IRB SOP 05.0 Reviews of Ongoing Research, 2018

Purpose:
The IRB conducts ongoing reviews for each study protocol to ensure the ongoing protection of the rights and welfare of research subjects. This includes any amendments/modifications to studies and review of any unanticipated problems that may arise while conducting the study.

Responsible Personnel:

Background:
Any changes to a study will need IRB review and approval before that change can be implemented. Additionally, a serious adverse event or an unanticipated problem may develop after a study is already approved. These problems may cause research teams to change their study or their consent forms.

Regulation and Guideline Reference(s):
KUMC References:

Definitions:

Procedure:

5.1 Modifications (Changes or Additions) to Approved Research

I. This standard operating procedure applies to research conducted under the KUMC Federalwide Assurance #00003411. It also applies to all research that is greater than minimal risk, regardless of funding source.

II. Investigators must report planned changes in the conduct of a study and receive approval from the institutional review board (IRB) prior to implementing these changes, except when a delay in implementation would place subjects or others at risk of harm. If a change was temporarily implemented without prior IRB approval in order to avoid harm, the investigator must notify the IRB within five working days, using the eIRB system:

A. The investigator should file a Report of New Information. The investigator should supply all relevant
information concerning the modification and the outcome to subjects’ safety.

B. The IRB will review the Report of New Information as a potential unanticipated problem involving risks to subjects or others, following SOP 5.3.

C. The investigator also must submit a Modification request if long-term implementation of the change is needed, along with revised study documents, as applicable.

III. Investigators should request modifications to approved research by submitting in the electronic IRB system (eIRB). The submission should be accompanied with relevant documentation including highlighted versions of any revised materials (protocol, consent forms, advertisements, etc.) and sponsor correspondence. If any subjects have been enrolled at KUMC, the submission should include the re-consenting/notification plan.

IV. All protocol modifications should be submitted as soon as feasible so that the project is conducted in a safe and ethical manner and so that data integrity is preserved. Beginning January 1, 2017, protocol modifications of multi-center studies must be submitted to the IRB within 45 days of receipt at the institution. Investigators are expected to be responsive to any requests for additional information from the IRB so that final approval or disapproval of the modification can be accomplished within 90 days of receipt.

A. Protocol modifications should be submitted as a Modification request within the eIRB system.

B. If either the sponsor or the local investigator determines that the modification requires prompt notification to subjects for safety reasons, then a Report of New Information should be submitted in the eIRB system as soon as the modification is received, even if the formal submission of the modification is still being prepared. The Report of New Information should describe the new information, the aspects that require urgent action, and the proposed method of contacting subjects who are impacted.

V. If enrollment at KUMC sites is permanently closed and either no subjects were enrolled at KUMC sites or all subjects are deceased, submission of protocol modifications or new risk information is not required.

VI. Investigators are notified in writing of the IRB's decision and of any changes required to obtain approval. Modification approval is not granted until all required changes have been made. Once approved, the investigator is sent a modification approval letter. The IRB may only approve modifications through the current approval expiration period. Upon receipt of the approval for the modification, the investigator may initiate the changes to the study.

5.2 Determination of Expedited, Full Board or Administrative Review of Modifications

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 eligible for expedited review as specified in the Federal Register, and do not otherwise affect the IRB's continuing approval of the research. Examples include, but are not limited to, study personnel changes, administrative protocol or consent form changes, addition of low risk procedures, recruitment materials, enrollment closures, additional survey questions, and participant newsletters.

II. The addition of new investigative sites to previously approved protocols may be reviewed using the expedited procedure. When the KUMC investigator is responsible for conduct at external sites, the investigator will document that the site staff is trained, the site provides adequate resources to safely conduct the study, and the investigator has a clear communication plan to inform the sites about updates to the study and to receive information about adverse events and other problems. When applicable, an
IRB Reliance Agreement must be in place prior to approving the involvement of the external site, as discussed in SOP 13. Other protocol specific requirements may apply.

III. The expedited review may be conducted by the IRB Chairperson or by one or more qualified reviewers designated by the chairperson from among members of the IRB. A qualified IRB member is defined as a voting member or alternate voting member who has received training relative to the expedited review categories and possesses the scientific or regulatory expertise needed to review the proposed research. The reviewer(s) will review all materials submitted with the modification and have ready access to the complete IRB file. In order to approve the modified research, the reviewer must determine that the regulatory criteria for approval continue to be met. If the modification is approved through expedited review, the IRB will be notified of the expedited approval through a report appended to the minutes.

IV. Modifications that indicate new risks, may impact the subjects' willingness to participate, or otherwise affect the IRB's continued approval of the research, are presented to the full board at a convened meeting. A primary reviewer will be assigned, as described in SOP 16.5. A secondary reviewer also may be assigned if the changes are significant (such as changes to study design, study intervention or information that warrants reconsideration of the overall risk/benefit ratio) or if the chair requests a secondary reviewer.

V. Primary/secondary reviewers receive all submitted materials regarding the modification. The primary/secondary reviewers must conduct an in-depth review of all submitted materials. Remaining members have electronic access to the entire submission. Remaining members must review provided materials in sufficient depth to discuss and vote at the meeting.

