Section 6: Review Mechanisms

6.1. Exemptions

Policy

- In accordance with federal regulations 45 CFR 46 and 21 CFR 50 and 56, UIR allows specific categories of research to be exempt from human subject review. Any research that falls within these categories must also present minimal risk and not be subject to any state laws that would prohibit an exemption. Of these categories, category 6 (see below) is the only one that is permissible if the research falls under the Food and Drug Administration regulation.
- The UIR IRB Chair or designee may determine that a human subject activity is exempt from UIR IRB review.
- The exemptions do not apply to research that involves prisoners. See Section 8 *Vulnerable Populations* for additional information about studies that involve prisoners.
- The exemption category for research that involves survey or interview procedures (category 2) is not allowed if the subjects are children.
- The exemption category for research involving observation of public behavior (category 2) when the subjects are children and the investigator does not participate in the activities being observed is permissible under this category.

Procedures

Accepted Exemption Categories

UIR will exempt from human research review only those research activities that involve human subjects that, fall within one ore more of the specified exempt categories. These categories are listed below. Categories considered exempt from UIR IRB review under 45 CFR 46.101 (b) are as follows:

Category 1: Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among the instructional techniques, curricula, or classroom management methods.

Category 2: Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subject's responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation.

For research that involves children as subjects, no exemptions are allowed under (b) when subjects are involved in observations in which the investigator participates in the activities being observed.

Category 3: Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

Category 4: Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

Category 5: Research and demonstration projects which are conducted by or subject to the approval of federal department or agency heads, and are designed to study or evaluate:

- Public benefit or service programs;
- 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 under those programs.

OHRP has determined that the following criteria must be satisfied to invoke the exemption for research and demonstration projects examining "public benefit or service programs" as specified under Department of Health and Human Services (DHHS) regulations at 45 CFR 46.101(b) (5):

1. The program under study must deliver a public benefit (e.g., financial or medical benefits as proved under the Social Security Act) or service (e.g., social, supportive, or nutrition services as provided under the Older Americans Act).
2. The research or demonstration project must be conducted pursuant to specific federal statutory authority.
3. There must be no statutory requirement that the project be reviewed by an Institutional Review Board (IRB).
4. The project must not involve significant physical invasions or intrusions upon the privacy of participants.

The funding agency must be contacted and provide approval to utilize this exemption category.

Category 6: Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or

environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Exemption Review Process

1. If an investigator believes that a study meets the criteria for exemption, the principal investigator (PI) is asked to complete the "*Claim of Exemption Form*." This and all other appropriate forms should be uploaded on IRBNet and submitted to Research Support Services (RSS).
2. The form asks for a brief summary of the research, and asks the investigator to indicate under which category the research is exempt.
3. The "*Claim of Exemption Form*" and all other appropriate documents are administratively reviewed by the RSS Specialist. Upon completion of this review it will then be submitted to the IRB Chair or designee. The reviewer will review the application to determine:
    - Risks to subjects are minimized.
    - There are adequate protections for privacy and confidentiality.
    - Whether some form of informed consent should still be obtained.
    - If necessary, subjects and/or the research will be appropriately monitored.
    - Whether any ethical concerns exist.
    - Whether the request meets the exemption criteria.
4. If the reviewer determines that the activity is exempt from review, the documents submitted in the initial protocol package found in IRBNet will be issued an approval. The investigator will be notified through IRBNet that the protocol has been approved.
5. Once a research study has been certified as exempt, annual reviews are not required. However, a 3 year expiration date is assigned from the date of approval.
6. It is the investigators responsibility to notify RSS of any changes or modifications that are made to the study's design, procedures, and so on, to ensure that all activities still remain exempt.
7. Investigators are required to submit a continuing review when the approval is about to expire if they wish to continue their research (see section 6.4), or submit a closing report.

DHHS Decision Chart: Is the Research Involving Human Subjects Eligible for Exemption? (Please see charts 3-7 for specific categories).

