3. IRB Review Process

3.1. Policy

All human subjects research under the auspices of the institution must meet the criteria for one of the following methods for determination/review:

- Exempt review ("exempt" or "exempt review");
- Expedited review ("expedited" or "expedited review"); or
- Full review by a convened IRB ("convened IRB review" or "convened IRB").

For all non-Exempt Human Subjects Research the IRB will ensure the research meets all required ethical and regulatory criteria for initial and continuing review and any modifications of approved research.

The following describes the procedures required for the review of research by the IRB.

3.2. Procedures

3.2.1. Electronic Submission System

UMKC utilizes an electronic submission system for the electronic administration and management of the IRB. The system offers electronic management of protocols and documents; on-line submissions; web-based protocol sharing and collaboration; automatic notifications; event tracking; and other important electronic features to facilitate oversight of human subjects protections at the institution. The University uses an electronic submission/review system to reduce manual and paper-based procedures, streamline and standardize protocol submission, and review processes throughout the research lifecycle.

3.2.1.1. Mandatory Electronic Submissions

All protocols must be submitted electronically and all review decision notifications will be issued electronically.

3.2.2. Human Subjects Research Determination

The responsibility for an initial assessment as to whether an activity constitutes human subjects research rests with the PI. The PI should make this assessment based on the definitions of human subject and research contained in section 1.4. Since the University will hold the PI responsible if the assessment is not correct, PIs are urged to request a determination from the RCO that an activity does not constitute human subjects research. All requests must include sufficient documentation of the activity to support a determination by the RCO.

Determinations as to whether an activity constitutes human subjects research will be made according to the definitions in section 1.4 and using the determination of human subjects research application. Determinations regarding activities that are either clearly or clearly not human subjects research will be made in writing and may be made by the CO or RCO Director. Determinations regarding less clear-cut activities may be referred to the Chair, who may make the determination or refer the matter for convened IRB review. If a clear determination cannot be

made, then, out of an abundance of caution, the activity should be deemed to constitute human subjects research for further determination/review (e.g., exempt, expedited or convened IRB review).

Documentation of all determinations made of whether or not an activity constitutes human subjects research are recorded and maintained by the RCO.

Regulations & Guidance: DHHS 45 CFR 46.101(a); FDA 21 CFR 56.101; AAHRPP I.3.C.

3.2.3. Exempt Studies

While all research using human subjects must be approved by the institution, through the RCO, exempt research is only subject to institutional review and must be determined by the CO, RCO Director or, IRB Chair (or their designee). The following sections describe activity that is exempt and the procedures for conducting exempt determinations.

3.2.3.1. Limitations on Exemptions

3.2.3.1.1. Children: The exemptions at paragraphs (d)(1), (4), (5), (6), (7), and (8) of this section may be applied to research subject to subpart D if the conditions of the exemption are met. Paragraphs (d)(2)(i) and (ii) of this section may only apply to research subject to subpart D involving educational tests or the observation of public behavior when the investigator(s) **do not** participate in the activities being observed. Paragraph (d)(2)(iii) of this section may not be applied to research subject to subpart D.

Prisoners: The exemptions at this section do not apply to research subject to subpart C, except for research aimed at involving a broader subject population that only incidentally includes prisoners.

3.2.3.1.2. International research: exemptions do not apply to international research. Review is required by either a convened IRB or by expedited review**.**

3.2.3.2. Categories of Exempt Research

Research activities involving human subjects that are exempt from the requirement they receive IRB, full or expedited review, approval are identified in 45 CFR 46.104and 21 CFR 56.104(d). The IRB may not create new categories of exempt research. Only the CO or higher may determine which activities qualify for exempt review. Investigators do not have the authority to make an independent determination that research involving human subjects is exempt and must contact the RCO or IRB concerning the status of proposed research or changes in ongoing research. An investigator may request a particular category of exemption, but the final determination of applicability will be made by the CO or higher.

Research may be granted exempt status if all research activities involve procedures listed in one or more of the specific categories under 45 CFR 46.104.

Note:

1. These categories do not apply to research involving prisoners and categories 1-8 do not apply to FDA regulated research.
2. The research involves no more than minimal risk to participants.
3. The exemptions at paragraphs (d)(1), (4), (5), (6), (7), and (8) of this section may be applied to research subject to subpart D if the conditions of the exemption are met. Paragraphs (d)(2)(i) and (ii) of this section only may apply to research subject to subpart D involving educational tests or the observation of public behavior when the investigator(s) do not participate in the activities being observed. Paragraph (d)(2)(iii) of this section may not be applied to research subject to subpart D.

Categories of exemption are:

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 §__.111(a)(7).

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 §__.111(a)(7).

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, 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 PaperworkReduction Act of 1995, 44 U.S.C. 3501 et seq.

HIPAA note: *under the health insurance portability and accountability act of 1996 (HIPAA), researchers may obtain access to de-identified health information without the consent of the study subjects. De-identified health information is data that does not identify an Individual and reasonably cannot be used to identify an Individual.*

Note: records considered private based on Federal and state statute, including medical records and education records, require written release by the study subject or by the custodian of the record. Researchers are cautioned that review of private records involving access to and recording of identifiable information is not exempt from IRB review and may require written consent of the study subject. Existing public records do not require prior consent of subjects to review the record.

Pathological or diagnostic specimens which are considered waste and are destined to be destroyed can be used in research and are considered exempt from IRB review if there are no patient identifiers linked to the specimen and if the data is not intended to be used in the diagnosis or treatment of a patient. (If either of these conditions applies, consent of the research subject is required and a higher level of IRB review is required.) Specimens retrieved as "extra" during a clinical procedure require review at a higher level and require written consent from the subject.

Inclusion of fetal tissue in the pathological specimens category of exempt research is prohibited by regulation and requires IRB review.

5. Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt

projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.

i. Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal website or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

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 food safety and inspection service of the US department of agriculture.

3.2.3.3. FDA Exemptions

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

- **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. [FDA 21 CFR 56.104(c)] see section 7.1.5 for a detailed discussion of this exemption.

- **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 EPA or the food safety and inspection service of the US DOA. [FDA 21 CFR 56.104(d)]

3.3. Additional Protections

Although exempt research is not covered by the Federal regulations, this research 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. Procedures for Exempt Determinations

3.3.1.1. Exempt Research Activities

a) The investigator submits a new study application.
b) The RCO CO, or higher, conducts an administrative determination of the research proposal. When one or more of the exemption categories are applicable to the research, the RCO CO, or higher, documents the applicable category(ies).
c) All exempt determinations are communicated to the investigator, and include the applicable category(ies) justifying the exemp determination.

3.3.1.2. Determination Process

a) The CO, or higher is responsible for reviewing the application to determine that all the research procedures fit one or more of the exempt categories specified in the Federal regulations. The CO confirms that the research meets ethical principles and standards for protecting research subjects.
b) The CO, or higher, makes one of the following determinations:
   i. Exemption is granted;
   ii. Additional information or modifications needed before a final determination can be made;
   iii. Proposed activity does not meet the definition of research involving human subjects;
   iv. Research proposal does not meet the criteria for exemption and must be reviewed by the IRB under expedited or convened review processes.

3.3.1.2.1. Amendments

It is recommended that any proposed changes to a project that has received a determination of exemption be submitted to the RCO prior to implementation. Amendments to research protocols that were granted an exemption are reviewed to determine whether or not the change to the research would alter the exempt status, thus requiring either expedited or convened IRB review. The RCO will notify the investigator regarding the determination of the amendment and its effect on the status of the protocol, if any.

3.3.1.2.2. Expiration

Studies granted exemptions from IRB review are not issued an expiration date.

Investigators are sent annual reminders near the anniversary date of the initial determination. This reminder serves:

- To reiterate the investigator's obligation to notify the RCO of any changes to the research;
- To request an amendment be submitted if such a change has occurred or being proposed; and
- To request a final report be submitted if the research has concluded.

All research conducted under an exempt determination category is subject to all applicable UMKC institutional and IRB policies and procedures.

Exempt research activities are subject to the same subject protections and ethical standards as outlined in *the Belmont report*.

