OFFICE OF
RESEARCH & GRADUATE STUDIES
CENTRAL MICHIGAN UNIVERSITY

Institutional Review Board

Human Research Protection Program
Standard Operating Procedures

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1 Human Research Protection Program (HRPP)

Central Michigan University (CMU) fosters a research environment that promotes respect for the rights and welfare of individuals participating in research conducted at or under the auspices of CMU. In reviewing and conducting research, CMU will be guided by the principles of respect for persons, beneficence, and justice set forth in the ***Ethical Principles and Guidelines for the Protection of Human Subjects of Research***. In addition, CMU will be guided by the idea of respect for community as well. The actions of CMU will also conform to all applicable federal, state, and local laws and regulations. CMU has established a Human Research Protections Program (HRPP) to fulfill this commitment.

1.1 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 timely and high-quality education, review and monitoring of human research projects; and
3. facilitate excellence in human subjects research.

The HRPP includes mechanisms to:

1. Establish a formal process to monitor, evaluate, and continually improve the protection of human research participants.
2. Dedicate resources sufficient to do so.
3. Exercise oversight of research protection.
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.

1.2 Institutional Authority

The CMU HRPP operates under the authority of the Central Michigan University policy “Human Subject Research (HSR)” adopted on July 1, 2011. Human subject research is defined as a systematic, scientific investigation that can be either interventional (a trial) or observational (no test article) and involves human beings as the research subjects. As stated in that policy, the operating procedures in this document “serve as the governing procedures for the conduct and review of all human research conducted under the auspices of CMU.” The HSR Policy and these operating procedures are made available to all CMU investigators and research staff and are posted on the HRPP website.

1.3 Definitions

Common Rule –The Common Rule refers to the "Federal Policy for the Protection of Human Subjects" adopted by a number of federal agencies. Although the Common Rule is codified by each agency separately, the text is identical to DHHS regulations in 45 CFR 46 Subpart A. For the purposes of this document, references to the Common Rule will cite the DHHS regulations.

The provisions of the revised Common Rule, which were is scheduled to be implemented in January 2018 but delayed until July 2018, have been adopted by the CMU. Until the revised Common Rule is formally implemented by the Common Rule agencies, CMU IRB will apply revised Common Rule provisions only to research not funded by or subject to regulation by federal agencies.

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

1. Intervention for research purposes with any human subjects of the research by performing invasive or noninvasive procedures.
2. Intervention for research purposes with any human subject of the research by manipulating the environment.
3. Interaction for research purposes with any human subject of the research.
4. Obtaining the informed consent of human subjects for the research.
5. Obtaining for research purposes identifiable private information or identifiable biological specimens from any source for the research. In general, obtaining identifiable private information or identifiable specimens includes, but is not limited to
    a. observing or recording private behavior;
    b. using, studying, or analyzing for research purposes identifiable private information or identifiable specimens provided by another institution; and
    c. using, studying, or analyzing for research purposes identifiable private information or identifiable specimens already in the possession of the investigators.

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

1. Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
2 Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

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 (as defined below), either as a recipient of the test article or as a control. A subject may be in normal health or may have a medical condition or disease. In the case of a medical device, a human subject/participant also includes any individual on whose tissue specimen an investigational device is used or tested.

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

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

Research – The Common Rule defines research as a systematic investigation, including research development, testing, and evaluation that is designed to develop or contribute to generalized knowledge.

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.

Additional Definitions: Sec 18.

1.4 Ethical Principles

Central Michigan University is committed to conducting research with the highest regard for the welfare of human subjects. It 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.

1.5 Regulatory Compliance

The HRPP is responsible for ensuring compliance with federal regulations, state law, and institutional policies. All human subjects research at CMU is conducted in accordance with federal regulations 45 CFR 46 and 21 CFR 50 and 56. The actions of CMU will also conform to all other applicable federal, state, and local laws and regulations.

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.

1.6 Federalwide Assurance (FWA)

Federal regulations require that federally-funded human subjects research only be conducted at facilities covered by a Federalwide Assurance (FWA) approved by the DHHS Office for Human Research Protections (OHRP). CMU has an OHRP-approved Federalwide Assurance. The FWA designates the Institutional Review Board that will review and oversee the research, specifies the ethical principles under which the research will be conducted, and names the individuals who will be responsible for the proper conduct of the research.

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 funded or otherwise subject to oversight by an agency that has adopted the Common Rule.

1.7 Research Covered by the HRPP

The CMU Human Research Protection Program Human covers all research involving human subjects that is conducted by agents of CMU or conducted under the auspices of CMU, regardless of funding.

1.8 Written Policies and Procedures

The “CMU Standard Operating Procedures for Human Research Protection” details the policies and regulations governing research with human subjects and the requirements for submitting research proposals for review by the CMU IRB. The Director of the Office 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 every 3 years or as needed to respond to regulatory changes. 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.

1.9 HRPP Organization

The HRPP is a comprehensive system to ensure the protection of human subjects participating in research. It consists of various individuals and committees, such as the IO, the DRC, the IRB, other committees or subcommittees addressing human subject protection (e.g., Biosafety, Radiation Safety, Conflict of Interest), investigators, IRB staff, research staff, and health and safety staff (e.g., Biosafety Officer, Radiation Safety Officer). 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 implementing the HRPP.

1.9.1 Institutional Official

The ultimate responsibility of the HRPP resides with the Vice President for Research and Dean of Graduate Studies (VPR/DGS), who serves as the Institutional Official (IO) of the HRPP. The IO is responsible for ensuring the CMU HRPP has the resources and support necessary to comply with all institutional policies, federal regulations, and state laws that govern human subjects research. The IO is legally authorized to represent CMU, is the signatory of the FWA, and assumes the obligations of the FWA.

The IO also holds ultimate responsibility for:

1. oversight of the Institutional Review Board (IRB);
2. oversight over the conduct of research conducted by all CMU investigators;

3. assuring that IRB members are appropriately trained to review research in accordance with ethical standards and applicable regulations;
4. assuring that all investigators are appropriately trained to conduct research in accordance with ethical standards and applicable regulations.

1.9.2 Director Office of Research Compliance

The Director of the Office of Research Compliance (DRC) is appointed by and reports to the IO and is responsible for:

1. 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.
2. Advising the IO on key matters regarding research at CMU.
3. Implementing the institution's HRPP policy and standard operating procedures.
4. Submitting, implementing, and maintaining an approved FWA through the VPR/DGS and the Department of Health and Human Services Office of Human Research Protection (OHRP).
5. Submits reports to AAHRPP to maintain accreditation.
6. Managing the budget of the CMU HRPP.
7. Assisting investigators in their efforts to carry out Central Michigan University's research mission.
8. Developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program.
9. Developing and implementing educational plans for IRB members, staff, and investigators.
10. Developing training requirements as mandated and appropriate for investigators, subcommittee members, and research staff, and ensuring that training is completed on a timely basis.
11. Exercising day-to-day responsibility for the operation of the HRPP office, including supervision of HRPP staff.
12. Responding to questions from faculty, students, and staff.
13. Working closely with the Chair of the IRB and on the development of policy and procedures as well as organizing and documenting the review process.

1.9.3 Institutional Review Board (IRB)

IRB members are appointed by the IO. The IRB prospectively reviews and make decisions concerning all human subjects research conducted at CMU facilities by its employees or agents or under its auspices. The IRB is responsible for protecting the rights and welfare of human research subjects at the CMU. It discharges this duty by complying with the requirements of the Common Rule, state regulations, the FWA, and institutional policies [See Section 2 for a detailed discussion of the IRB].

1.9.4 Investigator

The investigator is the ultimate protector of the human subjects who participate in research. The investigator must abide by the highest ethical standards and must a protocol that incorporates the principles of the *Belmont Report*. The investigator is expected to conduct research in accordance with the approved research protocol and to oversee all aspects of the research by providing

supervision of support staff, including oversight of the informed consent process. All subjects must give informed consent (unless this condition is explicitly waived by the IRB), and the investigator must establish and maintain an open line of communication with all research subjects within his/her responsibility. 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 investigator is responsible for providing and following written procedures for their storage, security, dispensing, and disposal.

1.9.5 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.

1.9.6 Office of Sponsored Programs

Office of Sponsored Programs staff review all research agreements with federal and state sponsors, and research agreements from foundation or non-profit sponsors that are not processed through the CMU Advancement Office. This institutional review ensures that all terms of the award are in compliance with institutional policies. Only designated senior individuals within the Office of Sponsored Programs have the authority to approve research proposals and to execute research agreements on behalf of the institution. As a further control, internal documents retained by the Office of Sponsored Programs as part of the application process for extramural funding include a copy of the proposal submitted to the external agency, the proposed budget, the financial disclosure statement, and the internal transmittal document.

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 subcontract is executed between CMU and the collaborating institution. If human subject research is involved, the subcontract 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.

1.9.7 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; offer technical assitance to investigators developing applications to conduct research involving human subjects; and offer educational presentations for the board.

1.9.8 Office of Risk Management

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

1.9.9 Relationship Among Components

The IRB functions independently of, but in coordination with, other institutional regulatory committees. The IRB, however, makes its independent determination whether to approve, require modifications in order to secure approval, or disapprove a protocol based upon whether human subjects are adequately protected.

1.10 HRPP Operations

1.10.1 HRPP Office

Operation of the office is the responsibility of the DRC assisted by clerical and other support staff in the Office of Research Compliance.

1.10.2 Director of the Office of Research Compliance

The Director of the Office of Research Compliance (DRC) is responsible for all aspects of the IRB throughout the review process of a research proposal involving human subjects. This responsibility includes the initial review of documents and screening of research proposals prior to their review by the IRB as well as serving as the liaison, if needed, between the investigators and the IRB. The DRC reviews the IRB minutes for accuracy and ensures proper documentation of discussions, including controverted issues discussed and actions taken by the IRB during its convened meetings.

1.10.3 Selection, Supervision, and Evaluation of HRPP Supporting Staff

All HRPP staff who support the IRB and HRPP are selected by the DRC according to CMU Human Resources policies and procedures.

1.11 HRPP Resources

The HRPP Office is located in Foust Hall and has the necessary office, meeting, and storage space and equipment to perform the functions required by the HRPP. The adequacy of personnel and non-personnel resources of the HRPP program is assessed annually by the DRC in consultation with the HRPP staff.

The CMU IO provides resources to the IRB and HRPP Office, including adequate meeting and office space, and staff for conducting IRB business. Office equipment and supplies, including technical support, file cabinets, computers, internet access, and copy machines, are made available to the IRB and staff. Resources provided for the IRB and HRPP Office are reviewed by the DRC and IO during the annual budget review process.

1.12 Conduct of Quality Assurance/Quality Improvement Activities

The objective of Central Michigan University's HRPP Quality Assurance / Quality Improvement Plan is 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 / Quality Improvement Plan will be managed and implemented by the DRC.

1.12.1 Investigator Audits and Compliance Reviews

Directed ("for cause") audits and periodic (not "for cause") compliance reviews will be conducted to assess investigator compliance with federal, state, and local laws as well as Central Michigan

University policies; identify areas for improvement; and suggest process improvements. Directed audits of IRB-approved research studies are authorized by the IRB Chair in response to identified concerns. Periodic compliance reviews are conducted using a systematic method to review IRB-approved research on a regular basis. The results are reported to the IO and the IRB Chair.

Activities of auditors during directed audits and periodic compliance reviews may include, but are not limited to:

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

1.12.2 External Site Audits and Compliance Reviews

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," to assess compliance with federal, state, and local law; research subject safety; and IRB policies and procedures. These reviews may include items listed in section 1.12.1 above. Operational deficiencies are discussed with the IRB Chair and remediation plans are developed.

1.12.3 Disposition of Quality Assurance Reports

The results of all quality assurance activities are reported to the DRC and the IRB Chair. Any noncompliance will be handled according to the procedures in Section 10. 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.

1.12.4 HRPP 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 VPR/DGS. The DRC or designee will:

1. Review the IRB minutes to determine that adequate documentation of the meeting discussion has occurred. This review will include assessing the documentation surrounding the discussion for protections of vulnerable populations as well as other risk/benefit ratio and consent issues that are included in the criteria for approval;
2. Assess the IRB minutes to assure that a quorum was met and maintained;
3. Assess the current adverse-event reporting process;

4. Assess privacy provisions, according to HIPAA, have been adequately reviewed, discussed, and documented in the IRB minutes;
5. Evaluate the continuing review discussions to assure they are substantive and meaningful and that no lapse has occurred since the previous IRB review;
6. Observe IRB meetings or other related activities;
7. Review IRB files to assure retention of appropriate documentation and consistent organization of the IRB file according to current policies and procedures;
8. Review the IRB database to assure tasks are completed accurately;
9. Verify that reviews are completed;;
10. Verify IRB approvals for collaborating institutions or external performance sites;
11. Review the appropriate metrics (e.g., time from submission to first review) to evaluate the quality, efficiency, and effectiveness of the IRB review process;
12. Review the workload of IRB staff to evaluate appropriate staffing level;
13. Perform other monitoring or auditing activities deemed appropriate by the IRB.

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

1.12.5 Quality Improvement

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.

1.12.6 Examples of Quality Improvement and Quality Assessment Activities

An example of an objective to achieve or maintain compliance would be determining whether IRB minutes meet standards listed at Sec 4.3 of these SOPs. The measure of compliance is the percentage of required elements that are consistently present in the minutes. The method to assess compliance is to use a checklist based on the required elements (at Sec 4.3 of these SOPs) and evaluate minutes for 6-month blocks of time.

An example of efficiency of IRB operations is timely review of protocols using exemption determinations, expedited review procedures and review at convened meeting. Efficiency is measured by time to complete a review of a protocol. The efficiency is assessed by comparing our data to data published by AAHRPP.

1.13 Collaborative Research Projects

In the conduct of collaborative research projects, CMU acknowledges that each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with applicable federal regulations. When CMU is engaged in only part of a cooperative research project, the CMU IRB only needs to approve the part(s) of the research in which the CMU investigator is engaged. For example, if CMU is operating the statistical center for a multicenter trial that receives identifiable private information from multiple other institutions, the CMU IRB reviews and approves the research activities related to the receipt and processing of the identifiable private information by the statistical center.

When a cooperative agreement exists, CMU may enter into a joint review arrangement, rely on the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort. A formal relationship must be established between Central Michigan University and the other institution through either a Cooperative Agreement or a Memorandum of Understanding. This relationship must be formalized before Central Michigan University will accept any human research proposals from the other institution or rely on the review of the other institution.

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

For collaborative research, the PI must identify all institutions participating in the research, the responsible IRB(s), and the procedures for dissemination of protocol information (e.g., IRB initial and continuing approvals, relevant reports of unanticipated problems, protocol modifications, and interim reports) among all participating institutions.

When CMU relies on another IRB, the DRC will review the policies and procedures of the IRB to ensure that they meet CMU standards. If the other IRB is part of an accredited HRPP, then it will be assumed that adequate protections are in place to protect human subjects.

2 Institutional Review Board

Note: In the following section and in the remainder of this document, 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. The membership of each board, the meeting schedule for each board, and, if appropriate, the special areas of review of each board, will be described in separate documents.

CMU has established an Institutional Review Board (IRB) to ensure the protection of human subjects in human subjects 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 the CMU IRB prior to the initiation of the research.

2.1 IRB Authority and Independence

The IRB derives its authority from the CMU HRPP policy. Under the federal regulations, this authority includes:

1. To approve, require modifications to secure approval, or disapprove all research activities overseen and conducted under the auspices of the CMU;
2. To suspend or terminate approval of research not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to participants;
3. To observe, or have a third party observe, the consent process; and
4. To observe, or have a third party observe, the conduct of the research.

Under certain conditions, detailed in Section 1.13, the Institutional Official may authorize other IRBs to carry out these functions.

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 if it has not been approved by the IRB. CMU officials may strengthen requirements and/or conditions or add other modifications to secure CMU approval or approval by another CMU committee. Previously-approved research proposals and/or consent forms must be re-approved by the IRB before the changes or modifications may be initiated.

2.2 Number of IRBs

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

CMU has two separately constituted and registered IRBs:

- IRB1 meets during the academic year (OHRP registration # IRB00001370)
- IRB2 meets during the summer months (OHRP registration # IRB00009405)

Membership of IRB2 is a subset of the membership of IRB1. Protocols presented to one board may be reviewed by the other board.

2.3 IRB Membership

The structure and composition of each IRB is be appropriate to the amount and nature of the research that is reviewed. Every effort is made to have members that understand the areas of specialty that encompasses most of the research performed at the CMU.

The IRB will include members who are knowledgeable about and experienced working with vulnerable populations that typically participate in CMU research.

Scientific members of the boards are drawn from colleges that submit most of the protocols: Liberal Arts and Social Sciences; Education and Human Services; Health Professions; and Medicine. In recognition of the increasing importance of data security in research, the information technology directors of the various colleges have been appointed as scientific members of the IRB.

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.

2.4 Composition of the IRB

The IRB will have at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.

~~The IRB will be sufficiently qualified through the experience and expertise of its members; 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 policies and regulations, applicable law, data security, 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, or cognitively impaired 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. (See Section 2.10.)~~

No IRB has members who are all males or all females. The IRB shall not consist entirely of members of one discipline or profession.

The IRB includes at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

The IRB includes at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

The IRB includes at least one member who represents the general perspective of participants.

One member may satisfy more than one membership category.

Staff of the CMU HRPP Office may be voting members of the IRB.

Per institutional policy, the CMU Privacy Officer may serve on the IRB as a voting member.

On an annual basis, the IRB Chairs and the DRC shall review the membership and composition of the IRB to determine if they continue to meet regulatory and Institutional requirements. Changes in IRB membership will be reported to the OHRP by the DRC.

2.5 IRB Coordinator

2.5.1 Qualifications

The IRB Coordinator is expected to be knowledgeable about regulations pertaining to human subjects research protections and be a resource for investigators and their research teams, especially those who may be inexperienced in research, about IRB requirements and human subjects protections training. Certification as either CIM or CIP, either at time of hiring or within 2 years of hiring, is a requirement for this position.

2.5.2 Responsibilities

The Coordinator is responsible for receiving and docketing new protocol applications and revisions and applications for continuing review; assigning reviewers for new and continuing applications; preparing correspondence on behalf of the IRB; developing agendas for convened meetings; and maintaining the IRB document management system. The Coordinator is an alternate member of the IRB and may review and approve minor modifications to approved protocols.

2.5.3 Evaluation

The performance of the Coordinator is evaluated on an ongoing by the DRC, with input from various sources, including the IRB Chair. An integral part of the evaluation process is giving constructive feedback to address any performance areas that are deficient or should be improved. If necessary, formal improvement plans are developed, implemented and reviewed at prespecified intervals.

2.6 Chair and Vice Chair of the IRB

2.6.1 Appointment

The CMU IO, in consultation with the IRB members and the DRC, appoints a Chair and Vice Chair of the IRB to serve for renewable three-year terms. Any change in appointment, including reappointment or removal, requires written notification.

The Vice Chair serves as the Chair of the IRB in the absence of the Chair and will have the same qualifications, authority, and duties as Chair.

2.6.2 Qualifications

The IRB Chair/Vice Chair should be a highly-respected individual, from within Central Michigan University, capable of managing the IRB and the matters brought before it with fairness and impartiality. The task of making the IRB a respected part of the institutional community will fall primarily on the Chair. 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, and other professional and nonprofessional sources.

2.6.3 Responsibilities

The IRB Chair/Vice Chair is responsible for:

- conducting the meetings.
- designating other IRB members (e.g., the Vice Chair) to perform duties, as appropriate, for review, and other IRB functions or;
- delegating responsibilities to IRB members or HRPP staff as appropriate;
- advising the IO and the DRC about IRB member performance and competence.

2.6.4 Evaluation

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

2.7 IRB Members

2.7.1 Appointment

The IRB Chair, Vice Chair, and/or the DRC identifies a need for a new, replacement, or alternate member. The IO solicits nominations from Deans and Chairs and sends the names of the nominees to the HRPP Office. Department Chairs and others may forward nominations to the IO, the HRPP Office, or the IRB Chair. The final decision in selecting a new member is made by the IO in consultation with the IRB Chair and the DRC. Appointments are made for an initial one-year term. Subsequent appointments may be made for a three-year 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 Chair. The IRB Chair and the DRC review the membership and composition of the IRB to annually to determine if they continue to meet regulatory and institutional requirements.

2.7.2 Qualifications

Required qualifications are willingness to: commit to serve on board and attend meetings; take required training course; take active part in discussions before the board; evaluate protocols assigned for expedited review; and present assigned protocols at convened meetings.

The process for identifying potential unaffiliated members is informal and has operated by the DRC reaching out to members of the Mt Pleasant community either directly or through CMU staff intermediates.

2.7.3 Responsibilities

The agenda, submission materials, protocols, proposed informed consent forms, and other appropriate documents are made available to members at least one week prior to the convened

meetings at which the research is scheduled to be discussed. Members review the materials before each meeting in order to participate fully in the review of each proposed project. IRB members will treat specific details regarding research proposals, protocols, and supporting data confidentially.

Members should attend all scheduled meetings.. If a member is unable to attend a scheduled meeting, he/she should inform the IRB Chair, Vice Chair, or an HRPP Office staff member.

If an IRB member is to be absent for an extended time, such as for a sabbatical, he/she must notify the IRB at least 30 days in advance so that an appropriate replacement can be obtained. If the member has a designated alternate (see Section AlternateMembersEvaluation74), the alternate can serve during the primary member's absence, provided the IRB has been notified in advance.

2.7.4 Alternate Members

The appointment, qualifications, and responsibilities of alternate members are the same as those of primary IRB members. Alternate members' expertise and perspective are comparable to those of the primary members with whom they are paired. A single alternate may be paired with more than one primary member and more than one alternate member may be paired with a single primary member.

CMU faculty consider the term "alternate" as indicating a lower level of membership with lower expectations and less credit for university service. Therefore, we have developed a separate nomenclature to describe a rotating voting member system in which:

- All appointments to the board are as undifferentiated "members";
- Rosters filed with OHRP do indicate primary and alternate members;
- Members are grouped according to subject area (eg, medicine, psychology, education, information technology) and rotate responsibilities for serving as either a voting member at convened meetings or an expedited reviewer; members conducting expedited reviews are usually not asked to review protocols at convened meetings;
- All members are encouraged to attend as many meetings as possible, even when they are not designated voting members for particular meetings; and
- All members receive the same training.

The role of the alternate member is to serve as a voting member of the IRB when the regular member is unavailable to attend a convened meeting. The IRB roster identifies the primary member(s) for whom each alternate member may substitute.

An alternate member may attend convened meetings but will not be counted as a voting member unless the primary member is absent or recuses. The IRB minutes will document when an alternate member replaces a primary member at a convened meeting.

To insure a quorum at a convened meeting, the IRB coordinator and the Office of Research Compliance secretary determine approximately 1 week in advance which members will be present and which will serve as voting members.. Voting members – whether primary or designated alternates – are announced at the beginning of each meeting and noted in the minutes.

Any experienced members may conduct expedited reviews.

The DRC is responsible for maintaining current rosters of IRB primary and alternates.

2.7.5 Evaluation

Members are evaluated on their ability to conduct expedited and full board reviews accurately and in a timely manner. If requested, a report of the members' times to complete assigned reviews will be provided. If needed, the DRC and IRB Chair or designee will discuss any issues that might negatively affect a members' ability to complete reviews in a timely manner.

Evaluation is an integral part of the HRPP Quality Assurance and Quality Improvement Programs, as such the results of HRPP QA/QI audits will be utilized for evaluating the effectiveness of protocol reviews. The results of QA/QI audits may be shared with the IRB Chair, the DRC, the IO or the full IRB or discussed with individual members of the IRB as appropriate.

2.8 IRB Member Conflict of Interest

An IRB Member Conflict of Interest is a situation in which a member's financial interest, scientific activities, or personal relationships are inconsistent with the member's ability to evaluate an application to the IRB without prejudice or prejudgment.

No member may participate in the review (initial, continuing, or modification) of any research project in which the member has a conflict of interest (COI), except to provide information as requested. It is the responsibility of each IRB voting member to disclose any COI in a study submitted for review and recuse him/herself from the deliberations and vote by leaving the room.

When first appointed and annually thereafter, all members of the IRB will complete an "IRB Member Human Research Conflict of Interest Assessment Form," which will be consistent with the forms used in connection with CMU's Financial Conflicts of Interest Policies. If a member discloses a potential financial conflict, the Executive Director of the Office of Research and Graduate Studies is notified, and, if necessary, coordinates development of a conflict of interest management plan.

Committee members may find themselves in any of the following conflicts of interest when reviewing research:

1. Where the member is involved in the design, conduct, and reporting of the research.
2. Where an immediate family member of the member or consultant is involved in the design, conduct, and reporting of the research.
3. Where the member holds significant financial interests related to the research being reviewed. (See Section 14.1 for a definition of significant financial interests.)
4. Any other situation where an IRB member believes that another interest conflicts with his/her ability to deliberate objectively on a protocol.

The IRB Chair polls members at each convened meeting to determine if a COI exists regarding any protocols to be considered during the meeting and reminds members that they should recuse themselves by leaving the room during the discussion and vote of the specific protocol. Members with a conflicting interest are excluded from being counted towards quorum, and all recusals are noted in the minutes.

If the Conflict of Interest status of an IRB member changes during the course of a study, the IRB member is required to declare this to the IRB Chair or the DRC.

2.9 Use of Consultants

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. The need for an external reviewer is determined in advance of the meeting by the DRC or the IRB Chair by reviewing the protocols scheduled to be reviewed at the convened meeting. The HRPP Office will ensure that all relevant materials are provided to the external reviewer prior to the convened meeting.

