Continuing Review

I. Definition and Regulatory Requirement for Continuing Review

Federal regulations require IRB review of research at intervals not greater than one year. This applies whether a study is reviewed by the convened IRB or through an expedited process. IRB review of human subjects research may be required at more frequent intervals [45CFR46.109 (e); 21CFR 56.109(f)], as appropriate for the degree of risk (for example: a Phase I protocol may be reviewed every 6 months due to the degree of risk).

Please note: The investigator is responsible for seeking continuing review and proving information for the review that is as complete as possible.

II. Submitting the Request for Continuing Review

A courtesy reminder notification is sent to the investigator and research team, via eIRB, 60 days before the study’s expiration date. If the PI does not receive the reminder notification, the study is accessible via eIRB. The continuing review should be submitted to the IRB for review well in advance of the protocol expiration date; approximately six weeks before expiration. It is the responsibility of the PI to assure that protocol continuing review submissions are in the IRB Office far enough in advance of the expiration date and at least six (6) weeks prior to protocol expiration to allow adequate time for processing and review prior to the expiration date. Extensions for submitting a continuing review must be submitted to the IRB Chair, or their designee, and will be granted based upon their determination, but this in no way guarantees that the protocol approval will not expire. The continuing review submission must be submitted regardless of the status of a pending protocol revision (amendment).

If the continuing review request is not submitted 30 days before the study expiration date, the protocol approval will expire on the protocol expiration date. A lapse in IRB approval of research occurs whenever an investigator does not provide continuing review information to the IRB or the IRB has not conducted a continuing review and re-approved the research by the expiration date. A lapse in approval can occur because the IRB did not receive the required materials from the investigator or because the IRB received the materials but did not grant continuing review because it requires additional actions by the IRB, the sponsor and/or the investigator. If the project is funded and the IRB approval expires, the funding may also be withheld. When a protocol expires, all study-related activities must cease. This includes...
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recruitment, advertising, screening, enrollment, obtaining research informed consent, interventions, interactions, and the collection of private identifiable information. Enrollment of new subjects cannot occur after IRB approval expires and the data collected on subjects after IRB approval expires cannot be included in the research analysis. Enrolling subjects after IRB approval expires is considered to be a protocol violation, which requires submitting this as a Reportable Event via eIRB. Subjects receiving test articles should be withdrawn in an orderly manner appropriate to the research medication. A plan for this procedure (safely withdrawing subjects) must be submitted in writing to the IRB for review as soon as possible per the Food and Drug Administration (FDA) regulations.

Per federal regulations, the IRB is not able to allow grace periods for extending the research beyond the expiration date. When IRB approval lapses and the investigator wishes to continue the study due to an immediate subject safety issue for which stopping the study would potentially affect subject adversely, the investigator must submit the continuing review expeditiously to allow the IRB to complete continuing review for the study as soon as possible. The investigator must provide justification for allowing the study to remain open due to an immediate subject safety concern to the IRB Chair as soon as possible. This request and justification may be sent to the IRB Chair via email at IRB@gru.edu. The determination may be made for all enrolled subjects as a group or for individual subjects. However, in all cases, the investigator should verify that the IRB agrees with this determination as soon as possible.

The IRB may allow continuation of the research intervention or interactions in already enrolled participants only when either: 1) the convened IRB, IRB Chairperson, or an IRB member or groups of IRB members designated by the IRB chairperson finds an over-riding safety concern or ethical issue involved such that it is in the best interests of individual subjects.

VA Studies

The IRB will notify the VAMC research administrative office for all protocols with a lapse in approval that list the VAMC as a performance site. The IRB will also notify the PI of the study.

Study Closure Due to Non-Receipt of Continuing Review Request

If the continuing review request is not submitted before the expiration date, no later than six (6) weeks, the study will close (lapse), per the expiration date. The continuing review report must be submitted and reviewed and approved by the IRB in order to continue the study. If the IRB subsequently re-approves the lapsed research, the IRB may approve the study for one year and establish a new anniversary date for the expiration of subsequent approval periods or may re-approve the study for less than one year, either to retain the original anniversary, or to address any study risks, in which case, a new date for continuing review is likely.
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III. IRB Review

In order to approve research, the IRB must determine that all of the following requirements are satisfied, which requires submission of the continuing review at least six weeks before the expiration date to ensure IRB review and approval:

- Risks to subjects are minimized;
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result;
- Selection of subjects is equitable;
- Informed consent will be sought from each prospective subject or the subject’s legally authorized representative, and appropriately documented;
- Where appropriate, the research plan adequately provides for monitoring the data collected to ensure the safety of subjects;
- Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data;
- Appropriate additional safeguards are included to protect vulnerable subjects; and
- Where the study involves children, the research complies with 21 CFR part 50, Subpart D.