6.2. Expedited Review

Policy

UIR permits the review of research protocols through the expedited review process governed by Food and Drug Administration (FDA) and Department of Health and Human Services (DHHS) federal regulations. Protocols that may be reviewed under expedited review are limited to 1) categories of research listed in 45 CFR 46.110 if the research involves no more than minimal risk and meet the applicability criteria and 2) minor changes in previously approved research during the period for which approval is authorized. Expedited review procedures may not be used for classified research. The IRB Chair or designee is responsible for final determination as to which protocols, revisions/amendments are eligible for expedited review and has the authority to perform the expedited review. For initial applications a primary and secondary reviewer will be assigned.

Procedures

Categories of Research That May be Reviewed through an Expedited Review

Applicability

1. Research activities that:
    - Present no more than minimal risk to human subjects, and
    - Involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through expedited review process. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review process when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.
2. The categories in the list below apply regardless of the age of subjects, except as noted.
3. The expedited review process may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability; be damaging to their financial standing, employability, insurability, or reputation; or be stigmatizing, unless reasonable and appropriate protections are implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
4. The expedited review process may not be used in classified research that involves human subjects.
5. Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

Research Categories

Category 1: Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.

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

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

- From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 mL in an eight week period and collection may not occur more frequently than two times per week; or
- 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/kg in an eight week period and collection may not occur more frequently than two times per week.

Category 3: Prospective collection of biological specimens for research purposes by non-invasive means.

Examples:

1. Hair and nail clippings in a non-disfiguring manner.
2. Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction.
3. Permanent teeth if routine patient care indicates a need for extraction.
4. Excreta and external secretions (including sweat).
5. 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.
6. Placenta removed at delivery.
7. Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor.
8. 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.
9. Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings.
10. Sputum collected after saline mist nebulization.

Category 4: Collection of data through non-invasive procedures (that do not involve general anesthesia or sedation) routine employed in clinical practice, excluding procedures that involve 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:

1. 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.
2. Weighing or testing sensory acuity.
3. Magnetic resonance imaging.
4. Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography.
5. Moderate exercise, muscle strength testing, body composition assessment, and flexibility testing, where appropriate, given the age, weight, and health of the individual.

Category 5: Research that involves materials (e.g., data, documents, records, specimens) that have been collected, or will be collected, solely for non-research purposes (e.g., medical treatment, diagnosis).

Category 6: Collection of data from voice, digital, or image recordings made for research purposes.

Category 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 that employs survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

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

1. Where
    - The research is permanently closed to the enrollment of new subjects;
    - All subjects have completed all research-related interventions; and
    - The research remains active only for long-term follow-up of subjects; or
2. Where no subjects have been enrolled and no additional risks have been identified; or
3. Where the remaining research activities are limited to data analysis.

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

DHHS Decision Chart: May the IRB Review be Done by Expedited Procedures?

New

Protocols that may be reviewed under the expedited review process are those listed by the Secretary of DHHS in the Federal Register, 45 CFR 46.110(a) and by the FDA in the Federal Register, 21 CFR 56.110 (a) (see below). To be eligible for expedited review, all procedures performed for research must be included in the expedited procedures categories, must be considered minimal risk as defined in the regulations, and must meet all of the applicability criteria. Classified research is not eligible for expedited review.

Any protocol that fits the criteria for expedited review must be submitted to RSS through IRBNet using the "*Initial Application Social & Behavioral Sciences*" form, or "*Initial Application Biomedical Sciences*" form and all other appropriate documents (e.g., questionnaires, informed consent documents, recruiting material, and appendix).

All protocols considered for expedited review will undergo administrative review by the Research Support Services (RSS) Specialist. The RSS Specialist will review all protocols for completeness and consistency and provide the investigator feedback, and questions or concerns that may need to be addressed. The RSS Specialist will also provide advice as to what will likely be acceptable within IRB policies and provide input on the protocol and consent document prior to being reviewed by a committee member(s). The investigator must respond to the issues raised and changes requested through the administrative review process before protocols are provided to a committee member(s) for expedited review.

The RSS Specialist also initially determines whether the protocol meets the criteria for expedited review as specified by the regulations which include the applicability criteria. In addition to meeting one of the categories on the expedited review list, the protocol, in total, must fall under the criteria for minimal risk. It is important to recognize that procedures that may be considered minimal risk in adults may not be minimal risk in children. This may be the result of psychological or emotional distress, even if the actual procedures present minimal physical risk to the subject. The IRB Chair or designee designates which protocols and which revisions/amendments may undergo expedited review and may designate any IRB member(s) as an expedited reviewer or review it themselves.