Written statements of consultants will be kept in IRB records, and key information provided by consultants at meetings will be documented in the minutes.

DRC reviews the conflict of interest policy with consultants, and consultants must sign a COI disclosure form prior to conducting a review. 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.

The consultant's findings will be presented to the full board or the member serving as an expedited reviewer for consideration either in person or in writing. If in attendance at a convened meeting, these individuals will provide consultation but may not participate in or observe the vote.

Ad hoc or informal consultations requested by individual members (rather than the full board) must be requested in a manner that protects the researcher's confidentiality and complies with the IRB conflict of interest policy (unless the question raised is generic enough to protect the identity of the particular PI and the title or specific details of the research protocol).

2.10 Training and Continuing Education of Chair and IRB Members

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

2.10.1 Orientation

New IRB members, including alternate members will meet with the IRB Chair and/or the DRC for an orientation session. At the session, the new member will receive electronic copies of the following documents:

- The Belmont Report;
- CMU Standard Operating Procedures of the Human Research Protection Program; and
- Federal regulations for protection of human subjects.

2.10.2 Initial Education

Prior to serving as primary or independent reviewers, new members are required to complete the Initial Education requirement for IRB members including CITI training; orientation to review procedures with the DRC and/or IRB Chair; orientation with the IRB Coordinator or HRPP staff on the use of the electronic management system for conducting reviews; and work with an experienced IRB member to conduct expedited reviews.

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

1. In-service training at IRB meetings;
2. Training workshops;
3. 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;

2.11 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.

2.12 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.

3 IRB Review Processes

All human subjects research conducted under the auspices of CMU must meet the criteria for one of the following methods for review:

- Exempt Review
- Expedited Review
- Review at Convened Meeting (Full Board Review)

The IRB will ensure that the research meets all required ethical and regulatory criteria for initial and continuing review as well as any modifications of approved research.

3.1 Definitions

Minimal Risk – The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Minor Change – A change that, in the judgment of the IRB reviewer, makes no substantial alteration in the level of risks to subjects. For example:

1. the research design or methodology (Note: Adding procedures that are not eligible for expedited review (see Section 3.5) would not be considered a minor change);
2. the number of subjects enrolled in the research (if research is greater than minimal risk, no greater than 10% of the total requested);
3. the qualifications of the research team;
4. the facilities available to support safe conduct of the research; and
5. any other factor that would warrant review of the proposed changes by the convened IRB.

Quorum – A simple majority of the voting membership, including at least one member whose primary concern is in a non-scientific area.

Suspension of IRB approval – A directive of the convened IRB or an authorized individual to temporarily stop some or all previously approved research activities. Suspended protocols remain open and require continuing review.

Termination of IRB approval – A directive of the convened IRB to stop permanently all activities in a previously approved research protocol. Terminated protocols are considered closed and no longer require continuing review.

3.2 Human Subjects 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" and "research" in Sec 18. Since Central Michigan University will hold them 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 HRPP Office.

Determinations as to whether an activity constitutes human subjects research will be made according to the definitions in Sec 18 using the form Determination Whether a Project Needs IRB

Review. Based on the checklist, determinations regarding activities that are either clearly or clearly not human subjects research may be made by the DRC or the Chair. Determinations regarding less clear activities will be referred to the IRB Chair, who may make the determination or refer the matter to the convened IRB.

Documentation of all determinations made through the HRPP Office will be recorded and maintained in the IRB documents management system. Formal submissions will be responded to in writing and a copy of the submitted materials and determination letter/email will be kept on file.

3.3 Exempt Determinations

Determinations regarding whether research involving human subjects qualifies for exempt status will be made by the IRB Chair or the Director of Research Compliance. The Chair may designate qualified IRB members to make exemption determinations and conduct exemption reviews. Exemption determinations may not be made solely by the researcher or by someone with a conflict of intertest in the research.

Although exempt research is not covered by the federal regulations, it is not exempt from the ethical guidelines of the Belmont Report. The individual making the determination of exemption will determine whether to require additional protections for subjects in keeping with the guidelines of the Belmont Report.

3.3.1 Limited IRB Review

When the research requires limited IRB review ategories mm, mm, and mmm), the review will be conducted by the IRB Chair or a Chair-designated member of the IRB and may be conducted using expedited review procedures limited to and focused on criteria 7. As with all other research subject to IRB review requirements, when conducting limited IRB review the IRB has the authority to approve, require modifications in (to secure approval), or disapprove all research activities.

Proposed modifications to the aspects of research subject to limited IRB review must be submitted to, and approved by, the IRB prior to implementation, except when necessary to eliminate apparent immediate hazards to the subject(s), in which case the change must be promptly reported to the IRB (within 5 business days if possible).

Continuing review is generally not required for research determined to be exempt, even when that research is subject to limited IRB review. However, the IRB may determine that continuing review is required for a particular study subject to limited IRB review, in which case it shall document the reasons for its determination in the IRB record and communicate the requirement to the investigator in the IRB determination letter.

3.3.2 Limitations on Exemptions

Children: Exemption #2(i) and (ii) for research involving survey or interview procedures or observations of public behavior 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. Exemption #2(iii), where identifiable information is obtained and the IRB conducts a limited IRB review, is NOT applicable to research in children. Exemption #3 does NOT apply to research involving children.

Prisoners: Exemptions do not apply EXCEPT for research aimed at involving a broader subject population that only incidentally includes prisoners.

3.3.3 Categories of Exempt Research

Unless otherwise required by law or a federal agency or department, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from the additional requirements of the revised Common Rule, except as specified.

Note: Other than exempt category 6, these categories do not apply to research that is also FDA-regulated.

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. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
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. 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; 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 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."
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; 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 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.

If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

4. Secondary research for which consent is not required: Secondary research uses 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); or
    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.

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.

3.3.4 Unused Exemption Categories

The CMU IRB has determined that exempt categories 5, 7 and 8 are not used, even though allowed by regulation. Protocols involving broad consent for future use of identified data or biospecimens will be reviewed by expedited processes or at convened meeting.

3.3.5 FDA Exemptions

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

1. Emergency use of a test article**. CMU IRB does not oversee emergency use of investigational or unlicensed test articles.**
2. 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 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 [21 CFR 56.104(d)].

3.3.6 Procedures for Exemption Determination

In order to obtain an exemption determination, investigators must submit

1. a completed IRB Application to Conduct Exempt Research;
2. all recruitment materials (e.g., letter of invitation, recruitment script, flyer), consent form (when appropriate);
3. all surveys, questionnaires, instruments, etc.;
4. letter(s) of permission from each non-Central Michigan University site of performance;
5. if sponsored, one copy of the grant application(s) and/or contract;
6. verification of current human research protection training for all members of the research team, including the faculty advisor.

Investigators will be given feedback by email as to the qualification of the application for exempt status. Once institutional review is completed, IRB staff or the DRC will send an email notification to the PI of the results of the review. Documentation must include the specific categories justifying the exemption. Exemptions have a five-year default termination date unless otherwise specified.

3.4 Expedited Review

Research that presents minimal risk to research subjects may be reviewed by expedited procedures. If the research is funded or supported by an agency that subscribes to the Common Rule, then the research must fall in one of the categories described below in Section 3.4.1. Otherwise, all other minimal risk research is eligible to expedited review (Section 3.4.2)

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. The designees must be voting members of the IRB (having successfully completed introductory training sessions in IRB procedures and carried out at least one expedited review under the guidance of an experienced member). The IRB Staff will select expedited reviewers from that list. 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 members with a conflict of interest in the research (see Section 2.8) will not be selected.

When reviewing research under an expedited review procedure, the IRB Chair or designated IRB member(s) will have access to all documentation associated with the protocol. The reviewer(s) conducting initial or continuing review will determine whether the research meets the regulatory criteria for approval by expedited review. If the research does not meet the criteria for expedited review, then the reviewer will indicate that the research requires full review by the IRB, and the protocol will be placed on the next agenda for an IRB meeting.

In reviewing the research, the reviewers will follow the Review Procedures described in Sections 3.7 and 3.8 below 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 described in section 3.8.

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.

3.4.1 Categories of Research Currently Authorized by HHS as Eligible for Expedited Review

The activities 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 previously noted.

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

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

Research Categories one (1) through seven (7) pertain to 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. (Note: 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.)

Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

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

(a) 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

from other adults and children [2], 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.

3. Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (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 gumbase 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 cleared/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 cleared medical devices for new indications.)

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

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). 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. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

Note 1: 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 under example (e) provided that the subject population meets the following criteria: Non-

pregnant; 18-45 years of age; in good health, with no medical indication(s) that would otherwise preclude them from engaging in vigorous exercise.

8. Continuing review of research previously approved by the convened IRB as follows:

a. where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; *or*

b. where no subjects have been enrolled and no additional risks have been identified; *or*

c. where the remaining research activities are limited to data analysis.

9. Continuing review of research not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Limited IRB Review. The limited IRB review that is required for certain exempt research (categories 2(iii) and 3(iii) (See Section 3.3)) may be conducted using expedited review procedures.

3.4.2 Additional Categories Eligible for Expedited Review (Flexibility Criterion)

The CMU IRB has determined that certain categories of research, beyond those described in Sec 3.4.1 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.

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.

3.4.3 Continuing Review and Annual Status Report

Continuing review of research is not required for research that qualifies for expedited review unless the IRB determines that it is required and documents the rationale within the IRB record.

Research that was approved by expedited process prior to implementation of the revised Common Rule by the CMU IRB in January 2018 will be evaluated on a case-by-case basis to determine whether continuing review will required.

Investigators conducting research approved by expedited process that does not require continuing review must submit annual status reports.

3.4.4 Informing the IRB

All members of the IRB will be apprised of all expedited review approvals by means of a list in the agenda for each scheduled meeting. Any IRB member can request access to the complete protocol file by contacting the IRB Office.

3.5 Convened IRB Meetings

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

3.5.1 IRB Meeting Schedule

The IRBs usually meet at least once per month during the academic year and summer. The schedule for IRB meetings and deadlines for submitting applications is posted on the HRPP website. Special meetings may be called at any time by the IRB Chair or the DRC.

3.5.2 Preliminary Review

The IRB Coordinator will perform a preliminary review of all protocol materials submitted to the HRPP Office for determination of completeness and accuracy. Only complete submissions will be placed on the IRB agenda for review. The 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. Individualized IRB consultations can be arranged for investigators who are submitting protocols for the first time or for investigator who may not be well-versed in the protocol submission procedures. Specific questions about the IRB policies and procedures, determination of whether a particular protocol is human research or not, and what particular forms are required for a particular study can be submitted to the DRC or IRB Chair for information and/or clarification.

3.5.3 Primary and Secondary Reviewers

After determining that the protocol submission is complete, the DRC or IRB Coordinator, in consultation with the IRB Chair, will assign protocols for review taking account of the scientific content of the protocol, the potential reviewer's area of expertise, and representation for vulnerable populations involved in the research. At least one reviewer will be assigned to each protocol and a reviewer may be assigned several protocols or other research items for review. Reviewers are assigned to all protocols requiring initial review, continuing review, and modifications. When the IRB is presented with a protocol that may be outside of the knowledge base or representative capacity of any of the IRB members, a consultant will be sought. [See Section 2.9] Protocols for which appropriate expertise cannot be obtained for a given meeting will be deferred to another meeting when appropriate expertise can be achieved.

The primary and secondary reviewers are responsible for:

1. Having a thorough knowledge of the details of the proposed research.
2. Performing an in-depth review of the proposed research.
3. Leading the discussion of the proposed research at the convened meeting, presenting both positive and negative aspects of the research.
4. Making suggestions for changes to the proposed research, where applicable.
5. Completion and submission of applicable IRB reviewer forms or comments prior to a convened meeting.

If both the primary and secondary reviewer are absent from the meeting, a new reviewer may be assigned, providing the s/he has reviewed the materials prior to the meeting. Additionally, an absent reviewer can submit written comments for presentation at the convened meeting, as long

as another reviewer present at the convened meeting can serve as the primary reviewer. All IRB members have access to, and are expected to review, all proposed studies.

3.5.4 Availability of Documents Before a Meeting

Investigators must submit all required materials (in full) 10 business days before the convened meeting for inclusion on the next IRB agenda. The meeting agenda will be prepared by the DRC or IRB Coordinator and made available to the IRB members prior to the meeting. All IRB members receive access to their review materials which include the IRB agenda, prior month's meeting minutes, applicable business items and audits, appropriate continuing education materials and protocol review materials no later than 5 business days before the scheduled meeting to allow sufficient time for review.

3.5.5 Materials Reviewed by the IRB

Each IRB member has access to the following documentation, as applicable, for all protocols on the agenda:

1. Complete Protocol Application form
2. Proposed Consent / Parental Permission / Assent Form(s)
3. Recruitment materials / subject information
4. Data collection instruments (including all surveys and questionnaires)

At least one primary reviewer must receive and review the following (when they exist): any relevant grant applications; the sponsor's protocol, the investigator's brochure, the DHHS-approved sample informed consent document, the complete DHHS-approved protocol.

Any IRB member may request access to any of the material provided to the primary and secondary reviewers by contacting the IRB Office.

Protocol reviewers will complete the Reviewer Checklist Worksheet. to document their review.

3.5.6 Quorum

A quorum consists of a simple majority (more than half) of the voting membership, including at least one member whose primary concern is in a non-scientific area. The IRB Chair, with the assistance of the IRB staff, 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.

At meetings of the IRB, a quorum must be established and maintained for the deliberation and vote on all matters requiring a vote. If a quorum is not maintained, the pending action item must be deferred or the meeting terminated. The IRB staff 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 (the same individual can serve in both capacities) will be present at all IRB meetings. Although the IRB may, on occasion, meet without this representation, individuals serving in these roles should be present for at least 80% of the IRB meetings.

A quorum worksheet is completed by the IRB staff to determine and document whether an IRB meeting is appropriately convened and maintained. A sign-in sheet is maintained for each convened meeting.

IRB members are considered present and participating at a duly convened IRB meeting when they are either physically present or participating through electronic means (e.g., tele/video-conferencing) 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 may be considered by the attending IRB members but will not be counted in any vote.

3.5.7 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;
- 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 HRPP 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 revisions/corrections are necessary, the minutes will be amended.

The IRB reviews all submissions for initial and continuing review, as well as requests for modifications. The Primary and Secondary Reviewer present an overview of the research. The chair 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 DRC or designee to record the proceedings of the session and to take minutes at each IRB meeting.

3.5.8 Guests

At the discretion of the IRB Chair, the Principal Investigator will be invited to the IRB meeting to answer questions about proposed or ongoing research.. The Principal Investigator may not be present for the discussion or vote on the proposal.

Other guests may be permitted to attend IRB meetings at the discretion of the IRB Chair and the DRC;. they may not speak unless requested by the IRB Chair and must sign a confidentiality agreement.

3.6 Criteria for IRB Approval of Research

3.6.1 Required determinations

For the IRB to approve human subjects research, either through expedited review or by review at a convened meeting, it must determine that the following criteria are satisfied:

1. Risks to subjects are minimized (i) by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
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 take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.
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.
5. Informed consent will be appropriately documented, in accordance with and to the extent required by the federal regulations.
6. When appropriate, the 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.

3.6.2 Additional considerations for vulnerable subjects

When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

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

These criteria must be satisfied for each review (initial, continuing, and modifications) for both expedited review and review by the convened IRB.

3.6.3 Risk-Benefit Assessment

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

1. judge whether the anticipated benefit, either of new knowledge or of improved health for the research subjects, justifies asking any person to undertake the risks;
2. disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits.

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

1. identify the risks associated with the research, as distinguished from the risks of therapies the subjects would receive even if not participating in research;
2. determine whether the risks will be minimized to the extent possible;
3. identify the probable benefits to be derived from the research;
4. determine whether the risks are reasonable in relation to the benefits to subjects, if any, and assess the importance of the knowledge to be gained;
5. ensure that potential subjects will be provided with an accurate and fair description of the risks or discomforts and the anticipated benefits;

3.6.4 Assessment of Scientific Merit

To assess the risks and benefits of the proposed research, the IRB must determine that the knowledge expected to result from this research is sufficiently important to justify the risk.

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 a funding agency or consultants. When scientific review is conducted by an individual or entity external to the IRB, documentation that the above questions were considered must be provided to the IRB for review and consideration.

When scientific review is conducted by an individual or entity external to the IRB, the Investigator may provide documentation that the above questions 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.

3.6.5 Equitable Selection of Subjects

The IRB will determine by viewing the application, protocol, and other research project materials that the selection of subjects is equitable with respect to sex, gender, age, socioeconomic status, and other characteristics of groups considered vulnerable or qualified for special protections under state or federal law.

The IRB will not approve a study that does not provide adequately for the equitable selection of subjects, given the research topic, or has not provided an appropriate scientific and ethical justification for excluding classes of persons who might benefit from the research. In making this determination, the IRB evaluates the purposes of the research; the setting in which the research occurs; scientific and ethical justification for including vulnerable populations such as children,

prisoners, decisionally-impaired persons, or economically or educationally disadvantaged persons; the scientific and ethical justification for excluding classes of persons who might benefit from the research; and the inclusion/exclusion criteria.

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.

The investigator will provide the IRB with all recruiting materials to be used in identifying participants, including recruitment methods, advertisements, and payment arrangements [See Section 3.7.7 for discussion of IRB review of advertisements and Section 3.7.8 for discussion of IRB review of payments].

3.6.6 Informed Consent

The IRB will ensure that informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116 and 21 CFR 50.20. In addition, the board will ensure that informed consent will be appropriately documented in accordance with, and to the extent required by 45 CFR 46.117 and 21 CFR 50.27 [See Section 5 below for detailed policies on informed consent].

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

1. Monitoring is commensurate with the nature, complexity, size, and risk involved.
2. Monitoring is timely with a determined frequency commensurate with risk. Results are reported to the IRB.
3. For low risk studies, continuous, close monitoring by the study investigator or other individual may be adequate and appropriate, with prompt reporting of problems to the IRB, sponsor, and regulatory bodies as appropriate.
4. For an individual Safety Monitor, the plan must include;
   a. Parameters to be assessed.
   b. Mechanism to assess the critical efficacy endpoints at intervals to determine when to continue, modify, or stop a study.
   c. Frequency of monitoring.
   d. Procedures for reporting to the IRB.
5. For a Data Safety Monitoring Board (DSMB), the plan must include;
   a. The name of the DSMB.
   b. When appropriate, the DSMB must be independent from the sponsor
   c. Availability of written reports
   d. Composition of the monitoring group (if a group is to be used). 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 and treatment under study should be part of the monitoring group or be available if warranted.
e. Frequency and content of meeting reports.
f. Frequency and character of monitoring meetings (e.g., open or closed, public or private).
In general, it is desirable for a DSMB to be established by the study sponsor for research that is blinded, involves multiple sites, involves vulnerable subjects, or employs high-risk interventions. The IRB has the authority to require a DSMB as a condition for approval of research when it determines that such monitoring is needed. When DSMBs are utilized, the IRB conducting continuing review of research may rely on a current statement from the DSMB 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.

3.6.8 Privacy and Confidentiality

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

3.6.8.1 Privacy

Privacy is defined as having control over the extent, timing, and circumstances of sharing oneself physically, behaviorally, or intellectually with others.

To determine that adequate procedures are in place to protect the privacy of subjects, the IRB must obtain information regarding how the investigators obtain access to 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 should be given to:

1. Methods used to identify and contact potential participants.
2. Settings in which an individual will be interacting with an investigator.
3. Appropriateness of all personnel present for research activities.
4. Methods used to obtain information about participants and the nature of the requested information.
5. Information that is obtained about individuals other than the "target participants" and whether such individuals meet the regulatory definition of "human participant" (e.g., a subject provides information about a family member for a survey).
6. That access will be limited to the minimum amount of information necessary to complete the study.

3.6.8.2 Confidentiality

Confidentiality refers to the methods used to ensure that information obtained by researchers about research subjects is not improperly divulged.

The level of confidentiality protection should be commensurate with the potential of harm from inappropriate disclosure. Confidentiality and anonymity are not the same. If anyone, including the investigator, can readily ascertain the identity of the subjects from the data, then the research is

not anonymous and the IRB must determine if appropriate protections are in place to minimize the likelihood that the information will be inappropriately divulged.

3.6.8.3 Review of measures to protect privacy and confidentiality

At the time of initial review, the IRB ensures that the privacy and confidentiality of research subjects is protected. The IRB assesses whether there are adequate provisions to protect subject privacy and maintain confidentiality. The IRB does this through the evaluation of the methods used to obtain information about:

1. subjects,
2. individuals who may be recruited to participate in studies,
3. the use of personally identifiable records, and
4. the methods to protect the confidentiality of research data.

The PI will provide the information regarding the privacy and confidentiality of research subjects at the time of initial review through the completion of the application, any necessary HIPAA Forms, research protocol, and/or other submitted, applicable materials. The IRB will review all information received from the PI and determine whether the privacy and confidentiality of research subjects are sufficiently protected. In some cases, the IRB may also require that a Certificate of Confidentiality be obtained to additionally protect research data [See Section 17.1].

In reviewing confidentiality protections, the IRB will consider the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research. It will evaluate the effectiveness of proposed de-identification techniques, coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections.

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

3.6.9 Vulnerable Populations

At the time of initial review, the IRB will consider the scientific and ethical reasons for including vulnerable subjects in research. The IRB may determine and require that, when appropriate, additional safeguards be put into place for vulnerable subjects.

For an extensive discussion about the IRB's review and approval process for individual populations of vulnerable subjects, please refer to Section 6.

3.7 Additional Considerations During IRB Review and Approval of Research

3.7.1 Approval Period

At the time of initial review and at continuing review, the IRB will determine the frequency of review of the research protocols. All protocols will be reviewed by the IRB at intervals appropriate to the degree of risk. The meeting minutes will reflect the IRB's determination regarding review frequency.

Unless specifically waived by the IRB, research that meets any of the following criteria will require review more often than annually:

1. Significant risk to research subjects (e.g., death, permanent or long-lasting disability or morbidity, severe toxicity) without the possibility of direct benefit to the subjects.
2. The involvement of populations likely to be subject to undue influence (eg, terminally ill).
3. A history of serious or continuing non-compliance on the part of the PI.

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

1. The probability and magnitude of anticipated risks to subjects.
2. The likely medical condition of the proposed subjects.
3. The overall qualifications of the PI and other members of the research team.
4. The experience of the Principal Investigator and other members of the research team in conducting similar research.
5. The nature and frequency of adverse events observed in similar research at this and other institutions.
6. The novelty of the research making unanticipated Adverse Events more likely.
7. 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 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 must be documented in the minutes.

3.7.2 Independent Verification That No Material Changes Have Occurred

The IRB recognizes that protecting the rights and welfare of subjects sometimes requires independent verification from sources other than the investigator that no material changes occurred during the IRB-designated approval period.

The IRB will determine the need for independent verification on a case-by-case basis and according to the following criteria:

1. Protocols where concern about possible changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources.
2. Protocols conducted by PIs who have previously failed to comply with federal regulations and/or the requirements or determinations of the IRB Protocols subject to internal audit.
3. Whenever else the IRB deems verification from outside sources is relevant.

The following factors will also be considered when determining which studies require independent verification:

1. The probability and magnitude of anticipated risks to subjects.
2. The likely medical condition of the proposed subjects.
3. The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed.

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 will decide the corrective action to be taken. [See Section 10.3]

3.7.3 Consent Monitoring

In reviewing the adequacy of informed consent procedures for proposed research, the IRB may determine that special monitoring of the consent process by an impartial observer (consent monitor) is required to reduce the possibility of coercion and undue influence. Such monitoring may be particularly warranted when the research presents significant risks to subjects or if subjects are likely to have difficulty understanding the information provided.

Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project [See Section 5.8 for further discussion of consent monitoring.]

3.7.4 Investigator Conflicts of Interest

The research application asks protocol-specific questions regarding conflict of interest for the investigators and key personnel. If a conflict of interest exists, final IRB approval of a protocol cannot be given until an approved conflict management plan that adequately protects the human subjects in the protocol is in place. [See Section 14 for a detailed discussion of Conflict of Interest.]

3.7.5 Significant New Findings

During the course of research, significant new knowledge or findings may develop about the treatment or test article and/or the condition under study. The PI must report any significant new findings to the IRB and the IRB will review them with regard to the impact on the subjects' rights and welfare. Since the new knowledge or 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 PI contact the currently enrolled subjects to inform them of the new information. The IRB will communicate this to the PI. The informed consent should be updated and the IRB may require that the currently enrolled subjects be re-consented, acknowledging receipt of this new information and for affirming their continued participation.

3.7.6 Advertisements and Recruitment Materials

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

1. The information contained in the advertisement.
2. The mode of its communication.
3. The final copy of printed advertisements.
4. The final audio/video-taped advertisements.

This information should be submitted to the IRB with the initial application.

3.7.6.1 General Considerations

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

1. The name and address of the investigator and/or research facility.
2. The condition being studied and/or the purpose of the research.
3. In summary form, the criteria that will be used to determine eligibility for the study.
4. The time or other commitment required of the subjects.
5. The location of the research and the person or office to contact for further information.
6. A clear statement that this is research and not treatment.
7. A brief list of potential benefits (*eg*, no cost for a health exam).

