Reserve Component and National Guard members in a federal duty status are considered for purposes of this issuance, to be adults. If a service member, reserve component or National Guard member in federal duty status, student at a Service Academy, or trainee is under 18 years of age, the IRB must carefully consider the research recruitment process and the necessity of including such member as a human subject.
- If the research involves DOD-affiliated personnel as subjects and if the research includes any risks to their fitness for duty (e.g. health, availability to perform job, data breach), the informed consent document must inform DOD-affiliated personnel about these risks and that they should seek command or Component guidance before participating.
- If the research involves DOD-affiliated personnel, the key investigator must receive command or Component approval to execute the research.
- Military and civilian supervisors, officers, and others in the chain of command are prohibited from influencing their subordinates to participate in research.
- Military and civilian supervisors, officers, and others in the chain of command must not be present at any research participant recruitment sessions or during the consent process for DOD-affiliated personnel. Excluded supervisors or those in the chain of command may participate in separate HSR recruitment sessions, if applicable.
- For greater than minimal risk research and where recruitment is conducted in a group setting, the IRB must appoint an ombudsman person. The ombudsperson:
    - Must not have a conflict of interest with the research or be a part of the research team.
    - Must be present during the research recruitment, monitoring that the recruitment and informed consent explain that participation is voluntary and that the information provided about the research is consistent with the IRB-approved script and materials, including digitally provided materials.

- Should be available to address DoD-affiliated personnel's concerns about participation.

Limitation on Compensation

Compensation to DOD-affiliated personnel for participation in research while on duty is prohibited in accordance with Title 5, U.S.C., with particular reference to Subparts G and H, with some exceptions for purposes consistent with Section 30 of Title 24, U.S.C.

Research Involving Large Scale Genomic Data (LSGD) Collection

DOD-conducted or DOD-supported research involving LSGD collected on DOD-affiliated personnel, or for which research the DOD provides assistance, is subject to additional requirements.

Certificate of Confidentiality (COC)

A DOD institution conducting human subjects research or non-DOD institution conducting human subjects research with DoD support may request a CoC pursuant to Section 241 of Title 42, U.S.C. All studies involving LSGD collected on DOD-affiliated personnel will apply an HHS CoC.

Other DOD-Specific Requirements

Reporting Requirements

The following must be promptly reported to the HRPO (generally within 30 days of the event):

- IRB-approved changes to research that involve changes to key investigators or institutions; decreased benefit or increased risk to subjects in greater than minimal risk research as defined in Part 219 of Title 32; addition of vulnerable populations, or DOD-affiliated personnel as subjects.
- Transfer of research oversight to a different IRB.
- Notification by any federal body, State agency, official governing body of a Native American or Alaskan native tribe, other entity, or foreign government that the nonDOD institution's DOD-supported research is under investigation.
- Any unanticipated problems involving risks to subjects or others, suspension or termination of IRB approval, or any serious or continuing noncompliance pertaining to DOD-supported research.
- The results of the IRB's continuing review, if required.
- Change in status when a previously enrolled human subject becomes pregnant, or when the researcher learns that a previously enrolled human subject is pregnant, and the protocol was not reviewed and approved by the IRB in accordance with Subpart B of 45 CFR 46.

- Change in status when a previously enrolled human subject becomes a prisoner, and the protocol was not reviewed and approved by the IRB in accordance with Subpart C of 45 CFR 46.
- A DOD-supported study's closure.

Recordkeeping

Consistent with CMU policy, research records must be maintained for at least 3 years after the completion of the research. The DOD may require that research records be transferred to the DOD Component rather than being retained by CMU.

Records that document compliance or noncompliance with DOD regulations must be made accessible for inspection and copying by authorized representatives of the DOD at reasonable times and in a reasonable manner as determined by the supporting DOD Component.

Civilian researchers attempting to access military subjects should seek collaboration with a military researcher familiar with service-specific requirements.

Department of Education

Research conducted or supported by the Department of Education (ED) is reviewed following the Common Rule since the ED is a signatory to the Common Rule with equivalent regulations under 34 CFR 97. The Common Rule is described throughout this manual.

A variation and additional requirement are:

- ED has not adopted Subpart B (Pregnant Women, Fetuses, or Neonates) or Subpart C (Prisoners) of the Common Rule.
- ED requires reporting of **alleged**
    - unanticipated problems involving risks to subjects or others; and,
    - serious or continuing noncompliance with the Common Rule or Subpart D (protection of children in research).

If the research is funded or sponsored by Department of Education, mandated reports outlined in *Section 18, Reporting to Regulatory Agencies and Institutional Officials* are submitted to ED instead of OHRP. For incident reporting, CMU IRB will use the *ED's Protection of Human Subjects in Research* website as the guide for required information necessary.

Family Educational Rights and Privacy Act

The Family Educational Rights and Privacy Act (FERPA) is a federal law regarding the privacy of student records and the obligations of the institution, primarily in the areas of release of the records and the access provided to these records. Any educational institution that receives funds under any program administered by the U.S. Secretary of

Education is bound by FERPA requirements. Institutions that fail to comply with FERPA may have funds administered by the Secretary of Education withheld.

Student education records are considered confidential and may not be released to third parties without written consent from the student unless disclosure is permitted through one of the FERPA signed consent exceptions. However, FERPA allows schools to disclose personally identifiable information from an education record of a student without consent if the disclosure is to organizations conducting studies for, or on behalf of, educational agencies or institutions to:

- Develop, validate, or administer predictive tests.
- Administer student aid programs.
- Improve instruction. [34 CFR 99.31(a)(6)]

Education records are defined as records, files, documents and other materials that contain information directly related to a student and are maintained by an education agency or institution or by a party acting for such agency or institution. Education records take many forms, including paper and electronics. Examples of education records are transcripts, class rosters, email containing information about a student, computer screen displaying student information.