Once the continuing review is submitted and the administrative analysis is completed, by the assigned IRB Administrator, the submission is sent to an expedited reviewer (for protocols approved via the expedited procedure) or scheduled for an IRB meeting (for protocols originally approved by the fully convened IRB). This is to ensure that the review occurs before the expiration date. Continuing reviews that are presented to the fully convened IRB are to no less than two experienced primary reviewers, according to their expertise.

The IRB must review the following:

- Current, approved, stamped documents:
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- Informed consent document(s) children’s assent document(s)

- Summary of IND Safety Reports (required for sponsored, multi-center studies) in which the sponsor sends IND safety reports to the study teams

- Progress report/brief project summary to include:
  - Number of subjects accrued (for multi-site studies, the number of subjects accrued at the local site and the number accrued study-wide)
  - A brief summary of any amendments approved by the IRB since the initial review or the last continuing review
  - Any new and relevant information, published or unpublished, since the last IRB review, especially pertaining to risks associated with the research
  - A summary of any unanticipated problems as per protocol (or a statement that there have been no unanticipated problems i.e., adverse events have occurred at the expected frequency and level of severity as documented in the protocol, the informed consent document, and Investigator’s Brochure) (if applicable)
  - A summary of any subject withdrawals since the last IRB review and the reasons for withdrawal, if known
  - A summary about any complaints about the research from subjects enrolled at the local site since the last IRB review
    - The latest version of the protocol and sample informed consent document in use at the site
    - Any proposed modifications to the informed consent document or protocol
    - The current Investigator’s Brochure (if applicable)
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- Any other significant information related to subject risks, such as the most recent report from the data monitoring committee (DMC)

- Any information regarding relevant regulatory actions occurring since the last review that could affect safety and risk assessments (e.g., withdrawal or suspension from marketing in any country on the basis of safety, reports of recalls and device disposition)

- The IRB may request additional information from the investigator as they deem necessary to assist them in making a risk/benefit assessment.

- IRB reviewers must have access to all prior relevant IRB records

Risk Assessment

The IRB must assess risk during continuing review and must determine whether the information provided at the time of continuing review would alter the conclusion 1) that the risks to subjects are minimized, or 2) that the risks to subjects are reasonable in relation to anticipated benefits (21 CFR 56.111(a)(1) and (2)). The IRB will consider any new information that has been received since the date that the IRB last reviewed the study (e.g., sponsor’s annual report, periodic aggregate reports, any analysis by the sponsor performed since then).

Informed Consent Document

The IRB will review the informed consent document to ensure the site is using the most currently approved version, and ensure the consent contains accurate, up-to-date information about the study. The IRB will ensure that information about any significant new findings identified since the last continuing review that may relate to the subjects’ willingness to continue participation will be provided to enrolled subjects

Local Context Issues

The IRB will consider local concerns during both initial and continuing review, including:

- Changes in the investigator’s situation or qualifications (e.g., suspension of hospital privileges, medical license; involvement in numerous clinical trials);

- Evaluation, investigation, and resolution of complaints related to the research;
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- Changes in the acceptability of the proposed research in terms of institutional commitments (e.g., personnel and financial resources, adequacy of facilities) and regulations, applicable state and local law, or standards of professional conduct or practice;

- Reports from third party observation of the research (including the informed consent process) carried out under 21 CFR 56.109(f); and

- Investigator concerns about trial conduct at the local site (e.g., study coordinator ineffectiveness, inability of subjects to understand sections of the informed consent document required by institutional policies).

Continuing Review via the Expedited Procedure

The IRB may use an expedited review procedure to conduct continuing review of research projects that:

- Involve only procedures described in one or more of the nine categories of research activities published in the Federal Register (see 63 FR 60364-60367, November 9, 1998, also available at http://www.hhs.gov/ohrp/policy/expedited98.html); and

- Are found by the reviewers to involve no more than minimal risk to the subjects (45 CFR 46.110(b)).