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

After initial screening by the RSS Specialist and pre-review, the RSS Specialist will give access to the protocol in IRBNet to the IRB Chair and to a primary and secondary reviewer for initial applications. Members are asked to declare if any conflict of interest exists for any protocol they are assigned to review through expedited procedures. If this is the case, the review access granted to the reviewer with the conflict of interest will be removed and the protocol will be reassigned. Any member may serve as an expedited reviewer. If a protocol involves prisoners and is eligible for expedited review, the prisoner representative must be designated one of the

expedited reviewers. The IRB Chair may also refer any protocol to the full Committee for review at a convened meeting. Even when expedited review is allowed in accordance with federal regulations, the IRB Chair reserves the right to request full Committee review. The IRB Chair's determination is final. No member with a conflict of interest may serve as a reviewer for any expedited item.

The primary reviewers who conduct the expedited review will receive access to the IRBNet submission and will find the following in the package:

- Protocol application
- Appropriate appendices
- Informed consent/Assent/HIPPA authorization Form
- Financial Disclosure (as pertinent)
- Investigational Drug Data (as pertinent)
- Investigational Device Data (as pertinent)
- Waiver of Parental Permission (as pertinent)
- Pregnant Women and Fetuses Form (as pertinent)
- Prisoners Form (as pertinent)
- Recruitment notices, postings, letters
- Letter of Support (as pertinent)
- Surveys, Questionnaires, and any other study tools
- Any other documents requested by reviewers

All of the criteria specified in 45 CFR 46 are applied as part of the expedited review process. The expedited reviewers are required to complete a worksheet which contains all of the regulatory criteria for approval. Any questions, comments, or requests for revisions (including any that concern the informed consent document) that are received from the reviewers are composed by the RSS Specialist and investigators are notified by a letter found within the IRBNet package. The primary reviewers will indicate whether they want to receive the investigator's response or whether the RSS Specialist can verify that the changes have been made. If an investigator is not willing to accept the recommendations and requirements presented as part of the expedited review process, the protocol and correspondence to date will be placed on the agenda for the next scheduled convened meeting. Once all issues are resolved and the informed consent finalized, approval will be given.

The designated reviewers may at any time determine that the protocol be forwarded to the full Committee for review if they feel it does not meet the requirements for expedited review, or if they are unable to come to an agreeable decision. The primary expedited reviewers may not disapprove an expedited protocol.

A summary of each protocol that undergoes expedited review, including a designation of expedited review categories, is to be prepared for the full Committee at its next scheduled meeting.

6.3. Full Committee Review

Policy

UIR has established and maintains an Institutional Review Board, that reviews research protocols for any issues in design and conduct that may potentially affect the safety, rights, and welfare of human subjects. The UIR has as its primary responsibility the protection of research subjects. The IRB establishes procedures to ensure a consistent review process for all initial reviews, continuing reviews, amendments/revisions, and unanticipated problems that involve risk to subjects or others. The review procedures must comply with federal and state regulations, and with institutional policies.

Procedures

Meeting Frequency

The UIR IRB meets monthly as appropriate. UIR IRB members will have access to all protocol materials on IRBNet after the RSS Specialist has completed his/her review. On the day of the meeting reviewers will be provided with hard copies upon request of the protocol found within the IRBNet package. The protocol will also be projected for Committee members to reference during discussion of the protocol.

Administrative Pre-Review

The RSS Specialist will review all protocols for completeness and consistency and provide the investigator with feedback, questions or concerns to be addressed. The RSS Specialist will also provide advice as to what will likely be acceptable within IRB policies and provide input on the protocol and consent document prior to being reviewed. The investigator must respond to the issues raised and changes requested through the pre-review process before the protocols are placed on the IRB meeting agenda or provided to committee members.