"Directory" information may be disclosed by schools to researchers without student consent. Directory information could be name, major, campus, degrees and awards, sports and athletic information. Student can request that Directory information be blocked from distribution.

School officials may not disclose a student's educational record, nor permit inspections of these records without written permission unless such action is covered by exceptions permitted by FERPA. Researchers must obtain signed and dated permission from the parent or eligible student for the release of their records. The written release must:

- Specify the records that may be disclosed,
- State the purpose of the disclosure, and
- Identify the party or class of partied to whom the disclosure may be made.

Note that this may require researchers to obtain signatures from subjects in instances where human subjects research regulations do not require signatures. In these cases, researchers must comply with the more restrictive FERPA regulations. The IRB does NOT have the authority to waive any part of this requirement. When signed releases are obtained to access student records, they should be stored indefinitely.

When FERPA applies, investigators must provide the IRB with information describing how they will ensure compliance with the rule. A letter of support or other documentation from the school supporting the conduct of the research should be provided. The IRB will review the information provided to verify compliance, including verification that permission for the use of the records will be obtained or that it is not required under an allowed use or exception.

Protection of Pupil Rights Amendment

The Protection of Pupil Rights Amendment (PPRA) affords parents of elementary and secondary students certain rights regarding the conduct of survey, collection and use of information for marketing purposes, and certain physical exams. PPRA applies to the programs and activities of a state educational agency (SEA), local educational agency (LEA), and any other recipient of ED funds. These rights transfer from parents to students when they reach the age of 18 or are an emancipated minor. This section is not intended to address PPRA as a whole; rather it addresses PPRA requirements as they most commonly relate to research.

Definitions:

Instructional Material: Means instructional content that is provided to a student, regardless of its format, including printed or representational materials, audio-visual materials, and materials in electronic or digital formats (such as materials accessible through the Internet). The term does not include academic tests or academic assessments.
Invasive Physical Examination: Means any medical examination that involves the exposure of private body parts, or any act during such examination that includes incision, insertion, or injection into the body, but does not include a hearing, vision, or scoliosis screening.
Personal Information: Means individually identifiable information including: (1) a student's or parent's first and last name; (2) a home or other physical address (including a street name and the name of a city or town); (3) a telephone number; or, (4) a Social Security Number.
Research or Experimentation Program or Project: Means any program or project in any program that is designed to explore or develop new or unproven teaching methods or techniques.

Rights under PPRA

When **research is funded by ED**, no student can be required to submit **without prior consent** to a survey that concerns one or more of the following protected areas:

- Political affiliations or beliefs of the student or the student's parent.
- Mental and psychological problems of the student or his or her family.
  Sex behavior and attitudes.
- Illegal, anti-social, self-incriminating, and demeaning behavior.
- Critical appraisals of other individuals with whom the student has close family relationships.
- Legally recognized privileged and analogous relationships, such as those of lawyers, physicians, and ministers.
- Religious practices, affiliations, or beliefs of the student or student's parent.
- Income, other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under a program.

Parents have the right to **receive notice and an opportunity to opt a student out** of:

- Any other survey that concerns any of the above protected areas, **regardless of funding**.
- Any non-emergency, invasive physical exam or screening required as a condition of attendance, administered by the school or its agent, that is not necessary to protect the health and safety of a student, except for hearing, vision, or scoliosis screenings, or any physical exam or screening permitted or required under state law.
- Activities involving collection, disclosure, or use of personal information collected from students for marketing or to sell or otherwise distribute the information to others. (This does not apply to the collection, disclosure, or use of personal information collected from students for the exclusive purpose of developing, evaluating, or providing educational products or services for, or to, students or educational institutions).

Parents also have the **right to inspect** upon request and before administration or use:

- Surveys that concern any of the protected areas and surveys created by third parties.
- Instruments used to collect personal information from students for any of the above marketing, sales, or other distribution purposes.
- Any instructional material used as part of the educational curriculum for the student.
- Instructional material, including teachers' manuals, films, tapes, or other supplementary instructional material, which will be used in conjunction with any research or experimentation program or project.

Procedures

When PPRA applies, investigators should review the school's PPRA policies and must provide the IRB with information describing how they will ensure compliance with the rule and the school's policies. A letter of support or other documentation from the school supporting the conduct of the research and its compliance with PPRA should be provided. The IRB will review the information provided to verify compliance.

Department of Energy

Research conducted or supported by the Department of Energy (DOE) is reviewed following the Common Rule since the DOE is a signatory to the Common Rule with equivalent regulations under 10 CFR Part 745. DOE has published additional requirements for research it supports or conducts as describe in DOE Order 443.1C. Protection of Human Research Subjects. The Common Rule is described throughout this manual.

The requirements outlined below apply to all research conducted with DOE funding, at DOE institutions (regardless of funding source), or by DOE or DOE contractor personnel (regardless of funding source or location conducted), whether done domestically or in an international environment, including classified and proprietary research.

For additional guidance see: https://science.osti.gov/ber/human-subjects/Regulations-and-Requirments/DOE-Specific-Requirements

Special Considerations for DOE-supported Research

Expansion of the Definition of Research with Human Subjects for Research Involving Intentional Modification of the Human Environment DOE has expanded the definition of human subjects research found at 45 CFR 46 as follows:

- Research involving human participants also includes studies that involve the intentional modification of the human environment; generalizable includes the study of tracer chemicals, particles, and/or other materials to characterize airflow.
- Generalizable also includes studies in occupied homes or offices that:
    - Manipulate the environment to achieve research aims.
    - Test new materials
    - Involve collecting information on occupants' views of appliances, materials, or devices installed in their homes or their energy-saving behaviors through surveys and focus groups.