3.4. Expedited Review

Expedited review ("expedited review") is used by the IRB for either or both of the following:

- Some or all of the research appearing on the list of categories of research eligible for expedited review unless the reviewer determines that the study involves more than minimal risk;and/or
- Minor changes in previously approved research during the period for which approval is authorized. [DHHS 45 CFR 46.110; FDA 21 CFR 56.110(b)].

Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers 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 nonexpedited procedure set forth in §46.108(b).

Expedited review does not mean that institutional review is less rigorous or happens more quickly than convened IRB review. OHRP has published decision trees that are available online to help in determining whether a research proposal fits the criteria for expedited review (http://www.HHS.gov/OHRP/policy/checklists/decisioncharts.html).

3.4.1. Categories of Research Eligible for Expedited Review

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 activities listed below should not be deemed to be of minimal risk simply because they are included on this list.

The expedited review procedure may not be used for the following:

- 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 risk.

- The availability of expedited review contained in paragraphs one (1) through nine (9) of this section below apply regardless of the age of subjects, unless specifically excepted as noted.

The standard requirements for consent (or its waiver or alteration) apply regardless of the type of review (i.e., expedited review or convened IRB review) used by the IRB. It should be noted

that, while paragraphs one (1) through seven (7) below pertain to both initial review and continuing review of research, paragraphs eight (8) and nine (9) below only pertain to continuing reviews.

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
    a) Research on drugs for which an IND [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 produce is not eligible for expedited review.)
    b) Research on medical devices for which (i) an IDE [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. Collections of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
    a) From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
    b) From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples:
    a) Hair and nail clippings in a non-disfiguring manner;
    b) Deciduous teeth at time of exfoliation or if routine patient care Indicates a need for extraction;
    c) Permanent teeth if routine patient care Indicates a need for extraction;
    d) Excreta and external secretions (including sweat);
    e) Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue.
    f) Placenta removed at delivery;
    g) Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
    h) Supra-and sub-gingival 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 non-invasive 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 non-research purposes (such as medical treatment or diagnosis). [**Note**: some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See exempt categories and 454 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 DHHS regulations for the protection of human subjects. See exempt categories and 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.]

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
   a) Where no subjects have been enrolled and no additional risks have been identified; or
   b) Where the remaining research activities are limited to data analysis.

Of note, category (8) identifies three situations in which research that is greater than minimal risk and has been initially reviewed by a convened IRB may undergo subsequent continuing review by the expedited review procedures.

For a multi-center protocol, an expedited review procedure may be used by the IRB at a particular site whenever the conditions of category (8)(a), (b), or (c) are satisfied for that site. However, with respect to category 8(b), while the criterion that "no subjects have been enrolled" is interpreted to mean that no subjects have ever been enrolled at a particular site, the criterion that "no additional risks have been identified" is interpreted to mean that neither the investigator nor the IRB at a particular site has identified any additional risks from any site or other relevant source.

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 by 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.

Under category (9) the determination that "no additional risks have been identified" does not need to be made by the convened IRB.

3.4.2. Expedited Review Procedures

Under an expedited review procedure, the review may be carried out by the IRB Chair or by one or more reviewers designated by the IRB Chair from among IRB members. IRB members who serve as designees to the IRB Chair for expedited review will be matched as closely as possible with their field of expertise to the study under review.

On an annual basis , the IRB Chair will designate a list of IRB members eligible to conduct expedited review. This designation will be noted on the IRB roster. The designees must be experienced members of the IRB, serving either as a primary member or an alternate. An experienced IRB member is one who has served on the IRB for at least six months and/or who, in the opinion of the IRB Chair, has gained over a period of time sufficient knowledge and skill in conducting IRB reviews to serve as an expedited reviewer. At that time, the Chair grants the RCO Director and/or CO's the authority to assign expedited reviewers from the list of designees. Selected reviewers must 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 COI in the research (see section 2.8) will not be selected to serve as expedited reviewers. An IRB member designated as an expedited reviewer remains on the list of eligible members for one year until:

- The list is renewed the following year;
- The member requests removal; or
- The IRB Chair revokes the eligibility of the member to act as an expedited reviewer.

In the second or third case, the IRB member or IRB Chair must notify the RCO Director and/or the CO's of the intent to remove the member from the list of eligible reviewers. The RCO Director and/or the CO's will then remove the member from the list.

When reviewing research under an expedited review procedure, the IRB Chair, or designated IRB member(s), should receive and review all documentation that would normally be submitted for convened IRB review including the complete protocol, as appropriate. This includes review of the following: (1) the complete protocol, as appropriate, (2) for research qualifying for expedited review but requiring continuing review, an **application for continuing review** that summarizes research activities since the previous annual review (including modifications and AEs); (3) notes from screening conducted by the RCO staff; (4) the current consent documentation; (5) recruitment materials; (6) study measures; and (7) copies of grants and/or sponsor materials (e.g. Investigator brochure, FDA form 1572, etc.) If applicable.

Protocols submitted for expedited review will be screened by RCO staff to ensure the application is complete. The reviewer(s) conducting initial or continuing reviews will determine whether the research meets the criteria allowing review using the expedited procedure, and if so, whether the research meets the regulatory criteria for approval. If the research does not meet the criteria for expedited review, then the reviewer will indicate that the research requires convened IRB review and the protocol will be placed on the agenda for the next IRB meeting.

In reviewing the research, the reviewers will follow the review procedures described in sections **3.8, Additional Considerations During IRB Review and Approval of Research** & **3.9 Compliance with all Applicable Laws and Regulations** and may exercise all of the authorities of the IRB except the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth below.

Reviewers will indicate approval, required modifications or referral to convened IRB and return the application to the RCO. If modifications are required, the RCO staff will inform the investigator(s). Modifications made by the investigator(s) will be sent back to the IRB member(s) for further review.

In the event that expedited review is carried out by more than one IRB member and the expedited reviewers disagree, the IRB Chair may make a final determination. Upon the

discretion of the RCO Director or IRB Chair, the protocol will be submitted to the IRB for convened IRB review.

Regulations & Guidance: DHHS 45 CFR 46.100; FDA 21 CFR 46.110; categories of research that may be reviewed by the IRB through an expedited review procedure—FDA & DHHS; OHRP Guidance on written IRB procedures; OHRP Guidance on use of expedited review procedures; OHRP Guidance on continuing review; FDA information sheets: continuing review after study approval; AAHRPP II.2.b.

3.4.2.1. Informing the IRB

All members of the IRB will be apprised of all expedited review approvals that were reviewed by the IRB Chair or designated IRB member(s). This notification is accomplished by means of a list in the agenda of the next scheduled meeting. Any IRB member can request to review the full protocol by contacting the RCO.

3.5. Convened IRB Review

Convened IRB review (or "convened IRB") means review by a fully convened IRB. Except when an expedited review procedure is used, the IRB will conduct initial and continuing reviews of all research at convened meetings at which a quorum (see section 3.5.7 below) of the members is present. [OHRP 45 CFR 46.108(b); FDA 21 CFR 56.108(c); AAHRPP II.2.C].

3.5.1. IRB Meeting Schedule

The IRB meets on a regular basis throughout the year. The schedule for the IRB may vary due to holidays or lack of quorum. The schedule for IRB meetings is found on the IRB website http://ORS.UMKC.edu/research-compliance/institutional-review-board-(IRB). Special meetings may be called at any time by the IRB Chair and/or RCO Director.

3.5.2. Screening

The RCO staff will perform a screening of all protocol materials submitted to the IRB for determination of completeness and accuracy. Only complete submissions will be referred for further consideration (i.e., expedited or convened IRB review).

The investigator will be informed of missing materials and to resubmit corrections before further review can take place. The PI is responsible to provide the RCO with an active e-mail address and current contact information.

Specific questions regarding the HRPP policies and procedures; determining whether a particular protocol is human subjects research or not; and which application is necessary for a particular study, can be submitted in writing and/or via telephone to the RCO for further information and/or clarification. Individual appointments with the IRB Chair, RCO Director, and/or RCO staff can also be arranged and are strongly recommended for first-time submissions.