3.7.6.2 Additional Considerations Relevant to Biomedical Research

The IRB reviews the material to assure that it is accurate and is not coercive or unduly optimistic, creating undue influence to the subject to participate, which includes but is not limited to:

1. Statements implying a certainty of favorable outcome or other benefits beyond what was outlined in the consent document and the protocol.
2. Claims, either explicit or implicit, that the drug, biologic, or device is safe or effective for the purposes under investigation.
3. Claims, either explicit or implicit, that the test article was known to be equivalent or superior to any other drug, biologic, or device.
4. Using terms like “new treatment,” “new medication,” or “new drug” without explaining that the test article is investigational.
5. Promising “free medical treatment” when the intent is only to say participants will not be charged for taking part in the investigation.
6. Emphasis on payment or the amount to be paid, such as bold type or larger font on printed media.
7. The inclusion of exculpatory language.

Coupons. Advertisements may not include compensation for participation in a trial offered by a sponsor to involve a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

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

3.7.7 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 expenses 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 coercing or unduly influencing research subjects.

Investigators who wish to pay research subjects must indicate in their research project application the justification for such payment. Such justification should:

1. demonstrate that proposed payments are reasonable and commensurate with the expected contributions of the subject;
2. state the terms of the subject participation agreement and the amount of payment in the informed consent form; and
3. 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.

3.7.8.1 Partial Payment

Credit for payment should accrue and not be contingent upon the participant completing the entire study. The IRB does not allow the entire payment to be contingent upon completion all parts of a multipart study. Any amount paid as bonus for completion of the entire study should not be so great that it becomes unduly influential.

The consent form must describe the terms of payment and the conditions under which subjects would receive partial payment or no payment (e.g., if they withdraw from the study before their participation is completed).

3.7.8.2 Lotteries

Incentives in the form of entering a research subject's name in a lottery are permitted and must conform to the terms of Michigan Lottery Law [SOM Act 382, Section 432.105d]

1. Total cash value of prizes (cash, gift certificates/cards, merchandise) awarded on any day cannot exceed $100.
2. 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 SOM "single gathering" criteria.
3. There is no pre-sale of raffle/lottery tickets
4. The informed consent document must include a description of the lottery/raffle process

3.7.8.3 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. Investigators who wish to have CMU issue compensation payments directly to research subjects should seek guidance from the CMU Accounting office. Investigators who wish to be reimbursed for compensation payments made directly to research subjects should contact the CMU Payroll/Travel office.

3.7.8 Compliance with Applicable State and Local Laws and Laws of Foreign Countries

The HRPP and the IRB rely on the 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.

3.7.9 IRB Review of Grant Applications

Although the revised Common Rule removes the requirement that the IRB review Federal grant applications or proposals, the CMU HRPP will continue to review grant and contract proposals submitted to internal and external funding programs to ensure congruency upon request by Office of Sponsored Programs.

3.8 Possible IRB Actions

Approval. The study is approved as submitted.

Conditional Approval. The protocol and/or consent form require minor revisions, such as wording changes, with replacement language provided. For protocols reviewed at a convened IRB meeting, the needed revisions are agreed upon at the IRB meeting and the board votes to approve the protocol subject to satisfactorily responding to the stipulation. Depending on the stipulations, the changes are reviewed by either the Chair or a member designated by the Chair or by an IRB staff member.

Note 1**:** The expiration date for the protocol is calculated based on the date of conditional approval and NOT on the final approval date.

Note 2: Conditional approval is NOT used when an application is reviewed by expedited procedures.

Deferred for substantive issues regarding the protocol and/or consent form that must be addressed. This action is taken if substantial modification or clarification is required or there is insufficient information to judge the application adequately (*eg*, the risks and benefits cannot be assessed with the information provided).

To receive approval for a protocol deferred for substantive issues,

1. For review at convened meeting, IRB members will have access to. the investigator's response package. The item is placed on the agenda for re-review at the next meeting.
2. For expedited, the investigator's response package is assigned to the same reviewer(s) for re-review (if possible).
3. The outcome of the IRB's deliberations is communicated to the investigator in writing.

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

Note: 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 has determined that the research cannot be conducted at the CMU or by employees or agents of CMU or otherwise under the auspices of CMU.

Note: A protocol reviewewed by expedited procedures cannot be disapproved. The matter must be referred for consideration at a convened meeting.

3.9 Suspension, Termination, and Investigator Hold

3.9.1 Suspension and Termination

IRB approval may be suspended or terminated if research is not being conducted in accordance with IRB or regulatory requirements or has been associated with unexpected problems or serious harm to subjects [See Section 8 for a discussion of unexpected problems and Section 10 for a discussion of noncompliance].

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 short of stopping them permanently. Suspension directives made by the IRB Chair or DRC must be reported to a meeting of the convened IRB. Suspended protocols remain open and require continuing review.

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

The IRB shall notify the PI in writing of such suspensions or terminations and shall include a statement of the reasons for the IRB's actions. The terms and conditions of the suspension must be explicit. The investigator shall be provided with an opportunity to respond in person or in writing.

When study approval is suspended or terminated, in addition to stopping all research activities, the HRPP will notify any subjects currently participating that the study has been suspended or terminated. The HRPP will consider whether procedures for withdrawal of enrolled subjects are necessary to protect their rights and welfare of subjects, such as: transferring participants to another investigator; making arrangements for care or follow-up outside the research; allowing continuation of some research activities under the supervision of an independent monitor; or requiring or permitting follow-up of participants for safety reasons.

If follow-up of subjects for safety reasons is permitted/required by the HRPP, subjects will be informed and any adverse events/outcomes will be reported to the IRB and the sponsor.

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.)

Suspension or termination of research conducted under protocols approved by the IRB can be issued by CMU officials acting outside of and unrelated to the HRPP. Such action can be taken by the President, Provost, and Deans, and can be made for any reason in furtherance of the Institution’s interest provided. The affected investigator is entitled to all rights and procedures afford to him/her under the Grievance Policy of the university. The PI must report any suspension or termination of the conduct of research by CMU officials to the IRB. The IRB will then determine if suspension or termination of the IRB approval protocol is warranted.

3.9.2 Investigator Hold

An investigator may initiate an Investigator Hold to temporarily or permanently stop some or all approved research activities. Investigator Holds are not suspensions or terminations.

Investigators must notify the IRB in writing of the following:

1. They are voluntarily placing a study on Investigator Hold.
2. A description of the research activities that will be stopped
3. Proposed actions to be taken to protect current participants.
4. Actions that will be taken prior to IRB approval of proposed changes in order to eliminate apparent immediate harm.

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

The IRB Chair and/or DRC, in consultation with the investigators, determine whether any additional procedures need to be followed to protect the rights and welfare of current participants as described in "Protection of Currently Enrolled Participants" below.

The IRB Chair and/or DRC, in consultation with the investigators, determine how and when currently enrolled participants will be notified of the Investigator Hold.

Investigators must notify the IRB before removing an Investigator Hold.

3.10 Continuing Review and Status Reports

3.10.1 Ongoing research that presents greater than minimal risk

The IRB will conduct continuing review of ongoing research that presents greater than minimal risk to subjects at intervals that are appropriate to the level of risk for each research protocol but not less than once per year.

3.10.2 When continuing review is not required

The revised Common Rule modifies when continuing review is required. Unless CMU IRB determines otherwise, continuing review of research is not required for research subject to the revised Common Rule in the following circumstances:

1. Research eligible for expedited review in accordance with §46.110; and research eligible for expedited review under flexibility criteria listed in Sec 3.4.2.
2. Exempt research reviewed by the IRB in accordance with limited IRB review as described in Section 3.3;
3. 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:
    a. Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
    b. Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care

If continuing review is not required, periodic status reports must be submitted to the IRB Office for the protocol to remain active.

3.10.3 Approval Period

Determination of the approval period and the need for additional supervision is made by the IRB on a protocol-by-protocol basis. Approval period of less than one year might be warranted if the is particularly risky; research by an investigator who has recently had a protocol suspended by the IRB due to regulatory concerns, an on-site review by a subcommittee of the IRB might occur or

approval might be subject to an audit of study performance after a few months of enrollment or after enrollment of the first several subjects.

For each initial or continuing approval, the IRB will indicate an approval period with an approval expiration date specified. IRB approval lapses on the expiration date of the approval. For a study approved by the convened IRB, the approval period starts on the date that the IRB conducts its final review of the study, that is, the date that the convened IRB approved the research or the date the convened IRB gave conditional approval. For a study approved by expedited review procedures, the approval period begins on the date the IRB reviewer gives final approval to the protocol.

The approval date and approval expiration date are clearly noted on all IRB certifications sent to the PI and must be strictly adhered to. Investigators should allow sufficient time for development and review of renewal submissions.

Review of a change in a protocol ordinarily does not alter the date by which continuing review must occur.

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.

3.10.4 Local Implementation (as of January 2018)

In most cases in accordance with the new final rule, continuing review will no longer be required. Reviewers will note whether continuing review is required and if yes, will justify the need for continuing review.

Status Report. For research that meets criteria listed in Sec 3.10.2, the CMU IRB will require 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. If a status report is not submitted within 90 days of the anniversary of the approval date, the protocol will be administratively closed.

Legacy Protocols. Research 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 give an explanation as described above) or may be discontinued. The determination will be documented in the protocol file, and investigators will be required to submit an annual status report.

3.10.5 When Continuing Review Might be Required

The CMU 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:

1. Required by other applicable regulations (e.g., FDA);
2. The research involves topics, procedures, or data that may be considered sensitive or controversial;

3. The research involves particularly vulnerable subjects or circumstances that increase subjects' vulnerability;
4. An investigator has minimal experience in research or the research type, topic, or procedures; and/or
5. An investigator has a history of noncompliance

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

3.10.6 Continuing Review Process

The IRB Office staff will send renewal notices to investigators three months, two months, and one month in advance of the expiration date; however, it is the investigator's responsibility to ensure that the continuing review of ongoing research is approved prior to the expiration date. By federal regulation, no extension to that date can be granted.

Investigators must submit the following for continuing review:

1. the continuing review form, updated with any changes,
2. the Protocol Change form if applicable,
3. the current consent document,
4. any newly proposed consent document, and

In conducting continuing review of research not eligible for expedited review, all IRB members are provided with and review all of the above material and the Primary Reviewer will review the complete protocol, including any modifications previously approved by the IRB. At the meeting, the Primary and Secondary Reviewers lead the IRB through the completion of the regulatory criteria for approval in the "Institutional Review Board – Protocol Review/Continuing Review" checklist.

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

3.10.7 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 will occur even if the investigator has provided the continuing information before the expiration date. Therefore, investigators must allow sufficient time for IRB review before the expiration date.

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

If research participants are currently enrolled in the research project and their participation is ongoing, once notified of the expiration of approval the PI must immediately submit to the IRB Chair a list of research subjects for whom suspension of the research would cause harm.

Enrollment of new subjects cannot occur and continuation of research interventions or interactions for already enrolled subjects should only continue when the IRB or IRB Chair finds that it is in the best interest of the individual subjects to do so.

Failure to submit continuing review information on time is noncompliance and will be handled according to the noncompliance policy. (See Section 10.3).

Once approval has expired, IRB review and re-approval must occur prior to re-initiation of the research. If the study approval has lapsed more than 90 days and the PI has not provided the required continuing review information, the PI must submit a new application to the IRB for review and approval. If the study approval has lapsed 90 or less and the PI provides the required continuing review information, the existing protocol may be reviewed for consideration of continued IRB approval.

If a research protocol receives contingent approval at the time of the continuing review and the approval expires before the PI responds to the contingencies, the PI may not enroll any new subjects or access medical records after the approval expiration date. Once the PI responds, the existing protocol will be reviewed for continuation.

3.11 Amendment of an Approved Protocol

Investigators wishing to modify or amend an approved protocol must seek IRB approval before making any changes unless the change is necessary to eliminate an immediate hazard to the subject (in which case the IRB must then be notified at once).

This requirement applies to all research approved by the CMU IRB, including any aspects of exempt research subject to limited IRB review (See Section 3.3), and research for which continuing review is not required.

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

Modifications may be approved if they are within the scope of what the IRB originally authorized. Modifications that substantially alter the scope of the originally approved protocol will require a new application.

Investigators must submit documentation about the changes to e study, including, but not limited to:

1. Completed “Request for Protocol Change” form.
2. Revised Investigator’s protocol application or sponsor’s protocol (if applicable).
3. Revised approved consent/parental permission/assent documents (if applicable) or other documentation that would be provided to subjects when such information might relate to their willingness to continue to participate in the study.
4. Revised or additional recruitment materials.
5. Any other relevant documents provided by the investigator.

IRB Office staff will determine whether the proposed changes may be approved through an expedited review process, if the changes are minor, or whether the modification warrants full board review. The reviewer(s) using the expedited procedure has the ultimate responsibility to

determine that the proposed changes may be approved through the expedited review procedure and, if not, must refer the protocol for full board review.

3.11.1 Expedited Review of Protocol Modifications

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

The reviewer(s) completes a reviewer worksheet/checklist to determine whether the modifications meet the criteria allowing review of the amendment using the expedited procedure and, if so, whether the research with the proposed modifications continues to meet the regulatory criteria for approval.

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

3.11.2 Review of Protocol Modifications at Convened Meeting

When a proposed change alters the risks or benefits of a protocol that is more than minimal risk or changes a minimal risk protocol to more than minimal risk , 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 modifications and leads the IRB through the completion of the regulatory criteria for approval. The IRB will determine whether the research with the proposed modifications continues to meet the regulatory criteria for approval.

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

3.12 Closure of Protocols

The completion or termination of the study, whether premature or not, is a change in activity and must be reported to the IRB. Although subjects will no longer be "at risk" under the study, a final report to the IRB allows it to close its files and provides information that may be used by the IRB in the evaluation and approval of related studies. Investigators must submit an *End of Project Report Form* to the IRB.

3.13 Reporting IRB Actions

All IRB actions are communicated to the PI, or designated primary contact person for the protocol, in by email within ten (10) working days via a template letter prepared by the IRB staff

For an approval, along with written notification of approval, a copy of the approved consent form containing the stamped approval with the dates of the approval and expiration (if applicable) on

each sheet will be made available to the investigator. For a deferral, the notification will include the modifications required for approval along with the basis for requiring those modifications. For a disapproval, termination or suspension, the notification will include the basis for making that decision.

All letters to investigators are filed in the protocol files maintained by the IRB.

The IRB reports its findings and actions to the institution in the form of its minutes, which are distributed by IRB staff to the CMU Institutional Official and are stored permanently and securely in the IRB Office.

3.14 Review and Reconsideration of IRB Decisions

When an IRB protocol presented at a convened meeting is disapproved or deferred, the IRB will notify the PI in writing about the specific deficiencies and the modifications that are necessary for 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 cases where there is disagreement between the IRB and the PI regarding the nature and extent of the requested changes and these disagreements cannot be resolved amicably, the PI and/or the IRB may ask the IO to assist in resolving the matter. The IO may organize a meeting to help facilitate discussion between the IRB and the PI. While the IO may provide input and make recommendations to the IRB for resolution of the matter, final determinations for approval remain under the purview of the IRB.

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

3.15 Use of Other IRBs

The IO may authorize use of other IRBs to review and oversee certain research projects that involve human subjects.

3.15.1 Situations in which use of another IRB would be appropriate:

1. CMU physicians wish to conduct research involving patients under care at an affiliated hospital or need to access facilities at an affiliated hospital. In this case, the hospital IRB would have responsibility for review and oversight.
2. CMU investigators wish to participate in sponsored research involving human subjects and the sponsor proposes using a central IRB that would oversee the research at several centers.
3. A CMU investigator wishes to participate in research sponsored by a component of the National Institutes of Health that has designated a central IRB to review and oversee the research.

3.15.2 CMU responsibilities prior to accepting oversight for a study by an external IRB

When the submission packet is received, the DRC or designee will review the materials and sponsor protocol, including:

1. The policies, procedures and resources of the external IRB. Preference is for an accredited IRB. However, if this is not feasible, then the DRC must assure that the policies are at least as rigorous as CMU's.
2. Principal Investigator's experience and assessment of prior noncompliance issues, if any.
3. Local resources available to the CMU investigator.
4. Involvement of special populations, e.g., minors/minor assent, adults unable to consent form themselves.
5. Lack of conflict with existing CMU Policies and Procedures.

Once the review is completed, CMU and the external IRB will execute an inter-institutional agreement. The IO or designee will sign on behalf of CMU. This document will describe the responsibilities of both institutions including: any financial aspects of IRB review (when a commercial IRB is involved); providing any training necessary to conduct the research; monitoring the research; communication of relevant information, especially information related to safety of participants; and procedures for responding to allegations of noncompliance by CMU investigators. The PI will be required to confirm that institutional processes for financial disclosure/COI management requirements, budget review, and contract negotiation are either in process or completed. Additional reminders of local policies concerning special topics (minor assent, incapable adults etc) may also be included in the notification to the independent IRB.

3.15.3 CMU and IRB responsibilities after approval

Reports of site monitoring activities (conducted either by CMU or another entity) with any finding that potentially impacts human subject protections will be shared between the external IRB and CMU. The external IRB copies the CMU IRB on all documents submitted to the PI of the study in question. CMU investigators approved through an independent IRB must report Unanticipated Problems to the CMU IRB Office, in addition to reporting such events to the external IRB.

3.16 Posting of Clinical Trial Consent Forms

The revised Common Rule includes a requirement for the posting of one IRB-approved consent form to a publicly available Federal website for each clinical trial conducted or supported by a Common Rule department or agency after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject. This requirement may be satisfied by either the awardee or the Federal department or agency. 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 website (e.g., confidential commercial information), the department or agency may permit or require redactions to the information posted.

If CMU is the awardee and is responsible for posting the consent form, the the Office of Sponsored Programs would be responsible for making it available on the designated site.

3.17 Multisite Studies

The following information must be supplied to the CMU IRB when the CMU investigator is the Lead Investigator on a Multi-Center Study or if the CMU site is the Coordinating Center for a Multi-Center Study.

3.17.1 Role of the Lead Investigator

A detailed description of the role of the lead investigator specifying his/her authorities and responsibilities (as distinct from those as principal investigator responsible for conduct of research at CMU). Reporting requirements to sponsor (if any).

3.17.2 Study sites

Name of site; site investigator; name and registration number of IRB responsible for oversight; research activities to be conducted.

3.17.3 Site approvals

Approval by IRB overseeing project at site. Letter from signatory authority approving research at the site.

3.17.4 Communication among sites

Plan to manage communication of information relevant to the protection of human subjects, such as reporting unexpected problems; protocol modifications; and interim results.

Plan for monitoring and auditing at sites.

4 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.

4.1 IRB Records

IRB records include but are not limited to:

1. Written operating procedures.
2. IRB membership rosters [See Section 4.5].
3. Training records. The IRB Administrator maintains accurate records listing research investigators, IRB members, and IRB staff who have fulfilled the facility's human subject training requirements. Electronic copies of documentation are maintained in the official IRB records located in the IRB Office.
4. IRB correspondence (other than protocol related).
5. IRB Study Files
6. Documentation of exemptions].
7. Documentation of convened IRB meetings minutes [See Section 4. 4 for information included in the minutes].
8. Documentation of review by another institution's IRB when appropriate.
9. Documentation of cooperative review agreements, e.g. Memoranda of Understanding (MOUs).
10. Federal Wide Assurances.
11. Protocol violations submitted to the IRB.
12. Quality assurance reviews.

Documentation for off-site IRBs include:

1. On-line access to all applicable protocol documents.
2. MOU/Agreements of IRB Services.
3. Workflow/SOPs.
4. Notes/documents pertaining to administrative reviews.

4.2 IRB Study Files

The IRB will maintain a separate IRB study file for each research application (protocol) that it receives for review. Protocols will be assigned a unique identification number by the IRB document management system and entered into the IRB tracking system.

Accurate records are maintained of all communications to and from the IRB. Copies are filed in the PI's project file. The CMU IRB maintains a separate file for each research protocol that includes, but is not limited to:

1. Protocol and all other documents submitted as part of a new protocol application.
2. Investigator brochure, if any.

3. Scientific evaluations when provided by an entity other than the IRB.
4. All other documents submitted as part of an application for continuing review/termination of research application.
5. Documents submitted and reviewed after the study has been approved, including reports of modifications to research/amendments and Adverse Event reports.
6. Copy of IRB-approved Consent Form.
7. DHHS-approved sample consent form document and protocol, when they exist.
8. IRB reviewer forms.
9. Documentation of type of IRB review.
10. For expedited review, documentation of any determinations required by the regulations and protocol-specific findings supporting those determinations, including waiver or alteration of the consent process, research involving pregnant women, fetuses, and neonates; research involving prisoners; and research involving children.
11. Documentation of all IRB review actions.
12. Notification of expiration of IRB approval to the PI, and instructions for submitting relevant continuing review materials.
13. Notification of suspension or termination of research.
14. Correspondence pertaining to appeals.
15. Copies of approval letters and forms that describe what the PI must do before beginning the study.
16. IRB correspondence with research investigators and IRB correspondence relevant to the research
17. For devices, a report of prior investigations.
18. Reports of unanticipated problems involving risk to subjects or others and adverse events.
19. Documentation of audits, investigations, reports of external site visits.

4.3 Documentation of Expedited Reviews

IRB records for initial and continuing review by the expedited procedure must include the specific permissible category; that the activity described by the investigator satisfies all of the criteria for approval under expedited review; the approval period and any determinations required by the regulations including protocol-specific findings supporting those determinations.

Additionally, records must include:

1. The rationale for conducting continuing review of research that otherwise would not require continuing review.
2. The rationale for a determination that research appearing on the expedited review list published in the Federal Register is more than minimal risk.

4.4 IRB Minutes

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

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:

1. Attendance
2. Names of members present.
3. Names of members or alternate members who are participating through videoconference or teleconference and documentation that those attending through videoconferencing or teleconferencing received all pertinent material prior to the meeting and were able to actively and equally participate in all discussions.
4. Names of alternates attending in place of specified (named) absent members. (Alternates may substitute for specific absent members only as designated on the official IRB membership roster.)
   Note: The initial attendance list shall include those members present at the beginning of the meeting. The minutes will indicate, by name, those members who enter or leave the meeting. The vote on each action will reflect those members present for the vote on that item. Members who recuse themselves because of conflict of interest are listed by name and their reasons are documented.
5. Names of consultants, investigators, and guests present.
6. Announcements made by the Chair regarding member conflict oif interest and confidentiality of discussion at meetings.
7. The presence of a quorum throughout the meeting, including the presence of one member whose primary concern is in a non-scientific area.
8. Business items discussed.
9. Continuing education.
10. Actions taken, including separate deliberations, actions, and votes for each protocol undergoing initial review, continuing review, or review of modifications by the convened IRB.
11. Votes on these actions (total number voting, number voting for, number voting against, number abstaining; number of those excused, number of those recused).
12. Basis or justification for these actions including required changes in research.
13. Summary of controverted issues discussed and their resolution.
14. Approval period for initial and continuing approved protocols, including identification of research that warrants review more often than annually and the basis for that determination.
15. Risk level of initial and continuing approved protocols.
16. Review of interim reports, e.g. unanticipated problems or safety reports, amendments, report of violation/deviations, serious or continuing non-compliance, suspensions/terminations, etc.
17. Review of Plans for Data and Safety Monitoring and Review of Data Safety Monitoring Board (DSMB) summary if applicable.
18. Justification for deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document.
19. Protocol-specific documentation that the research meets the required criteria [45 CFR 46.116(d)] when approving a consent procedure that does not include or that alters some or all the required elements of informed consent or when waiving the requirement to obtain an informed consent.
20. Protocol-specific documentation that the research meets the required criteria [45 CFR 46.117(c)] when the requirements for documentation of consent are waived.

21. When approving research that involves populations covered by Subparts B, C, or D of 45 CFR 46, the minutes will document the IRB's justifications and findings regarding the determinations stated in the Subparts or the IRB's agreement with the findings and justifications as presented by the investigator on IRB forms.
22. Special protections warranted for other groups of subjects who are likely to be vulnerable to coercion or undue influence, such as cognitively impaired persons or economically or educationally disadvantaged persons, regardless of source of support for the research.
23. The rationale for significant risk/non-significant risk device determinations.
24. Determinations of conflict of interest.
25. 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.
26. A list of research approved since the last meeting utilizing expedited review procedures.
27. An indication that, when an IRB member has a conflicting interest (see Section 2.8) with the research under review, the IRB member was not present during the deliberations or voting on the proposal and that the quorum was maintained.
28. Key information provided by consultants will be documented in the minutes or in a report provided by the consultant.

4.5 IRB Membership Roster

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

1. Name.
2. Earned degrees.
3. Affiliated or non-affiliated status(described in Section 1.3)
4. Status as scientist or nonscientist
5. Indications of experience, such as board certifications or licenses sufficient to describe each member's chief anticipated contributions to IRB deliberations.
6. Representative capacities of each IRB member; which IRB member is a prisoner representative (as required by Subpart C), and which IRB members are knowledgeable about or experienced in working with children, pregnant women, cognitively impaired individuals, and other vulnerable populations locally involved in research.
7. Role on the IRB (Chair, Vice-Chair, etc.).
8. Voting status.
9. For alternate members, the primary member or class of members for whom the member could substitute.

The DRC is an *ex officio* member of the IRB and may participate in discussions and render opinion about interpretation of regulations, but does not participate in voting.

The HRPP office must keep IRB membership list current. The DRC must promptly report changes in IRB membership to the Office for Human Research Protections, Departments of Health and Human Services.

4.6 Access to IRB Records

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

1. 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.
2. 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 (eg, 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.
3. Records are accessible for inspection and copying by authorized representatives of f regulatory agencies during regular business hours.
4. Records may not be removed from the IRB Office; however, the IRB staff will provide copies of records for authorized personnel if requested.
5. All other access to IRB study files is prohibited.

4.7 Record Retention

IRB minutes are retained indefinitely.

IRB records of protocol reviews must be retained by the facility for at least three (3) years after completion of the research.