IRB Review of Research Involving Expanded Definition states even if the IRB does not view a project as meeting the literal definition of human subjects research as defined in 45 CFR Part 46, DOE requires an initial review of the application and supporting materials by the IRB to determine whether the individuals included in the research will be properly informed and protected. The IRB must consider if additional protections are required for research involving DOE employees and contractors.

- The chair decides the level of review.
- The IRB assesses risks associated with the research and whether the individuals to be included in the research will be properly informed and protected.
- The chair sends a letter to the researcher indicating that the research has been approved in accordance with DOE expectations and will be monitored and tracked by the IRB.

Research involving multiple DOE sites (e.g., members of the research team from more than one DOE site and/or data or human subjects from more than one DOE site) must be reviewed and approved by one of the Central DOE IRBs prior to initiation, or if authorized by the DOE and/or NNSA HSP Program Manager, other appropriate IRB of record. In all cases, an IRB Authorization Agreement (IAA) or Memorandum of Understanding (MOU) must be in place between the organization(s) conducting the HSR and the organization responsible for IRB review.

Research that uses social media data must be submitted to the appropriate IRB for human participant research review and determination.

Research involving Personally Identifiable Information (PII) is any information collected or maintained about an individual, including but not limited to, education, financial transactions, medical history, and criminal or employment history, and information that can be used to distinguish or trace an individual's identity, such as his/her name, Social Security number, date and place of birth, mother's maiden name, biometric data, and any other personal information that is linked or linkable to a specific individual.

Personally identifiable information collected and/or used during human participant research projects must be protected in accordance with the requirements of DOE Order 206.1, Department of Energy Privacy Program.

For research that involves PII, investigators must complete and comply with the requirements outlined in "*Checklist – Reviewing Protocols that Use PII*" developed in coordination with the National Nuclear Security Administration. The IRB must verify compliance with those requirements in its review of the project.

DOE and DOE site employees and contractors are considered vulnerable subjects when participating in research and additional care must be taken to ensure their participation is truly voluntary (e.g., by ensuring they do not report to members of the research team), and that data collected about them is kept confidential.

Informed consent documents must contain the identity of the sponsoring agency unless the sponsor requests that it not be done because doing so could compromise intelligence sources or methods; the research involves no more than minimal risk to participants; and the IRB determines that by not disclosing the identity, the investigators will not adversely affect the participants.

The DOE Human Subjects Protection Manager (HSP) should be notified within 48 hours of any:

- Significant adverse events, unanticipated problems, or complaints about the research, with a description of any corrective actions taken or to be taken.
- Study suspensions or terminations of IRB approval of research with a description of any corrective actions taken or to be taken.
- Significant noncompliance with HRPP procedures or other requirements with a description of any corrective actions taken or to be taken.

The HSP should be notified immediately (i.e., upon discovery):

- When there is a breach of PII in printed or electronic form. The incident must also be reported to the DOE-Cyber Incident Response Capability in accordance with the requirements of DOE O 206.1.

    - Within 48 hours the DOE or NNSA HSP Program Manager must also be notified of any corrective actions taken and consulted regarding the plan for any remaining corrective actions.
- Upon learning of a serious adverse event. The HSP Program Manager(s) shall also be informed of any corrective actions taken and consulted regarding the plan for any remaining corrective actions.

The HSP should be notified prior to initiation of the HSR portion of a new project, even if it meets the regulatory definition of exempt HSR that involves:

- An institution without an established IRB.
- A foreign country.
- Potential for significant controversy (e.g., negative press or reaction from stakeholder or oversight groups).
- Research subjects in a protected class (prisoners, children, individuals with impaired decision-making, or DOE/NNSA federal or DOE/NNSA contractor employees as human subjects, who may be more vulnerable to coercion and undue influence to participate) that are outside of the reviewing IRB's typical range/scope; or
- The generation or use of classified information.

Environmental Protection Agency

Research conducted or supported by the Environmental Protection Agency (EPA) is reviewed following the Common Rule since the EPA is a signatory to the Common Rule with equivalent regulations under 40 CFR 26. EPA has published additional requirements for research it supports or conducts and for research intended for submission to the EPA as describe in EPA Order 1000.17A. The Common Rule is described throughout this manual.

For research conducted or sponsored by the EPA, IRB determinations and approval must be submitted to the EPA Human Subjects Research Review Official (HSRRO) for final review and approval before research may begin.

Special Considerations for EPA-supported Research

Prohibited Research involves the intentional exposure of pregnant women, nursing women, or children to any substance regulated by the EPA is prohibited. (40 CFR 26.203). Such research will not be approved by the IRB.

Intentional Exposure Research involves the intentional exposure of adults (except pregnant or nursing women) which must comply with 40 CFR 26.

Observational research (i.e., that does not involve intentional exposure) of pregnant women and fetuses is subject to the requirements of 40 CFR 26 subpart C and 45 CFR

46 subpart B (the requirements for research of pregnant women or fetuses prescribed by HHS).
Observational research (i.e., that does not involve intentional exposure) of children is subject to the requirements of 40 CFR 26 subpart D and 45 CFR 46 subpart D.