3.5.3. Reviewers

After it has been determined that the protocol submission is complete, the RCO staff, assigns protocols for review based on the scientific content of the protocol, reviewer's area of expertise, and requirements for representation of vulnerable populations involved in the research. For applications submitted to the IRB for convened IRB review, the Chair or designee is assigned as the primary reviewer and all other members assigned as secondary reviewers. For applications submitted to the IRB qualifying for expedited review, one or more reviewing members are assigned as primary reviewer based upon the type of submission.

When the IRB is presented with a protocol which, in the opinion of the IRB Chair, may be outside of the knowledge base or representative capacity of all of the IRB members, an outside consultant will be sought (see section 2.9). Proposals for which appropriate expertise cannot be obtained for a given meeting will be deferred to another meeting when appropriate expertise can be achieved.

Reviewers are responsible for:

- Having a thorough knowledge of all details of the proposed research;
- Performing an in-depth review of the proposed research and supporting documents;
- Discussing the proposed research at the convened meeting, presenting both positive and negative aspects of the research, and going through the regulatory criteria for approval (see sections 3.6); and
- Making suggestions for changes to the proposed research, where applicable.

For convened IRB review all IRB members have access to all information available and are expected to review all IRB proposals.

3.5.4. IRB Agenda

The meeting agenda for the IRB will be prepared by the RCO staff and distributed to IRB members prior to the scheduled meeting.

3.5.5. Pre-meeting Distribution of Documents to IRB Members

IRB members must have sufficient time in advance of an IRB meeting to review documents in connection with IRB agenda items. For this reason, the RCO strives to furnish all required materials to IRB members at least five (5) business days before the scheduled date upon which the IRB meeting will take place (except for emergency IRB meetings in which the material should be furnished with as much advance lead-time as reasonable).

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

- The IRB agenda for the upcoming meeting;
- Minutes from the previous month's meeting;
- Educational materials (as appropriate);
- Convened IRB initial submissions;

- Convened IRB continuing reviews;
- Convened IRB amendments or other submissions;
- Any deferred and/or compliance items for discussion; and
- Applicable business items and items related to audits.

In addition, each IRB member will be given access to the following documentation, as applicable, for each protocol on the agenda:

- IRB initial application, continuing review, amendment, or other applicable forms;
- Proposed consent form(s), assent form(s), and HIPAA authorization as applicable;
- Recruitment materials/subject information, advertisements;
- Data collection instruments (including all surveys and questionnaires);
- FDA form 1572;
- For research subject to ICH-GCP requirements, the investigator's curriculum vitae may be requested.

If an IRB member requires additional information to complete the review they may contact the RCO to make the request of the investigator.

Regulations & Guidance: AAHRPP II.1.F; II.2.D; ICH-GCP 8.2.10.

3.5.6. Pre-meeting Distribution of Documents to Reviewers

All members are able to review all materials submitted for review, including: any relevant grant applications; the protocol (when one exists); the investigator's brochure (when one exists); and the consent document (when one exists).

3.5.7. Quorum

A quorum ("quorum") consists of a simple majority (more than fifty percent (50%) of the voting IRB membership, including at least one member whose primary concern is in a non-scientific area. If a regular IRB member and his/her alternate are present at a convened IRB meeting, only one counts towards the quorum and the IRB member (not the alternate) is the only one entitled to vote.

Additional quorum requirements include the following:

- For FDA regulated research involving an IND or IDE, the convened meeting must include a licensed physician member. For all other FDA or non-FDA regulated research, the IRBs will rely upon the scientific expertise appropriate and relevant to the research being reviewed, which may or may not require the presence of a licensed physician member.
- When reviewing a protocol in which a prisoner is a subject or potential targeted subject, at least one IRB member present at the meeting shall be a prisoner, or a prisoner advocate/representative with appropriate background and experience to serve in that capacity. The prisoner/prisoner representative must be a voting IRB member

who is present for the discussion and for the review of any studies (including initial review, continuing review, modification, or report of Unanticipated Problems involving risks to participants and others) that involve prisoners.

At meetings of the IRB, a quorum must be established and maintained for the deliberation and vote on all matters requiring a vote. The IRB Chair, with the assistance of the RCO 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 IRB meeting remains appropriately convened. If a quorum is not maintained, the proposal or pending action item must be deferred or the meeting terminated. The RCO staff document the time of arrival and departure for all IRB members and notify the IRB Chair if a quorum is not present.

IRB members are considered present and participating at a duly convened IRB meeting when either physically present or participating through electronic means (e.g., teleconferencing or video conferencing) that permits them to listen to and speak during IRB deliberations and voting.

When not physically present, the IRB member must have received all pertinent materials prior to the meeting and must be able to participate actively and equally in all discussions.

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

RCO staff contact IRB members by e-mail and/or outlook calendar approximately 5 business days before a scheduled IRB meeting date to confirm their planned attendance to ensure appropriate notification of IRB alternate members.

3.5.8. IRB Meeting Procedures

3.5.8.1. Call to Order and Quorum

The IRB Chair (or designee in the event that the IRB Chair is absent) will call the IRB meeting to order, once it has been determined that a quorum exists.

3.5.8.2. Conflict of Interest of IRB Members

Where there is a COI involving an IRB member, the IRB Chair (or designee) will remind the IRB member to recuse him/herself from the discussion and vote by leaving the room when there is a conflict for the particular action item under review.

3.5.8.3. Review & Acceptance of Prior Meeting Minutes

The IRB will review and discuss the IRB meeting minutes from the previous 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 and presented to the Chair for

approval. A majority of the members present at a duly constituted IRB meeting is required to accept the minutes.

3.5.8.4. Initial & Continuing Review & Requests for Modification

The IRB reviews all submissions for initial review and continuing review, as well as requests for modifications. In order for the research to be approved, it must receive the approval of a majority of those voting members present at a duly constituted IRB meeting.

Regulations & Guidance: DHHS 45 CFR 46.103(b)(4); 45 CFR 46.108(b); 45 CFR 46.109; 45 CFR 46.116(b)(5); FDA 21 CFR 50.25(b)(5); 21 CFR 56.108; OHRP Guidance on Written IRB Procedures; OHRP Guidance on Continuing Review; FDA Information Sheets: Continuing Review after Study Approval; AAHRPP II.2.A.

3.5.8.5. Recording of Proceedings

It is the responsibility of the RCO to take minutes at each IRB meeting.

In order for a research activity to be approved, it must receive the approval of a majority of those voting members present at a duly constituted IRB meeting. The recording of the vote by IRB members will denote the number of votes for, against, and abstained.

3.5.8.6. Consultant Advice – Children

The institution has a signed Institutional Review Board agreement with Children's Mercy Hospital ("CMH") whereas CMH, a duly constituted pediatric IRB may be called upon for consulting advice. If needed, non-voting consultants may be invited to assist with the review if additional expertise is needed.

3.5.8.7. Consultant Advice – Vulnerable Populations

When reviewing studies with other vulnerable (by regulation) or potentially vulnerable populations, including pregnant women, fetuses, neonates, handicapped persons, and cognitively impaired persons, the IRB may request review by expert consultant. If the IRB regularly reviews research involving a vulnerable category of subjects, one or more Individuals who are knowledgeable about and experienced in working with these subjects should be included as IRB members (refer to policy on vulnerable subjects for more detail section 6).

3.5.8.8. Prisoner Representatives

When reviewing a protocol in which a prisoner is a subject:

- A majority of the IRB (exclusive of prisoner members or prisoner advocates) must have no association with the prison(s) involved, apart from their membership on the IRB.
- At least one IRB member present at the meeting shall be a prisoner, or a prisoner advocate/representative with appropriate background and experience to serve in that capacity. The prisoner/prisoner representative must be present and a voting member. The prisoner/prisoner representative must be present for the discussion and for the

review of any studies (including initial review, continuing review, modification, or report of anticipated problems involving risks to participants and others) that involve prisoners.

