

5.0 Reviews of Ongoing Research

5.1 Amendments (Changes or Additions) to Approved Research

- I. Investigators must report planned changes in the conduct of a study and receive approval from the HSC prior to implementing these changes, except when a delay in implementation would place subjects or others at risk of harm. The documentation sent to investigators when the project is first approved notifies them of the requirement for prior approval of future changes. If a modification was implemented without prior HSC approval in order to avoid harm, the investigator must notify HSC within five working days and supply all relevant information concerning the modification and the outcome to subjects' safety. The HSC will review the modification as an unanticipated problem involving risks to subjects or others, following SOP 5.3.
- II. Investigators should request amendments to approved research by using the appropriate Request for Amendment form. The form should be accompanied with relevant documentation including highlighted versions of any revised materials (protocol, consent forms, advertisements, etc) and sponsor correspondence.
- III. Investigators are notified in writing of the decision of the HSC and of any changes required. Amendment approval is not granted until all required changes have been made and submitted for review and approval. Once approved, the investigator is sent an amendment approval letter indicating the date of the next study expiration. The HSC may only approve amendments through the current approval expiration period, unless considered at the time of continuation review. The amendment approval letter reminds the investigator that further changes in research activity may not be initiated without HSC review and approval except when necessary to eliminate apparent immediate hazards to subjects. Upon receipt of the approval for the amendment, the investigator may initiate the modification.

5.2 Determination of Expedited or Full Committee Review of Amendments

- I. Regulations permit the use of expedited procedures for review of minor changes to previously approved research. Minor changes are those that do not alter the risk/benefit ratio, do not impact the subjects' willingness to participate, include only the addition of procedures in categories 1 – 7 allowing review using the expedited procedure, and do not otherwise affect the committee's continuing approval of the research. Examples include, but are not limited to, study personnel changes, administrative protocol or consent form changes, recruitment materials, enrollment closures, additional survey questions, and participant newsletters.
- II. The expedited review may be conducted by the HSC Chairperson or by one or more experienced reviewers designated by the chairperson from among members

- of the HSC. An experienced HSC member means a voting member or alternate voting member who has served on the HSC for at least one year, has received training relative to the expedited review categories, and possesses the scientific expertise needed to review the proposed research. The reviewer(s) will review all materials submitted with the amendment and have ready access to the complete HSC file. The reviewer(s) must conduct an in-depth review of all submitted materials. In order to approve the modified research, the reviewer must determine that the regulatory criteria for approval continue to be met. If the amendment is approved, the committee will be notified of the expedited approval through the meeting minutes.
- III. Modifications that may alter the risk/benefit ratio, impact the subjects' willingness to participate, or otherwise affect the committee's continued approval of the research, are assigned to a primary and secondary reviewer and presented to the full committee at a convened meeting. Primary and secondary reviewers are assigned, as described in SOP 16.5.
 - IV. Primary/secondary reviewers receive the all submitted materials regarding the amendment. The primary/secondary reviewers must conduct an in-depth review of all submitted materials. Remaining members of the committee receive a copy of the Request for Amendment Form, sponsor communication, and revised consent form (if applicable). Remaining HSC members must review provided materials in sufficient depth to discuss and vote at the meeting. All members, including the primary/secondary reviewers, may obtain access to the complete HSC file.
 - V. For amendments referred to the convened committee, the essence of the study should be summarized by the primary/secondary reviewers for HSC members and the reviewers should state what the proposed modification is and how it will affect the conduct of the study, whether the modified research meets the regulatory criteria for approval, and whether or not the amendment should be approved as written. If the amendment requires a change in the informed consent document, then the reviewer must review that change and recommend appropriate committee action.
 - VI. In order to approve the modified research, the HSC must determine that the regulatory criteria for approval continue to be met. Study amendments reviewed by the convened committee may be given approval, disapproval, deferred, conditional approval, tabled or restricted approval, as outlined in SOP 2.7.
 - VII. The HSC will determine whether current or past subjects must be informed of information related to study amendments. After the study amendment is approved, investigators must provide new information to current subjects if it alters their study participation, if the new information relates to safety or risks, or if the new information could otherwise impact subjects' willingness to continue in the study. Former subjects must be notified if the study modifications or new

information impact their safety and welfare. Unless otherwise approved by the HSC, the new information will be given to subjects by having them sign a revised consent form.