Quorum and Voting

In order for the IRB to hold a meeting at which actions can be taken a quorum of members must be present, including at least one member whose primary concerns are non-scientific, and one member who is not affiliated with the University. One member may serve more than one of these roles. A physician member must be present during the review of any clinical research

study that involves the use of a Food and Drug Administration-regulated drug, device, or biologic. A quorum consists of more then half of the IRB members. If a member is unable to attend, the member will be allowed to participate in the meeting by telephone conferencing. This member will have access to all materials (within IRBNet) other members receive in preparation for the meeting. The IRB Chair or designee will assume responsibility to make sure a quorum is present at all times. If a quorum is lost during a meeting, no further actions will be taken. In order for the research to be approved, it shall receive the approval of the majority of those members present at the meeting.

UIR policy does not allow an IRB member to participate in the initial or continuing review, requests for amendments, modifications, and unanticipated problems involving risk or incidents of non-compliance of any project in which the member has a conflicting interest, except to provide information requested by the IRB. IRB members are expected to advise the rest of the committee if they have a conflict of interest prior to discussion of any item on the agenda.

Actions

Approval

Approval is based upon an acceptable risk/benefit ratio and all other regulatory requirements pertaining to the protocol.

Conditional Approval

Conditional Approval means that at the time when the IRB reviews and approves a research study (or proposed changes to a previously approved research study), the IRB requires as a condition of approval that the investigator:

1. make specified changes to the research protocol or informed consent document(s),
2. confirm specific assumptions or understandings on the part of the IRB regarding how the research will be conducted, or
3. submit additional documents, such that, based on the assumption that the conditions are satisfied, the IRB is able to make all of the determinations required for approval under the HHS regulations.

When a protocol is conditionally approved, verification procedures must be included as part of the IRB approval process, under which the IRB Chair and/or designated individuals will review responsive materials from the investigator as required by the IRB, and determine whether the conditions of approval have been satisfied.

The Office for Human Research Protections (OHRP) does not consider the verification process to represent review and approval of minor changes under an expedited review procedure. Therefore, a person other than an IRB member may be designated to verify that the conditions have been satisfied if they have the appropriate expertise or experience.

Deferred for further review by full IRB

The changes proposed or questions raised by the IRB prevent the IRB from making one or more of the determinations required for approval by the regulations. The lack of information or concerns raised result in the IRB being unable to make the required determinations about research risks and benefits, the adequacy of privacy and confidentiality protections, or the adequacy of the informed consent process because the research protocol provides insufficient information and the IRB is unable to specify changes to the research protocol that would allow the IRB to make the required determinations.

Some examples of reasons for a deferral are:

- The protocol was poorly written, lacking significant amounts of information regarding scientific justification, procedures, risk reduction, and recruitment procedures.
- There are significant ethical concerns that do not permit a favorable risk/benefit determination. More information is required or changes in design and procedures must be implemented.
- There are clarifications and modifications requested directly relevant to determinations required by the regulations such as the data and safety monitoring plans.

Disapproved

After consultation with the investigator, the IRB determines that the research presents subject risks that far outweigh the benefit or value of the knowledge to be gained; or the research raises such serious ethical questions as to be unacceptable. In the event disapproval is foreseen, the investigator is invited to attend the meeting to discuss the protocol.

Tabled

A study that is unable to be reviewed at the meeting due to lack of time, no quorum present, lack of IRB panel expertise, and/or other extenuating circumstances. The protocol will be placed on the agenda for the next scheduled meeting.

Modifications Required

This term is used in IRBNet and by RSS staff and IRB committee members to indicate *minor* revisions that need to be made by the PI in order to secure approval of the protocol. Some requested revisions might be verbiage in a consent document, grammar/spelling within application forms, more detail and clarification of the protocol, and the completion of absent application forms.

Termination

Some or all activities on a protocol are permanently discontinued. There has been a determination that serious or continuing non-compliance or unanticipated problems involving risks have occurred and no further work on the protocol may continue. See Section 5.5

6.3.1. Initial Review of New Protocols: Full Review

New research protocol applications that do not meet the criteria for exemption or expedited review are placed on the agenda for full IRB review. All members of the Committee will be granted access to the protocol in IRBNet by the RSS Specialist.

