Continuing reviews

My study is closed to enrollment. Do I still have to renew it?

If **any** study procedures are ongoing, the study should be renewed if the study is FDA regulated. This includes studies with subjects still on study drug(s), undergoing study procedures, or being followed, or studies for which data is still being collected or analyzed. Even if the subject's own involvement in the study is finished, if you are still working with identifiable subject data IRB approval is needed. You should submit continuing review documents at the appropriate time.

If all study-related procedures are complete, and you are not planning to do any further data analysis, then the study can be terminated. If data analysis will be done at another site, and this site has completed all study procedures, the study can be terminated at this site, unless you feel that the sponsor may request additional data from your site. If you still need to look at subjects' medical records for information to report to the sponsor, you will need to keep the study active.

If your study is not FDA-regulated, and the IRB has determined that continuing review is not required, you will be formally notified by the IRB during the approval process that continuing review is not required. If you are not certain whether your approval letter indicates that continuing review is required, please contact the IRB office.

If your study is not FDA-regulated, but subjects remain on study, continuing review may or may not still be required. Please check your approval letter or contact the IRB office.

My study was finally approved 5 months ago. Why is the IRB already sending me reminder notices about renewing the study?

Federal regulations require that studies requiring continuing review be reviewed by the IRB at least once every year. This means that the IRB has one year from the date a protocol is reviewed at a convened meeting, or in the case of expedited reviews, the day the expedited approval is reviewed and approved, to review the study again, either at a convened meeting or through expedited review procedures.

If your protocol was last reviewed at a meeting in March, but did not get final approval until September, it must still be reviewed prior to one year from the day in March it was reviewed at a meeting.

Researchers should check the IRB website for renewal deadlines posted on the Meeting Dates page. Typically continuing reviews should be submitted 90-120 days prior to their expiration date.

Note that for studies that cannot be expedited, it is imperative to meet renewal deadlines, as renewal forms must be reviewed at a convened meeting. If there is no meeting scheduled before your study's expiration date, it will expire.

The AURA-IRB system sends out renewal reminders approximately 4 months before studies expire. These are automatically sent to the email address on the "Profile" page for the PI and primary contact from the email address _aura-irb@uchicago.edu. This is not a monitored email address; please do NOT use this email to communicate with the IRB office.

The goal is to review the studies at the meeting 1-2 months before the expiration. If any problems arise during the review or revised documents are requested, the PI thus has time to respond before the protocol's expiration date. Note that the IRB makes every effort to notify investigators prior to study expiration regarding the need for renewal; however, **the principal investigator is ultimately responsible** for ensuring a protocol's continued approval.

What materials are needed for a continuing review submission? What is the IRB looking for?

To be accepted for processing, all questions on the continuing review (CR) form should be completed and any applicable documentation uploaded, including any relevant data monitoring committee reports. Please see the Checklist below for the necessary materials to be accepted for processing:

CRs: Accepted for Processing Checklist

After a CR has been submitted, the IRB administrative team will review the submission and determine if any information is missing or if more information or documentation is needed. The IRB administrative team uses a "pre-review checklist" to document the administrative review. Any outstanding items or issues noted in this pre-review will be communicated to the study team via email. The administrative pre-review checklist is provided below for your reference:

CR Pre-review Administrative Checklist

Why do I have to do a literature search?

Ideally, a PI should always be well informed of the literature relating to the particular field of study and should be conducting reviews of the available literature on a regular basis. The need for a literature search to assess the risk level and alternatives to participation of each study was given additional emphasis following the federally-imposed halt on research at Johns Hopkins University in 2001. A volunteer on a Hopkins research study died after being exposed to a drug for which the government determined that risk information had not been adequately researched.

Consequently, the federal agencies governing research have heightened their emphasis on the need for a thorough review of available applicable literature both before research is started and

as an ongoing process throughout the research. The University of Chicago BSD/UCMC IRB therefore requires that a literature search be conducted and the results presented to the IRB at the time of original submission as well as at each continuing review (renewal). During the original submission, references in a written protocol may suffice in lieu of a literature search.

How should I conduct the literature search? What does the IRB require?

PIs should search on one or more web-based search engines for articles relating to 1) the condition being studied and 2) the specific drug/device/process/intervention being studied. For example, for studies of a new drug for IBD, researchers should not only search for articles on the risk of that drug, but should also search for articles on new treatments for IBD that would present available alternatives to study procedures. The Committee is also concerned with the applicability of the proposed research; that is, if a literature search reveals that the study being proposed replicates studies that have already been completed with definite results, the PI should consider whether the study is likely to yield new information and if not, if the study should be performed.

While the IRB has faith that investigators are responsibly conducting research, the IRB does not accept merely a statement that a literature search has been performed. The Committee requests that PIs provide the IRB with the **name of the search engine** that is used, the **search strategy** (keywords), and the **results** of the search, along with a description of the **results' impact on the risk level and/or alternatives to participation of the research**.

Example of an acceptable literature search for a renewal:

SEARCH ENGINE: PubMed
SEARCH TERMS: Drug Name (generic), Drug Name (brand), Disorder Name
RESULTS: 1200 articles.
SUMMARY: Most of the articles were not applicable to the study at hand as they dealt with the risks of or descriptions of standard of care drugs for this disorder. Searching on the drug itself yielded only a few results having to do with animal studies; these are already covered in the investigator's brochure. One article, "DRUG XYZ in Disease Y" by A. Jones, indicated a possible new alternative therapy, but this is still in Phase I development. Overall, there is nothing in the literature to indicate any new information on the risks or benefits of this study. Risks found in the literature are already covered in the protocol and consent form for this project.