3.5.9. Guests & *ex officio* Guests

At the discretion of the IRB, the PI (or designee such as a sub-investigator) may be invited to the IRB meeting to answer questions about the proposed or ongoing research (PI attendance may be required for initial submission). The PI may not be present for the discussion or vote on the study or action under review by the IRB.

Other invited guests may be permitted to attend IRB meetings at the discretion of the IRB Chair and/or RCO Director. Invited guests may participate in the discussion and provide relevant input but are not voting members and must sign a confidentiality agreement prior to the convened meeting.

Certain Individuals (e.g., RCO Director, and RCO staff) regularly attend IRB meetings. While they may or may not be voting members of the IRB, they may participate in the IRB discussion and may provide additional information to the IRB.

3.6. Criteria for IRB Approval of Research

At the time of initial and continuing review, the IRB must determine that the following requirements are satisfied in order to approve research involving human subjects:

- **Risks to subjects are minimized:**
  - By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk; and
  - Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

- **Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result**. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

  Selection of subjects is equitable. In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB 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.

- **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.**

- **Consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117.**

- **When appropriate, the research plan makes adequate provisions for monitoring the data collected to ensure the safety of subjects.**

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

    - The Secretary of HHS will, after consultation with the Office of Management and Budget's privacy office and other Federal departments and agencies that have adopted this policy, issue guidance to assist IRBs in assessing what provisions are adequate to protect the privacy of subjects and to maintain the confidentiality of data.

When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, 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.

Regulations & Guidance: DHHS 45 CFR 46.111; FDA 21 CFR 56.111.

3.6.1. Risk-Benefit Assessment

The goal of a risk-benefit assessment is to ensure that the risks to research subjects posed by participation in a research study are justified relative to the anticipated benefits for the subjects or society. The IRB must:

- 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; and
- Disapprove research, when the investigator(s) are unwilling to modify the research, in which the risks are judged unreasonable in relation to the anticipated benefits,

The assessment of the risks and benefits of the proposed research - one of the major responsibilities of the IRB - involves a series of steps:

- **Identify the risks** associated with the research, as distinguished from the risks of therapies the subjects would receive even if not participating in research;
- **Determine whether the risks to subjects will be minimized** to the extent possible. This can be done, for example by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk. This also can

be accomplished, as appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes;
- **Identify the probable benefits** to be derived from the research;
- **Determine whether the risks to subjects are reasonable in relation to the benefits** to subjects, if any, and assess the importance of the knowledge to be gained. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research – as distinguished from risks and benefits 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 (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility;
- **Ensure that potential subjects will be provided with an accurate and fair description** of the risks or discomforts and the anticipated benefits.

Based on this assessment, risk associated with the research will be classified as either no more than minimal risk or greater than minimal risk, which will be based on the interpretation of minimal risk.

Regulations & Guidance: DHHS 45 CFR 46.111(a); FDA 21 CFR 56.111(a); AAHRPP I.1.B; & I.4.A.

3.6.1.1.1. Scientific Merit

In order to assess the risks and benefits of the proposed research, the IRB must determine that:
- The research uses procedures consistent with sound research design;
- The research design is sound enough to reasonably expect the research to answer its proposed question; and
- The knowledge expected to result from this research is sufficiently important to justify the risk.

In making this determination, the IRB may draw on its own knowledge and disciplinary expertise, or the IRB may draw on the knowledge and disciplinary expertise of others, such as reviews by a funding agency, or department/unit head review.

Regulations & Guidance: DHHS 45 CFR 46.111(a)(1); FDA 21 CFR 56.111(a)(1); AAHRPP I.1.B.

3.6.2. Equitable Selection of Subjects

The IRB determines by viewing the IRB proposal that the selection of subjects is equitable with respect to gender, age, class, etc. The IRB will not approve a study that does not provide adequately for the equitable selection of subjects or has not provided an appropriate scientific and ethical justification for excluding classes of persons who might benefit from the research. In making this determination, the IRB evaluates:

- The purpose of the research;
- The setting in which the research occurs;
- Scientific and ethical justification for including vulnerable or potentially vulnerable populations such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons;
- The scientific and ethical justification for excluding classes of persons who might benefit from the research; and
- The inclusion/exclusion criteria.

At the time of the continuing review, the IRB will determine that the PI has followed the subject selection criteria that he/she originally set forth at the time of initial IRB review and approval.

Regulations & Guidance: DHHS 45 CFR 46.111(a)(3); FDA 21 CFR 56.111(a)(3); AAHRPP II.5.A.

3.6.2.1. Recruitment of Subjects

The PI will provide the IRB with all recruiting materials to be used in identifying participants including recruitment methods, advertisements, and payment arrangements.

See SOP 17 regarding off site research requirements and section 3.7.8 for a discussion of IRB review of advertisements, and section 3.7.9 for a discussion of IRB review of payments/compensation to subjects.

Regulations & Guidance: DHHS 45 CFR 46.111(a)(3); 45 CFR 46.116; FDA 21 CFR 50.20; 21 CFR 56.111(a)(3); AAHRPP II.5.b.

3.6.3. Consent

The IRB will ensure that consent ("consent" or "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 IRB will ensure that consent will be appropriately documented in accordance with, and to the extent required by 45 CFR 46.117 and 21 CFR 50.27.

Regulations & Guidance: DHHS 45 CFR 46.111(a)(4) & (a)(5); FDA 21 CFR 56.111(a)(4) & (a)(5).

3.6.4. Safety Monitoring

For all research that is more than minimal risk, the investigator is asked to address the presence or absence of a safety monitoring plan. If present, the initial plan submitted to the IRB should describe the procedures for safety monitoring, reporting of Unanticipated Problems involving risks to subjects or others, descriptions of interim safety reviews and the procedures planned for transmitting the results to the IRB. This description should include information regarding an

Independent Data and Safety Monitoring Board ("DSMB"), if one exists, or an explanation why an Independent Data Safety Monitor is not necessary.

The IRB determines that the data safety monitoring plan makes adequate provision for monitoring the reactions of subjects and the collection of data to ensure the safety of subjects. The overall elements of the monitoring plan may vary depending on the potential risks, complexity, and nature of the research study. The method and degree of monitoring needed is related to the degree of risk involved. 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 PI in a small, low risk study to the establishment of an Independent DSMB for a large phase III clinical trial.

Factors the IRB will consider in determining whether the safety monitoring plan is adequate for the research are as follows:
Monitoring is commensurate with the nature, complexity, size and risk involved.

1. Monitoring is timely. Frequency should be commensurate with risk. Conclusions are reported to the IRB.
2. For low risk studies, continuous, close monitoring by the study investigator or an Independent Individual may be an adequate and appropriate format for monitoring, with prompt reporting of problems to the IRB, sponsor and regulatory bodies as appropriate.
3. For an Individual safety monitor, the plan must include:
    - Parameters to be assessed
    - Mechanism to assess the critical efficacy endpoints, at intervals, in order to determine when to continue, modify, or stop a study
    - Frequency of monitoring
    - Procedures for reporting to the IRB
4. For a DSMB, the plan must include:
    - The name of the data safety monitoring board
        - Where appropriate, is Independent from the sponsor
    - Availability of written reports
    - 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
    - Frequency and content of meeting reports
    - The 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. For some studies the national institutes of health ("NIH") require a DSMB. The IRB has the

authority to require a DSMB as a condition for approval of research where it determines that such monitoring is needed. When DSMBs are utilized, IRBs 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 AEs, 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.

Regulations & Guidance: DHHS 45 CFR 46.111(a)(6); FDA 21 CFR 56.111(a)(6); AAHRPP II.4.B.

3.6.5. Privacy and Confidentiality

Under the research regulations, the IRB is required to determine whether adequate procedures are in place to protect the privacy of subjects and to maintain the confidentiality of the data. This duty is unrelated to HIPAA privacy requirements, which is addressed in section 16.

3.6.5.1. Definitions

Confidentiality: methods used to ensure that information obtained by researchers about their research subjects is not improperly divulged. Do not confuse this research term with HIPAA privacy requirements.