5 Informed Consent

No investigator conducting research 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 5.8 of these procedures.

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

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

5.1 Definitions

Legally Authorized Representative (LAR) – A legally authorized representative (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 legally authorized representative includes, but is not limited to, not only a person appointed as a health care agent under a Durable Power of Attorney for Health Care (DPAHC)or a court appointed guardian of the person but also next-of-kin in the following order of priority unless otherwise specified by applicable state law: spouse, adult child (18 years of age or older), parent, adult sibling (18 years of age or older), grandparent, or adult grandchild (18 years of age or older).

Legal guardian – A person appointed by a court of appropriate jurisdiction.

5.2 Basic Requirements

The requirement to obtain the legally-effective informed consent of individuals before involving them in research is one of the basic protections provided for by the federal regulations and the CMU HRPP. Investigators are required to obtain legally-effective informed consent from a subject or the subject's legally authorized representative. When informed consent is required, it must be sought prospectively and documented properly.

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

Informed consent is more than just a signature on a form. It is a process of information exchange to include reading and signing the informed consent document. The informed consent process is the critical communication link between the prospective human subject and an investigator, beginning with the initial approach of an investigator and continuing through the completion of the research study. Investigators must have received the appropriate training and be knowledgeable about the study protocol so they can answer questions to help provide understanding to the study participant or potential study participant. The exchange of information between the investigator and study participant can occur via one or more of the following modes of communication, among others: face-to-face contact, mail, telephone, email, internet, or fax. .

Investigators must obtain consent prior to entering a subject into a study and/or conducting any procedures required by the protocol, unless consent is waived by the IRB.

If someone other than the investigator conducts the interview and obtains consent from a participant, 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 be able to answer questions about the study.

Sample or draft consent documents may be developed by a sponsor or cooperative study group. However, the IRB-of-record is the final authority on the content of the consent documents that is presented to the prospective study participants.

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.

5.3 General Requirements for Informed Consent

Informed consent must be obtained under the following circumstances:

1. Informed consent may only be obtained from subjects who have the legal and mental capacity to give consent. For subjects without that capacity, consent must be obtained from a legal guardian or a legally authorized representative.
2. The informed consent process will be sought under circumstances that provide the subject (or legally authorized representative) with sufficient opportunity to discuss and consider whether or not to participate.
3. The informed consent process shall be sought under circumstances that minimize the possibility of coercion or undue influence.
4. 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 to 8th grade level and in non-technical terms should be used in the description of the research.
5. For subjects whose native language is not English, informed consent must be obtained in a language that is understandable to the subject or the subject's LAR. In accordance with this policy, the IRB requires that informed consent conferences include a reliable translator when the prospective subject does not understand the language of the person who is obtaining consent.
6. 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
7. Generally, the beginning of an informed consent should include a concise explanation of the following:
   a. The fact that consent is being sought for research and that participation is voluntary;
   b. The purposes of the research, the expected duration of the prospective subject's participation, and the procedures to be followed in the research;
   c. The reasonably foreseeable risks or discomforts to the prospective subject;

d. The benefits to the prospective subject or to others that may reasonably be expected from the research; and
e. Appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the prospective subject.

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

Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or LAR's understanding of the reasons why one might or might not want to participate

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

The PI is responsible for insuring that each prospective subject is adequately informed about all aspects of the research and understands the information provided.

5.4 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 and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental, a description of any reasonably foreseeable risks or discomforts to the subject,

1. A description of any benefits to the subject or to others that may reasonably be expected from the research.
2. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
3. A statement describing the extent, if any, to which confidentiality of records identifying the subject must be maintained.
4. For research involving more than minimal risk, an explanation as to the availability of medical treatment in the case of research-related injury, including who will pay for the treatment and whether other financial compensation is available.
5. An explanation of whom to contact on the research team for answers to pertinent questions about the research or to voice concerns or complaints about the research, and whom to contact in the event of a research-related injury to the subject.
6. Contact information for the IRB to obtain answers to questions about the research, to voice concerns or complaints about the research, to obtain answers to questions about their rights as a research participant, in the event the research staff could not be reached, and in the event the subject wishes to talk to someone other than the research staff.
7. 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.

8. One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:
    a. 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
    b. 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.
    c. Data will be destroyed.

5.4.1 FDA regulated studies

For FDA-regulated studies, the possibility that the Food and Drug Administration may inspect the records needs to be included in the statement regarding subject confidentiality.

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

1. A statement that the particular treatment or procedure may involve risks to the subject, which are currently unforeseeable. (For example, include when the research involves investigational test articles or other procedures in which the risks to subjects is not well known.)
2. A statement that if the subject is or becomes pregnant, the particular treatment or procedure may involve risks to the embryo or fetus, which are currently unforeseeable. (For example, include when the research involves pregnant women or women of childbearing potential and the risk to fetuses of the drugs, devices, or other procedures involved in the research is not well known.)
3. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent. (For example, include when there are anticipated circumstances under which the investigator may terminate participation of a subject.)
4. Any additional costs to the subject that may result from participation in the research. (For example, include when it is anticipated that subjects may have additional costs.)
5. The consequences of a subject's decision to withdraw from the research. (For example, include when withdrawal from the research is associated with adverse consequences.)
6. Procedures for orderly termination of participation by the subject. (For example, include when the protocol describes such procedures.)
7. 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. (For example, include when the research is long term and interim information is likely to be developed during the conduct of the research.)
8. The approximate number of subjects involved in the study. (For example, include when the research involves more than minimal risk.)
9. 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.

10. A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions.
11. 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).

5.4.3 General Data Protection Regulation (GDBP)

CMU investigators conducting research in one of the Member States of the European Union, or of Iceland, Liechtenstein, Norway, or the UK, 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.

5.5 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. Broad consent is not currently recognized in FDA regulation or guidance.

The following elements of broad consent [§46.116(d)] shall be provided to each subject or the subject's LAR:

1. A description of any reasonably foreseeable risks or discomforts to the subject;
2. A description of any benefits to the subject or to others which may reasonably be expected from the research;
3. A statement describing the extent, if any, to which confidentiality of records identifying the subject must be maintained;
4. 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;
5. 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;
6. 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);
7. 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;
8. 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;

9. 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);
10. 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;
11. Unless it is known that clinically relevant research results, including individual research results, will be disclosed to the subject in all circumstances, a statement that such results may not be disclosed to the subject; and
12. 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.

Investigators must include information regarding the circumstances under which broad consent will be obtained, the proposal for tracking of responses, and the proposed consent form(s) (or oral script if a waiver of documentation of consent is sought) and any other consent materials (e.g., information sheet, audio-visual materials, etc.) in their submission to the IRB. The CMU IRB will review the information provided with the aid of a checklist to ensure that all requirements are satisfied. The outcome of the IRB's review will be communicated to the investigator in writing.

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

5.6 Documentation of Consent

Unless the requirement for documentation of consent is waived by the IRB, informed consent must be documented by the use of written informed consent document (ICD) approved by the IRB and signed (including in an electronic format) by the subject or the subject's LAR. A written copy must be given to the person signing the ICD.

The ICD may be either of the following:

1. A written consent document that embodies the basic and required additional elements of informed consent. The investigator shall give either the subject or the subject's LAR adequate opportunity to read the informed consent form before it is signed; alternatively, this form may be read to the subject or the subject's legally authorized representative; or
2. A short form written consent document stating that the elements of informed consent have been presented orally to the subject or the subject's LAR and that the key information required by§46.116(a)(5)(i) (See Section 5.3 #5.a) was presented first to the subject before other information, if any, was provided. When this method is used:
   a. The oral presentation and the short form written document should be in a language understandable to the subject; and

b. There must be a witness to the oral presentation; and
c. The IRB must approve a written summary of what is to be said to the subject (the approved full consent document may serve as this summary); and
d. The short form document is signed by the subject;
e. The witness must sign both the short form and a copy of the summary; and
f. The person actually obtaining consent must sign a copy of the summary; and
g. A copy of the summary must be given to the subject or LAR, in addition to a copy of the short form.

5.7 Special Consent Circumstances

5.7.1 Non-English Speaking Subjects

Expected enrollment of non-English speaking subjects: In some protocols, the PI expects non-English speaking subjects to enroll because, for example, the protocol is studying a disease or condition that is likely to attract them or the PI is actively recruiting them. When the study subject population includes non-English speaking people or the PI and/or the IRB anticipates that consent discussions will be conducted in a language other than English, the IRB shall require a translated consent document to be prepared. In order to assure itself that the translation is accurate, the IRB may choose to require a certified translation, to have an independent back translation or to have a review of the consent document by an IRB member or other person who is fluent in that language. The subjects are given a copy of the signed translated consent document.

Unexpected enrollment of a non-English speaking subject: If a non-English speaking subject is unexpectedly eligible for protocol enrollment, there may not be an extant IRB-approved written translation of the consent document. 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 at the signing of the consent document or in subsequent discussions, his/her consent may not be informed, and therefore, not effective.

If a PI decides to enroll a subject into a protocol for which there is not an extant IRB-approved informed consent document in the prospective subject's language, the PI must receive IRB approval to follow the procedures for a “short form” written consent in as described in Section 12.6 (3b).

5.7.2 Use of interpreters in the consent process:

Unless the person obtaining consent is fluent in the prospective subject’s language, an interpreter will be necessary to deliver information in the IRB-approved script and to facilitate the consent conversation. Preferably someone who is independent of the subject (i.e., not a family member) should assist in presenting information and obtaining consent. Whenever possible, interpreters should be provided copies of the short form and the IRB-approved consent script well before (24 to 48 hours if possible) the consent conversation with the subject. If the interpreter also serves as the witness, she/he may sign the short form consent document and script as the witness and should note “Interpreter” under the signature line. The person obtaining consent must document that the “short form” process was used5.7.2 Braille Consent

For blind subjects who read Braille, the IRB may approve a consent document prepared in Braille. In order to assure itself that a Braille consent document is accurate, the IRB may require a transcription into print text or review of the document by an IRB member or other person who

reads Braille. If possible, the subject will sign the Braille consent; otherwise, verbal consent will be obtained, witnessed, and documented as described below.

5.7.3 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 (a) retains the ability to understand the concepts of the study and evaluate the risk and benefits of being in the study when it is explained verbally and (b) 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 5.10.

For more than minimal risk research, the consent form must be read to the subjects and the subjects must be given an opportunity to ask questions. An audio-recording approved by the IRB may 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 verbal 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 verbal consent. For medical research when appropriate, the consent process will also be documented in the medical record or in accord with the CMU's policy. Signed copies of the consent form are given to the subject and, whenever possible, these documents should be provided to the subject on audio or video tape.

5.8 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 (a 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

1. High risk studies.
2. Studies that involve particularly complicated procedures or interventions.
3. Studies involving highly vulnerable populations (e.g., ICU patients, children).
4. Studies involving study staff with minimal experience in obtaining consent to potential study participants.
5. Other situations when the IRB has concerns that the consent process is not being conducted appropriately.

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

5.9 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 may decide to terminate a subject's participation in research regardless of whether the subject wishes to continue participating. Investigators must plan for the possibility that subjects will withdraw from research and include a discussion of what withdrawal will mean and how it will be handled in their research protocols and informed consent documents.

Regulatory requirements regarding the retention and use of data after subject withdrawal or termination differ between research that is subject to FDA regulations and research that is not subject to FDA regulations. Under applicable FDA law and regulations, data collected on human subjects enrolled in an FDA-regulated clinical trial up to the time of subject withdrawal must remain in the trial database in order for the study to be scientifically valid. For research not subject to FDA regulations, investigators, in consultation with the funding agency, can choose to 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 seeking informed consent from subjects, the following information regarding data retention and use must be included:

1. 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.
2. For research not subject to FDA regulations, the investigator should inform subjects whether the investigator intends to either (i) retain and analyze already collected data relating to the subject up to the time of subject withdrawal, or (ii) 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.
3. For subjects from nations included under GDPR, these regulations must be also followed.
4. Sometimes a subject wants to withdraw from the primary interventional component of a study but is willing to allow the investigator to continue other research activities described in the IRB-approved protocol and informed consent document that involve participation of the subject, such as (a) obtaining data about the subject through interaction with the subject (e.g., through follow-up interviews, physical exams, blood tests, or radiographic imaging); or (b) obtaining identifiable private information from the subject's medical, educational, or social services agency records or from the subject's healthcare providers, teachers, or social worker. When a subject's withdrawal request is limited to discontinuation of the primary interventional component of a research study, research activities involving other types of participation for which the subject previously gave consent may continue. The investigator 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 continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through noninvasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.
5. If a subject withdraws from the interventional portion of the study but agrees to continued follow-up of associated clinical outcome information 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 informed consent form). IRB approval of informed consent documents would be required.
6. If a subject (a) withdraws from the interventional portion of a study, (b) does not consent to continued follow-up of associated clinical outcome information, and (c) does not request removal of their data, the investigator must not access for purposes related to the study the

subject's medical record or other confidential records requiring the subject's consent. 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.

5.10 Waiver or Alteration of Informed Consent

When reviewing research subject to the revised Common Rule, the CMU IRB will evaluate requests for waivers or alterations of informed consent in accordance with the requirements and criteria specified in the revised rule and summarized below. The IRB's determination will be documented in the IRB record and communicated to the investigator.

FDA regulations do not provide for waivers of informed consent except in emergency situations [which the CMU IRB does not review].

5.10.1 General Waiver or Alteration of Consent

In order to approve a request from an investigator to waive the requirement for informed consent, or to omit or alter one or more basic or additional element of consent (an "Alteration"), under this provision the CMU IRB must determine and document that the below criteria are satisfied.

1. The research involves no more than minimal risk to the subjects;
2. The research could not practicably be carried out without the requested waiver or alteration;
3. If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
4. The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
5. Whenever appropriate, the subjects or LARs will be provided with additional pertinent information after participation.
6. Investigators may be asked to provide justification, or additional information or documentation, to support that the above criteria are satisfied.

Restrictions:

Waivers

1. If an individual was asked to provide broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens in accordance with the requirements in Sections 8.1 and 8.3, and refused to consent, an IRB cannot waive consent for the storage, maintenance, or secondary research use of the identifiable private information or identifiable biospecimens.

Alterations

1. An IRB may not approve a request to alter or omit any of the general requirements for informed consent described in Section 8.1
2. If a broad consent procedure is used, an IRB may not alter or omit any of the elements described in Section 8.3.

5.10.2 Waiver or Alteration of Consent in Research Involving Public Benefit and Service Programs

In order to approve a request from an investigator to waive the requirement for informed consent, or to omit or alter one or more basic or additional element of consent (an "Alteration"), under this provision the CMU IRB must determine and document that the below criteria are satisfied.

1. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
    a. Public benefit or service programs;
    b. Procedures for obtaining benefits or services under those programs;
    c. Possible changes in or alternatives to those programs or procedures; or
    d. Possible changes in methods or levels of payment for benefits or services under those programs; and
2. The research could not practicably be carried out without the waiver or alteration.
3. Waivers –
    a. If an individual was asked to provide broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens in accordance with the requirements in Sections 8.1 and 8.3, and refused to consent, an IRB cannot waive consent for the storage, maintenance, or secondary research use of the identifiable private information or identifiable biospecimens.
4. Alterations
    a. An IRB may not approve a request to alter or omit any of the general requirements for informed consent described in Sections 8.1 and 8.3
    b. If a broad consent procedure is used, an IRB may not alter or omit any of the elements described in Section 8.3

5.11 Screening, Recruiting, or Determining Eligibility

The revised Common Rule removes the requirement for partial waivers of consent for the use of information or specimens for the purposes of screening, recruiting, or determining the eligibility of prospective subjects for inclusion in the research. Pursuant to the revised rule, the CMU IRB may approve a research proposal in which an investigator will obtain information or biospecimens for these purposes without the informed consent of the prospective subject or the subject's LAR if either of the following conditions is met:

1. The investigator will obtain information through oral or written communication with the prospective subject or LAR, or
2. The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

When research is subject to the revised Common Rule, and the above conditions are met, 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.

5.12 Waiver of Documentation of Informed Consent

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

1. The only record linking the subject and the research would be the consent document and the principle risk would be potential harm resulting from a breach of confidentiality.
   Note 1: Subjects must be asked whether they want documentation linking them with the research, and their wishes must govern. (For example, domestic violence research where the primary risk is discovery by the abuser that the subject is talking to researchers.)
   Note 2: In order to waive written documentation of consent where the only record linking the participant and the research would be the consent document, the IRB has to determine that the research was not FDA-regulated.
2. 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-researchers (e.g., marketing surveys, telemarketing).
3. The subjects or LARs are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects, and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

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

5.13 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 the following conditions are met:

1. There is an explicit statement, either in writing or verbally, of consent to participate;

2. the research presents no more than minimal risk to participants; and

3. the research is not supported by a Common Rule agency.

6 Vulnerable Subjects in Research

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

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

6.1 Involvement of Vulnerable Populations

When participants in a protocol are likely to be vulnerable to coercion or undue influence, the IRB should include additional safeguards to protect their rights and welfare. Examples of the vulnerable populations that might be involved in research include children, fetuses, neonates, prisoners, or individuals with impaired decision-making capability, students, employees, or homeless persons.

If the IRB reviews research that involves categories of participants vulnerable to coercion or undue influence, the review process will include one or more individuals who are knowledgeable about or experienced in working with these participants. 45 CFR 46 has additional subparts designed to provide extra protections for vulnerable populations that also have additional requirements for IRBs.

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

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

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

DHHS-funded research that involves any of these populations must comply with the requirements of the relevant subparts. Research funded by other federal agencies may or may not be covered by the subparts.

Under CMU's FWA, the subparts only apply to DHHS-funded research and research funded by another federal agency that requires compliance with the subparts. (FDA regulations include Subpart D, which applies to all FDA-regulated research). The following policies and procedures, which are based on the subparts, apply to all research regardless of funding. The individual sections describe how the subparts apply to DHHS-funded research.

6.2 Responsibilities

1. The PI is responsible for identifying the potential for enrolling vulnerable subjects in the research proposal. The PI is responsible for identifying participants who are at risk for impaired decisional capacity who are being asked to participate in a research study.
2. The IRB shall include representation, either as members or ad hoc consultants, individual(s) who have professional interest in or who have experience with the vulnerable populations involved in a research proposal.

3. The IRB reviews the PI's justifications for including vulnerable populations in the research to assess appropriateness of the research proposal.
4. The IRB must ensure that additional safeguards have been included in each study to protect the rights and welfare of vulnerable subjects as needed at the time of initial review of the research proposal.
5. Information reviewed as part of the continuing review process should include the number of participants considered as members of specific vulnerable populations.
6. For studies that do not have or are not required to have a Data and Safety Monitoring Board (DSMB) or a Data Monitoring Committee and have entered vulnerable subjects, the IRB needs to carefully review the safety monitoring plan.
7. The IRB should be knowledgeable about and experienced in working with populations who are vulnerable to coercion and undue influence. If the IRB requires additional qualification or expertise to review a protocol, it should obtain consultation.

6.3 Procedures

6.3.1 Initial Review of Research Proposal

1. The PI should identify the potential to enrol vulnerable subjects in the proposed research at initial review and provide the justification for their inclusion in the study.
2. The IRB evaluates the proposed plan for consent of the specific vulnerable populations involved. If the research involves adults unable to consent, the IRB evaluates the proposed plan for permission of legally authorized representatives.
3. The IRB evaluates and approves the proposed plan for the assent of participants.
4. The IRB evaluates the research to determine the need for additional protections and consider the use of a Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee as appropriate.
5. The PI should provide appropriate safeguards to protect the subjects' rights and welfare, which may include the addition of an independent monitor. The independent monitor is a qualified individual not involved in the research study who will determine the subject's capacity to provide voluntary informed consent.
6. The IRB assesses and documents the adequacy of additional protections for vulnerable populations provided by the PI.

6.4 Research Involving Pregnant Women, Human Fetuses, and Neonates

CMU IRB does not review research on neonates or fetuses of uncertain viability.

6.4.1 Research Involving Pregnant Women or Fetuses

The following applies to all research regardless of funding source. Since, according to the CMU FWA, Subpart B of 45 CFR 46 applies only to DHHS-funded research, the funding-source specific requirements are noted in the appropriate sections.

6.4.1.1 Research Not Funded by DHHS

For research not funded by DHHS, 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.

Pregnant women or fetuses may be involved in research not funded by DHHS involving more than minimal risk to fetuses if all of the following conditions are met:

1. Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing riskrisks to pregnant women and fetuses.
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus.
3. Any risk is the least possible for achieving the objectives of the research.
4. If the research holds out the prospect of direct benefit to the pregnant woman and/or the prospect of a direct benefit both to the pregnant woman and the fetus, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent.
5. If the research holds out the prospect of direct benefit solely to the fetus, then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6. Each individual providing consent under paragraph (4) or (5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
7. For children who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent.
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
10. Individuals engaged in the research will have no part in determining the viability of a neonate.

6.4.1.2 Research Funded by DHHS

For DHHS-funded research, 45 CFR Subpart B applies to all research involving pregnant women. Under 45 CFR Subpart B, pregnant women or fetuses may be involved in research funded by DHHS if all the following conditions are met:

1. Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing risk to pregnant women and fetuses.
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means.
3. Any risk is the least possible for achieving the objectives of the research.
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical

knowledge that cannot be obtained by any other means, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent.

5. If the research holds out the prospect of direct benefit solely to the fetus, then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6. Each individual providing consent under paragraph (4) or (5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
7. For children who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in Section .
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
10. Individuals engaged in the research will have no part in determining the viability of a neonate.

6.4.2 Research Involving 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 of IRB Review Process and Research Involving Children.

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

Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, 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 this manual are applicable.

6.5 Research Involving Prisoners

6.5.1 Applicability

The following applies to all research involving prisoners, regardless of funding source. The requirements in this section are consistent with Subpart C of 45 CFR 46, which applies to DHHS-funded research.

Even though CMU IRB may approve a research protocol 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 law [See 45 CFR 46.301].

6.5.2 Composition of the IRB and Role of the Prisoner Representative

In addition to satisfying the general requirements detailed in the IRB section of this manual, when reviewing research involving prisoners, the IRB must also meet the following requirements:

1. 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.
2. At least one voting member of the IRB must be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB, only one IRB need satisfy this requirement.
   The prisoner representative may be listed as an alternative member who becomes a voting member when needed.
3. The prisoner representative must review research involving prisoners, focusing on the requirements in Subpart C or equivalent protections.
   The prisoner representative must receive all review materials pertaining to the research (same as primary reviewer)
4. The prisoner representative must be present at a convened meeting when the research involving prisoners is reviewed. If the prisoner representative is not present, research involving prisoners cannot be reviewed or approved.
   The prisoner representative may attend the meeting by phone, video-conference, or webinar, as long as the representative is able to participate in the meeting as if they were present in person at the meeting.
5. The prisoner representative must present his/her review either orally or in writing at the convened meeting of the IRB when the research involving prisoners is reviewed.
6. Minor modifications to research may be reviewed using the expedited procedure described below, using either of the two procedures described based on the type of modification.
7. 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).
8. 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).

If no participants have been enrolled, the research may receive continuing review using the expedited procedure under expedited category #8.

6.5.3 Use of Expedited Review Procedures

1. For research involving interaction with prisoners reviewed by the expedited procedure:
2. 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.
3. The prisoner representative must concur with the determination that the research involves no greater than minimal risk.
4. The prisoner representative must review the research as a reviewer, designated by the chair, or consultant. This may be as the sole reviewer or in addition to another reviewer, as appropriate.
5. Review of modifications and continuing review must use the same procedures for initial review using this expedited procedure including the responsibility of the prisoner representative.

6. For research that does not involve interaction with prisoners (e.g. existing data, record review) reviewed by the expedited procedure:
    a. Research that does not involve 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.
    b. Review by a prisoner representative is not required.
    c. The prisoner representative may review the research as a reviewer or consultant if designated by the IRB chair.
    d. Review of modifications and continuing review must use the same procedures as initial review.

6.5.4 Exempt Determinations

The CMU IRB does not make exempt determinations when reviewing prisoner research.

6.5.5 When a Participant Becomes a Prisoner

If a participant becomes a prisoner while enrolled in a research study that was not reviewed according to Subpart C, then the following steps must be carried out by the IRB and the investigator:

1. Confirm that the participant meets the definition of a prisoner.
2. Terminate enrollment or review the research study under Subpart C if it feasible for the participant to remain in the study.
3. Before terminating the enrollment of the incarcerated participant the IRB should consider the risks associated with terminating participation in the study.
4. If the prisoner's participation cannot be terminated for health or safety reasons, then the IRB may:
    a. Allow the prisoner to remain enrolled in the study and review the research under Subpart C.
    b. If some of the requirements of Subpart C cannot be met, but it is in the best interests of the participant to remain in the study, then the IRB may allow the prisoner to remain enrolled and inform OHRP of the decision along with the justification.
    c. Remove the participant from the study and keep the participant on the study intervention under an alternate mechanism such as compassionate use, or off label use.

6.5.6 Additional Duties of the IRB when prisoners are involved

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

1. The research falls into one of the following **permitted categories** [See 45 CFR 46.306]:
    a. 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;
    b. 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;

c. Research on conditions particularly affecting prisoners as a class (e.g., research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults);
d. Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subjects.

2. 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/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.
3. The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers.
4. 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 principal investigator provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project.
5. The information is presented in language which is understandable to the subject population.
6. Adequate assurance exists that Parole Board will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole.
7. Where the IRB finds there may be a need for follow-up examination or care of subjects after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences and for informing subjects of this fact.