- IRBs may approve observational research involving children only if it finds that no greater than minimal risk to children is presented and only if the IRBs find that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.
- IRBs may approve research involving an intervention or procedure that presents more than minimal risk to children, only if it finds and documents that:
    - The intervention or procedure holds out the prospect of direct benefit to the individual subject or is likely to contribute to the subject's well-being;
    - 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 approaches; **and**
    - Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

Research Intended for Submission to the EPA

Similar to the requirements for EPA-supported research, research to be submitted to the EPA (but not conducted or supported by any federal agency that has regulations for protecting human research subjects, 40 CFR 26 subpart K and subpart L) is subject to the same requirements as above:

- Prohibited research involving the intentional exposure of pregnant women, nursing women, or children to any substance regulated by the EPA is prohibited. (40 CFR 26.203) Such research will not be approved by the IRB.
- Intentional Exposure Research involving the intentional exposure of adults (except pregnant or nursing women) must comply with 40 CFR 26.

Department of Justice

Research conducted or supported by the Department of Justice (DOJ) is reviewed following the Common Rule since the DOJ is a signatory to the Common Rule with equivalent regulations under 28 CFR 46. DOJ has chosen not to adopt Subparts B, C and D. The National Institute of Justice (NIJ) serves as DOJ's research arm. The Common Rule is described throughout this manual.

This section summarizes additional requirements for the conduct and IRB review of human subjects research conducted or supported by DOJ/NIJ (including funding through grants, subgrants, contracts, subcontracts, cooperative agreements, and

interagency agreements) and human subjects research conducted in the Federal Bureau of Prisons.

National Institute of Justice

In addition to Common Rule requirements, research projects involving the NIJ must meet the requirements of 28 CFR 22 – Confidentiality of Identifiable Research and Statistical Information (CIPSEA). Researchers are responsible for consulting with their NIJ Program Officer to confirm that all NIJ requirements are met prior to beginning research. Among those requirements are the following:

- A Privacy Certificate must be approved by the NIJ Human Subjects Protection Officer, see NIJ Privacy Certificate Guidance;
- All investigators and research staff are required to sign Employee Confidentiality Statements, which are maintained by the responsible investigator;
- Informed Consent
  The informed consent document must include the following information:
    - The name of the funding agency;
    - A statement describing confidentiality of subject records
        - The subject must be informed that private, identifiable information will be kept confidential and will only be used for research and statistical purposes;
        - If due to sample size or some unique feature and the identity of the individual cannot be protected, the subject must be explicitly notified;
        - If the investigator intends to disclose any information, the participant needs to be explicitly informed what information would be disclosed, under what circumstances, and to whom. The participant must be informed of any risks that might result from this disclosure and must explicitly provide written consent prior to participating in the research;
        - Researchers are not required to report child abuse unless the subject signs another consent document to allow child abuse reporting.
- A copy of all data must be de-identified and sent to the National Archive of Criminal Justice, including copies of the informed consent document, data collection instruments, surveys, or other relevant research materials. See NIJ Guidance for Applicants and Awardees.

Bureau of Prisons

Research conducted with/in the Federal Bureau of Prisons is subject to the requirements of the Common Rule and for the protection of prisoners found in Subpart C. Additional unique regulatory requirements are outlined in 28 CFR 512. These unique requirements involve the following points:

- Research Proposal and Design.
- Subject Selection and Incentives.
- Investigator Requirements and Responsibilities.
- Confidentiality, Privacy, and Access to Records.
- Informed Consent.

Section 28: Student Research or Participation

Student Conducted Research

Human Subject Research and Course Projects

Learning how to conduct ethical human subjects research is an important part of a student's educational experience. Research activities that are designed as part of a course requirement for purposes of learning experience only and are **NOT** designed *to develop or contribute to generalizable knowledge* will generally **NOT** require IRB review and approval if all of the following conditions are true:

- Results of the research are viewed only by the course instructor for teaching purposes and discussed within the classroom for teaching and learning purposes.
- Results of the research are not made public through presentation (outside of the classroom) and are not published in conference proceedings, paper, or electronic format (e.g., cannot be made available on the internet, cannot be published in a journal, etc.).
- When appropriate, an informed consent process is in place.

Responsibility of Course Instructor

The course instructor is responsible for ensuring the protection of human subjects (including a process for obtaining voluntary informed consent from research subjects when appropriate), and for monitoring the students' progress.

When designing a project, students should be instructed on the ethical conduct of research and on the preparation of the IRB application when such is required. Instructors and students should:

- Understand the principles of the Belmont Report and their application.
- Develop appropriate consent documents.
- Plan appropriate strategies for recruitment.
- Identify and minimize potential risks to subjects or others.
- Assess the risk-benefit ratio for the project.
- Establish and maintain strict guidelines for protecting privacy and confidentiality.
- Allow sufficient time for IRB review, if applicable, and completion of the project.

During the IRB review, the following will be considered:

- Research procedures should be no more than minimal risk.
- Permissions are obtained from any facilities or organizations where research activities, including recruitment, will take place.
- Vulnerable populations are not targeted (e.g., children under age 18, prisoners, persons who are cognitively impaired, etc.).

- Data collected are recorded in such a manner that the subjects are not identifiable (images in videotapes and photographs and voices on audiotape are identifiable).

In making a determination of whether or not a class research project requires IRB review, the instructor is encouraged to contact the IRB Coordinator for assistance or to submit a for a determination following the procedures outlined in *Section 5 Human Subjects Research Determination*.

Individual Research Projects Conducted by Students

When students conduct, or participate as a research team member, in Human Subjects Research other than class work as described above, they must follow the standard procedures for research described throughout this manual, as applicable to the research.

Capstone, Theses, Dissertations, and similar activities must be independently submitted for IRB review. It is important to keep in mind that any human subjects research activity that will ultimately contribute to part or all of a thesis, dissertation, or other type of publication or presentation must go through the IRB review process prior to enrolling subjects and collecting data.

IRB review *cannot* occur after a study has begun. Furthermore, any Human Subjects Research project initiated without IRB review and approval is considered non-compliance and in violation of CMU's Human Subjects Research Policy. Students and advisors should contact the IRB Office with any questions.