Identifiable information: for research privacy purposes, this means information where the identity of the subject is or may readily be ascertained by the investigator or associated with the information. This term should not be confused with individually identifiable health information (IIHI) used with HIPAA.

Individually identifiable private information: is information where, for research purposes, the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

Obtain (or "obtaining"): means to receive or access individually identifiable private information (or identifiable specimens) for research purposes. This includes an investigator's use, study, or analysis for research purposes of individually identifiable private information (or identifiable specimens) already in the possession of the investigator.

Private information: for research privacy purposes, this means information about behavior that occurs in a context in which an Individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an Individual and which the Individual can reasonably expect will not be made public (e.g., a medical record). [45 CFR 46.102(f)]. Do <u>not</u> confuse this research term with HIPAA privacy requirements.

3.6.5.2. Privacy

The IRB must determine whether the activities in the research constitute an invasion of privacy. In order to make that determination, the IRB must obtain information regarding how the investigators are getting access to subjects or subjects' private, identifiable information

("Individually Identifiable Private Information") and the subjects' expectations of privacy in the situation. Investigators must have an appropriate authorization to access subjects or the subjects' information.

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

- Methods used to identify and contact potential participants;
- Settings in which an Individual will be interacting with an investigator;
- Appropriateness of all personnel present for research activities;
- Methods used to obtain information about participants and the nature of the requested information;
- Information that is obtained about Individuals other than the "target participants," and whether such Individuals meet the regulatory definition of human subject (e.g., a subject provides information about a family member for a survey); and
- How to access the minimum amount of information necessary to complete the study.

3.6.5.3. Confidentiality

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. The level of confidentiality protections should be commensurate with the potential of harm from inappropriate disclosure.

At the time of initial review, the IRB ensures that the privacy and confidentiality of research subjects are 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 subjects;
- About Individuals who may be recruited to participate in studies;
- The use of personally identifiable records; and
- The methods to protect the confidentiality of research data.

The PI will provide information regarding the privacy and confidentiality of research subjects at the time of initial review through the completion of the IRB application, and/or other submitted, applicable materials. The IRB will review all information received from the PI and determine whether or not the privacy and confidentiality of research subjects is sufficiently protected. In some cases, the IRB may also require that a certificate of confidentiality be obtained to additionally protect research data from compulsory disclosure (see section 18.1).

In reviewing confidentiality protections, the IRB shall consider the nature, probability, and magnitude of harm that would be likely to result from a disclosure of collected information outside the research. It shall evaluate the effectiveness of proposed de-identification techniques,

coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections.

Regulations & Guidance: DHHS 45 CFR 46.111(a)(7); FDA 21 CFR 56.111(a)(7); AAHRPP II.6.a; & II.6.b.

3.6.6. Vulnerable or Potentially Vulnerable Populations

At the time of initial review, the IRB will consider the scientific and ethical reasons for including vulnerable or potentially vulnerable subjects in research. The IRB may determine and require that, when appropriate, additional safeguards are put into place for vulnerable or potentially vulnerable subjects, such as those without decision-making capacity.

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

Regulations & Guidance: DHHS 45 CFR 46.111(b); 45 CFR 46 Subpart B, Subpart C & Subpart D; 45 CFR 46.205; FDA 21 CFR 50.3; 21 CFR 56.111(b)-(c); 21 CFR Subpart D; AAHRPP II.4.C.

3.7. Additional Considerations During IRB Review and Approval of Research

3.7.1. Determination of Risk

At the time of initial review and continuing review, the IRB will make a determination regarding the risks associated with the research proposals. Risks associated with the research will be classified as either "no more than minimal risk" or "greater than minimal risk" based on the absolute interpretation of minimal risk. The meeting minutes will reflect the IRB's determination regarding risk levels.

3.7.2. Frequency of Review

At the time of initial review and at continuing review, the IRB will make a determination regarding the frequency of review of the research protocol. All protocols will be reviewed by the IRB at intervals appropriate to the degree of risk but no less than once per year. In some circumstances, a shorter review interval (e.g. Semi-annually, quarterly, or after accrual of a specific number of participants) may be required (see below). The meeting minutes will reflect the IRB's determination regarding review frequency.

Regulations & Guidance: DHHS 45 CFR 46.109(e); FDA 21 CFR 56.109(f).

3.7.3. Review More often than Annually

Unless specifically waived by the IRB, research that meets any of the following criteria, although not inclusive of all scenarios, may require review more often than annually:

1. Significant risk, as determined by the IRB, 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 especially vulnerable populations likely to be subject to coercion (e.g., terminally ill); or
3. A history of serious or continuing Non-Compliance on the part of the PI.

The following factors will be considered when determining which studies require review more frequently than on an annual basis:

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 specific experience of the PI and other members of the research team in conducting similar research;
5. The nature and frequency of AEs observed in similar research at this and other institutions;
6. The novelty of the research making unanticipated AEs more likely; or
7. Any other factors the IRB deems relevant.

In specifying an IRB 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 1 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 1 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.

3.7.4. Independent Verification that no Material Changes have Occurred

The IRB recognizes that protecting the rights and welfare of subjects sometimes requires that the IRB Independently verify, utilizing sources other than the investigator, that no material changes occurred during the IRB-designated approval period. Independent verification from sources other than the investigator may be necessary at times (e.g., in cooperative studies, or other multi-center research).

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

1. Protocols where concern about possible material changes occurred 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;
3. Protocols randomly selected or for “cause audit” for internal audit; or
4. Whenever else the IRB deems verification from outside sources is relevant.

The following factors also will 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; or
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 prospectively require that such verification take place at predetermined intervals during the approval period, or may retrospectively require such verification at the time of continuing review, 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.

3.7.5. Consent Monitoring

In reviewing the adequacy of subject consent procedures for proposed research, the IRB may on occasion determine that special monitoring of the consent process by an impartial observer (i.e., a 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 that will be 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 5.4.6 for a detailed discussion of consent process monitoring.

Regulations & Guidance: DHHS 45 CFR 46.109(e); FDA 21 CFR 56.109(f); AAHRPP II.7.g.

3.7.6. Investigator Conflicts of Interest

The research application asks protocol-specific questions regarding COI for investigators and key research personnel. As part of its review process, the IRB communicates with the University's Office of Research Services ("ORS") regarding the potential conflict. See section 14 for details regarding Conflicts of Interest.

Regulations & Guidance: 42 CFR 50.603; 42 CFR 50.606(a); FDA 21 CFR 50.606(a): 21 CFR 54.1; 21 CFR 54.2; 21 CFR 54.4; 21 CFR 312.64(d); 21 CFR 812.110(d); 45 CFR 690; AAHRPP III.1.A.

3.7.7. Significant New findings

During the course of research, significant new knowledge or findings about the medication or test article and/or the condition under study may develop. The PI must report any significant new findings to the IRB and the IRB will review such findings with regard to potential 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 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.

Regulations & Guidance: OHRP Guidance on Written IRB Procedures; OHRP Guidance on Continuing Review; FDA Information Sheets: Continuing Review after Study Approval; AAHRPP II.2.D.

3.7.8. Advertisements

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

- The information contained in the advertisement;
- The mode of its communication;
- The final copy of printed advertisements, prior to posting; and
- The final audio/video taped advertisements.

This information should be submitted to the IRB with the initial application or as an amendment request to the protocol along with the submittal.

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

- Statements implying a certainty of favorable outcome or other benefits beyond what was outlined in the consent document and the protocol;
- Claims, either explicitly or implicitly, that the drug, biologic or device was safe or effective for the purposes under investigation;
- Claims, either explicitly or implicitly, that the test article was known to be equivalent or superior to any other drug, biologic or device;
- Using terms like "new treatment," "new medication," or "new drug;"
- Promising "free medical treatment" when the intent was only to say participants will not be charged for taking part in the investigation;
- Emphasis on payment or the amount to be paid, such as bold type or Larger font on printed media; or
- The inclusion of exculpatory language.
- Advertisements will 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.