Reference:

45 CFR 46.110

5.3 Unanticipated Problems Involving Risks to Subjects or Others

I. Regulatory requirements

- A. Federal regulations require institutions to ensure prompt reporting of unanticipated problems involving risk to research subjects or others to the IRB, regulatory agencies, and appropriate institutional officials.
- B. The HSC reviews reported problems to determine whether they are unanticipated problems involving risks to subjects or others and to determine what actions are needed to ensure the continued safety and welfare of subjects.

II. Definition of unanticipated problems involving risks to subjects or others

- A. Unanticipated problems involving risks to subjects or others are those events that (1) are not expected given the nature of the research procedures and the subject population; (2) are related to the research, and (3) suggest that the research places subjects or others at greater risk of harm or discomfort than was previously known or recognized
- B. Unanticipated problems involving risks to subjects or others may arise from physical, psychological, social, economic or legal risks.

III. Investigators must promptly report the following events:

- A. Certain adverse drug events (see Item V. below)
- B. Unanticipated adverse device events
- C. Reports of non-compliance, such as protocol violations or deviations (described in SOP 17.1)
- D. Complaints
- E. Local monitoring reports indicating non-compliance or other issues that could increase risk to subjects
- F. Incarceration of a study subject
- G. Breach of confidentiality or loss of data
- H. Other problems with the study, such as a equipment problems; unavailability of study-related materials or resources; or other problems that impact the integrity of the study or the welfare of subjects
- I. New information about the study, such as:

1. All interim reports or status reports from a Data and Safety Monitoring Board, Data Monitoring Committee or other central monitoring entity
 2. Summaries of study-wide adverse events
 3. Suspension or termination of the study by the sponsor or regulatory agency related to risk
 4. Publications that indicate a negative change to the risk/benefit ratio of the study
 5. FDA Alert or change in FDA labeling or withdrawal of a marketed drug, device or biologic used in the study
- J. Other events that, in the opinion of the principal investigator, are unanticipated, related to study participation and affect the welfare of current, previous or future subjects.
- K. Any type of new information about current or closed studies that impacts the welfare of current, previous or future subjects.

IV. Internal versus External Problems

- A. Internal problems are those that occur to subjects under the responsibility of the KUMC principal investigator.
- B. External problems are those that occur to subjects at sites that are not under the responsibility of the KUMC investigator and are thus not under the jurisdiction of the KUMC Human Subjects Committee.

V. Investigators must promptly report the following adverse events:

- A. Unanticipated adverse device events
- B. All adverse drug events, serious or non-serious, that are unexpected **and** that are judged by the KUMC principal investigator to be related or possibly related to participation in the research; or
- C. Adverse drug events that are expected in some subjects, but are determined to be occurring at a significantly higher frequency or severity than expected; or
- D. Other unexpected adverse drug events, regardless of severity, that may alter the HSC's analysis of the risk versus potential benefit of the research and as a result warrant consideration of substantive changes to the research protocol or informed consent process/document.
1. Evaluation of events by the investigator
 - a. "Unexpected" events are those that differ in nature, severity or frequency from what is described in the investigator's brochure or investigational plan and in the informed consent document. Investigators are required to maintain current knowledge of the protocol, consent form, and investigator's brochure (if applicable) in order to make this determination.
 - b. "Related or possibly related" events are those that are, in the opinion of the KUMC investigator, most likely attributable to

the study participation. In determining whether the event is most likely attributable to study participation, the KUMC investigator uses his or her expertise about the condition under study, experience with the study drug, available data from related studies, and information from the study sponsor in the case of multi-center trials. The KUMC investigator also evaluates the temporal relationship with study interactions or interventions and whether symptoms decrease or disappear when a test article is withdrawn. Events are not considered to be related if they are judged to be caused by the clinical state or clearly attributable to unrelated circumstances.