6.5.6.1 Certification to HHS

Under 45 CFR 46.305(c), the institution responsible for conducting research involving prisoners that is supported by HHS shall certify to the Secretary (through OHRP) that the IRB has made the seven (7) findings required under 45 CFR 46.305(a). For all HHS 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 protocol in question and any relevant HHS grant application or protocol. HHS conducted or supported research involving prisoners as subjects may not proceed until OHRP issues its approval 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, any relevant HHS 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.

The above requirement does not apply to research that is not HHS conducted or supported.

6.5.6.2. 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:

1. The sole purposes are:
   a. to describe the prevalence or incidence of a disease by identifying all cases, or
   b. to study risk factor associations for a disease, and
2. The IRB has approved the research and fulfilled its duties under 45 CFR 46.305(a)(2)–(7) and determined and documented that
   a. the research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and
   b. prisoners are not a particular focus of the research.
3. The specific type of epidemiological research subject to the waiver involves no more than minimal risk and no more than inconvenience to the human subject participants. The waiver would allow the conduct of minimal risk research that does not now fall within the categories set out in 45 CFR 46.306(a)(2).
4. The range of studies to which the waiver would apply includes epidemiological research related to chronic diseases, injuries, and environmental health. This type of research uses epidemiologic methods (such as interviews and collection of biologic specimens) that generally entail no more than minimal risk to the subjects.
5. In order for a study to be approved under this waiver, the IRB would need to ensure that, among other things, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data.

6.6 Research Involving Children

The following procedures apply 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.

6.6.1 Allowable Categories

Research on children must be reviewed and categorized by the IRB into one of the following groups:

1. Research not involving physical or emotional risk greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (i.e., minimal risk). Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 6.7.2.
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject:
   a. the risk is justified by the anticipated benefit to the subjects; and
   b. adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 6.7.2.

3. Research involving greater than minimal risk and no reasonable prospect of direct benefit to the individual subject but likely to yield generalizable knowledge about the subject's disorder or condition:
    a. the risk represents a minor increase over minimal risk;
    b. 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;
    c. adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 6.7.2.
4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children:
    a. federally-funded research in this category must be approved by the Secretary of Health and Human Services;
    b. FDA-regulated research in this category must be approved by the Commissioner of Food and Drugs;
    c. for non-federally-funded, non-FDA research, the IRB will consult with a panel of experts in pertinent disciplines (e.g., science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research based on whether
        i. the research in fact satisfies the conditions of the previous categories, as applicable; or
        ii. the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
    d. the research will be conducted in accord with sound ethical principles; and
5. adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 6.7.2.

6.6.2 Parental Permission and Child Assent

6.6.2.1 Parental Permission

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

Parents or guardians must be provided with the basic elements of consent and any additional elements the IRB deems necessary, as described in Section 5.5.

The IRB may find that the permission of one parent is sufficient for research to be conducted under Categories (a) and (b) above. The IRB's determination of whether consent must be obtained from one or both parents will be documented in the consent checklist when a protocol receives expedited review and in meeting minutes when reviewed by the convened committee.

Consent from both parents is required for research to be conducted under Categories (c) and (d) above unless:

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

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

1. the research meets the provisions for waiver in Section 5.8, or
2. if the IRB determines that the research protocol is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (e.g., neglected or abused children) provided 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; the risk and anticipated benefit to the research subjects; and their age, maturity, status, and condition.

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

Permission from parents or legal guardians must be documented in accordance with and to the extent required by Section 5.6 and 5.9.

6.6.2.2 Assent from Children

Because “assent” means a child’s affirmative agreement to participate in research, the child must actively show his/her willingness to participate in the research, rather than just complying with directions to participate and not resisting in any way. When judging whether children are capable of assent, the IRB is charged with taking into account the ages, maturity, and psychological state of the children involved. The IRB has the discretion to judge children’s capacity to assent for all of the children to be involved in a proposed research activity or on an individual basis.

The IRB should take into account the nature of the proposed research activity and the ages, maturity, and psychological state of the children involved when reviewing the proposed assent procedure and the form and content of the information conveyed to the prospective subjects. For research activities involving adolescents whose capacity to understand resembles that of adults, the assent procedure should likewise include information similar to what would be provided for informed consent by adults or for parental permission. For children whose age and maturity level limits their ability to fully comprehend the nature of the research activity but who are still capable of being consulted about participation in research, it may be appropriate to focus on conveying an accurate picture of what the actual experience of participation in research is likely to be (e.g., 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.

The IRB presumes that children ages 7 and older should be given an opportunity to provide assent. Generally, oral assent through the use of a script should be obtained from children 7 - 11 years of age. Written assent using a written document for the children to sign may be sought for older children.

At times there may be inconsistency between parent permission and child assent. Usually a "no" from the child overrides a "yes" from a parent, but a child typically cannot decide to be in research over the objections of a parent. Obviously, there are individual exceptions to these guidelines (such as when the use of an experimental treatment for a life threatening disease is being considered). The general idea, however, is that children should not be forced to be research subjects, even when their parents consent to it.

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 when the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances detailed in the Waiver of Informed Consent section of this manual.

6.6.2.3 The Assent Form

When the IRB determines that assent is required, it will also determine whether and how assent must be documented.

Researchers should try to draft a form that is age appropriate and study specific, taking into account the typical child's experience and level of understanding, and composing a document that treats the child respectfully and conveys the essential information about the study. The assent form should:

1. tell why the research is being conducted,
2. describe what will happen and for how long or how often,
3. say it's up to the child to participate and that it's okay to say no,
4. explain if it will hurt and if so for how long and how often,
5. say what the child's other choices are,
6. describe any good things that might happen,
7. say whether there is any compensation for participating, and
8. ask for questions.

For younger children, the document should be limited to one page if possible. Illustrations might be helpful, and larger type makes a form easier for young children to read. Studies involving older children or adolescents should include more information and may use more complex language.

6.6.2.4 Children Who Are Wards

Children who are wards of the state or any other agency, institution, or entity can be included in research involving greater than minimal risk and no prospect of direct benefit to individual subjects but likely to yield generalizable knowledge about the subject's disorder or condition, **only if such research** is:

1. related to their status as wards; or
2. conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

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

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

6.7 Persons with Impaired Decision Making Capacity

The requirements in this section apply to all research involving persons with mental disabilities or persons with impaired decision-making capacity regardless of funding source.

Research involving persons with impaired decision-making capability may be approved only when the following conditions apply:

1. Only incompetent persons or persons with impaired decision making capacity are suitable as research subjects. Competent persons are not suitable for the proposed research. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as subjects. Incompetent persons or persons with impaired decision-making capacity must not be subjects in research simply because they are readily available.
2. The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Incompetent people or persons with impaired decision-making capacity are not to be subjects of research that imposes a risk of injury, unless that research is intended to benefit that subject and the probability of benefit is greater than the probability of harm.
3. Procedures have been devised to ensure that participant's representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision making capacity. Health care agents, appointed under Durable Power of Attorney for Health Care (DPAHC), and next-of-kin, or guardians, must be given descriptions of both proposed research studies and the obligations of the person's representatives. They must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest.

6.7.1 IRB Composition

The IRB membership must include at least one member who is an expert in the area of the research. Consideration may be given to adding another member who is a member of the population, a family member of such a person, or a representative of an advocacy group for that population. The IRB may utilize a consultant as necessary.

6.7.2 Determination of Decision-Making Capacity

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.

For research protocols that involve subjects with mental disorders that may affect decision-making capacity, the IRB may determine that capacity assessments are necessary, unless the investigator can justify why such assessments would be unnecessary for a particular group.

For research that poses greater than minimal risk, the IRB may require investigators to use independent and qualified professionals to assess whether potential subjects have the capacity to give voluntary, informed consent. Even in research involving only minimal risk, the IRB may require that the study include a capacity assessment if there are reasons to believe that potential subjects' capacity may be impaired. It is not necessary to require a formal capacity assessment by an independent professional for all potential research subjects with mental disorders.

For research protocols involving subjects who have fluctuating or limited decision making capacity the IRB may ensure that investigators establish and maintain ongoing communication with involved caregivers. Periodic re-consent should be considered in some cases. Third party consent monitors may be used during the recruitment and consenting process, or waiting periods may be required to allow more time for the subject to consider the information that has been presented.

It is often possible for investigators and others to enable persons with some decisional impairments to make voluntary and informed decisions to consent or refuse participation in research. Potential measures include repetitive teaching, group sessions, audiovisual presentations, and oral or written recall tests. Other measures might include follow-up questions to assess subject understanding, videotaping or audio-taping of consent interviews, second opinions, use of independent consent observers, 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 give consent, a re-consenting process with surrogate consent may be.

Though competent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives.

In the event research participants become incompetent or impaired in decision making capacity after enrolment, the PI is responsible for notifying the IRB and HRPP office. The PI is responsible for developing a monitoring plan which follows the guidelines outlines above for incompetent and impaired decision-making research participants.

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

1. ability to communicate a choice,
2. ability to understand relevant information,
3. ability to appreciate the situation and its likely consequences, and
4. ability to manipulate information rationally.

A range of professionals and methods may be utilized to assess capacity. In general, the consent assessor should be a researcher or consultant familiar with dementias and qualified to assess and monitor capacity and consent in such subjects on an ongoing basis. The IRB will consider the qualifications of the proposed individual(s) and whether he/she is sufficiently independent of the research team.

A person who has been determined to lack capacity to consent to participate in a research study should be notified of that determination before permission may be sought from his or her legally authorized representative to enroll that person in the study. If permission is given to enroll such a person in the study, the potential subject should then be notified. If the person objects to participating, this objection should be heeded.

6.7.3 Informed Consent and Assent

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 5 above. When participants lack the capacity to give consent, investigators may obtain consent from the legally authorized representative of a subject (i.e., surrogate consent) as described below.

A person who is incompetent or has been determined to lack capacity to consent to participate in a research study should be informed about the research to the extent compatible with the subject's understanding and, if possible, the subject should give their assent to participate, and sign and date the written informed consent or a separate assent form

Surrogate consent may be obtained from a legally authorized representative as described in Section 5.2.

7 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 investigations of investigational drugs and biological products must be conducted according to FDA's IND regulations, 21 CFR Part 312, and other applicable FDA regulations. Evaluations of the safety or effectiveness of a medical device 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 by the Central Michigan University (CMU) IRB.

7.1 Definitions

Biologic. Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other technologies. In general, the term "drugs" includes therapeutic biological products.

Clinical Investigation. Clinical investigation means any experiment that involves a test article and one 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 520(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. [21 U.S.C. 321(ff)]

Emergency Use. Emergency use is defined as the use of a test article on 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) – 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

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.

The following articles are not considered HCT/P's: vascularized human organs for transplantation; whole blood or blood components or blood derivative products subject to listing under parts 607 and 207, respectively; secreted or extracted human products, such as milk, collagen, and cell factors; except that semen is considered an HCT/P; minimally manipulated bone marrow for homologous use and not combined with another article (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow); ancillary products used in the manufacture of HCT/P; cells, tissues, and organs derived from animals other than humans; in vitro diagnostic products as defined in 809.3(a); blood vessels recovered with an organ, as defined in 42 CFR 121.2, that are intended for use in organ transplantation and labeled "For use in organ transplantation only."

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 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.

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

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

IND. IND means an investigational new drug application in accordance with 21 CFR Part 312.

IDE. IDE means an investigational device exemption in accordance with 21 CFR 812.

In Vitro Diagnostic Product (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:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; or
2. Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or

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

7.2 FDA Exemptions

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

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

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

7.3 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:

1. 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.
2. 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.
3. The investigator is responsible for personally conducting or supervising the investigation. When 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.
4. 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 or sponsor), and identify the dates of involvement in the study. An investigator should maintain separate lists for each study conducted by the investigator.

5. The investigator is responsible for protecting the rights, safety, and welfare of subjects under their care during a clinical trial. This responsibility includes:
    a. Informing subjects that the test articles is being used for investigational purposes and ensuring that the requirements relating to obtaining informed consent are met
    b. 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
    c. 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)
    d. Adhering to the protocol so that study subjects are not exposed to unreasonable risks
    e. 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.
6. The investigator is responsible for reading and understanding the information in the investigator brochure or device risk information, including the potential risks and side effects of the drug or device.
7. 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, but are not limited to: correspondence with other investigators, the IRB, the sponsor, monitors, or the FDA; drug and device accountability records; case histories; consent forms; and documentation that consent was obtained prior to any participation in the study. Records must be obtained for a minimum of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such. For clinical investigations of medical devices, required records must be maintained for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. Other regulations, such as HIPAA, organizational policies, or contractual agreements with sponsors may necessitate retention for a longer period of time.
8. The investigator is responsible for controlling test articles according to FDA regulations and the Controlled Substances Act, if applicable.
9. For research reviewed by the 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.
    a. The investigator is responsible for investigational drug accountability that includes storage, security, dispensing, administration, return, disposition, and records of accountability. Such details will be provided in the IRB submission and reviewed by the IRB for acceptability.

b. The investigator may delegate in writing, as part of the IRB submission, the responsibility detailed in 'a' above to the Pharmacy Service.

c. Investigational drugs and devices must be labeled in accordance with federal and state standards.

d. 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.

10. The investigator shall furnish all reports required by the sponsor of the research including adverse events, progress reports, safety reports, final reports, and financial disclosure reports.
11. The investigator will permit inspection of research records by the sponsor, sponsor representatives, HRPP and IRB representatives, the FDA, accrediting bodies, and any other agencies or individuals entitled to inspect such records under regulation, organizational policy, or contractual agreement.

7.4 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 analyze 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 analyze clinical laboratory test or other device data, results, and findings; and

- Not intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system; and
    - Is intended for the purpose of displaying, analyzing, 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.

7.5 Human Cells, Tissues, or Cellular or Tissue-based Products (HCT/Ps)

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).

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

7.7 Clinical Investigations of Articles Regulated as Drugs or Devices

7.7.1 IND/IDE Requirements

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

1. Industry sponsored study with IND/IDE number indicated on the protocol;
2. Letter/communication from FDA;
3. Letter/communication from industry sponsor; or
4. 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 IDE-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 IDE-exempt or NSR; or,
3. If neither of the above, whether an IND is necessary, or that a device study is exempt or NSR, or whether the study must be submitted to the FDA, 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.

7.7.2 IND Exemptions

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

1. 21 CFR 312.2(b)(1): The drug being used in the research is lawfully marketed in the United States and all of the following requirements are met:
    a. 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;
    b. In the case of a prescription drug, the research is not intended to support a significant change in the advertising for the product;
    c. 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;
    d. The research is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
    e. The research is conducted in compliance with the requirements of 21 CFR 312.7 (i.e., the research is not intended to promote or commercialize the drug product); and
    f. The research does not intend to invoke FDA regulations for planned emergency research [21 CFR 50.24].

    Please Note: FDA has provided specific guidance for evaluating whether this exemption applies to studies of marketed drugs/biologics for the treatment of cancer.
2. 21 CFR 312.2(b)(2): For clinical investigations involving defined (blood grouping serum, reagent red blood cells, and anti-human globulin) in vitro diagnostic biological products, an IND is not necessary if a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and b) it is shipped in compliance with 312.160

3. 21 CFR 312.2(b)(5): A clinical investigation involving use of a placebo is exempt from the requirements of part 312 if the investigation does not otherwise require submission of an IND.
4. 21 CFR 320.31(b) and (d): Bioavailability or Bioequivalence (BA/BE) studies if all of the following conditions are met:
    a. The drug product does not contain a new chemical entity [21 CFR 314.108], is not radioactively labeled, and is not cytotoxic;
    b. 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;
    c. The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively]; and
    d. 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)].
5. 21 CFR 361.1: Research using a radioactive drug or biological product if all of the following conditions are met:
    a. It involves basic research not intended for immediate therapeutic, diagnostic, or similar purposes, or otherwise to determine the safety and efficacy of the product;
    b. The use in humans is approved by a Radioactive Drug Research Committee (RDRC) that is composed and approved by FDA;
    c. The dose to be administered is known not to cause any clinically detectable pharmacological effect in humans, and
    d. 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.
6. FDA practices enforcement discretion for research using cold isotopes of unapproved drugs if all of the following conditions are met:
    a. 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;
    b. The research is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject;
    c. 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;
    d. The quality of the cold isotope meets relevant quality standards; and
    e. The investigation is conducted in compliance with the requirements for IRB review and informed consent. [21 CFR parts 56 and 50, respectively]

7.7.3 IDE Exemptions

For clinical investigations of medical devices, an IDE is not necessary if:

1. 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;
2. 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);
3. The research involves a diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
    a. Is noninvasive,
    b. Does not require an invasive sampling procedure that presents significant risk,
    c. Does not by design or intention introduce energy into a subject, and
    d. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure;
4. 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;
5. The research involves a device intended solely for veterinary use;
6. The research involves a device shipped solely for research on or with laboratory animals and labeled in accordance with 21 CFR 812.5(c);
7. 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.

7.7.4 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:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
2. 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;
3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or

4. 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 7.7.1. The FDA's determination is final, and the IRB does not have to make the device risk determination.

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

The sponsor or sponsor-investigator is responsible for providing the IRB with an explanation describing the basis for their initial determination of NSR and any other information that may help the IRB in evaluating the risk of the study (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 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 when applicable, with the determination in writing.

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

1. 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):
    a. Labels the device in accordance with 812.5;
    b. Obtains IRB approval of the investigation after presenting the reviewing IRB with an explanation of why the device is not a significant risk device, and maintains such approval;
    c. 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 the requirement is waived by the IRB;
    d. Complies with the requirements of 812.46 with respect to monitoring investigations;
    e. 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);

f. 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); and

g. 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.

7.8 Diagnostic or Treatment Use of Humanitarian Use Devices

7..8.1 Definitions

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

7.8.2 IRB Review Requirements

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

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

7.8.3 Procedures

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

The health care provider seeking approval for diagnostic or treatment use of a HUD at CMU facilities is responsible for obtaining IRB approval prior to use of the HUD at the facility and for

complying with the applicable regulations, including those for medical device reporting, organizational policies, and the requirements of the IRB.

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

1. Application Form – Humanitarian Use Devices (non-research uses);
2. A copy of the HDE approval letter from the FDA;
3. A description of the device, such as a device brochure;
4. The patient information packet for the HUD;
5. The proposed clinical consent process/form; and
6. Other relevant materials (e.g., training certificates) as identified in the Application Form

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

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

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

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

The IRB will review these reports via either expedited or convened review, as appropriate, and will consider whether any changes are needed to the IRB-approved plan or patient materials.

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

The Humanitarian Use Devices Continuing Review Form

1. The most recent periodic report to the FDA by the HDE holder;
2. The current patient information packet, if applicable;
3. The current consent, if applicable;
4. Other materials as identified on the Humanitarian Use Devices Continuing Review Form; and
5. Any other new relevant information or materials

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

7.8.4 Emergency Uses of HUDs

If an appropriately trained and licensed health care provider in an emergency situation determines that IRB approval for the use of the HUD at the facility cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be used without prior IRB approval. The health care provider must, within 5 days after the emergency use of the device, provide written notification of the use to the CMU Pediatric IRB Chair including the identification of the patient involved, the date of the use, and the reason for the use. [21 CFR 812.124]

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

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

7.9 Expanded Access to Investigational Drugs, Biologics and Devices

Note: The content in this section has been developed from current regulation and guidance and for single-patient expanded access.

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/uncleared 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.

7.9.1 Expanded Access to Investigational Drugs and Biologics

The FDA's expanded access rule for investigational drugs, including biologics classified as drugs, is intended to improve access to investigational drugs for patients with serious or immediately life-threatening diseases or conditions who lack other therapeutic options and may benefit from the investigational agent. Expanded access is sometimes referred to as compassionate use or treatment use.

For the purposes 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" for the purposes of these SOPs.

Under the FDA's expanded access rule, access to investigational drugs for treatment purposes is 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]

The following section addresses expanded access for individual patients. Investigators seeking expanded access for intermediate-size populations or widespread use should consult with the HRPP/IRB office. Convened IRB review is generally required for intermediate or widespread expanded access unless the FDA has issued a waiver.

Physicians seeking access to investigational drugs under expanded access should work closely with the sponsor or manufacturer, the FDA, and the 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 FDA's contact information.

7.9.1.1 Expanded Access to Investigational Drugs 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 a FDA website. Form FDA 3926 includes a section where an investigator can request approval from the FDA for alternative IRB review procedures; these alternative procedures enable review by the IRB Chair (or a Chair-designated IRB member) in lieu of review by the convened IRB. This alternative review procedure is referred to as a "concurrence review" in FDA guidance; however, the IRB Chair must review the same materials and make the same determinations as the convened board would. IRB Chair review can also be used for any post-approval reviews (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 Section 7.9.1.2.

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

IRB Review:

Unless the conditions that permit an emergency use exemption (see Section 7.9.1.2) are satisfied, 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 via IRB Manager:

1. A completed Expanded Access Application and any additional documentation noted within it;
2. A copy of the Letter of Authorization (LOA) from the Commercial Sponsor or Manufacturer or other documentation supporting sponsor/manufacturer approval;
3. A copy of the information submitted to the FDA (and FDA approval, if available);
4. A copy of the Investigator's Brochure or similar documentation that provides information regarding the potential risks and benefits of the investigational drug;
5. A copy of the plan for treating and monitoring the patient (If not described elsewhere); and
6. A copy of the draft informed consent document specific for expanded access use.

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 office, to discuss IRB reliance for expanded access protocols.

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 7 business days of the date of submission to the FDA.

7.9.1.2 Emergency Use of Investigational Drugs

FDA regulations permit the use of an investigational drug without IRB approval when an appropriately trained and licensed health care provider determines that IRB approval for the use of the drug 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 and to have substantial reason to believe that benefits will exist. The criteria and requirements for this Emergency Use Exemption are explained in Section 7.9.1.2.1 below.

Approval from the FDA and the Sponsor/Manufacturer must be obtained prior to initiating treatment with the drug.

Providers invoking the emergency use exemption must comply with any applicable FDA follow-up requirements including submission of safety reports, amendments, a summary following completion of treatment, and annual reports.

A copy of reports or amendments submitted to the FDA and any related correspondence must be submitted to the IRB office.

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.

7.9.1.2.1 Emergency Use Exemption from Prospective IRB Approval

Under FDA regulations at 21 CFR 56.104(c), FDA exempts the emergency use of an investigational drug (or biologic classified as a drug) from the requirement for prospective IRB approval, provided that the conditions described below are satisfied and that the emergency use is reported to the IRB within 5 working days. Any subsequent use of the investigational drug in the facility requires IRB approval. 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 it appears likely that the investigational drug may need to 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.

- **Life-threatening** means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.
- **Severely debilitating** means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Unless the provisions for an emergency exception from the informed consent requirement are satisfied (see Section 7.9.1.3), 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 **5 working days** after an emergency exemption is used. The IRB Chair or designated IRB member will review the report to verify that circumstances of the emergency use 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). Reports of emergency uses will be brought to the convened IRB for their information.

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

7.9.1.3 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 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 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; and
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 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

The IRB must be notified within **5 working days** when an emergency consent exception is invoked by submitting an event report. The Pediatric IRB Chair or designated IRB member will review the report to verify that circumstances of the emergency exception conformed to FDA regulations.

7.9.2 Expanded Access to Investigational and Unapproved Medical Devices

As with investigational drugs, unapproved medical devices may normally only be used in humans in an approved clinical trial under the supervision of a participating clinical investigator. However, there are circumstances under which a health care provider may use an unapproved device outside of a clinical study when it is not possible to enroll a patient in a clinical study and the patient is facing life-threatening circumstances or suffering from a serious disease or condition for which no other alternative therapy or diagnostic exists or is a satisfactory option for the patient.

FDA has made the following mechanisms available for these circumstances:

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

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

FDA has made information about expanded access to medical devices available on a website.

7.9.2.1 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:

1. The patient has a life-threatening or serious disease or condition; and
2. 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:

1. A description of the device (provided by the manufacturer);

2. Authorization from the device manufacturer for the use;
3. 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;
4. 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; and
5. The patient protection measures that will be followed, including:
    a. A draft of the informed consent document that will be used;
    b. Clearance from the institution as specified by their policies (see below);
    c. Concurrence (approval) of the IRB Chair or Chair-designated IRB member (prior to FDA request when possible); and
    d. 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, 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 via the IRB Manager system]:

1. A completed Expanded Access Application and any additional documentation noted within it;
2. A copy of the information submitted to the FDA (and FDA approval, if available);
3. 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;

4. A copy of the plan for treating and monitoring the patient (If not described elsewhere); and
5. 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 office, to discuss IRB reliance for Compassionate Use protocols.

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 7 business days of the date of submission to the FDA.

7.9.2.2 Treatment Use of Investigational/Unapproved Medical 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:

1. The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition;
2. There is no comparable or satisfactory alternative device available to treat or diagnose the disease or condition in the intended patient population;
3. 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; and
4. 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. Investigators should follow the standard procedures for applying for review of a clinical investigation.

CMUwill 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 office, to discuss IRB reliance for Treatment Use IDEs.

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 7 business days of receipt.

7.9.2.3 Emergency Use of Investigational Devices

FDA regulations permit the emergency use of an investigational or unapproved device without prior approval by the FDA or IRB when an appropriately trained and licensed health care provider determines that:

- The patient has a life-threatening or serious disease or condition that needs immediate treatment;
- No generally acceptable alternative treatment for the condition exists; and
- Because of the immediate need to use the device, there is no time to use existing procedures to obtain FDA approval for the use.

FDA expects the provider to make the determination that the above criteria are satisfied, to assess the potential for benefit from the use of the unapproved device, and to have substantial reason to believe that benefits will exist. Because prior FDA approval is not required, FDA expects providers planning the emergency use of an investigational device to obtain as many of the following as possible:

- An independent assessment from an uninvolved physician;
- Authorization from the device manufacturer;
- Concurrence of the IRB Chair or designee;

- Institutional clearance; and

Informed consent from the patient or legally authorized representative.