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:

- The name and address of the PI and/or research facility;
- The condition being studied and/or the purpose of the research;
- In summary form, the criteria that will be used to determine eligibility for the study;
- The time or other commitment required of the subjects;
- The location of the research and the person or office to contact for further information;
- A clear statement that this is research and not treatment;
- A brief list of potential benefits (e.g. No cost of health exam); or
- IRB project number, the date of original IRB approval, and the date of IRB approval of the advertisement.

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

Note: an advertisement may be modified to include the appropriate contact person and contact information.

Regulations & Guidance: DHHS 45 CFR 46.111(a)(3); 45 CFR 46.116; FDA 21 CFR 50.20; 21 CFR 56.111(a)(3); AAHRPP II.5.B.

3.7.9. Payment to Research Subjects

Payment to research subjects may be an incentive for participation or a way to reimburse a subject for time, travel, parking, 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 coercion of subjects. Payments should reflect the degree of risk, inconvenience, or discomfort associated with participation. The amount of compensation must be proportional to the risks and inconveniences posed by participation in the study.

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

The IRB must review both the amount of payment and the proposed method of disbursement to assure that neither entails coercion or undue influence.

For research studies involving multiple visits, the IRB may not allow the entire payment to be contingent upon completion of the entire study. As such, credit for payment should accrue and not be contingent upon the participant completing the entire study. Any amount paid as bonus for completion of the entire study should not be so great that it becomes coercive.

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). Researchers are required to follow University policy regarding methods of payment to research participants.

3.7.10. Recruitment Incentives

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. UMKC prohibits the use of payment(s) in exchange for the referral of research participants outside those outlined in the "refer a friend" guidelines for clinical research center at UMKC School of Dentistry. Similarly, payments designed to accelerate recruitment that are tied to the rate or timing of enrollment ("bonus payments") also are not permitted. PIs are strongly encouraged to consult with the University of Missouri system Office of General Counsel (OGC) if they have any questions or concerns about recruitment incentives.

3.8. Compliance with all Applicable Laws and Regulations

The RCO and UMKC IRB rely on the University's OGC for interpretation and application of Federal and state law and the laws of any other jurisdiction where research is conducted as they apply to human subject research. It is ultimately the PIs responsibility to understand and adhere to the applicable, Federal, state and local laws in the jurisdictions where the research is being carried out.

All consent forms also must be consistent with applicable state and local laws.

3.9. Possible IRB Actions

The IRB or reviewer(s) may arrive at the following decisions:

- Approval (or "approve" or "approved");
- Deferred with minor modifications;
- Tabled for major modifications;
- Tabled;
- Disapproval (or ("disapprove" or "disapproved");
- Approval in principal;
- Suspension or termination; and
- Investigator hold.

The following sections provide clarification with respect to each of these decision options.

3.9.1. Approval

Approved (or "approved," "approval," or "IRB approval"): means the determination by the IRB that the investigation and protocol, as submitted, has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and other institutional and Federal

regulations. The research may begin as of the IRB approval date. [DHHS 45 CFR 46.102(h); FDA 21 CFR 56.103(m)].

3.9.2. Deferred with minor modifications

3.9.2.1. Definitions

Deferred with minor modification: is a situation where the IRB cannot approve the research as submitted or where the proposal and/or **consent form** require minor revisions (e.g., wording changes, with replacement language provided). For proposals submitted for convened IRB review, the needed revisions are agreed upon at the IRB meeting. For proposals submitted in expedited review, the needed revisions are designated by the reviewer(s). These revisions are presented to the PI for incorporation.

3.9.2.2. Policy

In order to receive approval for a protocol deferred with minor modifications:

- For proposals initially submitted for convened IRB review, the PI's response, the revised proposal and the previously submitted proposal is given to the IRB Chair and/or a designee of the IRB for review. The reviewer(s) may approve the study upon receipt and approval of the revisions without further action by the convened IRB.
- For proposals initially submitted for expedited review, the PI's response, the revised proposal and the previously submitted proposal is given to the same reviewer(s) for re-review.

Approval of the protocol application will not be granted and the approval letter will not be issued until all deficiencies, if any, are corrected to the satisfaction of the IRB or the reviewer(s).

The outcome of the IRB's deliberations or reviewer(s) findings is communicated to the PI in writing, which notice shall be issued within ***10 working days*** of determination. The PI may not proceed with the research until receipt of notice of IRB/reviewer(s) approval of the research.

The IRB's determination concerning the revision will be documented.

IRB deferred with minor modification letters are automatically generated.

3.9.3. Tabled for Major Modifications

3.9.3.1. Definitions

Tabled for major modification: is a situation where the IRB cannot approve the research as submitted because (1) the proposal and/or **consent form** require major modification or clarification; or (2) insufficient information is provided to adequately judge the protocol application (e.g., the risks and benefits cannot be assessed with the information provided). IRB approval of the proposed research must not occur until subsequent review by the convened IRB of the requested major modification or clarification.

3.9.3.2. Policy

For proposals initially submitted for convened IRB review, in order to receive approval for a protocol tabled for major modifications, the investigator's response must be submitted for review at a subsequent, convened meeting of the IRB. The RCO provides the IRB with the PI's response, the revised proposal and the previously submitted proposal. The item is placed on the agenda for review at the next meeting.

IRB approval of the proposal will not be granted and an approval letter will not be issued until all deficiencies, if any, are corrected to the satisfaction of the IRB.

The IRB's determination concerning the subsequent revised proposal will be documented. The outcome of the IRB action is communicated to the PI in writing.

3.9.3.3. Time Limit for Submitting Requested Changes for New Research Protocol Application Deferral or Tabling

Failure to submit a response to IRB stipulated changes or inquires related to new research protocols deferred for minor modifications or tabled for major modifications within **90 days** will result in deactivation of the new research protocol application. The PI will receive written notification of the withdrawal of the IRB file including an explanation for this action. PIs wishing to re-open their file must re-apply to the IRB following procedures outlined in this document. An extension beyond 90 days may be granted by the IRB if sufficient cause is provided by the PI. After the 90-day deadline, the IRB Compliance Officer will withdraw the study application at which time an email notifying the PI of the withdrawn study application will be delivered.

3.9.4. Tabled (for reasons other than major modification)

The IRB may also table a protocol where it does not have a member with expertise adequate to the scope and complexity of the proposed research and thus seeks review by an expert in the appropriate field. The protocol PI may suggest an expert to the IRB for this purpose.

A protocol requiring convened IRB review may be tabled for lack of appropriate expertise in attendance, lack of time, loss of quorum, etc. In the event a research protocol application is tabled for such administrative reasons, the RCO will assign it for review at a future meeting of the convened IRB.

When a protocol is tabled for reasons other than major modifications, the RCO shall draft and transmit to the protocol PI a memorandum setting forth the reasons for this action.

3.9.5. Disapproved

The IRB action of disapproved means that it cannot approve the protocol as written. The IRB has determined that the research cannot (1) be conducted on institutional premises, or other facilities; (2) cannot involve University students, employees or patients; (3) be conducted on or by institutional employees or institutional agents; and/or be conducted under the auspices of UMKCs IRB. Written notice of disapproval will be issued by the IRB.

The expedited reviewer(s) may exercise all of the decisional authorities of the IRB, except that expedited reviewer(s) may not disapprove the research application. If there are concerns about whether or not an Individual research project meets the definition of minimal risk or if the project may involve procedures that cannot be reasonably reviewed via the expedited review process, the application will be submitted for consideration at a convened IRB meeting.

3.9.6. Approved in Principle

Approval in principle is IRB approval, as requested by a sponsor, without the IRB having reviewed all of the study procedures and consent documents. [DHHS 45 CFR 46.118].

There are two circumstances in which the IRB may grant approval required by a sponsoring agency without having reviewed all of the study procedures and consent documents [45 CFR 46.118]. One is if study procedures are to be developed during the course of the research, but human subject approval is required by the sponsoring agency. The other is if the involvement of human subjects depends on the outcomes of work with animal subjects. The IRB may then grant approval without having reviewed the undeveloped recruitment, consent, and intervention materials. However, if the proposal is funded, the PI must submit such materials for approval at least 60 days before recruiting human subjects into the study, or into any Pilot studies or pre-tests. Approval in principle is granted to satisfy sponsoring agency requirements or to allow investigators to have access to funding to begin aspects of the project that do not involve human subjects. Approval in principle may be done via expedited review.