All new protocols are assigned a primary and secondary reviewer. At least one of the two reviewers must have the appropriate expertise to review the topic of the protocol. If there is not appropriate expertise, either an outside consultant would be sought or the protocol will be rescheduled for review when the expertise is obtained. The primary and secondary reviewers are responsible for a complete review and summary of the protocol application. These reviewers present the protocol to the entire IRB committee at a convened meeting. The primary reviewer presents a brief summary of the protocol, followed by his or her comments. The secondary reviewer presents his or her comments only. Following presentation by the primary and secondary reviewers, the full board is invited to provide additional comments. All members are asked to review all protocols and informed consents in preparation for the discussion.

Primary and secondary reviewers receive a reviewer worksheet that must be completed and uploaded in the protocol package found within IRBNet. The use of this worksheet is mandatory. The worksheet requires that reviewers consider all the regulatory criteria required for approval. Their comments at the meeting are structured to discuss the issues within the context of the regulatory criteria.

Protocols are discussed on an individual basis. Any IRB member who has a conflict of interest (e.g., is involved in the protocol or has other conflicts) must leave the room during the final discussion and vote. These individuals may be asked questions about the content of the protocol but must not be present beyond the discussion of questions and answers.

Following presentation by the assigned primary and secondary reviewers, discussion is opened to the full board. The primary and secondary reviewers suggest an action to be taken (see *Actions*, listed above). Following discussion, the IRB Chair calls for a Committee vote. The IRB Chair tries to continue discussion until it appears that a consensus is reached, but a vote may be called at any time.

A vote is taken and recorded. The total number of votes is always to equal the total number of members present at the meeting. The vote is recorded as follows:

- The number of members who vote **for** the action recommended
- The number of members who vote **against** the action recommended

- The number of members who wish to **abstain** from voting
- The number and name of members who are **present at the meeting, but who are not present in the room when the vote is called**
- The number and names of **members who leave the room for reasons of conflict of interest**

The decision about the protocol will be determined by the majority vote. A second vote will take place regarding informed consent documents. Members will also vote on the informed consent/assent documents and hold a separate vote for an authorization document as well. Votes must be unanimous in favor of approval of each document. If not, documents will be revised until a unanimous vote is reached.

In addition, the Committee determines the time frame for the subsequent continuing review. The continue review time period must be set to occur within 1 year of the approval date.

6.3.2. Revisions/Amendments: Full Review

All revisions/amendments that do not meet the criteria for expedited review are placed on the agenda for full IRB review. Each amendment is assigned a primary and secondary reviewer.

Reviewers get a reviewer worksheet that needs to be completed and uploaded in IRBNet. The procedures listed above apply to the review and voting process for revisions/amendments. All members will be granted access to the revision/amendment application in IRBNet. As part of the review, the Committee will determine whether subjects who have previously been enrolled in the research should be provided with information about the amendment when such information may impact a subject's willingness to participate in the research and whether re-consent is required.

6.4. Continuing Review

Policy

An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research 45 CFR 46.109(e).

Procedures

With the exception of those continuing reviews that meet the regulatory criteria for expedited review, all continuing reviews are placed on the agenda for full IRB review. These include protocols that were initially approved under expedited review procedures and still meet those regulatory criteria in addition to expedited review DHHS criteria 8 and 9.

- **Category 8:** Continuing review of research previously approved by the convened IRB as follows:
    - (a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
    - (b) where no subjects have been enrolled and no additional risks have been identified; or
    - (c) where the remaining research activities are limited to data analysis
- **Category 9:** Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply, but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Each expedited continuing review is assigned a primary reviewer. A reviewer worksheet is provided and needs to be uploaded in IRBNet. The worksheet is structured so that the reviewer can determine whether the regulatory criteria continue to be met. The primary reviewer is provided with a copy of the continuing review form and all other appropriate documents uploaded within the package. The procedures listed above also apply to the review and voting process for continuing reviews requiring a convened meeting. In addition, the reviewer determines the time frame for subsequent continuing review.

6.5. Amendments/Revisions

Policy

The UIR IRB must review and approve any requested changes/modifications to human subject protocols before implementation. The only exception to this requirement is a protocol deviation or change that may be necessary to eliminate an apparent immediate hazard to a given research subject. If an investigator needs to modify a protocol to remove an immediate safety hazard or risk to the subject, this must be reported to the IRB within 2 business days. These changes will be reviewed by the IRB as events that may represent unanticipated problems involving risk to participants or others and to determine whether the change was consistent with ensuring the participant's continued welfare.