- c. In addition to judging whether the event is unexpected and related, investigators are asked to evaluate whether the event negatively impacts the safety or welfare of current subjects or previous subjects
- E. The reporting criteria for internal or external adverse events are identical; however, internal events must be reported in a shorter time frame, as described below.

VI. Reporting time frames

- A. Except for study deaths described below, internal problems must be reported to the HSC within five working days.
- B. External problems requiring prompt reporting must be reported to the HSC within twenty working days.
- C. The HSC requires the following time frames for reporting the death of a KUMC subject:
 - 1. Projects involving a study drug/biologic
 - a. Deaths that occur within thirty days of the last dose of study drug/biologic must be reported verbally or by fax within 24 hours of notification to the PI or research team, followed by a written report within five working days.
 - b. Deaths that occur more than thirty days after the last dose of study drug/biologic, that may be possibly, probably or definitely related to the study drug/biologic must be reported within five working days of notification.
 - 2. Projects involving a study device
 - a. Deaths that are possibly, probably or definitely related to the study device must be reported verbally or by fax within 24 hours of notification to the PI or research team.
 - b. A written report must follow within five working days.
 - 3. Projects that do not involve a test article
 - a. Deaths in projects that do not involve a drug, biologic or device must be reported within five working days of notification if the death may be related or possibly related to study participation.

4. Other deaths of KUMC subjects
 - a. Death of a KUMC study subject that does not fit the above criteria does not require prompt reporting to HSC.
 - b. If the subject died during study participation, the death should be reported on the Continuing Review Form as a study withdrawal.
 - c. If the study team learns of a subject's death after his or her study participation is over, the death should be reported only if the investigator suspects it is indicative of a previously unrecognized risk related to study participation.
- D. The death of a non-KUMC subject is reportable if it meets the criteria discussed in Section V. above.

VII. Report forms

- A. Investigators must report problems using one of the following forms:
 1. Internal Adverse Drug Event Report Form
 2. External Adverse Drug Event Report Form
 3. Unanticipated Adverse Device Event Report Form
 4. Report of Non-Compliance
 5. Study-Related Compliant Form
 6. Monitoring/Audit Report Form
 7. Incarceration of a Study Participant Form
 8. Breach of Confidentiality/Loss of Data Report Form
 9. Other Problems Report Form
 10. New Information Reporting Form
- B. Additional documentation describing the event should be attached to the form.

VIII. Administrative processing of reports

- A. The HSC staff will review the submission to confirm that the report has been completed in its entirety and that the event appears to meet KUMC reporting criteria.
- B. If the form has omissions or contradictory information, the staff will contact the KUMC investigator by phone or email. Additional information will be documented and dated by the staff or received in writing from the investigator. The additional information will be appended to the report.
- C. If the report indicates that subjects are at risk for imminent harm, the HSC staff will immediately contact the HSC Chair or Vice Chair.
 1. The Chair determines whether immediate suspension is warranted. The Chair may consult with the IO and HRPP Director. In the Chair's absence, the IO or HRPP Director can suspend a study on an urgent basis.