Students should also check with their department, program advisor, and the Office of Research and Graduate Studies to determine if there are additional requirements to be met that are not covered in this document. When CMU students conduct, or participate as a research team member, in research at or with another organization, they must contact CMU IRB Coordinator to determine if review by the CMU IRB is required, or if a Reliance Agreement is needed, prior to engaging in the activity.

Students may not serve as PIs. They must have a faculty sponsor who fulfills the PI eligibility criteria and who will serve as PI and faculty advisor on the study.

Theses and Dissertations

It is important to keep in mind that these research activities are generally considered to meet the federal definition of Human Subjects Research and an IRB application must be submitted to the CMU IRB by the student-researcher's faculty advisor. A faculty member ultimately is responsible for the protection of the subjects, even if the student is the primary researcher and directing the project. Advisers assume the responsibility for students engaged in independent research. IRB review/approval cannot occur after a study has begun.

Research in K-12 Schools

Use of students maybe integral to a research protocol, in some research situations. This is particularly true of research related to teaching methods, curricula, as well as other areas related of teaching and learning. Special conditions are required be put in place to ensure the safety and welfare of student participants. Issues particular to students in grades K-12 include gaining access to school sites and obtaining parental consent and child assent for students under the age of majority at the study location.

An underlying principle of the regulations governing use of human subjects in research is that the subject's participation is voluntary and based upon full and accurate information. The student-teacher relationship raises the issue of volunteer participation. Students may volunteer to participate in the belief that doing so will place them in a favorable situation (e.g., better grade, good recommendation, employment possibilities), or that failure to participate will negatively affect their relationship with the investigator or teacher (e.g. lower grade, less favorable recommendation, being "uncooperative", and not part of the scientific community).

Care should be taken to eliminate or reduce the risk that undue influence of faculty/teachers or coercion affects student participation in research. The following guidelines are offered to assist faculty/teachers who engage in research projects in which students will be asked to be research subjects.

Site permission

K-12 school sites are autonomous institutions that retain the right to approve/reject any Human Subjects Research to be conducted at their site, in their facilities, and/or with their teachers, staff or students. Therefore, research in schools, requires site permission documentation. Each K-12 site may have different procedures for approving external research. It is the expectation of the IRB that researchers will contact the appropriate authority.

Depending on the specific site, permission may be granted by a superintendent, a principal, and/or by a committee at the district level for where they have their own external research review committees. If a district uses a committee to review research proposals, it is important to plan additional time into the approval process since the project will be reviewed by both the IRB and the school's review committee. If the school appropriate authority requires IRB approval before issuing its letter of support, please contact IRB Coordinator for assistance.

Engagement

If teachers or school staff are engaged in research activities taking place in their school or classroom, they must complete human subjects protection training and be listed as part of the project team. The IRB defines engagement based on involvement in any research activities including recruitment, consenting, data collection, data analysis, answering questions about the project, etc.

Teachers and school staff would NOT be engaged in research activities if they only facilitate the distributing of recruitment material and/or consent document. They could also assist in collecting any signed forms to be given to the investigators.

Use of instructional time for research purposes

Verify with the schools/districts/administrators if research activities will be allowed to take place during normal class time. The protocol should indicate whether the research will be presented in classrooms as part of the school/district standard curriculum, as this distinction will often affect the type of IRB review. When study participation of the student consumes a significant portion of a class sessions, this should have no impact or a positive impact on student learning. Coordinate study participation with the class teacher so the research activity does not negatively impact their instruction.

Program Evaluation

When the project involves program evaluation, the IRB protocol must clearly differentiate between the teaching program (which may be conducted regardless of the evaluation) and the evaluation procedures. Often, the evaluation procedures are what constitute “research” and are what require the approval of the IRB rather than the procedures conducted in the actual teaching program.

Student Participation

Solicitation of volunteer student subjects for research must be done in a non-coercive manner. To avoid undue influence, subjects should be recruited by a general announcement, central posting or announcement mechanism and should include a clearly written description of the project and a statement of the proposed student participation.

When extra credit is to be given to students who participate in research, students choosing not to participate in the research are to be given other options for extra credit, for example: short papers, special projects, book reports, and brief quizzes on additional readings, or completing a similar project. These projects should be comparable in terms of time, effort and educational benefit to participation as research subject to further reduce the potential risk of coercion. Alternatives offered to subjects need prior IRB approval.

The rationale for the study, the process of data collection, and the intent of the researcher could be provided after participation. This would be a teaching opportunity in the form of an "educational debriefing" so students understand what the objective of the research is.

Parental Consent/Child Assent

Parental permission is required for minors (under 18 years of age) to be included as research subjects. It is important to plan for an appropriate method to obtain consent from parents (i.e. send the study information and consent forms to parents for review, ensure clear understanding of research procedures, answer questions, etc.). If teachers or school staff is used to facilitate in the process of providing research material to parents (e.g., 'backpack mail' or through school email), the research's contact information should be included with the materials. Plan for a method for the collection consent form(s) from the parents that will not "engage" teachers or school staff.

Parental permission and assent procedures should be clear as to the activities that are considered research. For example, a program of instruction that is presented to the entire class in a conventional manner is not a research activity (even if it is novel) and parental permission forms should not imply that they are. Student interviews or questionnaires administered for research purposes are activities for which parental permission and assent are sought. Individual student performance data that are part of the instruction can be included as research data only with explicit permission and assent for this additional use.

Waiver or Alteration of Documentation of Parental Consent

Student may become unwitting participants if, for example, parent never receive the letter, don't read English, or are simply confused by the instructions. The IRB only approves "passive" procedure if the federal criteria for waiving informed consent are met.