The IRB will determine whether subjects who have been previously been enrolled in the research should be provided with information about the amendment or revision and whether they require re-consent.

Definition of Minor Revisions and Amendments

A minor modification is defined as a change that would NOT materially affect an assignment of the risks and benefits of the study, or does not substantially change the specific aims or the design of the study. Examples of minor modifications may include:

- Changes in the research staff/personnel for a protocol, minor revisions in the informed consent document, and/or change in the number of subjects to be enrolled
- The substitution of assessments with alternate assessments that present minimal risk
- An increase or decrease in proposed human research subject enrollment supported by a statistical justification
- Narrowing the range of inclusion criteria
- Broadening the range of exclusion criteria only if the risk/benefit assessment remains unchanged
- Decreasing the number or volume of biological sample collections, provided that such a change does not affect the collection of information related to safety evaluations
- An increase in the length of confinement or number of study visits for the purpose of increased safety monitoring, provided the risk/benefit ratio does not change
- Alterations in human research subject payment that do not add element of undue inducement
- Changes to improve the clarity of statements or to correct typographical errors, provided that such changes do not alter the content or intent of the statement
- The addition or deletion of qualified investigators
- The addition or deletion of study sites
- Revisions or modifications in the informed consent to provide better clarification, revised lay language, or inclusion or missing elements

Addition of recruitment notices, recruitment sites, or a population, provided there is not change in the risk/benefit determination

Procedures

IRB approval of modifications to research protocols and informed consent documents may be requested at any time. **The approval of an amendment request by the IRB does not alter the original approval date or expiration date assigned to the research protocol/informed consent.**

Prior to use or distribution, the IRB must also review and approve any additional recruitment materials or other materials given to subjects during their participation in the study (i.e. reminders, letters, etc.) or following their participation (study results, thank-you letters).

Process to Submit

Investigators may submit any amendment/revision by completing an *Amendment Form*. The form must be complete, and the investigator may attach additional information as pertinent.

Investigators are advised to submit not only a list of the changes, but to provide a rationale for the changes. This applies to both the protocol and the informed consent documents. The investigator should specifically discuss whether the changes result in any substantive changes in the study design. If the amendment requires modifications of the informed consent document, the investigator should also provide specific justification for whether re-consent of subjects who have already been enrolled will be required. The protocol application, protocol, consent, recruitment notices, etc. should be revised to incorporate all changes; however, it is important for the investigator to save all approved older versions as well. Documents should be submitted with the changes highlighted.

Amendments/Revisions Review Process

A proposed change in research related activities that does not materially affect an assessment of the risks and benefits of the study and does not substantially change the specific aims or design of the study may be approved through expedited review procedures. This includes minor changes to previously approved research.

Upon receipt of the Amendment Form, the RSS Specialist makes an initial determination as to whether the requested amendment warrants review by the full IRB Committee, or whether the amendment can be reviewed through the IRB's expedited procedures. If the RSS Specialist is unsure as to whether the amendment requires review by the full Committee or expedited review, the RSS Specialist will check with the IRB Chair.

The individual who is performing the expedited review is granted access to the protocol in IRBNet and will find a copy of the amendment application, and all other documents that might be affected by the proposed amendment. The reviewer will also be provided with a worksheet to complete to ensure the regulatory criteria continues to be met. The expedited reviewer may ask for further justification from the principal investigator for the requested amendment. If there are any questions or concerns that the PI needs to address, the RSS Specialist will communicate these concerns to the PI. If there are no issues for the PI to address, the amendment can be approved. As part of the review, the reviewer will determine whether the amendment qualifies as a minor revision or amendment that qualifies for expedited review and whether the subjects who have previously enrolled in the research should be provide with information about the amendment when such information may impact a subject's willingness to participate in the research. The expedited reviewer will also determine whether they wish to see the changes back or whether the RSS Specialist may verify the changes have been made.

Amendments/revisions and modifications that are approved through expedited review are shared with the IRB Committee at the scheduled meeting. Similar proceedings will occur for projects that have been previously determined to be exempt.