3.10. Study Suspension, Termination and Investigator Hold

3.10.1. Suspension or 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 Unanticipated Problems and section 10 for a discussion of Non-Compliance)

Suspension of IRB approval is a directive of a convened IRB, IRB Chair or Vice Chair or RCO Director to temporarily stop either some or all previously approved research activities to ensure protection of the rights and welfare of study participants or for Non-Compliance. Suspension directives made by the IRB Chair or Vice Chair or RCO Director 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 permanently stop some or all activities in a previously approved research protocol. If all research activities are terminated, the research no longer requires continuing review.

The IRB shall notify the PI in writing of such suspensions or terminations and shall include an explanation of the reasons for the decision. The PI shall be provided with an opportunity to respond in person or in writing.

When a study is suspended or terminated, the convened IRB or authorized Individual will:

- Have any Unanticipated Problems reported to the IRB;
- Consider actions to protect the rights and welfare of subjects;
- Consider whether procedures for withdrawal of enrolled subjects take into account their rights and welfare; and
- Consider informing current subjects of the suspension or termination.

All suspensions or terminations must be reported to the IO and reporting agency.

As it relates to the actions of the IRB suspension or termination of research, that involves an IRB-approved protocol, also can be issued by University officials acting outside the HRPP (i.e., not necessarily related to protecting the rights and welfare of study participants and therefore not necessarily reportable to any reporting agency(ies)). In the event of such action, it is the responsibility of the PI or University official to inform the IRB immediately. The convened IRB, IRB Chair Vice Chair or RCO Director will take such action as necessary to ensure the rights and welfare of study participants is being protected as well as informing the relevant governmental institutions.

Regulations & Guidance: DHHS 45 CFR 46.113; FDA 21 CFR 56.113; AAHRPP II.4.d.

3.10.2. Investigator Hold

A PI or sponsor may request an investigator hold on a protocol when the PI/sponsor wishes to temporarily or permanently stop some or all approved research activities. Investigator holds are not suspensions or terminations.

3.10.2.1. Procedures

PIs must notify the IRB in writing:

- Providing a description of the research activities that will be stopped;
- Describing proposed actions to be taken to protect current participants; and
- Describing actions that will be taken prior to IRB approval of proposed changes in order to eliminate apparent immediate harm.

Upon receipt of written notification from the PI the IRB Chair or RCO Director, in consultation with the PI, determines 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 in section 2.4.3. If additional procedures need to be followed to protect the rights and welfare of the current participants the IRB CO places the research study on the agenda for review.

The IRB Chair and/or RCO Director, in consultation with the PI, determine how and when currently enrolled participants will be notified of the administrative hold, if applicable.

PIs may request a modification of the administrative hold by submitting a request for a modification to previously approved research.

3.10.3. Protection of Currently Enrolled Participants

Before an investigator hold, termination, or suspension is put into effect, the convened IRB, IRB Chair (or designee) considers whether any additional procedures need to be followed to protect the rights and welfare of current participants. Such procedures might include:

- Transferring participants to another PI;
- Making arrangements for clinical care outside the research;
- Allowing continuation of some research activities under the supervision of an Independent monitor;
- Requiring or permitting follow-up of participants for safety reasons;
- Requiring AEs or outcomes to be reported to the IRB and the sponsor;
- Notification of current participants; and/or
- Notification of former participants.

3.11. Continuing Review

Unless an IRB determines otherwise, continuing review of research is not required in the following circumstances:

(i) Research eligible for expedited review in accordance with §__.110;

(ii) Research reviewed by the IRB in accordance with the limited IRB review described in §__.104(d)(2)(iii), (d)(3)(i)(C), or (d)(7) or (8);

(iii) 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.

For research requiring continuing review, the IRB will conduct such a review of ongoing research at intervals that are appropriate to the level of risk for each research protocol, but not less than once per year. Continuing review must occur as long as the research remains active for long-term follow-up of participants, even when the research is permanently closed to the enrollment of new participants and all participants have completed all research-related interventions.

Regulations & Guidance: DHHS 45 CFR 46.109(e); FDA 21 CFR 56.109(f).

3.11.1. Approval Period

At UMKC, determination of the approval period and the need for additional supervision and/or participation is made by the IRB on a protocol-by-protocol basis. For example, for an

investigator who is performing particularly risky research, or for 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 is considered to have lapsed at midnight on the expiration date of the approval.

*When the IRB reviews and approves research **without conditions** at a convened meeting*
When an IRB conducts the initial review of a research project at a convened meeting and approves the research for one year *without* requiring either (a) changes to the protocol or consent document(s), or (b) submission of clarifications or additional documents, the effective date of the initial approval is the date of that IRB meeting. In such circumstances, the expiration date of the initial approval period may be as late as one year after the date of the IRB meeting at which the research project initially was approved (45 CFR 46.109(e)).

*When the IRB reviews and approves research **with conditions** at a convened meeting without requiring further review at a subsequent convened meeting*
Often the IRB conducts the initial review of a research project at a convened meeting and approves the research for one year **and**;

- As a condition of approval, requires either (a) changes to the protocol or consent document(s), or (b) submission of confirmations of specific assumptions or understandings on the part of the IRB or additional documents; and
- Directs that the IRB Chairperson (or other Individual(s) designated by the IRB) to review and determine on behalf of the IRB whether the changes, clarifications, and/or additional documents to be submitted by the investigator(s) are satisfactory.

Under this scenario, further review by the IRB at a subsequent convened meeting is not necessary in order for the initial approval to become effective, and the effective date of the initial approval is the date on which the IRB Chairperson (or any other Individual(s) designated by the IRB Chair) has reviewed and accepted as satisfactory all changes to the protocol or consent documents, or any other responsive materials, required by the IRB from the investigator. In such circumstances, the expiration date of the initial approval period, which is the date by which the first continuing review must occur, may be as late as one year after that effective date of initial IRB approval (45 CFR 46.109(e)).

*Determining the date for **continuing reviews** for research reviewed by the IRB at convened meetings and approved for one year intervals*
The IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year (45 CFR 46.109(e)). Given this requirement, it is important to recognize that the use of the "effective date" of IRB approval (i.e., the date on which the IRB Chairperson or any other Individual(s) designated by the IRB has determined

that the conditions of approval have been satisfied) – as opposed to the date of the convened meeting at which the IRB approved a research study with conditions– to determine the latest permissible date for continuing review *only applies to the first continuing review*. For all subsequent continuing reviews of a research study, since there will be an on-going approved study, *the date of the convened meeting* when the IRB conducts continuing review and approves the study (with or without conditions) determines the latest permissible date of the next continuing review.

It is noted that when the IRB approves research with conditions at the time of continuing review before the expiration date of the preceding IRB approval period, IRB approval does not lapse even if the investigator needs additional time – beyond the date on which the preceding IRB approval would have expired – to satisfy some or all of the IRB's conditions.

The approval date and approval expiration date are noted on initial approvals and subsequent continuing review approvals 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 research ordinarily does not alter the date by which continuing review must occur. This is because continuing review is review of the full protocol, not simply a change to it.

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.

3.11.2. Continuing Review Process

To assist PIs, courtesy reminders are sent to investigators in advance of the study expiration date. It is the PI'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.

Information and documentation to be uploaded by PIs includes the following:

- The application for continuing review with protocol edits, if applicable, to reflect any changes from the prior submission;
- The current approved stamped **consent form**;
- Any newly proposed **consent form** document clean and with track changes to reflect any changes from the prior submission, if applicable
- The current word version copy of the approved consent form, if no changes have been made;
- The full protocol or a protocol summary containing the relevant information necessary to determine whether the proposed research continues to fulfill the criteria for approval;
- A status report on the progress of the research that includes:

- A summary since the last IRB review of:
- Unanticipated Problems involving risks to participants or others;
- AEs, untoward events, and adverse outcomes experienced by participants.
- Participant withdrawals;
- The reason for withdrawals;
- Complaints about the research;
- Amendments or modifications;
- Any relevant recent literature; and
- Any interim findings.