VI. For modifications referred to the convened board, the essence of the study should be summarized by the primary/secondary reviewers 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 modification should be approved as written. If the modification involves a change to the informed consent document, then the reviewers must review that change and recommend appropriate board action.

VII. In order to approve the modified research, the IRB must determine that the regulatory criteria for approval continue to be met. Study modifications reviewed by the convened board may be given approval, disapproval, deferred, or conditional approval, as outlined in SOP 2.7.

VIII. The IRB will determine whether current or past subjects must be informed of information related to study modifications. After the study modification 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 IRB, the new information will be given to subjects in a revised consent document (for active participants) or a notification letter (for participants in follow-up).

IX. Institutional policy dictates which study personnel must be included in the IRB submission. Proposed changes to study personnel, other than a change in the principal investigator, are administrative in nature and not changes to the research. Proposed changes to study personnel may be reviewed and approved by IRB members or office staff. Prior to administrative approval, the new study personnel must demonstrate current training in human subjects protection and a current conflict of interest disclosure. Additional compliance requirements, such as an unaffiliated investigator agreement or IRB reliance agreement, may apply if the study personnel are not affiliated with KUMC, as described in SOP 13. A change to the principal investigator must be reviewed and approved by the IRB Chair, Vice Chair or
Chair’s designee.

X. An additional category of post-approval changes includes a one-time request for prospective approval of an enrollment exception or other type of exception to the IRB-approved study protocol. The request must be documented in the Exception Request Form. In submitting the request, the investigator will provide the rationale, explain the protocol element that applies to the request and clarify why the exception would not negatively impact subject safety or data integrity. Requests for studies with external sponsors must include the sponsor’s approval for the exception. The one-time request is submitted in the electronic IRB system as a Report of New Information, unless a permanent protocol change is being proposed. The IRB may inquire as to whether a permanent protocol change is warranted. If the investigator provides appropriate justification for the one-time request, it can be reviewed on an expedited basis by the IRB Chair, Vice Chair or designated IRB member.

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 IRB reviews reported problems to determine whether they are potential unanticipated problems involving risks to subjects or others, to determine what immediate actions are needed to ensure the continued safety and welfare of subjects, and to determine the need for additional review by other institutional representatives or committees.

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 new information, using the Report of New Information (RNI) function in the eIRB system. The term "prompt" is defined in section VI below.

A. Certain adverse drug events (see Item V. below)

B. Any information that indicates a new or increased risk, or a safety issue. For example:

   1. New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) indicates an increase in the frequency or magnitude of a previously known risk, or uncovers a new risk.

   2. Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol

   3. Protocol violation that harmed subjects or others or that indicates subjects or others might be at increased risk of harm
4. Complaint of a subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm

5. Any changes significantly affecting the conduct of the research

C. Any harm experienced by a subject or other individual, which in the opinion of the investigator are unexpected and probably related to the research procedures.
   1. A harm is "unexpected" when its specificity or severity are inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population.
   2. A harm is "probably related" to the research procedures if in the opinion of the investigator, the research procedures more likely than not caused the harm.
   3. A harm can be fatal or non-fatal.

D. Non-compliance with the federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance (See also SOP 17.1).

E. Audit, inspection, or inquiry by a federal agency.

F. Certain monitoring reports from industry sponsors (See also SOP 17.1).

G. Failure to follow the protocol due to the action or inaction of the investigator or research staff (See also SOP 17.1).

H. Breach of confidentiality.
   I. Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject (See also SOP 17.1).
   J. Incarceration of a subject in a study not approved by the IRB to involve prisoners, if the study team intends to continue data collection or intervention with that subject.

K. Complaint of a subject that cannot be resolved by the research team.

L. Premature suspension or termination of the research by the sponsor, investigator, or institution.

M. Unanticipated adverse device effect (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.)

N. Because of characteristics in the eIRB system, an investigator brochure, package insert, or device labeling that is revised to indicate an increase in the frequency or magnitude of a previously known risk, or describe a new risk should be submitted as a Modification in the eIRB system, not as an RNI, so that current study documents are appropriately updated.

O. If the new information does not meet the above criteria, the report will be returned without review.

IV. Internal versus External Problems

A. Internal problems are those that occur to subjects under the responsibility of the KUMC principal investigator, regardless of the location of the problem.
   1. Internal events include those that happen at non-KUMC study sites when the KUMC IRB is the IRB of Record for the project.
   2. Internal events also include those that happen to subjects under the responsibility of the KUMC
principal investigator even when an external IRB is the IRB of Record.

B. External problems are those that occur to subjects at sites that are not under the responsibility of the KUMC investigator or the KUMC IRB.

V. Investigators must promptly report the following adverse drug events:

A. All internal adverse drug events, serious or non-serious, that are unexpected and that are judged by the KUMC principal investigator to be related or probably related to participation in the research;
   1. "Unexpected" events are those that differ in nature, severity or frequency from risk information previously reviewed and approved by the IRB.
   2. "Related or probably related" events are those that are, in the opinion of the KUMC investigator, more likely than not attributable to study participation. In determining whether the event is 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.