If the protocol was originally reviewed via the expedited procedure and continues to qualify as such, then the Chairperson or designee will review the submission and/or attachments (e.g., advertisement, informed consent document, etc.). If approved, these results are reported to the full Committee at the next IRB meeting via the agenda. If the reviewer determines that they cannot approve the Continuing Review; then the Investigator is notified and the Continuing Review is placed on the Full Board Agenda. Disapproval of a research study at the time of the continuing review can only occur after review by the IRB at a convened meeting, not by the expedited review process.

Expedited review categories (1) to (7) apply to both initial and continuing review, whereas review categories (8) and (9) apply only to continuing review. Per DHHS guidance, in general, a research study that was eligible for initial review under an expedited review procedure will qualify for an expedited review procedure at the time of continuing review; however, the IRB should be aware that a research study previously approved under an expedited review procedure in some circumstances will need to undergo continuing review by the IRB at a convened meeting.

If the protocol was originally reviewed as full review and may now be reviewed via the expedited method, the fully convened IRB will review the submission and determine that the study can be reviewed via the expedited criteria for future continuing review per the federal regulations listed below:
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8. Continuing review of research previously approved by the convened IRB as follows 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
(iv) Where no subjects have been enrolled and no additional risks have been identified; or
(v) Where the remaining research activities are limited to data analysis.

9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) (Hotlink to Categories) 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.

1 Children are defined in the DHHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." 45 CFR 46.402(a).

IV. Frequency of Continuing Review

The IRB must conduct continuing review of research at intervals appropriate to the degree of risk posed to the subject but no less than one year. More frequent review may be required based upon the degree of risk. The frequency of continuing review is based upon:

- The nature of and any risks posed by the clinical investigation;
- The degree of uncertainty regarding the risks involved;
- The vulnerability of the subject population;
- The experience of the clinical investigator in conducting clinical research;
The IRB’s previous experience with that investigator and/or sponsor (e.g., compliance history, previous problems with the investigator obtaining informed consent, prior complaints from subjects about the investigator);

- The projected rate of enrollment; and
- Whether the study involve novel therapies.

The PI is notified of the interval at which continuing review will occur at the initial approval and subsequent continuing review.

**Continuing Review Approval and Expiration Dates**

The IRB determines the continuing review approval and expiration dates based upon the date when the IRB conducts continuing review and approves the study (with or without conditions). For example, a protocol was initially approved from August 1, 2012 to July 31, 2013. The continuing review of the protocol is reviewed and approved at the IRB meeting on July 6, 2013. The continuing review approval date will be July 6, 2013 to July 5, 2014.

**V. Outcome of IRB Review**

The IRB may complete the following actions for continuing review:

- Approve
- Approve with Stipulations
- Disapprove

**Approval**

If the continuing review is approved, a notification and approval letter will be sent via eIRB. The approval letter will indicate the effective date of the approval and the expiration date.

**Approval with Stipulations**

The IRB will approve the protocol for continuing review on a contingent basis pending (with stipulations) the satisfactory response by the investigator. The approval will be held until the requested items are received. This approval will be for a defined time period and may be extended upon receipt of the requested items. If the requested items are not received in a timely manner, the convened IRB may disapprove the protocol.

The investigator must ensure that the sponsor and/or the FDA and the NIH are informed of actions, if any, taken by the IRB as a result of its continuing review. The IRB may set conditions
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under which a protocol can be approved for continuing review. For submissions reviewed by
the fully convened IRB, if the conditions are substantive regarding the protocol or informed
consent process/documents then the approval must be deferred until the next convened IRB
meeting. If the conditions are not substantive the investigator’s response may reviewed and
approved by the Chair and/or his designee.

For continuing review via the expedited procedure, the investigator must respond to reviewer
requested revisions/stipulations before the expiration date or the study will be closed. The
investigator is notified of the study closure via eIRB.

Disapproval

Disapprovals may only be determined by the fully convened IRB. If a continuing review is
disapproved by the fully convened IRB, this determination will be communicated to the PI via a
letter from eIRB. Disapproval means the study activities must cease and the study will not be
continued. If the protocol is sponsored, the IRB will notify the sponsor regarding the
disapproval and the reason(s) for the disapproval determination. If a continuing review of a
protocol conducted at the Charlie Norwood VA Medical Center is disapproved, the CNVAMC
Director is notified of the disapproval and the reason(s) for the disapproval determination.