6.6. Modifications: Exceptions and Deviations

Policy

Federal regulations require that all protocol modifications (*any* change from the approved protocol) must be submitted to the IRB for review, and receive approval prior to implementation, unless the change is to eliminate an immediate harm to a research subject. Most of these changes are submitted as amendments which undergo expedited or full committee review (see policy on *Amendments section 6.5*).

When an investigator anticipates a one time **significant**, time sensitive, intentional action or process that departs from an IRB approved protocol, the investigator may request that a one time **exception** be granted by the IRB.

Modifications that are noted or recognized after they occur are referred to as **deviations**. These changes may be classified as **significant or minor deviations**.

Significant deviations/exceptions are events that actually or have the potential to:

- Impact subject safety, welfare, or rights
- Alter the risks or benefits to the subject in a more significant, serious, or negative way
- Impact the integrity of the data
- Effect a subject's willingness to participate

It is important to note that although a deviation/exception may not fit within one of the above categories, the fact that it had the potential to result in a negative outcome classifies the event as significant. Investigators will need to use their discretion when making this determination.

Significant deviations must be reported to the IRB within 2 business days of their recognition through the unanticipated events process.

Minor deviations/exceptions are deviations/exceptions that do not meet these criteria, must be tracked by the investigator and reported as applicable to the sponsor, FDA and through the data and safety monitoring process. Minor deviations and exceptions should also be reported to the IRB as part of the continuing review application.

The IRB will make a determination for all significant deviations that are submitted whether they constitute serous or continuing non-compliance or an unexpected problem that creates potential or actual risks to subjects. Need for regulatory reporting is detailed in section 5.5.

Definitions

Protocol Amendment	A *permanent, intentional* action or process that revises/amends a previously approved research protocol. There is a documented approval from the IRB, Sponsor, Data Safety Monitoring Board or Study Coordinating Center. The IRB has a form investigators may use to submit amendments for review and approval. Once approved, no further IRB follow-up is required. See section 6.5.
Protocol Exception	A *one time, intentional, time sensitive* action or process that departs from the IRB approved study protocol, intended for one occurrence. If the impact on the protocol and/or human subjects is deemed *significant*, prior documented IRB approval is required. If the impact on the protocol and/or human subjects is deemed *minor*, a report of the exception should be submitted to the IRB with the next continuing review.
Protocol Deviation	A *one time, unintentional* action or process that departs from the IRB approved study protocol, involving one incident and identified retrospectively (after the event). If the impact on the protocol is deemed *significant*, the deviation must be reported to the IRB within 2 business days. If the impact on the protocol is deemed *minor*, a report of the deviation should be submitted to the IRB with the next continuing review.

Procedures

Minor vs. Significant Exceptions or Deviations

Protocol Deviations and Exceptions are classified as either *Minor* or *Significant*, based on both the actual direct or potential effect of the action or process on the specific subject(s), the entire subject population, and/or the overall integrity of the study design and results. While examples of each type will be provided, it is ultimately the PI's responsibility to determine whether the protocol deviation or exception is Minor or Significant, based on the following definitions.

Significant Deviation or Exception meets at least one of the following criteria:

Events that actually or potentially

- Impact the subject safety, welfare, or rights
- Alter the risks or the benefit to the subject in a more significant, serious, or negative way
- Impact the integrity of the data
- Effect a subject's willingness to participate

Protocol Deviation Documentation and IRB Reporting

Once a protocol deviation is identified, it should be promptly reviewed and assessed by the PI and documented in the study records. The PI must make and include a determination as to whether the deviation's impact on the study is Minor or Significant.

It is up to the PI and research staff to determine a suitable method of documentation, such as a summary log, or a note to be filed in the investigator's study records. Whatever method is determined, it must include the following information:

- Date Deviation Occurred
- Date Deviation Identified
- Name of Research Staff that identified the deviation
- Description of Deviation
- Explanation why Deviation Occurred
- Corrective actions taken/Preventative measures implemented
- PI assessment whether Minor or Significant, and reason for choice
- PI signature and date

If the PI determines the deviation is Minor as specified above, no further action is required to meet IRB reporting requirements. File documentation and submit copies at the next continuing review. If the PI determines the deviation is Significant as specified above, the PI must submit to the IRB within 2 business days of identification. The "Prompt Reporting to IRB" form should be used. Report the deviation to the sponsor, FDA, and DSMB as appropriate.

