

6.0 Continuing Review Procedures

6.1 Federal Requirements for Continuing Review

- I. The HSC conducts continuing review for each study protocol to ensure the continued protection of the rights and welfare of research subjects. Continuing review of human subjects research will occur at intervals appropriate to the degree of risk, but not less frequently than once a year. The HSC applies the same criteria for approval of continuing review as it does for initial applications. In accordance with SOP 2.7, the Committee may set approval periods and requirements for continuing review at intervals of less than one year or at intervals dependent on subject accrual or at any time when unanticipated problems are encountered. The HSC has the discretion to increase the frequency of review if new information negatively impacts the risk/ benefit ratio or if the Committee is notified of a complaint or alleged compliance violation.
- II. Federal regulations require that continuing review of research must be substantive and meaningful. In accordance with HHS regulations at 45 CFR 46.108(b) and at 46.115(a)(2), continuing review by the convened HSC, with recorded vote on each study, is required unless the research is otherwise appropriate for expedited review under Section 46.110. At continuing review, the HSC will determine whether the research continues to meet the criteria for HSC approval as set forth in 45 CFR 46.111. These criteria include, among other things, determinations by the HSC regarding risks, potential benefits, informed consent, and safeguards for human subjects.
- III. Continuing review is required at least annually as long as the study remains active. Studies are considered “active” while they are recruiting and enrolling subjects, performing study interventions, conducting long-term follow-up, collecting identifiable data, or analyzing identifiable data.
- IV. Unless the research qualifies for expedited continuing review, the HSC must review proposed research at a convened meeting at which a majority of the members of the HSC are present, including at least one member whose primary concerns are in nonscientific areas.

6.2 HSC Office Notifications

- I. The HSC Office sends notifications to investigators about the schedule for continuing review. For cancer-related studies, reminder notices are mailed approximately 90 days before the project’s expiration date, to allow time for review by the Protocol Review and Monitoring Committee. For studies that are not cancer-related, reminder notices are mailed approximately sixty days before study expiration. A Continuing Review form, which acts as the application for recertification, must be returned by the indicated deadline to allow the Committee

sufficient time to complete its review prior to the project's expiration date. Once completed continuing review materials are received, a determination is made whether the continuing review is eligible for expedited review or if it should be scheduled for full committee review.

- II. Upon return of a completed Continuing Review form to the HSC Office, if expedited review is not applicable, the application for recertification will be placed on the agenda for review at the next regularly scheduled meeting.

6.3 Continuing Review Submission Materials

- I. To request continuing review, investigators submit a written report of the research on a Continuing Review form. The form includes information on the status of the project, number of subjects, unanticipated problems, complaints, numbers of withdrawals and reasons for withdrawals, relevant literature, significant new information, oversight activities at non-KUMC sites, when applicable.
- II. In addition to the Continuing Review form, investigators submit the following documents:
 - a. Protocol summary
 - b. Current protocol
 - c. Current informed consent document(s)
 - d. The most recent safety monitoring report, for studies being monitored by a data monitoring committee or data and safety monitoring board
 - e. Any correspondence from the FDA
 - f. A copy of any FDA audits of sites under the auspices of the KUMC investigator
 - g. The most recent FDA progress report, for studies in which the KUMC investigator holds the IND or IDE.
- III. At the time of submission, a member of the HSC office staff will review the submission for completeness. If any required materials are missing, office staff will contact the investigator to obtain the missing information prior to assignment for review. If the administrative reviewer notes that there are unresolved issues from previous reviews, those issues will be noted on the administrative sheet that is provided to the primary reviewer.
- IV. If investigators are requesting changes to the protocol or consent form at the time of continuing review, the changes should be submitted on a Request for Amendment form. If the changes are minor, they will be reviewed under expedited procedures described in SOP 5.2. The revised consent form is stamped with the new approval dates determined by the committee when the continuing review is considered. If the changes are not minor, they will be sent to the reviewer who is providing the continuing review for the project and discussed at the convened meeting.