2. When a study is suspended, the Chair or HRPP Director notifies the IO. The Chair or HRPP Director notifies the investigator by phone call and in writing.
 3. The IO notifies federal authorities of the suspension. The IO files a preliminary report within five working days. The report is filed as described below in section X.A.
 4. The Chair works with investigator to provide for continued safety and welfare for subjects. Depending on the nature of the event and the subjects' best interests, they may be continued on an investigational drug, transferred to clinical care, placed under additional safety monitoring, or provided with other protective measures.
 5. The HSC is notified of the suspension at its next meeting and reviews the entire set of documentation about the event. The HSC Chair has the prerogative to call a special meeting to discuss the suspension.
- D. If the initial evaluation establishes that the report meets reporting requirements and does not indicate imminent threat of harm, the Chair or Vice Chair evaluates the report to determine whether it potentially represents an unanticipated problem involving risk to subjects or others. In making the evaluation of non-fatal events, the Chair or Vice Chair uses information including, but not limited to: seriousness of the event, the investigator's assessment of potential harm, available data about the study population or test article, experience of similar trials, and information from safety monitoring entities. All fatal events that meet the criteria for prompt reporting are sent to the convened committee for review.
- E. Any internal event that is unexpected and related to the research and suggests that subjects are at greater risk of harm than was previously known or recognized will be referred to the convened HSC for review. Prior to the referral, the Chair or Vice Chair evaluates the report to decide whether additional information is needed before the HSC reviews. If additional information is needed, the HSC staff will notify the investigator. Otherwise, the report is placed on the agenda of the next HSC meeting.
- F. An individual external event that is unexpected and related to the research and suggests that subjects are at greater risk of harm than was previously known or recognized will be reviewed by the HSC Chair, and possibly the convened HSC, if the sponsor provides (a) supporting information about why the event potentially represents an unanticipated problem involving risk to subjects or others and (b) a plan of action to address the problem. External adverse events without such supporting information may be returned without review.
- G. If the event does not potentially represent an unanticipated problem involving risk to subjects or others, the Chair or Vice Chair signs the form and it is placed in the file. A copy of the signed form is mailed to the

investigator. The report is marked with a colored tab to easily identify similar reports in the file.

IX. Evaluation by the Convened Human Subjects Committee

- A. All reports that may represent unanticipated problems involving risk to subjects or others are referred to the full committee for review at a convened meeting.
 - 1. A primary reviewer is assigned as described in SOP 16.5. The primary reviewer will have access to the report, the study protocol, consent form and investigator's brochure (if applicable). The remaining members are provided with the report and the current consent form. During the meeting, the primary reviewer presents the report to the committee, makes an initial recommendation and begins the discussion.
 - 2. After discussion, the HSC may defer the review in order to obtain more information from the investigator or other sources.
 - 3. If the review is not deferred, the committee determines whether it represents an unanticipated problem involving risks to subjects or others. If so, the HSC considers taking one or more of the following actions:
 - a. Require modifications of the study protocol;
 - b. Require modifications to the informed consent document;
 - c. Require additional information be provided to past subjects;
 - d. Require notification of current subjects;
 - e. Require that current subjects re-consent to participation;
 - f. Increase the frequency of continuing review;
 - g. Monitor the conduct of the research;
 - h. Monitor the consent process;
 - i. Suspend the study pending further information;
 - j. Terminate the study;
 - 4. If the HSC directs more than minor modifications to the protocol or consent form, the modifications are reviewed by the convened committee. Minor changes may be reviewed by the HSC Chair or experienced member, as described in SOP 5.2
 - 5. If the HSC determines the report does not represent an unanticipated problem involving risk to subjects or others, then the report is accepted with no further action.
- B. The investigator is notified in writing about the committee's decision.

X. Reporting to federal agencies

- A. When the HSC determines the event represents an unanticipated problem involving risk to subjects or others, the IO files a letter of notification to

federal authorities and others. The letter is drafted by the HRPP Director, with final approval by the IO. The letter of notification will include:

1. The name of the institution
 2. Title of the research project and/or grant proposal in which the problem occurred;
 3. Name of the principal investigator on the protocol;
 4. The HSC number assigned to the protocol
 5. A detailed description of the problem and the reason for the suspension or termination (if applicable); and
 6. Actions the institution is taking or plans to take to address the problem (including those actions described above in IX.A.2.)
- B. The notification will be sent, as applicable, to:
1. OHRP
 2. FDA, if the study is subject to FDA regulations
 3. Other federal agencies (if applicable) that are conducting or funding the study
 4. Sponsor, if the study is sponsored
 5. Principal investigator
 6. Department Chair, Center Director or Dean
 7. The HSC
- C. A copy of the letter is placed in the HSC file.

References:

45 CFR 46.103
45 CFR 46.109
21 CFR 56.108
21 CFR 312.32
21 CFR 812.150