The IRB will review the report and will determine whether the deviation meets the criteria for regulatory reporting to OHRP, FDA, or the sponsor. Once the IRB reviews and accepts that appropriate follow-up action has occurred, an official acknowledgement will be documented in the IRBNet package.

Protocol Exception Documentation and IRB Reporting

When a protocol exception is anticipated, the PI should promptly assess the impact the exception may have on the study or on the welfare of the subjects, and make a determination as to whether the impact will be Minor or Significant. All protocol exceptions should be documented and include the following information:

- Date or Time Frame of Proposed Exception

- Description of Protocol Exception
- Reason and Rationale of Proposed Exception
- Explanation why action will be one time, rather than permanent
- PI assessment whether Minor or Significant, and reason for choice
- PI signature and date

If a protocol exception is deemed Significant, the PI is required to submit the request to the IRB and receive approval **prior to implementation**. There is Significant Exception Request form that should be used which is available in IRBNet. If there is an outside study sponsor, obtain approval for the exception request (if applicable) **prior** to IRB submission. Once the IRB reviews and approves the anticipated exception, a letter will be posted in IRBNet documenting approval. Minor exceptions should be tracked and reported to the IRB at the next continuing review. All exceptions should be reported as appropriate to the sponsor, FDA, and through the data and safety monitoring plan.

Notification to Subjects

When the IRB reviews the exceptions and deviations, a determination will be made as to whether information related to protocol changes should be provided to participants based on whether such information might relate to their willingness to continue to take part in the research. The investigator will be advised if subjects need to be informed.

Examples of Minor vs. Significant

When a study deviations or exceptions are identified, it is the responsibility of the PI to make an independent determination as to whether it should be classified as Minor or Significant. Examples of common Protocol Deviations and Exceptions and how they may be classified are provided below. However, based on protocol specific details, sometimes what may be considered minor for one study may be significant in another. This is not an all inclusive list of all potential events. Please contact RSS if there are questions.

Minor:

1. Missing signed informed consent document, but the PI can verify by other methods consent was obtained
2. Inappropriate documentation of informed consent including
   a) Missing signatures (other than subject and/or parent/legal guardian)
   b) Copy of consent not given to subject
   c) Wrong dates
   d) Wrong signature lines
   e) Missing documentation or relationship of person providing parental permission

3. Use of invalid consent for a small number of subjects as long as the consent of the form contains all information that is included in the valid consent
4. Study visits/procedures that are either omitted, conducted outside the visit window or in a different sequence that specified in the protocol as long as this has not potentially impacted the safety and welfare of the subject
5. Over enrollment of subjects in research that has produced additional data of potential scientific value
6. Study personnel involved in research without appropriate training
7. Use of recruitment materials and processes that include small modifications from those that are approved
8. Assent obtained but not appropriate documented

Please note, for all these events a single or infrequent occurrence may be considered minor, however, if it is discovered these events have involved a majority of research subjects or the frequency is increasing, this may signify a more systematic problem with the conduct of the research and this could lead to reclassification of the events as Significant.

Significant:

1. Failure to obtain informed consent prior to initiating research procedures
2. Informed consent obtained after research procedures are initiated
3. Performing study procedures not approved by the IRB unless to eliminate immediate potential harm to the subject
4. Failure to perform a test approved in the protocol that is important to subject safety or data integrity
5. Drug medication (dosing and dispensing) errors regardless of whether a subject was negatively impacted
6. Failure to follow data and safety monitoring plan
7. Failure to report a serious, unanticipated adverse event that is thought to be possibly or definitively related to research interventions
8. Use of a recruitment process not approved by the IRB
9. Enrollment of new subjects after IRB approval has expired
10. Enrolling a subject that does not meet inclusion/exclusion criteria
11. Enrolling an incarcerated youth or a ward of state in a protocol not previously approved to include these populations
12. Parental permission granted by someone other than the parent or legal guardian
13. Assent not obtained when required by the IRB
14. Verbal consent obtained when IRB requires written consent