6.4 Expedited Continuing Review

- I. If a project qualifies for expedited continuing review, the 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 current voting member or alternate voting member who has received training relative to the expedited review categories, and possesses the expertise needed to review the proposed research. The reviewers have ready access to the entire HSC file, which includes the complete protocol, consent form and all other documents that have been submitted to the HSC. Continuing review may be expedited when the project was:
 - A. Approved by expedited review on initial approval and no changes in risk have occurred.
 - B. Approved by the convened committee but the research is permanently closed to 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 and all of the following are true:
 1. The remaining follow-up involves minimal risk to subjects;
 2. If identification of the subjects or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, reasonable and appropriate protections have been implemented so that risks related to invasions of privacy and breach of confidentiality are no greater than minimal;
 3. The research is not classified research.
 - C. Approved by the convened committee but no subjects have been enrolled, no additional risks have been identified, and the research is not classified.
 - D. Approved by the convened committee but the remaining activities are limited to data or specimen analysis and all of the following are true:
 1. The remaining follow-up involves minimal risk to subjects;
 2. If identification of the subjects or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, reasonable and appropriate protections have been implemented so that risks related to invasions of privacy and breach of confidentiality are no greater than minimal;
 3. The research is not classified research.
- II. The HSC Chair or experienced member(s) conduct an in-depth review of the Continuing Review form and all other submitted materials, including the current protocol and the current consent form, to ensure compliance with current regulations and standards. Reviewers should:

- A. Examine the current protocol submitted with the continuing review, to confirm that any changes in the research were reported to and approved by the HSC;
 - B. Consider if new or additional risks have been identified (e.g. unanticipated problems) that would require changes to the protocol, consent form, review frequency, etc;
 - C. Consider if any new information may impact subjects' willingness to continue participation;
 - D. Verify, with the additional assistance from separate HIPAA reviewers, that applicable requirements of the HIPAA Privacy Rule have been met;
 - E. Report to the IRB Administrator, HSC Chair or HRPP Director if it appears that the research is not being conducted in accordance with HSC requirements;
 - F. Evaluate whether new HSC policies might necessitate changes in the protocol;
 - G. Confirm, in light of the above information, that the current consent is still accurate and complete;
 - H. Determine, in light of the above review, whether or not the study continues to meet federal criteria for approval.
- III. If expedited continuing review is permitted, the review must occur prior to the study expiration date. If an investigator has failed to provide continuing review information to the HSC or the HSC has not reviewed and approved the study prior to the expiration date, the research must stop, unless the HSC finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. Enrollment of new subjects cannot occur after the expiration of HSC approval.
- IV. If the research is approved for continuation through an expedited review procedure, the full committee is notified of the approval through the minutes of the next meeting.

6.5 Full Committee Continuing Review

- I. At each meeting, members may conduct continuing reviews of ongoing, approved protocols. The reviews are designed to ensure that the rights and welfare of subjects continue to be protected. Continuing reviews include protocols that are determined to require more than annual review, as well as those with only annual review requirements. In continuing review, the HSC ensures that the same standards as applied in the original review are still present (e.g., minimized risk, risks reasonable in relation to benefits, equitable selection, adequate informed consent process and documents, monitoring data to ensure subject safety, privacy protections, confidentiality protections, and appropriate safeguards for vulnerable populations).

- II. Each continuing review will undergo a primary review by an HSC member. Whenever feasible, the primary reviewer will be one of the two members who reviewed the proposal at the time of initial review. If an initial reviewer is not available, the review will be assigned to an HSC member who has expertise relevant to the study.
- III. The primary reviewer will receive all materials in the continuing review submission. Continuing review materials are distributed to HSC members along with all other review assignments, approximately 4 – 5 days prior to the meeting. The remaining members who are scheduled to attend the meeting, and who do not act as a primary reviewer, receive the Continuing Review form, the protocol summary, and the current or proposed consent form. All HSC members have access to the complete file, which is maintained in the HSC Office.
- IV. Primary reviewers conduct an in-depth review of the provided materials. These reviewers should:
 - A. Examine the current protocol submitted with the continuing review, to confirm that any changes in the research were reported to and approved by the HSC;
 - B. Consider if new or additional risks have been identified (e.g. unanticipated problems) that would require changes to the protocol, consent form, review frequency, etc;
 - C. Consider if any new information may impact subjects' willingness to continue participation;
 - D. Report to the committee any indication that the research is not being conducted in accordance with HSC requirements;
 - E. Make a preliminary determination that the current or proposed consent is accurate and complete;
 - F. Make a preliminary determination on whether or not the study continues to meet federal criteria for approval.
- V. Each continuing review is separately discussed at the meeting. Any member who has a conflicting interest on the study leaves the room during discussion and voting. The primary reviewer summarizes the activity and progress of the study and initiates discussion of the research. After discussion, the HSC determines whether the study continues to meet federal approval criteria and votes on one of the actions listed in section 6.6. The approval period is set, based upon the continuing review schedule determined by the committee. Approval and expiration dates are calculated as described in SOP 2.10.
- VI. At the time of submission and review, the HSC has the discretion to require external verification that no material changes have occurred since the previous review. External verification may be required when the study is classified as high risk, when the investigator has previously failed to comply with HSC requirements, when materials submitted for continuing review include