At CMU, providers planning the emergency use of an investigational or unapproved device must contact the HRPP/IRB office as early in the process as possible and submit the Emergency Use Report and the supporting documentation called for in the form for review by the IRB Chair or designee. The IRB Chair or designee will review the information provided and determine whether the use conforms with FDA's requirements and expectations and whether the provisions for the protection of the patient appear adequate using the applicable criteria at 21 CFR 50 and 56 as guidelines (e.g., minimization of risks, risk/benefit, safety monitoring, informed consent, etc.).

The emergency use must be reported to the FDA by the IDE Sponsor, when one exists, or by the provider if no IDE exists. Information regarding what to include in the report and where to submit it is available on FDA's website. When the provider is responsible for the FDA report, a copy of the report and any related correspondence must be submitted to the IRB office. Reports of emergency uses will be brought to the convened IRB for their information.

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

9.10 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 investigator's and IRB's responsibility to minimize risks to subjects (Beneficence), to ensure that the risks and burdens associated with research are equitably distributed (Justice), and to ensure that subjects are properly informed and not unduly influenced to accept an otherwise unacceptable risk or cost in order to access a benefit (Respect for Persons). Any costs to subjects or insurers must be described in the IRB application and informed consent document.

9.10.1 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)].

9.10.2 Charging for Investigational Drugs and Biologics

In 2009, FDA updated its rules at 21 CFR 312 regarding charging for Investigational Drugs Under an IDE. 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.

8 Reportable Events, Non-Reportable Events and Unanticipated Problems Involving Risks to Subjects or Others

CMU complies with DHHS and FDA regulations which state that institutions must have written policies on reporting unanticipated problems involving risks to subjects or others to the IRB, institutional officials, and relevant federal agencies and departments.

The following procedures describe how unanticipated problems involving risk to subjects or others are handled in research under the auspices of CMU.

8.1 Definitions

UPIRSO - Unanticipated problems involving risk to subjects or others –Any incident, experience, outcome, or new information that meets all of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

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 protocol-related documents, such as the IRB-approved research protocol and informed consent documents, and the characteristics of the subject population being studied.

Unanticipated adverse device effect - 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 relates to the rights, safety, or welfare of subjects [See 21 CFR 812.150(a)].

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 – Any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article.

Note: Only a fraction of Adverse Events are UPIRSOs and not all UPIRSOs are Adverse Events.

8.2 Reportable Event Procedures

8.2.1 Reporting by Investigator

Investigators must promptly (according to reporting schedule in 8.2.2) report the following problems to the IRB:

1. Adverse events involving direct harm to participants which, in the opinion of the principal investigator, meet the criteria for an unanticipated problem involving risk to subjects or others.
2. An unanticipated event related to the research that exposes participants to risk but that does not involve direct harm to participants.
3. An unanticipated event related to the research that exposes individuals other than the research participants (e.g., investigators, research assistants, students, the public, etc.) to risk.
4. IND Safety Reports from sponsors that meet the criteria for an unanticipated problem involving risk to subjects.
   Note: CMU will not conduct research on drugs that require an IND
5. New information that indicates a change to the risks or potential benefits of the research. For example,
   a. An interim analysis or safety-monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB.
   b. A paper is published from another study that shows that the risks or potential benefits of your research might be different than initially presented to the IRB.
   c. A breach of confidentiality.
   d. Incarceration of a participant in a protocol not approved to enroll prisoners.
   e. Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial.
   f. Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team.
   g. Protocol violation (meaning an accidental or unintentional change to the IRB approved protocol) that harmed participants or others or that indicates participants or others may be at increased risk of harm.
   h. Sponsor imposed suspension for risk.
   i. Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
   j. Unanticipated adverse device effect.
   k. Any other event that indicates participants or others might be at risk of serious, unanticipated harms that are reasonably related to the research.

8.2.2 Submission of Reports by Investigator

Investigators must report possible unanticipated problems to the IRB promptly (according to reporting schedule in 8.2.2).

If the event requires immediate intervention to prevent serious harm to participants or others, the investigator must report the event within five (5) days of receiving notice of the event.

Investigators must report all other possible unanticipated problems occurring at the local research site and non-local research sites to the IRB as soon as possible but no later than ten (10) business days or as soon as practicable from the date of the event or from the date the investigator is notified of the event.

Problems occurring within thirty (30) days after participants' active participation or treatment must be reported according to the above schedule.

Investigators or the study team must report possible unanticipated problems to the HRPP Office in writing using the **Adverse/Reportable Event Form**. The written report should contain all of the following:

1. Detailed information about the possible unanticipated problems, including relevant dates.
2. Any corrective action, planned or already taken, to ensure that the possible unanticipated problems is corrected and will not occur again.
3. An assessment of whether any subjects or others were placed at risk as a result of the event or suffered any physical, social, or psychological harm and any plan to address these consequences.
4. Any other relevant information.
5. Any other information requested by the HRPP Office.
6. A report of a possible unanticipated problem involving risks to participants or others will be immediately forwarded to the IRB Chair if the IRB staff believes that immediate intervention may be required to protect participants or others from serious harm.

Upon receipt of a report of a possible unanticipated problem from someone other than the investigator or study staff, the DRC will notify the PI on the study when appropriate.

8.2.3 Processing Reports of Possible Unanticipated Problems

8.2.3.1 Review by IRB Staff and Chair

1. Upon receipt of an Adverse/Reportable Event form from a PI, the IRB support staff checks the form for completeness. If any applicable sections of the form are incomplete or have been answered unsatisfactorily, the IRB staff will contact the investigator or the designated contact person to obtain additional information. Corrections are documented in the IRB file, indicating the date, the person spoken with, and the IRB staff making the correction.
2. The IRB chairperson and/or other experienced IRB member(s), or compliance office staff designated by the IRB chairperson receives and reviews the report of the event(s) considered to be an unanticipated problem. The IRB chairperson (or designee) will make the final determination as to whether the event is to be regarded as an unanticipated problem.
3. Based on the information received from the investigator, the IRB Chair or designee may suspend research to ensure protection of the rights and welfare of participants. Suspension directives made by the IRB Chair or designee must be reported to a meeting of the convened IRB.
4. The IRB or the IRB chairperson (or designee) has authority to require submission of more detailed contextual information by the PI, the sponsor, the study coordinating center, or DSMB/DMC about any Adverse Event occurring in a research protocol as a condition of the continuation of the IRB's approval of the research.
5. The reviewer will assess whether a reported event:
   a. Was anticipated or unanticipated

b. If participants or others were harmed or at increased risk of harm.

6. If the reviewer considers that the problem was foreseen (was expected):
   a. the reviewer indicates that the problem is not an unanticipated problem.
   b. A report is filed in the protocol record, the determination is communicated to the investigator, and no further action is taken.
   c. The reviewer advises the investigator that anticipated problems that are adverse events may be reported in summary form at time of continuing review or status report and that anticipated problems that are not adverse events are non-reportable (see section X.3).
7. If the reviewer considers that the problem was not foreseen (was unexpected/unanticipated) AND determines that participants or others were not harmed, potentially harmed or are at increased risk of harm:
   a. The reviewer indicates that the event, while unanticipated, is not a UPIRSO,
   b. A report is filed in the protocol record and the determination is communicated to the investigator
   c. The investigator is advised to report unanticipated problems affecting the research but NOT involving risks to subjects or others in summary form at time of continuing review or status report (see section X.3).
8. If the reviewer considers that the problem is an unanticipated problem involving, or potentially involving risks to subjects or others, but that the risk is no more than minimal, the reviewer will:
   a. Review the currently approved protocol, consent document and investigators brochure/recruitment documents (if one exists) and;
   b. Review previous reports of unanticipated problems involving risks to participants or others, and
   c. After reviewing all of the materials, the reviewer will take appropriate action depending on the nature of the risk involved, including requiring modification of the protocol or the consent form, if applicable.
   d. The results of the review will be recorded in the protocol record, communicated to the investigator, and reported to the IRB.
   e. All events determined to be unanticipated problems will be reported to the relevant regulatory agencies and institutional officials according to the procedures in Section 11.

8.2.3.2 IRB Review

All reported unanticipated problems where the risk is more than minimal will be reviewed at a convened IRB meeting. If a report suggests that participant safety is at risk, the IRB may immediately suspend or terminate the research.

1. The reviewer will conduct their assessment as outlined in section 5 above with the following exceptions:
   a. The reviewer will provide a report summarizing the problem
   b. The convened IRB will review the report and make the final determination regarding how to classify the problem based on the following considerations:
      i. Whether the reported event is an unanticipated problem involving risks to participants or others according to the definition in this policy.
      ii. What action in response to the report is appropriate.
      iii. Whether suspension or termination of approval is warranted.
      iv. Whether further reporting to Institutional and/or federal officials is required.

c. The convened IRB will specify actions to be taken or will designate a subcommittee or individual(s) with appropriate expertise to ensure that appropriate corrective actions are taken, including but not limited to:
    i. Requiring modifications to the protocol.
    ii. Revising the continuing review timetable.
    iii. Modifying the consent process.
    iv. Modifying the consent document.
    v. Providing additional information to current participants (e.g., whenever the information may relate to the participant's willingness to continue participation).
    vi. Providing additional information to past participants.
    vii. Requiring additional training of the investigator and/or study staff.
    viii. Taking other actions appropriate for the local context.
    ix. Additional actions that may be taken if the event is determined to be a UPIRSO:
        1) Reconsidering approval.
        2) Requiring that current participants re-consent to participation.
        3) Monitoring the research.
        4) Monitoring the consent.
        5) Making referral to other organizational entities (e.g., legal counsel, risk management, Institutional Official).
        6) Suspending the research.
        7) Terminating the research.
d. The determination of the IRB will be communicated to the investigator along with any corrective actions required

8.2.3.3 Reporting

1. Any suspension or termination of research by the IRB must be promptly reported to the IO, and OHRP (if supported by PHS), and FDA (if FDA-regulated research) through the IO. This should be done in writing.
2. 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 (eg, NSF, OHRP, and FDA).

8.3 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.

9 Protocol Exceptions & Deviations

Protocol exceptions and deviations must be reported to the IRB.

9.1 Exceptions

A protocol exception is a one-time, intentional action or process that departs fro m the IRB-approved protocol.

It is the responsibility of the Investigator to report exceptions to the IRB. The IRB will perform an expedited review of the Request for Protocol Change form submitted by the PI along with documentation of sponsor justification and approval. Exceptions must be approved by the sponsor and IRB before being implemented.

Exceptions may not increase risk or decrease benefit, affect the participants' rights, safety, welfare, or affect the integrity of the resulting data.

9.2 Deviations

A protocol deviation is defined as a violation that is unanticipated and happens without any prior agreement (*eg*, protocol visit scheduled outside protocol window, blood work drawn outside protocol window, etc.)

It is the responsibility of the PI not to deviate from the protocol approved by the IRB, except to avoid an immediate hazard to the participant. The PI must submit an amendment request to the IRB and receive written approval prior to implementation of any change to the protocol.

Deviations that increase risk, have potential to recur, or are undertaken to eliminate an immediate hazard would be considered an Unanticipated Problem and should be handled according to Section 8.

When a sponsor requests that the IRB be notified of a deviation, the completed form will be forwarded to the IRB chair or designate for review of the Request for Protocol Change form submitted by the PI.

Deviations may be ruled by the IRB to constitute non-compliance resulting in suspension of IRB approval.

9.3 Reporting & Review

Deviation/Exception Reports are to be completed for those events that qualify as a protocol deviation or exception. These reports should be filed with the IRB Office. The IRB Office will forward the report to the IRB Chair or designee for review. An acknowledged report will be sent back to the PI for the study file. The Chair may choose to place any deviation or exception on the agenda of the next convened IRB meeting for discussion. The PI may be asked to appear at that meeting to answer any questions or clarify issues for the IRB.

10 Complaints, Concerns and Non-Compliance

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

All PIs and other study personnel involved in human subjects research are required to comply with all laws and regulations governing their research activities, as well as with requirements and determinations of the IRB. Study personnel include the PI and any staff member directly involved with participants or the informed-consent process.

The following procedures describe how complaints and allegations of non-compliance are handled by the IRB.

At CMU 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 reports received by the ORC are recorded on a log by the Director of Research Compliance (DRC) or designee. All IRB related reports are relayed to the IRB Chair by the Office of Research Compliance.

10.1 Definitions

Noncompliance –Failure to comply with any of the regulations and policies described in this document and failure to follow the determinations of the IRB. Non-compliance may be minor or sporadic or it may be serious or continuing.

Serious noncompliance –Failure to follow any of the regulations and policies described in this document or failure to follow the determinations of the IRB, and which, in the judgment of either the IRB Chair or the convened IRB, increases risks to participants, decreases potential benefits, or compromises the integrity of the HRPP. Research being conducted without prior IRB approval or participation of subjects in research activities without their prior consent (i.e., in studies where consent was not specifically waived by the IRB) is considered serious noncompliance.

Continuing noncompliance – A pattern of non-compliance that, in the judgment of the IRB Chair or convened IRB, suggests a likelihood that instances of non-compliance will continue without intervention. Continuing non-compliance also includes failure to respond to a request to resolve an episode of non-compliance.

Allegation of Noncompliance – An unproved assertion of non-compliance.

Finding of Noncompliance – 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 that the protocol was wilfully not followed would represent reports of non-compliance that would require no further action to determine their truth and would therefore represent findings of non-compliance. A finding of non-compliance may also occur subsequent to investigation when either the IRB Chair or convened IRB determines that the

evidence supports the allegation of non-compliance. Once a finding of non-compliance is made, it must be categorized as serious, non-serious, or continuing.

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.

10.2 Complaints

The Chair of the IRB will promptly handle (or delegate ORC or IRB staff to handle) and, if necessary, investigate all complaints, concerns, and appeals received by the IRB. This includes complaints, concerns, and appeals from investigators, research participants, and others.

All complaints, written or oral (including telephone complaints), and regardless of point of origin, are recorded on a complaint form and forwarded to the IRB Chair and DRC.

Upon receipt of the complaint, the Chair or DRC will make a preliminary assessment of whether the complaint warrants immediate suspension of the research project. If a suspension is warranted, the procedures in Section 3.10.1 will be followed.

If the complaint meets the definition of non-compliance, it will be considered an allegation of non-compliance according to Section 10.4

If the complaint meets the definition of an unanticipated problem involving risk to subjects or others, it will be handled according to Section 8.

Within three (3) business days of receipt of the complaint (or as soon as is practicable), the IRB Chair and/or DRC will generate a letter to acknowledge that the complaint has been received and is being investigated. Afollow-up contact name will be provided to the complainant/relator unless the complainant/relator has indicated they do not wish to be contacted or the report was submitted anonymously.

10.3 Noncompliance

Investigators and their study staff are required to report instances of possible non-compliance. The PI is responsible for reporting any possible noncompliance by study personnel to the IRB. Common reports to the IRB that are not serious or continuing are typically protocol violations. However, any individual or employee may report observed or apparent instances of noncompliance 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.

10.3.1 Review of Allegations of Noncompliance

All allegations of non-compliance will be reviewed by the IRB Chair or designee in the Office of Research Compliance, who will review:

1. all documents relevant to the allegation;
2. the last approval letter from the IRB;
3. the last approved IRB application and protocol;
4. the last approved consent document;
5. the grant, if applicable; and
6. 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.

The IRB Chair will review the allegation and determine the truthfulness of the allegation. The Chair may request additional information or an audit of the research in question.

When the IRB Chair determines that noncompliance did not occur because the incident was within the limits of an approved protocol for the research involved, the determination is reported in writing to the PI and, if applicable, to the reporting party. The determination letter will be copied to the IO in cases where the IO and any other parties had been notified at the outset.

If, in the judgment of the IRB Chair, the reported allegation of non-compliance is true, the non-compliance will be processed according to Section 9.4.2 Review of Findings of Non-compliance.

If, in the judgment of the IRB Chair, any allegation or findings of non-compliance warrant suspension of the research before completion of any review or investigation to ensure protection of the rights and welfare of participants, the Chair may suspend the research as described in Section 3.10 with subsequent review by the IRB.

The IRB Chair may determine that additional expertise or assistance is required to make these determinations and may form an ad hoc committee to assist with the review and fact gathering process. When an ad hoc committee assists in the review process, the Chair is responsible for assuring that minutes of the meeting are generated and kept to help support any determinations or findings made by the ad hoc committee.

10.3.2 Review of Findings of Noncompliance

Noncompliance is not serious or continuing – When the IRB Chair determines that the noncompliance occurred, but the noncompliance does not meet definition of serious or continuing noncompliance, the determination is reported in writing to the PI and, if applicable, to the reporting party. The Chair will work with the PI to develop a corrective action plan to prevent future noncompliance. Reports of minor noncompliance and corrective action plans are submitted to the IRB individually by uploading these documents to the electronic protocol file and are presented individually or in summary form during a convened meeting. If, however, the PI refuses to cooperate with the corrective action plan, the matter is referred to a convened meeting of the IRB with notification to the IO.

Serious or Continuing Noncompliance – When the IRB Chair determines that noncompliance has occurred and that the noncompliance meets the definition of serious or continuing noncompliance, the report of noncompliance is submitted for review by the IRB at the next convened meeting.

However, the Chair may use discretion and call an emergency IRB meeting should the circumstances warrant such an urgent meeting.

All findings of serious or continuing non-compliance submitted to the IRB will be reviewed at a convened meeting. All IRB members will receive:

1. all documents relevant to the allegation,
2. the last approval letter from the IRB,
3. the last approved IRB protocol, and
4. the last approved consent document.

At this stage, the IRB may:

1. find that there is no issue of non-compliance,
2. find that there is noncompliance that is neither serious nor continuing and an adequate corrective action plan is in place,
3. find that there is serious or continuing non-compliance and approve any changes proposed by the Chair and/or ad hoc committee,
4. find that there may be serious or continuing non-compliance and direct that a formal inquiry (described below) be held, or
5. request additional information.

10.3.3 Inquiry Procedures

If the convened IRB is unable to make a determination regarding alleged non-compliance or requires additional information to substantiate an allegation, a determination may be made by the IRB that an inquiry is necessary. The IRB may choose to designate either a designee within the Office of Research Compliance or a subcommittee consisting of IRB members, ORC staff and non-members (if appropriate) to ensure fairness and expertise. ORC staff will work with the subcommittee (or designee) to ensure that records of the proceedings and findings of the subcommittee (or designee) are maintained and will draft any reports or letters that the subcommittee (or designee) requires. The subcommittee or ORC designee is given a charge by the IRB, which can include any or all of the following:

1. review of protocol(s) in question;
2. review of sponsor audit report of the investigator (if appropriate);
3. review of any relevant documentation, including consent documents, case report forms, subject's investigational and/or medical files, etc. as they relate to the investigator's execution of her/his study involving human subjects;
4. interview of appropriate personnel (if necessary);
5. prepare either a written or oral report of the findings, which is presented to the full IRB at its next meeting;
6. recommend actions if appropriate.

10.3.4 Final Review

The results of the inquiry will be reviewed at a convened IRB meeting where the IRB will receive a report from the subcommittee. If the results of the inquiry substantiate the finding of serious or continuing non-compliance, the IRB’s possible actions could include, but are not limited to the following:

1. Request a correction action plan from the investigator.
2. Verify that participant selection is appropriate and observe the actual informed consent.
3. Increase data and safety monitoring of the research activity.
4. Request a directed audit of targeted areas of concern.
5. Request a status report after each participant receives intervention.
6. Modify the continuing review cycle.
7. Request additional PI and staff education.
8. Notify current subjects if the information about the non-compliance might affect their willingness to continue participation.
9. Require modification of the protocol.
10. Require modification of the information disclosed during the consent process.
11. Require current participants to re-consent to participation.
12. Suspend the study (see below).
13. Terminate the study (see below)

In cases where the IRB determines that the event of noncompliance also meets the definition of unanticipated problem involving risks to subjects or others, the policy and procedure for review of such events will also be followed.

The investigator is informed of the IRB determination and the basis for the determination in writing and is given a chance to respond. 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 11.

11 Reporting to Institutional Officials, Regulatory Agencies, and AAHRPP

11.1 Reporting Triggers

Federal regulations require prompt reporting to appropriate institutional officials and, if the research is funded by an agency of the federal government, to the department or agency head of (a) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (b) any suspension or termination of IRB approval. The CMU HRPP will comply with this requirement, and the following procedures describe how these reports are handled.

Reporting procedures are initiated as soon as the IRB takes any of the following actions:

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

11.2 Preparation of Report

The DRC or designee is responsible for preparing reports or letters which include the following information:

1. The nature of the event (e.g., unanticipated problem involving risks to participants or others, serious or continuing non-compliance, suspension or termination of approval of research).
2. Name of the institution(s) conducting the research.
3. Title of the research project and/or grant proposal in which the problem occurred.
4. Name of the PI on the protocol.
5. Number of the research project assigned by the IRB and the number of any applicable federal award(s) (e.g., grant, contract, or cooperative agreement).
6. A detailed description of the problem including the findings of CMU and the reasons for the IRB's decision.
7. Actions the institution is taking or plans 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.).
8. Plans, if any, to send a follow-up or final report by the earlier of
    i. a specific date, or
    ii. when an investigation has been completed or a corrective action plan has been implemented.
9. The IRB Chair and the IO review the letter and modify the letter/report as needed.
10. The IO signs all correspondence from the facility.

11.3 Recipients of Report

The DRC or designee sends a copy of the report to the following:

1. The IRB, by including the letter in the next agenda packet as an information item.
2. The IO.
3. The following federal agencies:
   i. OHRP, if the study is subject to DHHS regulations or subject to a DHHS Federalwide Assurance.
   ii. FDA, if the study is subject to FDA regulations.
   iii. If the study is conducted or funded by any federal agency other than DHHS that is subject to "The Common Rule," the report is sent to OHRP or the head of the agency as required by the agency.
   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 Central Michigan University, and the agency has been notified of the event by the investigator, sponsor, another organization, or other mechanisms.
4. The PI.
5. The Sponsor, if the study is sponsored.
6. Contract research organization, if the study is overseen by a contract research organization.
7. Chairman or supervisor of the PI.
8. The Privacy Officer of a covered entity, if the event involved unauthorized use, loss, or disclosure of individually-identifiable patient information from that covered entity
9. The Information Security Officer of an organization if the event involved violations of information security requirements of that organization.
10. J. Office of Risk Management (if appropriate).
11. Others as deemed appropriate by the IO.

The DRC ensures that all steps of this policy are completed within ten (10) working days of the determination. For more serious actions, the DRC will expedite reporting.

11.4 Reporting to AAHRPP

CMU will report to AAHRPP will report:

1. 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.
2. Any litigation, arbitration, or settlements initiated related to human research protections, *subject to approval be university counsel*.
3 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.

12 Investigator Responsibilities

PIs are ultimately responsible for the conduct of research. PIs may delegate research responsibility. However, investigators must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibility.

The following procedures describe the investigator responsibilities in the conduct of research involving human participants.

12.1 Investigators

12.1.1 Principal Investigators

At CMU only a 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 VPR/DGS. The IRB recognizes one PI for each study.

12.1.2 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.

12.1.3 Research Team

These include the PI and other individuals, also known as key personnel, 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 thereof), or who analyze data and/or tissue samples derived from humans.

12.2 Responsibilities

To satisfy the requirements of this policy, investigators who conduct research involving human subjects must

1. develop and conduct research that is in accordance with the ethical principles in the *Belmont Report*;
2. develop a research plan that is scientifically sound and minimizes risk to the subjects;
3. have sufficient resources necessary to protect human subjects, including
    a. access to a population that would allow recruitment of the required number of subjects.
    b. sufficient time to conduct and complete the research.
    c. adequate number of qualified staff.
    d. adequate facilities.
    e. a process to ensure that all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions.
    f. availability of medical or psychological resources that subjects might require as a consequence of the research.

4. assure that all procedures in a study are performed with the appropriate level of supervision and only by individuals who are licensed or otherwise qualified to perform such under the laws of Michigan and the policies of CMU;
5. assure that all personnel are educated in the regulatory requirements regarding the conduct of research and the ethical principles upon which they are based;
6. protect the rights and welfare of prospective subjects;
7. ensure that risks to subjects are minimized: (i) By using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk; and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes;
8. recruit subjects in a fair and equitable manner;
9. obtain and document informed consent as required by the IRB and ensuring that no human subjects are involved in the research prior to obtaining their consent;
10. monitor the data collected for the safety of research subjects;
11. protect the privacy of subjects and maintain the confidentiality of data;
12. 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, include additional safeguards in the study to protect the rights and welfare of these subjects;
13. have a procedure to receive complaints or requests for additional information from subjects and respond appropriately;
14. ensure that pertinent laws, regulations, and institution procedures and guidelines are observed by investigators and research staff;
15. ensure that all non-exempt research involving human subjects receives IRB review and approval in writing before commencement of the research;
16. comply with all IRB decisions, conditions, and requirements;
17. ensure that protocols are submitted for timely continuing IRB review and approval, when required;
18. report unanticipated problems involving risk to subjects or other and any other reportable events to the IRB (see Section 8);
19. obtain documentation of IRB review and approval before changes are made to approved protocols or consent forms; and
20. seek IRB assistance when in doubt about whether proposed research requires IRB review.

12.3 Training and Ongoing Education of Investigators and Research Team

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

12.3.1 Initial Education

All personnel must complete the CMU Required Core Modules in the CITI Course in the Protection of Human Research Subjects.