B. 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

C. Other unexpected adverse drug events, regardless of severity, that may alter the IRB's analysis of the risk versus potential benefit of the research and as a result warrant consideration of changes to the research protocol or informed consent process/document; or

D. External adverse events or new information from a multi-center trial where the sponsor has determined that the event or new information constitutes an unanticipated problem involving risk to subjects or others and is implementing corrective actions such as changing the protocol, revising eligibility criteria, enhancing safety monitoring or updating informed consent documents. If the report involves an individual external event occurring in a multi-center trial, it should be accompanied by supporting information from the study sponsor. The supporting information must clarify (a) why the event potentially represents an unanticipated problem involving risk to subjects or others; and (b) the sponsor's plan of action to address the problem. External adverse events without such supporting information may be returned without review.

E. Proposed study changes resulting from an adverse event should be submitted concurrently with the RNI as a Modification request as described in SOP 5.1.

VI. Time frames for prompt reporting

A. Except for study deaths described below, internal problems must be reported to the IRB within five working days.

B. External problems requiring prompt reporting must be reported to the IRB within twenty working days.

C. The IRB requires the following time frames for reporting the death of a KUMC subject:
   1. Projects involving a study drug/biologic
      a. Deaths that are unexpected and related or probably related to the study drug/biologic must be reported to the IRB by phone or email within 24 hours of notification to the PI or
research team.

b. An RNI in the eIRB system must follow within five working days.

2. Projects involving a study device

a. Deaths that may be related to the study device must be reported by phone or email within 24 hours of notification to the PI or research team.

b. An RNI in the eIRB system must follow within five working days.

3. Projects that do not involve a test article

a. For projects that do not involve a drug, biologic or device, a subject’s death must be reported within five working days of notification if the death may be 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 IRB.

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 promptly reportable if (1) it is not expected given the nature of the research procedures and the subject population; (2) it is related to the research; (3) it occurs at an internal or external study site that is under the purview of the KUMC IRB, and (4) it suggests that the research places subjects or others at greater risk of harm than was previously known or recognized.

VII. Report form

A. Investigators report the above listed problems using the eIRB system function of "Reportable New Information."

B. The IRB requires a supplemental reporting form if the event concerns an adverse event or non-compliance.

VIII. Administrative Processing of Reports

A. The IRB 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. If the event does not meet reporting criteria, it may be returned without review or acknowledged administratively.

B. If the form has omissions or contradictory information, the staff will send a request for clarification through the eIRB system.

C. If the report indicates that subjects are at risk for imminent harm, the IRB staff will immediately contact the IRB 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 the 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 IRB is notified of the suspension at its next meeting and reviews the entire set of documentation about the event. The IRB Chair has the prerogative to call a special meeting to discuss the suspension.

D. If the initial evaluation establishes that the event meets reporting requirements and does not indicate imminent threat of harm, IRB staff ensure that the report is ready for review by the convened board. The Chair, Vice Chair or HRPP Director or IRB staff may request additional information from the investigator or other sources. The Chair, Vice Chair or HRPP Director also considers whether any interim actions should be taken prior to the IRB meeting to ensure the safety and welfare of participants. Once the appropriate information is obtained, the report is placed on the agenda of the next available convened IRB meeting.

IX. Evaluation by the Convened IRB

A. All reports of new information that may represent unanticipated problems involving risk to subjects or others are reviewed at a convened meeting.

1. A primary reviewer and secondary reviewer are assigned as described in SOP 16.5. All members have access to the electronic submission and the entire study history. During the meeting, the reviewers present the report to the board, make an initial recommendation and begin the discussion.

2. After discussion, the IRB may defer the review in order to obtain more information from the investigator or other sources.

3. If the review is not deferred, the board determines whether it represents an unanticipated problem involving risks to subjects or others. If so, the IRB 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 IRB requires more than minor modifications, these modifications are reviewed by the convened board.

5. If the IRB requires specific modifications, these directed changes may be reviewed by the IRB Chair or qualified member, as described in SOP 5.2

6. If the IRB 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 board’s decision.

X. Reporting to Federal Agencies

A. When the IRB 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 when required. As of January 17, 2018, KUMC extends its Federalwide Assurance only to research that is funded by a Common Rule department or agency. When required, 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 IRB 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 IRB Chair

C. A copy is available to IRB members upon request.

References:

45 CFR 46.103
45 CFR 46.109
21 CFR 56.108
21 CFR 312.32
Attachments:

Approval Signatures

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<tr>
<th>Approver</th>
<th>Date</th>
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<tbody>
<tr>
<td>Steffani Webb: Vice Chancellor for Administration</td>
<td>12/10/2019</td>
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<tr>
<td>Lisa Hoebelheinrich: Chief Compliance Officer</td>
<td>12/10/2019</td>
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<td>Annie Fors: QA Director</td>
<td>12/3/2019</td>
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<tr>
<td>Karen Blackwell: Director HRPP</td>
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<td>Kyle Stephens: Assistant Director</td>
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Applicability

KU Medical Center, KU SoM Wichita