unapproved modifications or inconsistent information, or when the HSC has been informed of non-compliance by another source.

- VII. If new issues arise during the course of the study that require additional expertise from outside the committee, any member may request that the IRB Administrator arrange a consultant for the continuing review, as described in SOP 2.8.

6.6 HSC Actions on Continuing Review

- I. The types of action possible at continuing review are listed below. Investigators should note that when the recertification is deferred or conditionally approved, all requirements must be fulfilled prior to the expiration date of the project. The investigator must plan ahead to meet relevant deadlines to assure that the project's approval does not lapse.
- A. **Reviewed and Recertified.** The project is approved for continuation until the next expiration date.
 - B. **Deferred-Additional Review by Committee Required.** Recertification in this category is deferred when the HSC requests substantive clarifications or modifications regarding the protocol or informed consent document(s) that are directly relevant to the federal criteria for human research approval (see section I.C). The investigator's responses to this category must be brought before the full Committee for action at a regularly convened meeting.
 - C. **Conditional Approval -Additional Chair Review Required Before Implementation.** When the HSC's stipulations are minor in nature, (such as non-substantive issues that do not require judgment by the reviewer) the HSC may vote to authorize the Chair or another HSC member designated by the Chair, to review the investigator's responses under an expedited review procedure. If the responses are considered satisfactory, the recertification will then be approved for implementation by the Chair or designee.
 - D. **Suspension or Termination.** This action indicates that the committee identifies major ethical conflicts or safety issues that warrant significantly revising or stopping the study.
- II. Notifications
- A. Investigators are notified in writing of the decision of the HSC and any changes required. Results of reviews are also posted to an internal website that investigators may access.
 - B. Continued approval is not granted until all required changes have been made and submitted for review and approval. Once approved, the investigator is sent an approval letter indicating the date of the next study expiration. The approval letter reminds investigators that changes in research activity may not be initiated without HSC review and approval

except when necessary to eliminate apparent immediate hazards to subjects. A re-certified consent form accompanies the approval letter.

- C. The KUMC Institutional Official (IO) is notified of committee action(s) through the meeting minutes. Copies of the minutes are maintained in the IO's office.

6.7 Study Expiration

- I. When continuing review of a research protocol does not occur prior to the end of the approval period specified by the HSC, approval expires automatically. The investigator will be notified in writing of the expiration. Such expiration of HSC approval does not need to be reported to OHRP as a suspension of HSC approval under HHS regulations.
- II. Federal regulations make no provision for a grace period after study expiration. If project approval has expired, all protocol-related activity must cease, including, but not limited to, recruitment, enrollment, data analysis and study visits for ongoing subjects.
- III. The full committee is notified of expired projects through the HSC minutes.
- IV. When informed of the expiration, the investigation should contact the HSC immediately if the expiration affects subject safety. Investigators may request continuation of protocol-related activity they deem necessary to ensure subject safety. If the investigator believes that some or all subjects may be harmed by study expiration, he/she must submit written documentation to the HSC chair, including a list of affected subjects. The HSC chair may determine that the specified activities may continue for affected subjects. At his/her discretion, the HSC chair may consult individual HSC members or the entire committee when making the determination. The HSC chair will provide written documentation to the investigator about the study activities that may continue for affected subjects.
- V. In order to re-instate the expired research, the investigator must submit a new application for approval to the HSC. If the research originally was reviewed by the convened committee, the application for reinstatement will be referred to the convened committee. If the research originally was reviewed under expedited review, the application for reinstatement will be reviewed under expedited procedures. When requesting reinstatement, the investigator must accompany the HSC application with a letter explaining the circumstances of the request, summarizing the activities (if any) that were temporarily approved to continue for the purposes of subject safety, and describing the activities that will be undertaken if reinstatement is granted.

