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.

3.3.4 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)].

3.3.5 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 expeditious 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.