The following are types of waiver or alterations to parental consent possible:

1. Waiver of parental consent: Parents are not provided information about the study and are not asked to provide permission.
2. Waiver of documented parental consent: Parents are informed of the research involving their child and provide consent, but their consent is not documented in any way.
3. Alteration of parental consent: Parents are informed of the research involving their child and provide consent in a method that does not include their signature (or by clicking a box).

Some examples for waiving or altering parental consent are:

- Research involving child abuse or neglect. In this example, gaining parental consent could put children in the research study at risk. Therefore, a waiver of parental consent could be appropriate.
- Research involving undocumented children. In this example, a signed consent document could put the child at risk of deportation. Therefore, a waiver of documented consent could be appropriate.
- Research involving a survey for children at a summer camp. In this example, it may not be practicable to gain parental consent and/or separate out surveys for children whose parents did not provide written consent. Therefore, the investigator could request an alteration of parental consent for an "opt-out"

option (i.e., parents could contact the investigator if they did not want their child to participate).

Note: A waiver of consent cannot be issued when research involves the collection of a child's educational records. Educational records are protected by law. In this case, a waiver of parental consent would compromise the rights of the research subject.

Use of Video or Audio Recording

Schools may place limitations on the use of video or audio recording in classrooms. If the research project is one where data are collected from a group or perhaps a videotape/audio recording of the group interaction, each student's consent is necessary for the use of that data in the research. If one student does not consent, the data may be used only if the non-consenting student's data can be effectively excluded. If a parent/participant has not agreed to be video recorded, then the researchers must make sure that these participants are out of the video shot range and/or that these persons are deleted from any video recordings collected during the research process. Subsequent use of video recordings must exclude participants who did not agree to be video or audio recorded. The video/audio recording procedure needs to be included as part of your description of the scope of research.

Additional Regulatory Requirements

Generally, researchers may not access classroom performance evaluations, grades, and/or information in a student's records without prior written permission from the student, regardless of the access a researcher may have in his/her academic role. FERPA protects student education records. For guidance on obtaining permission to access student records for research, CMU registrar is the campus FERPA official. Refer to *Section 26 Department of Education* for more FERPA information.

Research supported by the US Department of Education is subject to additional requirements and ethical standards. Their requirements may take precedent over OHRP Common Rule requirements. Refer to *Section 26 Department of Education* for more information.

The following regulations go beyond the basic IRB rules that may apply to research conducted in the K-12 setting.

***FERPA**:* Family Educational Rights and Privacy Act is a federal law that protects the privacy of personally identifiable information contained within a student's educational record. The IRB does not have the authority to waive written parental permission for research that falls under PPRA regulations. Refer to *Section 26 Department of Education* for more information.

PPRA: Protection of Pupil Rights Amendment is a federal law that affords certain rights to parents of minor students with regard to surveys that ask questions of a personal nature. Refer to *Section 26 Department of Education* for more information.

COPPA: Children's Online Privacy Protection Act administered by the Federal Trade Commission may apply to K-12 research conducted using online mechanisms. If minors will be recruited or possibly in the recruitment pool, parental permission must be addressed. Researchers are prohibited from collecting personal information from a child without posting notices about how the information will be used and without getting verifiable parental consent.

Students as Research Participants

An underlying principle of the regulations governing use of human subjects in research is that the subject's participation be voluntary and based upon full and accurate information. Students are a frequently accessed population in the social and behavioral sciences research; some students are studied directly in education-focused research and other students, particularly university students, are encouraged to participate in studies as part of their educational experience. When a researcher is also a student's instructor, the primary ethical concern is the instructor-student relationship. For example, a student may feel coerced into participating, believing that failure to participate will negatively impact their instructor-student relationship, their grade, and/or standing in class with fellow classmates.

Researchers Recruiting from Their Own Courses

The IRB recognizes, however, that in some research situations, use of one's own students is integral to the research. This is particularly true of research into teaching methods, curricula and other areas related to teaching and learning. In these situations special considerations should be made to recognize and reduce the potential for coercion.

Potential for Coercion

There are cases in which the research cannot be feasibly completed without recruiting students from a course. If the project has a reasonable change of yielding benefits, and the only feasible way to complete the study is to recruit in the instructor's course, the research may be permissible if the researcher is able to sufficiently reduce the potential for students to feel pressured to participate. The experience should be truly voluntary from the student perspective.

Reducing the Potential for Students to Experience Coercion

In the instances in which an instructor(s) recruits from their own class, researchers are expected to minimize the potential for students to feel pressured to participate. There are various strategies for minimizing the potential pressure to participate. One way that researchers can reduce the potential for perceived coercion is to design the study so that the instructor is blinded to the identity of the participants. If a researcher

designs a study this way, several points are crucial:

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

Course or Extra Credit

If course or extra credit is offered in exchange for participation, an alternate means of earning equivalent credit for an equivalent commitment of time and effort should be made available to all potential student subjects. These alternatives are to be outlined in your protocol so the IRB can be sure that students are not being coerced into becoming subjects. For example, the IRB is likely to view the choice between volunteering to fill out a short questionnaire or writing a five-page paper as coercive, since writing a five-page paper involves considerably more time, effort, and stress.

Recruitment

Researchers 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 should 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.

There are various ways students can be offered the opportunity to participate in research. For participation as part of a course requirement, Subjects Pools (e.g., SONA) is a means to offer multiple studies for a student to choose what to participate in. A comparable non-research alternative must be available as a choice.