6.8 Suspensions or Terminations for Cause

- I. The HSC has the authority to suspend or terminate approval of human subjects research that is not being conducted in accordance with the HSC's requirements or that has been associated with unexpected, serious, and related harm to subjects.
- II. Suspension is the temporary closing of some or all aspects of a human research project or discontinuing some or all of an investigator's privilege to conduct human subject research short of the permanent ending of all activities related to a human research project or an investigator's privilege of conducting human subjects research. Suspension may be for serious or continuing noncompliance with HSC policies or for inhibition of the rights and welfare of subjects. The suspension may be partial in that certain activities may continue while others may stop or it may be complete in that no activity related to the research may proceed. The HSC will make this determination. Termination is the permanent ending of all activities related to a human research project or an investigator's privilege of conducting human subject research at the University of Kansas Medical Center.
- III. Decisions to suspend or terminate approved research are considered at a convened HSC meeting. When action is required to ensure subject safety prior to a meeting of the convened HSC, research may be suspended or terminated by the HSC Chair, HSC Vice-Chair or the HRPP Director. Any notification of suspension or termination of approval includes a statement of the reasons for the HSC's action and is reported promptly to the investigator, the investigator's department chair, the Institutional Official. The Institutional Official is responsible for further notifications outside the institution, in accordance with SOP 17.0.
- IV. In its notification of suspension or termination, the HSC will require, when applicable, immediate actions to notify subjects of the suspension or termination and any necessary steps to ensure the safety and welfare of subjects. Additional requirements may include remedial action or education for the investigator or any other key personnel.
- V. Suspended research requires continuing review according to the previously-designated schedule, until such time as the research is terminated or closed or until the suspension is lifted. Terminated research does not require continuing review.

6.9 Sponsor-Imposed Suspensions

- I. Notification of suspension by a sponsor unrelated to risk is submitted to the HSC for review and approval as a modification to previously approved research. Such modifications are considered minor and may be reviewed by the expedited procedure.

- II. Notification of suspension by a sponsor possibly related to risk is submitted to the HSC for review by the full Committee for evaluation as a potential unanticipated problem involving risks to participants or others, and as a review of a modification to previously approved research.

6.10 Study Closure Procedures

- I. Closure Request Forms are used to notify the HSC of study closure. When an investigator has closed a study, this form should be completed and forwarded to the HSC. The HSC Chair reviews and acknowledges the Closure Request. If the Chair has any questions or conditions prior to approving the closure, the HSC Office sends a notification letter to the investigator. If there are no questions or conditions, the HSC Chair acknowledges receipt. A copy of the acknowledged form is returned to the investigator. HSC staff document the study closure by entering the date of closure in the database maintained in the HSC.

6.11 Activities related to Closed Studies

- I. If the investigator wishes to re-contact former subjects after study closure, to provide additional study-related information, the communication must first be approved by the HSC.
 - A. Requests to re-contact former subjects will be reviewed on an expedited basis by the HSC chair or other experienced member. At his/her discretion, the Chair may refer the request to the full committee.
 - B. Communications that relate to the safety of former subjects will be referred to a convened meeting. The Committee may request additional information to ensure that adequate follow-up occurs.
 - C. The HSC Office administratively re-instates the research for the limited purpose of communication with former subjects. The re-instatement is granted for 90 days. At the end of 90 days, the project is administratively closed again unless investigators need an extension to allow additional time for safety follow-up.
- II. Investigators must obtain prior approval from the HSC if they wish to use identifiable data from their previously closed study for additional analyses. A new HSC application will be required.
- III. Prior HSC approval is required if data from a closed study is used by persons not associated with the original study or if the data is to be used for purposes not covered by the original approval. This requirement applies for both identifiable and de-identified data. Investigators must submit a new HSC application. The

HSC will evaluate the proposed secondary use, to determine whether the new activity is exempt or requires expedited or full-committee review.

References:

45 CFR 46.109

21 CFR 56.109

45 CFR 46.110

21 CFR 56.109

45 CFR 46.111

21 CFR 56.111