- Any relevant multi-center trial reports;
- The investigator's current risk-potential benefit assessment based on study results, if applicable;
- **Application for continuing review**;
- **HIPAA authorization form,** if applicable;
- **Truman Medical Center research administration and privacy board approval,** if applicable; and
- **FDA form 1572s,** if applicable.

In conducting continuing review of research, ***all*** IRB members will be directed to review the above materials along with all prior materials.

The RCO staff will retrieve any additional materials should the IRB members request.

Review of currently approved or newly proposed consent documents must occur during the scheduled continuing review of research by the IRB. However, **consent documents should be reviewed whenever new information becomes available that would require modification** of information in the IRB-approved consent document. Changes to consent documents are amendments and will be reviewed according to the procedures in section 3.12.

Continuing review of a study must continue until:

- The research is permanently closed to the enrollment of new participants;
- All participants have completed all research-related interventions and long term follow up; and
- Collection and analysis of private identifiable information has been completed

3.11.3. Expedited Review of Continuing Review

Unless an IRB determines otherwise, continuing review of research is not required in the following circumstances:

(i) Research eligible for expedited review in accordance with §__.110;
(ii) Research reviewed by the IRB in accordance with the limited IRB review described in §__.104(d)(2)(iii), (d)(3)(i)(C), or (d)(7) or (8);

(iii) 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.

Records of continuing review activities, including the rationale for conducting continuing review of research that otherwise would not require continuing review as described in §__.109(f)(1).

Regulations & Guidance: DHHS 45 CFR 46.109 (f)(1); 45 CFR 46.115(a)(3)

3.11.4. Lapse in Continuing Review Approval

The regulations permit no grace period or approval extension after approval expiration. Research that continues after the approval period has expired is considered to be research conducted without IRB approval. If the continuing review approval does not occur within the timeframe set by the IRB, this is a lapse in approval. All research activities must stop. This includes cessation of subject recruitment (e.g., 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 required information for continuing review before the expiration date. Therefore, investigators must allow sufficient time for IRB review and approval.**

It is the responsibility of the PI to ensure that a lapse in approval does not occur. The RCO will notify the PI of the expiration of approval and that all research activities must cease.

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 a lapse in continuing review of the research would cause harm. Enrollment of new subjects cannot occur and continuation of research interventions or interactions for already enrolled subjects will only continue when either the IRB, IRB Chair, or RCO Director, finds that it is in the best interest of the Individual subjects to do so.

Failure to submit continuing review information in a timely manner is considered Non-Compliance and will be handled according to the Non-Compliance policy (see section 10).

Once approval has expired (i.e., lapse in continuing review approval), IRB review and re-approval must occur prior to re-initiation of the research. If the study approval has lapsed more than 30 days and the PI has not submitted an **application for continuing review**, the study may be closed by the IRB.

If the IRB requires revisions to obtain continuing review approval and no response has been received from the PI within 60 days following IRB correspondence, the study may be closed unless the IRB determines that study closure will harm subjects.

3.11.5. Calculating the "date of IRB approval"

3.11.5.1. Approval at a convened meeting. When the convened IRB committee approves the IRB application, the date of the convened IRB committee meeting is the "date of IRB approval" stamped on the ICF(s) and placed on the approval letter.

3.11.5.2. Approval pending changes at a convened IRB committee meeting. When the IRB application is approved with specific changes requested, pending review and approval by the Chair or designee, the date that the changes are verified by the Chairperson or his/her designee is the "date of IRB approval" stamped on the ICF(s) and placed on the approval letter.

3.11.5.3. Expedited review. When the IRB application is approved through an expedited review process, the date that final approval is extended by the Chairperson or his/her designee is the "date of IRB approval" stamped on the ICF(s) and placed on the approval letter.

3.11.5.4. Continuing review. OHRP recognizes the logistical advantages of keeping the IRB approval period constant from year to year throughout the life of each project. When continuing review occurs annually and 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.

3.11.5.5. Amendments. The "date of IRB approval" for amended ICFs is based on the type of review or determination as described above. For example, when an amendment is approved pending changes, the date that the changes are verified by the Chairperson or his/her designee is the date of IRB approval stamped on the ICF(s).

3.12. Amendment of an Approved Protocol

PIs who wish to modify or amend their approved applications **must seek IRB approval before making any changes in approved research**. This requirement exists even though the changes are planned for the period for which IRB approval has already been given. One noteworthy exception is for changes necessary to eliminate an immediate hazard to the subject, in which case the IRB must then be notified at once.

Amendments may be approved if they are within the scope of what the IRB originally authorized. For example, if a researcher wishes to add a population to an existing study, but not

alter the study procedures or purpose, an amendment request is usually appropriate. Likewise, amending a procedure without changing the study's purpose or study population may also be appropriate. If, however, the researcher wishes to add a population and revise study procedures, he or she may need to submit a new application for human subjects approval.

Investigators must submit documentation to inform the IRB about the changes in the status of the study. To this end, investigators are required to submit the changes as an amendment to the approved protocol:

- Completed **application for amendment**;
- Revised protocol (if applicable);
- Revised approved **consent(s)/assent(s)** 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;
- Revised or additional recruitment materials; or
- Any other relevant documents provided by the investigator

RCO staff or RCO Director will determine whether the proposed changes may be approved through an expedited review process, if the changes are minor, or whether the amendment warrants convened IRB 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 amendment of an approved protocol for convened IRB review.

Regulations & Guidance: AAHRPP II.2.E; OHRP Guidance on written IRB procedures.

3.12.1. Expedited Review of Protocol Amendments/Modifications

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

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

The reviewer 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.

3.12.2. Convened IRB Review of Protocol Modifications

When a proposed change in a research study is not minor (e.g., procedures involving increased risk or discomfort are to be added), 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 documents provided by the PI are accessible to all IRB members. 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.

3.12.3. Changes in the Consent Document

When a modification makes it necessary to change the informed consent document, regardless of whether any participants are enrolled, two copies of the revised consent document are to be submitted to the IRB. One "track changes" copy should show all changes from the previous version (i.e., highlighting all additions and striking through all deletions) and one clean copy for the IRB to affix the approval stamp without any outdated text.

3.13. Closure of Protocols

The completion or termination of a study is a change in activity that must be reported by the PI to the IRB on the **final report form**. Although subjects will no longer be at risk under the study, a final report to the IRB allows it to close the study as well as provide information that may be used by the IRB in the evaluation and approval of related studies involving the PI.

IRB staff will review the **final report form** for completeness, close out the study, and notify the IRB.

3.14. Notice to PI of IRB Actions

Barring extraordinary circumstances, all IRB letters are prepared by RCO staff and are distributed to the PI and research team within ***ten (10) working days***. For an approval, along with written notification of approval, a copy of the approved **consent(s)**/**assent(s)** document(s) containing the stamped approval with the dates of the approval and expiration on each sheet will be uploaded. For deferrals for minor modifications or tabling, communication will include the information that is required, the basis for requiring those modifications, and a deadline for response submission. For a disapproval, termination or suspension, the notification will include the basis for making that decision.

All formal correspondence between the IRB and investigators are retained.

The IRB reports its findings and actions to the institution in the form of its minutes, a copy of which is stored in the RCO files.

3.15. Appeal of IRB Decision to Disapprove

When an IRB protocol presented at a convened meeting is disapproved, deferred with minor modification, or deferred with major modification, the IRB will notify the PI in writing about the specific deficiencies and the modifications that are necessary for appropriate IRB approval. The IRB shall include in its written notification a statement of the reasons for its decision and give the PI an opportunity to respond in writing. The PI also is given the opportunity to schedule a meeting with the IRB to discuss this matter.

Regulations & Guidance: DHHS 45 CFR 46.109(d); FDA 21 CFR 56.109(e).

Approved by: Lawrence Dreyfus, PhD
Name of University Institutional Official

_____
Signature of University Institutional Official Date