Normal Educational Setting

Normal educational settings are not necessarily limited to a formal school setting. An educational setting encompasses any setting where one would go in order to have an educational experience. For example, a public school would certainly qualify, as would an after-school club or program, a Boy or Girl Scout meeting, 4H meeting or even a professional development seminar for school district personnel. Researchers must obtain permission to conduct the study at such a location.

In summary, due to the potential for undue influence, researchers generally should avoid recruiting participants from their own classes. If recruiting from their own class is the only practicable way to do a study, researchers are expected to design the research in

such a way that the potential for students to feel pressured is minimized.

Section 29: Transfer of Research Studies from Another IRB to CMU

This procedures in this section discuss the regulatory responsibilities of the CMU IRB and the original reviewing IRB when oversight of previously approved, ongoing clinical investigations or research projects under FDA's jurisdiction or subject to the regulations at 45 CFR 46 are transferred, from an IRB that originally reviewed the research, to the CMU IRB. Transfer of IRB oversight responsibility for a clinical investigation or research project must be accomplished in a way that assures continuous IRB oversight with no lapse in either IRB approval or the protection of human subjects, and with minimal disruption of research activities. The specific steps in the IRB transfer process may vary, depending on the reasons for the transfer, the parties involved, and the number and risk of the studies being transferred. The duration of the IRB transfer process may vary, depending on the speed at which the following steps can be completed.

Transfer Process

When transferring IRB review and oversight of clinical investigations or research projects to CMU, there must be a plan for the transfer process, documented in a written agreement between the original IRB's organization and CMU. The agreement should address how the IRBs should accomplish, and document as appropriate, the steps described in the subsequent subsections. Please note, this list is not meant to be all inclusive and additional actions may be necessary and/or appropriate.

Identify Studies Being Transferred

The original reviewing IRB and the CMU IRB must have a clear understanding of the studies being transferred to allow for effective planning. Several factors (e.g., the number of studies, the risk posed by the studies, and the circumstances leading to the transfer) may influence the transfer process. The written transfer agreement should identify the studies to be transferred.

Ensure the Availability and Retention of Pertinent Records

Before the CMU IRB accepts oversight of the transferred clinical investigations or research projects, it should obtain copies of pertinent IRB records in order to meet the review and ongoing oversight responsibilities once transferred. For example, the records should include documents such as the research protocol and significant amendments, the approved consent form(s), previous continuing review reports, the investigator's brochure (if applicable), reports of unanticipated problems involving risk to human subjects and others (UAPs), minutes of IRB meetings at which the research was reviewed (initial, continuing, amendments, UAPs, etc.), reports of IRB-conducted audits (if any) and relevant correspondence with the investigator, sponsor, and/or FDA/OHRP.

- Availability of pertinent IRB records.
  With concurrence of the sponsor, the original IRB should make the pertinent IRB records available to the CMU IRB by providing paper, or preferably, electronic

copies of the records. The sponsor's concurrence is necessary because, for example, the records may contain confidential commercial information. Alternatively, depending on the circumstances surrounding the transfer or if the records are not available from the original IRB, the CMU IRB may elect to obtain the records directly from the clinical investigator and/or sponsor. If records are obtained in this manner, the CMU IRB should also obtain meeting minutes from the original IRB, if possible, as this information may be critical to the CMU IRB's assessment of the adequacy of the previous review (e.g., discussion of controverted issues or inclusion of vulnerable populations, quorum, etc.).

Both the original IRB and the CMU IRB should maintain adequate records regarding the clinical investigations or research projects affected by the transfer; e.g., any written agreement between the original IRB and the CMU IRB, the title of the protocols being transferred, the identity of the original IRB and the date(s) on which the CMU IRB accepts responsibility for oversight of the clinical investigations. In addition, the original and CMU IRBs should keep complete records of communications to all affected stakeholders (sponsors, clinical investigators, and FDA/OHRP) and comply with all other recordkeeping requirements.

- Retention of IRB records.
  Under FDA and OHRP regulations, IRB records related to the review of a clinical investigation must be retained for at least three (3) years after the completion of the research, and the records must be accessible for inspection and copying by FDA or OHRP at reasonable times and in a reasonable manner. The CMU IRB must assure that FDA or OHRP know whether the original IRB, the CMU IRB, the institution that housed the original IRB, a CRO or other responsible third party will maintain the records once clinical investigation oversight has been transferred. The party that assumes responsibility for the records is responsible for ensuring that they are retained in accordance with federal regulations. Generally, the original and CMU IRBs have the flexibility to work out any suitable arrangement for handling the transfer and maintenance of the records as long as the records remain accessible for inspection and copying by authorized representatives of FDA/OHRP at reasonable times and in a reasonable manner. If the original and CMU IRBs agree to share record retention responsibilities, there must be a clear understanding of their respective roles to avoid confusion and to ensure appropriate responsibility for and access to the documents. There may be circumstances when the original IRB reaches an agreement with the CMU IRB to retain some of the documentation for the transferred trials but may not be able to commit to retaining the documents for at least 3 years after the completion of the research. In this situation, the original IRB should make arrangements to transfer the documents to the CMU IRB or to another, responsible party.

Establish a Date for Transfer of Records and IRB Oversight

It is highly recommended that a date for transfer of the records of each clinical investigation or research project for which oversight is being transferred be established (specified date or timeframe) to prevent confusion as to when review by the CMU IRB will occur or is projected to occur. When choosing a transfer date, the affected IRBs should allow enough time for all appropriate actions, communications and agreements to occur. When a large number of studies are being transferred, a plan will be developed as when the studies will be transferred (i.e., studies for which continuing review will be required immediately after transfer, protocols with submitted amendments, etc).