New research protocols and applications for continuing review will not be accepted from PIs who have not completed the initial education requirement.

While research protocols and applications for continuing review will be accepted and reviewed if the PI holds a current certification of training, final approval will not be granted until all co-investigators and members of the research team have completed the initial education requirement.

12.3.2 Waiver of Initial Education

If investigators or members of their research team can verify that they have successfully completed human subjects research training equivalent to that required by CMU, they may request a waiver of the requirement for Initial Education. However, all investigators or members of their research team must complete the requirements of Continuing Education.

12.3.3 Continuing Education and Recertification

All investigators and members of their research teams 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. In these cases the researcher should check with the IRB Office for a determination.

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 Office staff will satisfy the training requirements for IRB members and staff described in this policy under Section 2.13.

12.4 Investigator Concerns

Investigators who have concerns or suggestions regarding CMU's HRPP should convey them to the IO or other parties (e.g., college dean, departmental chair) regarding the issue, when appropriate. The IO will research the issue, and when deemed necessary, convene the parties involved to form a response for the investigator or make necessary procedural or policy modifications, as warranted. In addition, the IRB Chair or the DRC will be available to address investigators' questions, concerns, and suggestions.

13 Sponsored Research

These procedures apply to clinical research trials of drugs and medical devices that are conducted according to FDA regulations.

CMU Office of Sponsored Programs (OSP) will not enter into sponsored research agreements to conduct clinical trials that require Investigational New Drug Exemptions (INDs). As appropriate (*ie*, if trained investigators and adequate facilities are available), then OSP may enter into sponsored agreements to conduct research on approved drugs and on medical devices.

13.1 Definitions

Sponsor – The company, institution, individual donor, or organization responsible for the initiation, management, or financing of a research study.

Sponsored research – Research funded by external entities through a grant or contract that involves a specified statement of work (e.g., the research proposal) with a related transfer of value to the sponsor, including clinical trials involving investigational drugs, devices, or biologics.

13.2 Contracts

1. OSP will negotiate contracts for research involving human subjects, and OSP and the Office of Research Compliance (ORC) will share information as necessary to ensure that protocol, consent, and contract language are consistent.
2. Contracts for sponsored research involving human subjects will be reviewed for the following provisions by both OSP and ORC:
    a. All sponsor contracts will indicate that the CMU investigator will follow the protocol, applicable regulations, and applicable ethical standards.
    b. All sponsor contracts will define who will provide care for research-related injuries and who will pay for it.
    c. If the sponsor will monitor the conduct of the research, 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.
    d. 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. (See Sec 3.6.4 for further details regarding safety monitoring.)
    e. 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).
    f. 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.

14 Financial Conflicts of Interest in Human Subjects Research

It is policy to preserve public trust in the integrity and quality of research at CMU by minimizing actual or perceived conflict of interest in the conduct of research.

Note: CMU has separate Financial Conflict of Interest policies for research supported by the Public Health Service ("Managing Conflicts of Interest in Public Health Service Research Projects" [3-34]) and by all other sponsors, including the National Science Foundation ("Conflict of Interest Guidelines" [3-9]).

The policies differ in certain important definitions such as conflict of interest; immediate family members; dollar threshold amounts for reporting a financial interest; and training requirements. The policies should be consulted when making any required disclosures or reports.

14.1 Definition of Financial Conflict of Interest

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.

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.

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.

14.2 Training in Financial Conflict of Interest

PHS. Public Health Service regulations and CMU Policy require that all PHS grantees undergo training in financial conflict of interest at least every 4 years. This obligation can be satisfied by taking the CITI course in Conflicts of Interest in Research Involving Human Subjects.

All other sponsors. The Conflict of Interest module included in CMU' s mandatory CITI initial and refresher courses for biomedical and social and behavioral research satisfies all other COI training requirements. Refresher training must be taken every 3 years.

14.3 Personnel Who Must Disclose (also called Key Personnel or Participating Faculty/Staff)

PHS: The Project Director or Principal Investigator and any other person identified as senior/key personnel in Central Michigan University's grant application, progress report, or any other report submitted to the PHS by Central Michigan University.

CMU Policy 3-34: Participating faculty/staff members in a sponsored project include:

1. The project director/principal investigator.
2. Co-project director/co-principal investigator, and
3. 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.

14.4 Individual Conflicts of Interest

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

14.4.1 Disclosure and Evaluation of Investigator Financial Interests in Research

Investigators conducting externally sponsored research are required to file a Financial Disclosure Statement no later than the time when a grant proposal is submitted, then either annually or as new reportable financial interests are obtained. There are separate forms for PHS-sponsored projects and all other externally sponsored research.

All disclosures of financial interest are reviewed by the Executive Director of the Office of Research and Graduate Studies (XD/ORGS).

14.4.2 Management of COI

If the XD/ORGS determines that a significant financial interest in a research project presents a conflict of interest, then she will develop a COI Management Plan to protect the rights and welfare of human research participants and the integrity of the institution. The elements of a management plan might include:

1. Disclosure to subjects through the consent process.

2. Modification of the research protocol or safety monitoring plan.
3. Monitoring of research by independent reviewers.
4. Disqualification of the conflicted party from participation in all or a portion of the research.
5. Appointment of a non-conflicted PI.
6. Divestiture of significant financial interests.
7. Severance of relationships that create actual or potential conflicts.
8. Prohibition of the conduct of the research at CMU.

The XD/ORGS will communicate the COI Management Plan to the IRB, which will consider it when it reviews the protocol. The CMU IRB has final authority to decide whether the financial conflict of interest and its management, if any, allows the research to be approved.

If the conflict cannot be adequately resolved, the matter will be referred to the Conflict Review Committee (previously known as the Conflict of Interest Committee), which will consider the matter, develop a management plan, and refer it to the IRB for review and approval.

14.5 Institutional Conflict Of Interest

These procedures apply to all human subjects research conducted under the auspices of CMU. This policy applies to investigators, IRB members and staff, and institutional officials.

The policy of CMU is to ensure that the welfare of human subjects and the integrity of research will not be compromised, or appear to be compromised, by competing institutional interests or obligations. Although CMU policy has separated technology transfer functions from research administration, circumstances may exist in which separation of function is not sufficient to avoid the appearance of institutional conflict of interest.

14.5.1 Responsibilities

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.

14.5.2 Management of Conflict of Interest

As part of its review of institutional COI, the CRC will ask if any related research involves human subjects. If yes, any conflict management plan which is developed will be forwarded to the IRB.

Presumption of Conflict of Interest

If Central Michigan University retains a significant financial interest, or if an IO with direct responsibility for the HRPP holds a significant financial interest in the invention, then the CRC must

assess the potential conflict of interest and weigh the magnitude of any risk to human participants. When reviewing potential institutional conflict of interest, the CRC will assume an inclination against the conduct of human participants research at, or under the auspices, of the institution where a COI appear to exist. However, the assumption may be overturned by the Committee when the circumstances are compelling and the Committee has approved an effective conflict management plan.

Decision-Making

A key aspect in decision-making is to analyze when it would be appropriate and in the public interest to accept and manage a COI, rather than require that the COI be eliminated. In some cases, the benefits of conducting a proposed research activity at the institution will be potentially high, and the risks will be low. In other cases, the scientific advantages of conducting the research may be speculative and the risks may be great. In these latter instances, the conflict should be avoided by disapproving the research application.

Evaluation of Risk

Each case should be evaluated based upon the following:

1. The nature of the science.
2. The nature of the interest.
3. How closely the interest is related to the research.
4. The degree of risk that the research poses to human participants.
5. The degree to which the interest may be affected by the research.

The COIC will consider whether the institution is uniquely qualified, by virtue of its attributes (e.g., special facilities or equipment, unique patient population) and the experience and expertise of its investigators, to conduct the research and safeguard the welfare of the human subjects involved.

Potential Actions

Potential actions to be considered to better protect subjects are any or a combination of the following:

1. Public disclosure of the financial interest.
2. Not conducting proposed research at that institution or halting it if it has commenced.
3. Reducing or otherwise modifying the financial (equity or royalty) stake involved.
4. Increasing the segregation between the decision-making regarding the financial and the research activities.
5. Requiring an independent DSMC or similar monitoring body.
6. Modifying of role(s) of particular research staff or changes in location for certain research activities, e.g., a change of the person who seeks consent, or a change in investigator.
7. Establishing a research monitoring process, so that the research can be closely scrutinized to ensure that potential conflicts do not undermine the integrity of the work and of CMU.

15 Community Outreach

CMU is committed to ensuring that educational opportunities offered to research participants, prospective research participants, and community members will enhance their understanding of research involving human participants at CMU.

15.1 HRPP Outreach Activities

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.

15.2 University Outreach Activities

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.

15.3 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.

16 Health Insurance Portability and Accountability Act (HIPAA)

This section is under review in anticipation of moving it to the portfolio of the HIPAA Privacy Office.

Protected health information obtained by CMU may not be used internally or disclosed to any outside person or organization for research purposes without prior approval of the IRB or the privacy board or privacy office of the entity responsible for the records. CMU researchers must also abide by all corporate HIPAA policies regarding HIPAA privacy and security.

The following describe the procedures for conducting research at CMU in accordance with the *Health Insurance Portability and Accountability Act of 1996 (HIPAA)*.

16.1 Definitions

Access –The mechanism of obtaining or using information electronically, on paper, or other medium for the purpose of performing an official function.

Authorization – A detailed document that gives covered entities permission to use protected health information for specified purposes, which are generally other than treatment, payment, or health care operations, or to disclose protected health information to a third party specified by the individual.

Covered entity –The term applied to institutions that must comply with the Privacy Rule. These include

1. Health plans.
2. Health care clearinghouses.
3. Health care providers who conduct certain financial and administrative transactions electronically. These electronic transactions are those for which standards have been adopted by the Secretary under HIPAA, such as electronic billing and fund transfers.

Common Rule – A federal policy on human subject protection that provides for the primary source of regulation of research.

De-Identified Information – Health information that does not identify an individual and with respect to which there is no reasonable basis to believe that the information can be used to identify an individual. If information is de-identified, it no longer is subject to the Privacy Rule and is exempt from HIPAA.

Deletion – The removal, erasing, or expunging of information or data from a record.

Disclosure –The release, transfer, provision of access to, or divulging in any other manner information outside of the covered entity.

Health Information –Any information created or received by a health care provider or health plan that 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 payment for the provision of health care to an individual.

Identifiable Health Information –A subset of health information including demographic information collected from an individual.

Limited Data Set –Protected health information that excludes specific direct identifiers of the individual or of relatives, employees, or household members of an individual. A limited data set can only be used for the purposes of research, public health, or healthcare operations, and disclosed for the purpose of research.

Minimum Necessary –The principle that any access should be limited to the minimum amount of information needed to accomplish the intended purpose of the use or disclosure.

Privacy Board – A board comprised of members of varying backgrounds and appropriate professional competencies, as necessary, to review individual's privacy rights. It is an alternative to an IRB for privacy issues only. It cannot replace the IRB for Common Rule purposes.

Privacy Act –An Act of Congress that provides for the confidentiality of individually-identified and retrieved information about living individuals that is maintained in a system of records and permits the disclosure of records only when specifically authorized by the statute. The Act provides that the collection of information about individuals is limited to that which is legally authorized, relevant, and necessary.

Privacy Rule –Provides guidance on the use of protected health information in the conduct of research. It imposes requirements on those involved in research, both individuals and institutions. "Privacy" refers to a person's desire to control the access of others to information about him/herself. The evaluation of privacy involves consideration of how the investigator will access information from or about participants. The IRB members should know strategies to protect privacy interests relating to contact with potential participants and access to private information.

Protected Health Information – Individually identifiable health information transmitted or maintained electronically or in any other form or medium, except for education records or employment records, as excluded in the Privacy Rule.

Preparatory Research – The method applied to developing or designing a research study.

Waiver of Authorization –A means of requesting approval from an IRB or Privacy Board rather than asking each research subject for an authorization to access protected health information.

16.2 Research Under HIPAA

HIPAA defines research as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge." This definition is identical with the one used in the Common Rule. HIPAA describes privacy standards for protecting PHI and so only applies to research that involves humans' (not animals') health information.

16.2.1 Waiver of Authorization for Use or Disclosure of Protected Health Information in Research

Under the Privacy Rule, covered entities are permitted to use and disclose protected health information for research with individual authorization or without individual authorization under limited circumstances. A covered entity may use or disclose protected health information for

research when presented with documentation that an IRB has granted a waiver of authorization [See 45 CFR 164.512(i)(1)(i)]. This provision of the Privacy Rule might be used, for example, to conduct records research, epidemiological studies, or other research where de-identified data is unavailable or not suited to the research purpose.

The waiver of documentation presented to the covered entity must include the following:

1. Identification of the IRB or Privacy Board and the date on which the alteration or waiver of authorization was approved;
2. A statement that the IRB or Privacy Board has determined that the alteration or waiver of authorization, in whole or in part, satisfies the three criteria in the Rule;
3. A brief description of the protected health information for which use or access has been determined to be necessary by the IRB or Privacy Board;
4. A statement that the alteration or waiver of authorization has been reviewed and approved under either normal or expedited review procedures; and
5. The signature of the Chair or other member, as designated by the Chair, of the IRB or the Privacy Board, as applicable.

The following criteria must be satisfied for the IRB to approve a waiver of authorization under the Privacy Rule:

> *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:*

1. An adequate plan to protect the identifiers from improper use and disclosure; and
2. An adequate plan to destroy the 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
3. Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart; and
4. The research could not practicably be conducted without the waiver or alteration; and
5. The research could not practicably be conducted without access to and use of the protected health information.

16.2.2 Review Preparatory to Research

The Privacy Rule permits a covered entity to use or disclose protected health information to a researcher without authorization or waiver for the limited purpose of a "review preparatory to research." Such reviews may be used to prepare a research protocol, or to determine whether a research site has a sufficient population of potential research subjects. Prior to permitting the researcher to access the protected health information, the covered entity must obtain representations from the researcher that the use or disclosure of the protected health information is solely to prepare a research protocol or for similar purposes preparatory to research, that the researcher will not remove any protected health information from the covered entity, and that protected health information for which access is sought is necessary for the research purpose. Researchers should consult the covered entity regarding any forms or applications necessary to conduct a review preparatory to research.

Researchers conducting a review preparatory to research may not record information in identifiable form, nor may they use the information that they receive to contact potential subjects, unless the investigator is also the subject's treating physician. Because the Privacy Rule permits a covered entity to disclose protected health information to the individual who is the subject of the information, covered health care providers and patients may continue to discuss the option of enrolling in a clinical trial without patient authorization. Even when permitted by the Privacy Rule, however, any use of patient information for recruitment must comply with IRB recruitment policies (see discussion below).

1. All human subjects' research requires IRB review to determine either (i) exempt status or (ii) need for further review.

Reviews preparatory to research that are permitted under HIPAA may or may not be human subjects research, depending on the investigation being conducted:

a. Only those reviews of a database by an individual entitled to access that database intended to enumerate an available data set without reviewing PHI and for which no PHI is recorded do not require review. For example: medical records may be queried for information such as, "In the year XXXX, how many patients had a discharge diagnosis of [indicate disease/diagnosis]." IRB Privacy Board Review is required for all other uses of PHI as indicated.

b. If the research involves a de-identified data set, defined as removing the following identifiers, then a de-identified data set certification form must be completed submitted for administrative review and certified prior to accessing the data set. This activity also requires an IRB-determined exemption from review:

    1. Names
    2. Geographic information (city, state, and zip)
    3. Elements of dates (except years)
    4. Telephone #s
    5. Fax #s
    6. E-mail address
    7. Social Security #
    8. Medical record, prescription #s
    9. Health plan beneficiary #s
    10. Account #s
    11. Certificate /license #s
    12. VIN and Serial #s, license plate #s.
    13. Device identifiers, serial #s
    14. Web URLs
    15. IP address #s
    16. Biometric identifiers (finger prints)
    17. Full face, comparable photo images
    18. Unique identifying #s

IRB Privacy Board review and approval is required prior to initiating this research. Investigators are not authorized to contact potential research subjects identified in reviews preparatory to research unless they are directly responsible for care of the potential subject and entitled to PHI as a result of that duty.

Investigators who have previously obtained full consent and authorization to contact a research subject as a result of a previously approved research project, may contact his/her former research subjects provided that the subject agreed to be contacted for information on future research conducted by the same PI or co-investigator(s).

16.2.3 Research on Protected Health Information of Decedents

The protections of the Common Rule apply only to living human beings; by contrast, the Privacy Rule also protects the identifiable health information of deceased persons ("decedents"). The Privacy Rule contains an exception to the authorization requirement for research that involves the PHI of decedents. A covered entity may use or disclose decedents' PHI for research if the entity obtains representations from the researcher that the use or disclosure being sought is solely for research on the PHI of decedents, that the PHI being sought is necessary for the research, and, at the request of the covered entity, documentation of the death of the individuals about whom information is being sought. Researchers should submit the applicable IRB form for IRB approval when they intend to conduct research involving decedents' PHI.

16.2.4 Limited Data Sets with a Data Use Agreement

When a researcher does not need direct identifiers for a study but does require certain data elements that are not permitted in de-identified data, the Privacy Rule permits a covered entity to disclose a "limited data set" to the researcher without authorization or waiver, provided that the researcher has signed a data-use agreement. The limited data set is still considered to be protected health information, but it must exclude only specified direct identifiers of the individual or of relatives, employers, or household members of the individual.

If the research involves a limited data set, it is defined as removing the following 16 identifiers:

1. Names
2. Postal address information (if other than city, state and zip)
3. Telephone and fax #s
4. Email addresses
5. Social Security #s
6. Medical record, prescription numbers
7. Health plan beneficiary #s
8. Account #s
9. Certificate/license #s
10. Vin and serial #s, license plate #s
11. Device identifiers, serial #s
12. Web URLs
13. IP address #s
14. Biometric identifiers (finger prints)
15. Full face, comparable photo images

The Privacy Rule requires that the data-use agreement used in conjunction with the limited data set contain provisions that

1. Establish the permitted uses and disclosures of the limited data set by the recipient, consistent with the purposes of the research, and which may not include any use or disclosure that would violate the Rule if done by the covered entity; and

Limit who can use or receive the data; and

Require the recipient to agree to the following:

a. Not to use or disclose the information other than as permitted by the data-use agreement or as otherwise required by law; and

b. Use appropriate safeguards to prevent the use or disclosure of the information other than as provided for in the data use agreement; and

c. Report to the covered entity any use or disclosure of the information not provided for by the data-use agreement of which the recipient becomes aware; and

d. Ensure that any agents, including a subcontractor, to whom the recipient provides the limited data set agrees to the same restrictions and conditions that apply to the recipient with respect to the limited data set; and

e. Not to identify the information or contact the individual.

Researchers who will be receiving limited data sets must submit a signed copy of the covered entity's data use agreement to the CMU IRB for approval, prior to initiating the research. Transition Provisions

The Privacy Rule contains certain grandfathering provisions that permit a covered entity to use and disclose PHI for research after the Rule's compliance date of April 14, 2003, if the researcher obtained any one of the following prior to the compliance date:

2. An authorization or other express legal permission from an individual to use or disclose protected health information for the research; or

The informed consent of the individual to participate in the research; or

An IRB waiver of informed consent for the research.

Even if informed consent or other express legal permission was obtained prior to the compliance date, if new subjects are enrolled or existing subjects are re-consented after the compliance date, the covered entity must obtain the individual's authorization. For example, if there was a temporary waiver of informed consent for emergency research under the FDA's human subject protection regulations, and informed consent was later sought after the compliance date, individual authorization must be sought at the same time.

The transition provisions apply to both uses and disclosures of PHI for specific research protocols and uses or disclosures to databases or repositories maintained for future research.

16.3 HIPAA and Documentation Requirements

HIPAA documents include an authorization form, a waiver of authorization form, and a de-identification form. One of these documents must be used whenever PHI is utilized in the research.

16.4 Patient Rights and Research

Under HIPAA, patients have certain rights. Those that may affect research include the right to receive a Notice of Privacy Practices, the right to access, inspect, and receive a copy of one's own PHI, the right to request an amendment to one's own PHI, and the right to an accounting of certain disclosures of PHI that occur outside the scope of treatment, payment, and health care operations that have not been authorized.

16.5 HIPAA and Existing Studies

Any research subject enrolled in a study that uses PHI from a covered entity must sign a HIPAA-compliant authorization form. This form is in addition to the existing Informed Consent document and is federally required. In a few cases, the Informed Consent document may be combined with a HIPAA authorization.

16.6 Waivers to HIPAA Authorization Form

In some cases, the CMU IRB may approve a waiver to use of the HIPAA authorization form. This may occur when the IRB finds that the research could not be practically done without the waiver, not without access to and use of the PHI, and that disclosure poses minimal risk to privacy.

17 Special Topics

17.1 Certificate of Confidentiality (CoC)

The privacy of the research subjects referred to in §301(d) is protected through the issuance of Certificates of Confidentiality. These certificates of Confidentiality provide protection against compelled disclosure of identifying information about subjects enrolled in sensitive biomedical, behavioral, clinical, or other research. This protection is not limited to federally supported research.

Certificates of Confidentiality are issued by the National Institutes of Health (NIH) and other HHS agencies to protect identifiable research information from forced or compelled disclosure. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in civil, criminal, administrative, legislative, or other proceedings, whether federal, state, or local. Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects, such as damage to their financial standing, employability, insurability, or reputation. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help to minimize risks to subjects by adding an additional level of protection for maintaining confidentiality of private information.

Certificates of Confidentiality protect subjects from compelled disclosure of identifying information but do not prevent the voluntary disclosure of identifying characteristics of research subjects. Researchers, therefore, are not prevented from voluntarily disclosing certain information about research subjects, such as evidence of child abuse or a subject's threatened violence to self or others.

However, if a researcher intends to make such voluntary disclosures, the consent form should clearly indicate this. Furthermore, Certificates of Confidentiality do not prevent other types of intentional or unintentional breaches of confidentiality. As a result, investigators and IRBs must ensure that other appropriate mechanisms and procedures are in place to protect the confidentiality of the identifiable private information to be obtained in the proposed research.

17.1.1 Statutory Basis for Protection

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

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

17.1.2 Usage

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

Any investigator engaged in research in which sensitive information is gathered from human subjects (or any person who intends to engage in such research) may apply for a Certificate of Confidentiality. Research can be considered "sensitive" if it involves the collection of

1. information about sexual attitudes, preferences, practices;
2. information about personal use of alcohol, drugs, or other addictive products;
3. information about illegal conduct;
4. information that could damage an individual's financial standing, employability, or reputation within the community;
5. information in a subject's medical record that could lead to social stigmatization or discrimination; or
6. information about a subject's psychological well-being or mental health.

This list is not exhaustive. Researchers contemplating research on a topic that might qualify as sensitive should contact the IRB Office for help in applying for a certificate.

In the Informed Consent form, investigators should tell research subjects that a Certificate is in effect. Subjects should be given a fair and clear explanation of the protection that it affords, including the limitations and exceptions noted above. Every research project that includes human research subjects should explain how identifiable information will be used or disclosed, regardless of whether a Certificate is in effect.

17.1.3 Limitations

The protection offered by a Certificate of Confidentiality is not absolute. A Certificate protects research subjects only from legally compelled disclosure of their identity. It does **not** restrict voluntary disclosures.

For example, a Certificate does not prevent researchers from voluntarily disclosing to appropriate authorities such matters as child abuse, a subject's threatened violence to self or others, or from reporting a communicable disease. However, if researchers intend to make such disclosures, this should be clearly stated in the Informed Consent form that research subjects are asked to sign.

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

1. the subject (or, if he or she is legally incompetent, his or her legal guardian) consents, in writing, to the disclosure of such information;

2. 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; or
3. release of such information is required by the federal Food, Drug, and Cosmetic Act or regulations implementing that Act.

Here are the limitations as outlined by UCLA:

- Required by other Federal, State, or local laws, such as for reporting communicable diseases; OR,
- The subject has consented to such disclosure; OR,
- The disclosure is for the purposes of scientific research that is compliant with human subjects regulations

17.1.4 Application Procedures

Any person engaged in research collecting sensitive information from human research subjects may apply for a Certificate of Confidentiality.

NIH will automatically issue CoCs to all research funded by NIH that is collecting or using identifiable, sensitive information. Compliance requirements are outlined in the NIH Grants Policy Statement, which is a term and condition of all NIH awards.

If the PI is conducting a sensitive research project that is covered by the AHRQ confidentiality statute (42 U.S.C. section299a-1(c) entitled “limitation on use of certain information”) or the Department of Justice confidentiality statute (42USC section 3789g), then a CoC is not required.

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

For more information, see the NIH Certificates of Confidentiality Kiosk. (http://grants.nih.gov/grants/policy/coc/index.htm).

17.2 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 the Michigan Department of Social Services or relevant county social service office.

CMU policy requires the solicitation of informed consent from all adult research subjects and assent from children involved as research subjects, in addition to the consent 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.

Michigan’s Mandatory reporting Law can be found at MCL 722.623 et seq.

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

17.3 CMU Students and Employees as Subjects

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

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

17.4 Student Research

17.4.1 Human Subjects 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

Responsibility of the Course Instructor: The course instructor is responsible for communicating to the students the ethics of human subjects research, for ensuring the protection of human subjects (including a process is in place for obtaining voluntary informed consent from research subjects when appropriate), and for monitoring the students' progress.

When designing a project, students should be instructed on the ethical conduct of research and on the preparation of the IRB application when such is required. In particular, instructors and students should

1. understand the elements of informed consent;
2. develop appropriate consent documents;
3. plan appropriate strategies for recruiting subjects;
4. identify and minimize riskrisks to subjects;
5. assess the risk-benefit ratio for the project;
6. establish and maintain strict guidelines for protecting confidentiality; and
7. allow sufficient time for IRB review (if necessary) and completion of the project.