Also, it is imperative that an effective date for transfer of oversight for each clinical investigation or research project be established in order to promote continuity, prevent a lapse in IRB coverage and minimize confusion regarding which IRB is responsible for review and action (e.g., if an unanticipated problem should arise). When choosing an effective date for transfer of oversight, enough time should be allowed for all appropriate actions (i.e., review by the CMU IRB, communication to FDA/OHRP, sponsors and investigators, etc.) to occur. The effective date for transfer of IRB oversight may be established as follows or by some other method:

- In the written agreement, the exact date or a timeframe is specified in advance between the original IRB and the CMU IRB; or
- In the written agreement, the date is made contingent upon the review and acceptance of the clinical investigation by the CMU IRB. For example, if the CMU IRB decides to perform an initial review of the clinical investigation, the transfer may take effect on the date the CMU IRB makes its decision to approve, require modification in (to secure approval), or disapprove the clinical investigation. In this situation, the CMU IRB should notify the original IRB and other involved parties of the date of its actions and acceptance of oversight responsibilities.

Review of Studies by CMU IRB Prior to acceptance of Oversight

The regulations do not address transfer of IRB oversight; therefore, it is left to the CMU IRB to decide whether to conduct a review of the clinical investigation prior to the next continuing review date established by the original IRB. Generally, IRBs choose to perform some type of review before accepting responsibility for a study, as part of their own due diligence efforts.

According to FDA and OHRP Guidance, IRBs may decide to:

- Undertake an *initial review*, either by the convened IRB or under an expedited review procedure, if appropriate. Review by the CMU IRB will occur for higher risk studies, such as those involving an exception from the informed consent requirements, unapproved therapies with a high risk of morbidity and/or mortality, novel therapies including new cellular or gene therapies, device studies to make an independent determination of significant or non-significant device risk, and those flagged by the original IRB for more frequent review. Initial review should also be considered where the CMU IRB has no familiarity with the original IRB and, as such, may not be comfortable with the original IRB's review and approval.

- Undertake a *continuing review at the time of transfer*, either by the convened IRB or under an expedited review procedure, if appropriate**.**
- Not undertake *a review until the next continuing review date*. This option may be used in certain situations. However, the CMU IRB will generally choose to perform one of the reviews described above. However, if this option is chosen, any request for CMU IRB approval of a protocol or informed consent modification or a report of an unanticipated problem will prompt the CMU IRB to perform either an initial or continuing review to ensure that they are sufficiently familiar with the study before approving substantive changes to the research or the informed consent document or acknowledge and report the unanticipated problem.

CMU will use the following procedures when reviewing studies that are being transferred to CMU:

- Conduct a continuing review, comparable to an initial review, for studies for which the approval period is expiring.
- For studies where a modification request was submitted for review during the transfer process but prior to a continuing review being required, review the modification request while concurrently completing a review comparable to an initial review.
- Conduct an initial review for studies where the original IRB's review determination was either "Deferral" or "Contingent Approval" and the IRB's conditions for approval had not been satisfied prior to the transfer.
- For the remaining studies, a qualified IRB staff member will complete an administrative review to determine regulatory compliance and determine whether the CMU IRB should undertake IRB review sooner than the next continuing review date (established by the original IRB).
    - If the administrative review indicates the need to document IRB determinations that perhaps were not clearly documented by the original IRB, a review, comparable to an initial review, will be completed sooner than the next continuing review date.
- For each transferred study requiring consent from a subject or the subject's Legally Authorized Representative (LAR), the CMU IRB will provide the researcher with an IRB approved consent form addendum for notifying subjects of the change in IRB contact information.

In addition, Federal regulations make no provision for a grace period extending the conduct of research beyond the expiration date of IRB approval. Therefore, if the CMU IRB's review of the transferred research does not occur prior to the end of the approval period specified by the original IRB, IRB approval expires automatically and all research activities involving human subjects must stop. Enrollment of new subjects cannot occur after the expiration of IRB approval.

Regulations also give authority to IRBs to suspend or terminate approval of research in circumstances where the clinical investigation or research project is not being conducted in accordance with the CMU IRB's requirements or has been associated with unexpected

serious harm to subjects. The CMU IRB must promptly report any suspension or termination of IRB approval to the investigator, institutional officials, sponsors and regulatory agencies in accordance with federal regulations and local policies and procedures.

Confirm or Establish the Continuing Review Date

If the CMU IRB conducts a review at the time of study transfer (whether an initial or a continuing review), it may choose to maintain the anniversary date of approval established by the original IRB or decide to establish a new anniversary date. If the CMU IRB decides to establish a new anniversary date, the new date must be within one year of the CMU IRB's review. If the CMU IRB does not conduct a review of the clinical investigation at the time of transfer, the date of clinical investigation approval by the original IRB will remain in effect for the full approval period established at the time of the most recent review by the original IRB.

Determine if Consent Form Revisions are Required

Federal regulations require the informed consent document to contain 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." Therefore, when CMU accepts oversight of a clinical trial or research project, new the contact information and/or whom to contact regarding subject rights or in the event of research-related injury must be provided to subjects. For subjects who were previously enrolled, this may be accomplished with a letter or postcard providing the relevant contact information. For new subjects, the informed consent, assent, and/or parental permission form must be revised to reflect the new contact information.

Other changes to the consent form may also be necessary, for example, if the CMU IRB requires modifications to the consent form as a condition of approval. If modifications are required, the principal investigator should be notified and make the revisions prior to conducting the research at CMU.

Notification of Key Parties

At the beginning of the transfer process, pertinent groups (e.g., investigator, Data Safety Monitoring Board, etc.) must be notified of the transfer of responsibility of IRB review and oversight, and to provide contact information for the CMU IRB.

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- OHRP and FDA regulations and guidance documents
- NIH HIPAA in Research documents