In determining whether a class research project requires IRB review, the instructor is encouraged to err on the side of caution and to contact the IRB office for assistance.

17.4.2 Individual Research Projects Conducted by Students

Senior theses, masters and advanced degree research, 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.**

Students and advisors should contact the IRB Office with any questions.

Students should also check with their department, program advisor, and the College of Graduate Studies to determine if there are additional requirements to be met that are not covered in this document.

17.4.3 Theses and Dissertations

These research activities are generally considered to meet the federal definition of human subjects research and must be independently submitted to the IRB by the student-researcher's faculty advisor. However, when students conduct research as part of a course of study, *a faculty member ultimately is responsible for the protection of the subjects*, even if the student is the primary researcher and actually directs the project. Advisers assume the responsibility for students engaged in independent research, and instructors are responsible for research that is conducted as part of a course.

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.

17.5 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, namely a systematic investigation designed to develop or contribute to generalizable knowledge. Investigators should consult the IRB Chair or the DRC. Pilot studies that do not meet the regulatory definition yet pose greater than minimal risk to subjects may be referred for separate review.

17.6 Case Reports Requiring IRB Review

In general, an anecdotal report on a series of patients seen in one's own practice and a comparison of these patients to existing reports in the literature is not research and would not require IRB approval. Going beyond one's own practice to seek out and report cases seen by other clinicians creates the appearance of a systematic investigation with the intent to contribute to generalizable knowledge and, therefore, would be considered research and would require IRB approval.

Single Case Report – The external reporting (e.g., publication or poster/verbal presentation) of an interesting clinical situation or medical condition of a single patient. Case reports normally contain detailed information about an individual patient and may include demographic information and information on diagnosis, treatment, response to treatment, follow-up after treatment, as well as a discussion of existing relevant literature. The patient information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience.

Case Series – The external reporting (e.g., publication or poster/verbal presentation) of an interesting clinical situation or medical condition in a series of patients (i.e., more than one patient). Case series usually contain detailed information about each patient and may include demographic information and information on diagnosis, treatment, response to treatment, follow-up after treatment, as well as a discussion of existing relevant literature. The information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience.

17.7 International Research

For international research where CMU is responsible for the conduct of 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.

Approval of research is permitted if “the procedures prescribed by the foreign institution afford protections that are at least equivalent to those provided in 45 CFR 46.”

All policies and procedures that are applied to research conducted domestically should be applied to research conducted in other countries, as appropriate.

The CMU IRB must receive and review the foreign institution’s or site’s IRB review and approval of each study prior to the commencement of the research at the foreign institution or site.

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:

1. When the foreign institution or site has an established IRB/IEC, the PI must obtain approval to conduct the research at the "not engaged" site from the site’s IRB/IEC or provide documentation that the site’s IRB/IEC has determined that approval is not necessary for the PI to conduct the proposed research at the site.
2. 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 are permitting the research to be conducted at the performance site.
3. IRB approval to conduct research at the foreign institution or site is contingent upon receiving documentation of the performance site’s IRB/IEC determination or letter of cooperation, as applicable.
4. It is the responsibility of the CMU PI and the foreign institution or site to assure that the resources and facilities are appropriate for the nature of the research.
5. It is the responsibility of the CMU PI and the foreign institution or site to confirm the qualifications of the researchers and research staff for conducting research in that country(ies).
6. It is the responsibility of the CMU PI and the foreign institution or site to ensure that the following activities will occur.
    a. Initial review, continuing review, and review of modification
    b. Post-approval monitoring
    c. Handling of complaints, non-compliance, and unanticipated problems involving risk to subjects or others.

The IRB will not rely on a local ethics committee that does not have policies and procedures for the activities listed above.

7. It is the responsibility of the CMU PI and the foreign institution or site to notify the IRB promptly if a change in research activities alters the performance site's engagement in the research (eg, performance site "not engaged" begins consenting research participants, etc.).
8. The IRB will consider local research context when reviewing international studies to assure protections are in place are appropriate to the setting in which the research will be conducted.
9. In the case where there is no local IRB review, the IRB may require an expert consultant, either from the local country where the research is conducted or from an international organization, with the expertise or knowledge required to adequately evaluate the research in light of local context.
10. The informed consent documents must be in a language understandable to the proposed participants. Therefore, the IRB will review the document and a back translation of the exact content contained in the foreign language informed consent document which must be provided by the PI, with the credentials of the translator detailed in the IRB application or amendment form. Verification of the back translation should be made available for the IRB file.

17.7.1 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 will both be involved in the review of research, there is a plan for coordination and communication with the local ECs.

The IRB will require documentation of regular correspondence between the CMU PI and the foreign institution or site and may require verification from sources other than the CMU PI that there have been no substantial changes in the research since its last review.

17.8 Community-Based Research (CBR)

Community-based research is research that is conducted as an equal partnership between academic investigators and members of a community. In CBR projects, the community participates fully in all aspects of the research process. *Community* is often self-defined, but general categories of community include geographic community, 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, PIs 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 HRPP Office will assist the PI in developing such arrangements.

The following are some questions that PIs should ask as they develop CBR. These are also the questions that the IRB should consider when reviewing CBR.

Background, purpose, objectives

1. How was the community involved or consulted in defining the need?

2. Who came up with the research objectives and how?
3. Is this research really justified with respect to community concerns?
4. Are there concrete action outcomes?
5. Who benefits? How?

Research methodology

6. How will the community be involved in the research? At what levels?
7. What training or capacity-building opportunities will be built in?

Procedures

8. Will the methods used be sensitive and appropriate to various communities (consider literacy issues, language barriers, cultural sensitivities, etc.)?
9. How will scientific rigor and accessibility be balanced?

Participants

10. Are the appropriate people being included to get the questions answered (e.g., service providers, community members, leaders etc.)?
11. How will the research team protect vulnerable groups?
12. Will the research process include or engage marginalized or disenfranchised community members? How?
13. Is there a reason to exclude some people? Why?

Recruitment

14. What provisions have been put in place to ensure culturally-relevant and appropriate recruitment strategies and materials?
15. Have "power" relationships been considered in the recruitment strategies to minimize coercion?
16. Who approaches people about the study and how?

Risks and potential benefits

17. What are the risks and potential benefits of the research for communities? For individuals?
18. Are the risks (including risks to the community) being presented honestly?
19. How will risks be minimized?

Privacy and confidentiality

20. Where will data be stored? Who will have access to the data? How?
21. What processes will be put in place to be inclusive about data analysis and yet maintain privacy of participants?
22. What will be the rules for working with transcripts or surveys with identifying information?
23. How will boundaries between multiple roles (e.g., researcher, counselor, peer) be maintained?

Compensation

24. How will people be reimbursed for their time and honored for their efforts without it becoming coercive?
25. How will compensation be approached?
26. What provisions have been made for minimizing barriers to participation (e.g., providing for food, travel, childcare)?
27. Who is managing the budget? How are these decisions negotiated?

Conflicts of interest

28. What happens when the PI/research staff is the friend, peer, service provider, doctor, nurse, social worker, educator, funder, etc.?
29. How will power differentials be appropriately acknowledged and negotiated?

Informed consent process

30. What does informed consent mean for "vulnerable" populations (e.g., children, mentally ill, developmentally challenged)?
31. What processes are in place for gathering individual consent?
32. Is written informed consent being obtained? If not, explain why.
33. What processes are in place for gathering community consent?
34. Where minors are to be included as participants, how will assent be obtained?
35. Are the consent processes culturally sensitive and appropriate for the populations being included?

Outcomes and results

36. How will the research be disseminated to academic audiences?
37. How will the research be disseminated to community audiences?
38. What are the new ways that this research will be acted upon to ensure community/ policy/social change?

Ongoing reflection and partnership development

39. Is there a partnership agreement or memorandum of understanding to be signed by all partners that describes how they will work together?
40. What internal process evaluation mechanisms are in place?
41. When plans change to accommodate community concerns (as they invariably do in CBR), how will this be communicated to the IRB?

18 IRB Reliance

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.

When relying upon another IRB or when serving as the reviewing IRB for an outside organization or external investigator, a formal relationship must be established between CMU and the outside organization or investigator through an IRB Authorization Agreement, Investigator Agreement, a Memorandum of Understanding, or other such written agreement. The written agreement must be executed before CMU will accept any human research proposals from the outside organization or investigator or rely on the review of an external IRB.

IRB reliance agreements establish the authorities, roles, and responsibilities of the reviewing IRB and the relying organization. The procedures for reliance, including for communication, information-sharing, and reports, may be outlined in the reliance agreement, in SOPs, or other written materials. IRB Staff utilize a checklist to ensure that reliance agreements and any accompanying materials address all requirements and are consistent with 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.

18.1 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. CMU 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:

1. The terms of the external organization's FWA;
2. Prior experience with the organization and investigators;
3. The accreditation status of the external organization's HRPP;
4. The compliance history of the organization and investigators (e.g., outcomes of prior audits or inspections, corrective actions);
5. The research activities conducted by or at the external organization;
6. The willingness of the external organization to accept CMU's reliance terms and procedures;
7. The ability of the organizations to collaboratively provide meaningful oversight of the proposed research, taking into account factors such as:
    a. The risks and procedures of the research;

b. 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;
c. The expertise and experience of the CMU IRB with the proposed research, subject population, and applicable regulations;
d. The familiarity of the CMU IRB with the relevant local context considerations of the external organization; and/or
e. 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.

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.

For example, alternative procedures may be used for any of the following:

1. Management and documentation of scientific review, other ancillary reviews, and institutional permissions for research;
2. Training requirements and verification of qualifications and credentials for external investigators and staff;
3. For-cause and not-for-cause compliance reviews;
4. The disclosure and management of conflicts of interest. In all cases, any COIs and CMPs identified and developed by the relying organization will be communicated to the reviewing IRB. The reviewing IRB will determine the acceptability of the plan in accordance with their policies and procedures.
5. Review and management of matters such as site-specific consent language, HIPAA (e.g., authorizations, waivers, alterations), noncompliance, unanticipated problems, and federal reports;
6. Ensuring concordance between any applicable grant and the IRB application/protocol.
7. Procedures for and type of IRB review (e.g., expedited, convened) of additional sites after the research protocol is IRB-approved;
8. Procedures for submission and review of interim reports and continuing review materials; and/or
9. The communication of IRB determinations and other information to external investigators and organizations.

18.2 External IRB Review of CMU Research

All non-exempt human subject research (or exempt research for which limited IRB review takes place pursuant to § __.104(d)(2)(iii) or (d)(3)(i)(C) that CMU is engaged in must be reviewed and approved by the CMU IRB or an external IRB that CMU has agreed to rely upon prior to the initiation of the research.

CMU has standing agreements in place to engage the services of external IRBs for the review of specific categories of research including:

- WCGClinical for gene therapy studies (pending)

- NCI's Pediatric CIRB for NCI research involving children (pending)

Research that falls within the above parameters must be registered with CMU prior to submission to the external IRB following the procedures outlined in Section 18.2.1. Post-approval requirements are summarized in Section 18.2.2.

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 by contacting the IRB Coordinator.

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

1. The accreditation status of the proposed IRB;
2. The compliance history of the IRB (e.g., outcomes of prior audits or inspections, corrective actions);
3. Prior experience with the IRB;
4. The federal IRB registration and organizational FWA, as applicable;
5. The expertise and experience of the proposed IRB (e.g., with reviewing the type of research, research procedures, and subject population(s));
6. The research activities that will be conducted at or by CMU;
7. The risks and complexities of the proposed research;
8. 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;
9. The plan for review and allowance of the incorporation of site-specific consent language; and
10. 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:

1. 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;
2. 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;
3. The willingness of the external IRB to accommodate requests for relevant minutes and other records of the proposed study and/or to copy CMU's HRPP office on correspondence such as determination letters and notices of suspensions or terminations of IRB approval;
4. 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; and/or
5. An assessment of the external IRB's policies and procedures.

The external IRBs that serve as the IRB of record for CMU research have the same authority as the CMU IRB and all determinations and requirements of the external IRBs are equally binding. Investigators must be familiar with and comply with the external IRB's policies and procedures and any additional requirements or procedures outlined in the IRB reliance agreement or companion materials (e.g., reliance SOPs). CMU will support compliance with the terms of reliance agreements by providing investigators with 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 the CMUHRPP.

18.2.1 Registration of Studies Reviewed by External IRBs

Investigators must register studies that will be reviewed by an external IRB by submitting basic information about the research to the HRPP/IRB office in an Application for Reliance on an External IRB. After opening the application form, when prompted, investigators should supply all requested information and upload all requested documents in the remaining sections of the application. The HRPP/IRB office staff 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 reviewing IRB in accordance with the reliance agreement. When applicable, and when the external IRB is not responsible for reviews of requests for waivers or alterations of HIPAA authorization (e.g., studies reviewed by the NCI CIRB), the HRPP/IRB staff will forward requests for waiver or alteration of HIPAA authorization and any relevant materials to the internal IRB Chair for review. The HRPP/IRB office 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 notice and any approved consent document(s) to the HRPP/IRB office via the electronic system. If the protocol was modified during the external IRB review process, the approved version of the protocol should be provided as well.

18.2.2 Post Approval Requirements

Investigators approved through external IRB review must still report local unanticipated problems, complaints, and any noncompliance to the CMU HRPP/IRB office 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 the corresponding IRB approval or acknowledgment.

Changes in PI and the addition of other research team members must be submitted to the IRB office using a Protocol Change Form prior to the new PI or research team member assuming any study responsibilities. The HRPP/IRB office must verify CITI training, COI review, and any other applicable requirements.

Notices about and reports from external monitors, auditors, or inspectors must be provided to the HRPP/IRB Office using an Adverse/Reportable Event Form.

Any of the following issues must be reported immediately (asap once aware) 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 indicated (classification as "OAI" is typically made after the FDA has the opportunity to review any responses to a 483), 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; and/or
- Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding CMU's HRPP.

Investigators are reminded that other CMU reporting requirements, such as to Compliance, Privacy, and Risk Management, remain applicable in addition to HRPP reporting requirements.

18.3 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.

18.3.1 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. The HRPP Director will consult with others within the organization as needed and make a recommendation to the IO for consideration. Requests for CMU to rely upon an external IRB as the sIRB should be submitted as early in the process as possible by an Application for Reliance on an External IRB.

When CMU will not be the prime awardee, investigators should, as early in the process as possible, submit a request for CMU to rely upon an external IRB as the sIRB by Application for Reliance on an External IRB.

18.3.2 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.

18.3.3 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 prior to submission to the external IRB following the procedures outlined in Section 18.2.1. Post-approval requirements are summarized in Section 18.2.2.

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 HRPP.

19 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.

19.1 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.

19.1.1 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.

19.1.2 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.

a) 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.

(b) 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.

19.1.3 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.

19.1.4 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, 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.

19.1.5 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.

19.1.6 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.

19.1.7 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.

19.1.8 Updating IRB Registration Information

If required, CMU will revise its OHRP registration.

20 Definitions

A –

Access –The mechanism of obtaining or using information electronically, on paper, or other medium for the purpose of performing an official function.

Adverse Event – Any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article.

Agent – Any person performing institutionally-designated activities or exercising institutionally delegated authority or responsibility.

Anonymized means that data or biospecimens do not contain any identifying information and they cannot be linked to any identifiable person.

Authorization – A detailed document that gives covered entities permission to use protected health information for specified purposes, which are generally other than treatment, payment, or health care operations, or to disclose protected health information to a third party specified by the individual.

C –

Children – persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. According to Michigan state law, minors are persons under the age of 18. The general rule is that a person may consent for his/her own medical care at the age of 18. Therefore, the CMU IRB generally defines children as persons under 18 years of age. Certain statutes and case law, however, provide minors with "majority" status in some circumstances, giving them the right to consent to their own medical care. For example, for emancipated minors, Michigan law enumerates certain categories of individuals who, although under the age of 18, have the right to make medical decisions on their own behalf, such as minors who are married, widowed, or divorced; minors who are parents; etc.; for mature minors, Michigan law recognizes that some minors may be sufficiently "mature" to give consent to medical treatment, even though they do not qualify as "emancipated"; or certain minors seeking care for drug addiction, sexually transmitted diseases, emotional disorders, or abortion or mental health treatment. Because Michigan law does not specifically address consent of children with majority status to research, the CMU IRB will review issues of consent related to enrollment of these children in research on a case-by-case basis.

Note: For research conducted in jurisdictions other than Michigan, the research must comply with the laws regarding the legal age of consent in all relevant jurisdictions. The CMU General Counsel's Office will provide assistance with regard to the laws in other jurisdictions.

Clinical Investigation (per FDA) - Clinical investigation means any experiment that involves a test article and one 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 520(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.

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

Common Rule –The Common Rule refers to the "Federal Policy for the Protection of Human Subjects" adopted by 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.

Community. The term "community" encompasses any group that is identified or self-identifies as a community (including ethnic, religious, occupational, social, or special interest group or group defined by a disease or physical condition), local community organizations and advisory boards, and/or formalized community partnerships.

Covered entity –The term applied to institutions that must comply with the Privacy Rule. These include health plans and health care clearinghouses.

Health care providers who conduct certain financial and administrative transactions electronically. These electronic transactions are those for which standards have been adopted by the Secretary under HIPAA, such as electronic billing and fund transfers.D –

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

Delivery – Complete separation of the fetus from the woman by expulsion, extraction, or any other means.

De-identified means that identifiers have been removed from data biospecimens; a code may link individual records or specimens to identifiable persons. The requirement for IRB review depends on who deidentified the data/biospecimens and who has access to the linking code.

De-Identified Information – Health information that does not identify an individual and with respect to which there is no reasonable basis to believe that the information can be used to identify an individual. If information is de-identified, it no longer is subject to the Privacy Rule and is exempt from HIPAA.

Deletion – The removal, erasing, or expunging of information or data from a record.

Disclosure –The release, transfer, provision of access to, or divulging in any other manner information outside of the covered entity.

E –

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

1. Intervention for research purposes with any human subjects of the research by performing invasive or noninvasive procedures.
2. Intervention for research purposes with any human subject of the research by manipulating the environment.
3. Interaction for research purposes with any human subject of the research.
4. Obtaining the informed consent of human subjects for the research.
5. Obtaining for research purposes identifiable private information or identifiable biological specimens from any source for the research. In general, obtaining identifiable private information or identifiable specimens includes, but is not limited to

   a. observing or recording private behavior;

   b. using, studying, or analyzing for research purposes identifiable private information or identifiable specimens provided by another institution; and

   c. using, studying, or analyzing for research purposes identifiable private information or identifiable specimens already in the possession of the investigators.

F –

Fetus – The product of conception from implantation until delivery.

Equivalent Protections – {define}

G –

Guardian – An individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care. In Michigan, a "guardian" of a minor means someone with the duty and authority to act in the best interests of the minor, subject to residual parental rights and responsibilities, to make important decisions in matters having a permanent effect on the life and development of the minor and to be concerned with his/her general welfare [See MCL 330.1100(b)(6)].

Note: For research conducted in jurisdictions other than Michigan, the research must comply with the laws regarding guardianship in all relevant jurisdictions. The CMU General Counsel's Office will provide assistance with regard to the laws in other jurisdictions.

H –

Health Information –Any information created or received by a health care provider or health plan that 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 payment for the provision of health care to an individual.

Human subject means a living individual about whom an investigator (whether professional or student) is 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.

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 (as defined below), either as a recipient of the test article or as a control. A subject may be in normal health or may have a medical condition or disease. In the case of a medical device, a human subject/participant also includes any individual on whose tissue specimen an investigational device is used or tested.

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

Human Subjects Research –This means any activity that meets the definition of "research" and involves "human subjects" as defined by either the Common Rule or FDA regulations.

I –

IDE – An investigational device exemption in accordance with 21 CFR 812.

Identifiable Health Information –A subset of health information including demographic information collected from an individual.

IND – An investigational new drug application in accordance with 21 CFR Part 312.

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.

Investigational Device – A medical device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. As further stated, a device is any healthcare product that does not achieve its primary intended purpose by chemical action or by being metabolized.

Investigational Drug – An investigational drug for clinical research use is one for which the PI or a sponsor has filed an IND application (21 CFR Part 312) or an approved drug that is being studied for an unapproved or approved use in a controlled, randomized, or blinded clinical trial.

Interaction includes communication or interpersonal contact between investigator and subject.

Identifiable private information is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

An **identifiable biospecimen** is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

Institutional Review Board (IRB) – An IRB is a board designated by Central Michigan University to review, to approve the initiation of, and to conduct periodic review of research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects in research. The IRB may be assigned other review functions as deemed appropriate by the VPR/DGS or the Provost of the University Central Michigan University.

Note: In the sections that follow, the singular form "IRB" will be used to mean all IRBs registered to CMU.

Institutional Official (IO) – The IO is responsible for ensuring that the HRPP at Central Michigan University has the resources and support necessary to comply with all federal regulations and guidelines that govern human subjects research. The IO is legally authorized to represent the institution, is the signatory official for all Assurances, and assumes the obligations of the institution's Assurance.

L –

Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research.

Limited Data Set –Protected health information that excludes specific direct identifiers of the individual or of relatives, employees, or household members of an individual. A limited data set can only be used for the purposes of research, public health, or healthcare operations, and disclosed for the purpose of research.

M –

Minimum Necessary –The principle that any access should be limited to the minimum amount of information needed to accomplish the intended purpose of the use or disclosure.

Minimal risk means that 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.

N –

Neonate – A newborn.

Non-Significant Risk (NSR) – An investigational device other than a significant risk device.

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

P –

Pregnancy – 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.

Preparatory Research – The method applied to developing or designing a research study.

Prisoner – Any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute; individuals detained in other facilities by virtue of statutes or commitment procedures that provide

alternatives to criminal prosecution or incarceration in a penal institution; and individuals detained pending arraignment, trial, or sentencing. *Minimal Risk for Prisoner Research*

The definition of minimal risk in Subpart C is different than in the rest of the federal regulations. According to 45 CFR 46.303(d), "minimal risk" is 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

Privacy Act –An Act of Congress that provides for the confidentiality of individually-identified and retrieved information about living individuals that is maintained in a system of records and permits the disclosure of records only when specifically authorized by the statute. The Act provides that the collection of information about individuals is limited to that which is legally authorized, relevant, and necessary.

Privacy Board – A board comprised of members of varying backgrounds and appropriate professional competencies, as necessary, to review individual's privacy rights. It is an alternative to an IRB for privacy issues only. It cannot replace the IRB for Common Rule purposes.

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 (*eg*, a medical record).

Privacy Rule –Provides guidance on the use of protected health information in the conduct of research. It imposes requirements on those involved in research, both individuals and institutions. "Privacy" refers to a person's desire to control the access of others to information about him/herself. The evaluation of privacy involves consideration of how the investigator will access information from or about participants. The IRB members should know strategies to protect privacy interests relating to contact with potential participants and access to private information.

Protected Health Information – Individually identifiable health information transmitted or maintained electronically or in any other form or medium, except for education records or employment records, as excluded in the Privacy Rule.

R –

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

Research (DHHS) – The **Common Rule** defines research as a systematic investigation, including research development, testing, and evaluation that is designed to develop or contribute to generalized knowledge.

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.

For purposes of implementing these Standard Operating Procedures, the following activities are deemed not to be research:

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

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

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

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

Research (FDA) - FDA regulations define Research as 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 the Food and Drug Administration under section 505(i) of the federal Food, Drug, and Cosmetic Act are those that include the use of a drug other than an approved drug in the course of medical practice [21 CFR 312.3(b)].

Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 520(g) of the Food, Drug, and Cosmetic Act are those that include 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)].

Research Under the Auspices of Central Michigan University – Research under the auspices of the institution includes research conducted at this institution, conducted by or under the direction of any employee or agent of this institution (including students) in connection with his or her institutional responsibilities, conducted by or under the direction of any employee or agent of this institution using any property or facility of this institution, or involving the use of this institution's non-public information to identify or contact human subjects.

S –

Secondary research means conducting research using data or biospecimens originally collected for another purpose, which may or may not have been research. The requirements for IRB review and informed consent depend on the circumstances under which the data were collected and whether the data can be linked to individuals.

Significant Risk (SR) – A significant risk device is an investigational device that

1. is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; or
2. is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or
3. is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
4. otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Surrogate Consent – Consent obtained from a legally authorized representative on behalf of a participant determined to lack decision-making capacity.

T –

Test Article – Test articles covered under the FDA regulations include the following:

1) **Human drugs** – The primary intended use of the product is achieved through chemical action or by being metabolized by the body. A “drug” is defined as “a substance recognized by an official pharmacopoeia or formulary; a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; a substance (other than food) intended to affect the structure or any function of the body; a substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device.” [http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm]

2) **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 [sic] 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]

3) **Biological Products** – These 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 cutting-edge 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]

4) **Food Additives** – In its broadest sense, a "food additive" is any substance added to food. Legally, the term refers to "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 characteristics of any food." This definition includes any substance used in the production, processing, treatment, packaging, transportation, or storage of food.

5) **Color Additives** – A "color additive" is any dye, pigment, or substance that, 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.

6) **Foods** – These include dietary supplements that bear a nutrient content claim or a health claim.

7) Infant Formulas – Infant formulas are liquid foods intended for infants and that substitute for mother's milk.

U –

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 protocol-related documents, such as the IRB-approved research protocol and informed consent documents, and the characteristics of the subject population being studied.

V -

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

W.

Waiver of Authorization –A means of requesting approval from an IRB or Privacy Board rather than asking each research subject for an authorization to access protected health information.