My study is closed to enrollment. Do I still need to perform a literature search?

If your study is still enrolling subjects OR if enrollment is closed, but subjects are still actively participating in study procedures or receiving study drug, then a literature review should be submitted.

If your study is permanently closed to enrollment and all subjects have completed all research-related interventions, then a literature review **may** not be required. However, the IRB does require that you provide a justification for not providing a literature search. ("Not applicable" is not considered a sufficient justification. Please explain why a search is not applicable.) Also, the IRB may determine that a literature search is needed to ensure that there is no new information that should be provided to subjects in follow up, e.g. new safety information about the drug tested in the study. Please contact the IRB staff for more guidance on your specific protocol, if needed.

Can a continuing review undergo expedited review?

If continuing review is required, continuing review (CR) must take place at a convened meeting at which a majority of the IRB members are present **unless** the research qualifies for review under an expedited review procedure (**45 CFR 46.108(b)**).

IRBs may use an expedited review procedure to conduct continuing review of research that:

- Involves only procedures described in one or more of the nine categories of expeditable research activities (see OHRP Expedited Review Categories); and
- Currently involves no more than **minimal risk** to the subjects (**45 CFR 46.110(b)**)

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. (45 CFR 46.102(j))

See attached decision tree for more information.

Amendments

In what circumstances do I submit an amendment?

Any change to an approved study, including changes to the consent form, advertisement, recruitment procedures, study personnel, or protocol design, should be submitted as an amendment to the protocol. Minor changes can be approved through expedited procedures, but still must be submitted for approval. All requested changes should be described in detail on the amendment submission form, which must be electronically signed by the PI and submitted along with any documents that are being changed.

No change should be implemented until it is approved by the IRB.

Amendments cannot be processed on protocols that have not yet been approved. Changes to protocols that have not yet been approved should be addressed through memos or responses to the IRB Committee.

Study activities **should NOT deviate in any way** from the protocol that is approved by the IRB unless a change is necessary to eliminate immediate hazard to an individual. The investigator should notify the IRB as soon as possible after a change is made to eliminate hazard(s) to subjects or others, and a formal amendment should follow within 5 working days of implementation of the change.

Studies for which continuing review is not required are still required to submit amendments prior to initiating changes to approved study procedures.

How do I enroll an otherwise ineligible subject on a study? How can I slightly alter approved study procedures for one subject?

The BSD/UCMC IRB does not have a protocol "exception" policy. Accordingly, when **any** revision to an approved research protocol is desired, including a change in research design or eligibility criteria, for one subject or multiple subjects, the investigator must submit an amendment. The amendment form should explain what changes are desired and provide a rationale for those changes. A revised copy of the pertinent original documents (e.g. protocol, consent form, etc.) should also be submitted with the changes identified.

Amendments to approved protocols may not be initiated until IRB approval has been obtained, except where necessary to eliminate apparent immediate hazards to the subject, in which case the IRB should be notified as soon as possible. Eliminating immediate hazards to a subject should be considered in the light of treatment rather than research. If it is in the best interests of the patient/subject to be given or removed from study drug/procedures, then this should be done regardless of the approved protocol or the need for an amendment. The appropriate paperwork may be completed later.

In other words, **treatment** decisions should be made separately from research decisions. An investigator/ physician may believe that the best treatment for a patient is an experimental drug. However, as an investigator, that same physician should note that if a **treatment** decision for a particular patient does not fit within or differs from approved **research** procedures, the patient may not be able to remain on or be enrolled in the **research**.

The IRB is often informed that "treatment" may be delayed if an amendment is not approved immediately. In practice, treatment decisions must be made by the treating physician regardless of a research opportunity. Participation on a research study is often not a patient's only treatment option. Alternative approved drugs/procedures or other drugs given off label may represent other treatment options for a potential patient for a study or a subject already enrolled on a study.

When a PI makes a decision as to whether to treat a person and/or to keep that person on a research study, there may be other entities involved in the decision regarding this person, including the study sponsor and IRB. A sponsor may or may not allow the person to remain on study if procedures for that individual will differ from study procedures. In addition, this event would require reporting to the IRB as an unanticipated problem if the PI has not requested prior

approval for the change to approved study procedures. The IRB may then determine that using data from that individual is not appropriate on the study. Again, this does not affect the treatment decision; it only affects the research.

An IRB is required by federal regulations to ensure prompt reporting of serious or continuing noncompliance with regulations or noncompliance with the IRB's own requirements and determinations. Deviations from the approved protocol, i.e., changes made without prior IRB approval, fall under the category of noncompliance. Deviations must be reported to the IRB. Once reported, the IRB can make a decision regarding appropriate response or remedial action, or determine that no remedial action is necessary. Remedial actions may include asking an investigator to exclude data that was obtained inappropriately or outside approved study parameters.

A protocol deviation occurs when the study departs from the IRB-approved protocol in any way, including use of a non-approved or outdated document (consent, advertisement, etc.), change in procedures (drug dosing, scheduling of study visits, re-ordering of study activities), change in personnel conducting study procedures, and inclusion of a subject not meeting eligibility criteria.

It is the expectation of the IRB that all approved protocol procedures are being followed without alteration unless the IRB has been informed of a protocol change (through an amendment) or deviation (through an Unanticipated Problem report or continuing review update).

Example #1:
Patient A was screened for a research study. All the necessary screening labs were done as well as a medical history review. Inclusion/exclusion criteria were verified by the PI and the patient was found to be eligible and started on study. Later, it was discovered that Patient A had a condition diagnosed at an outside facility that was not recorded in the medical history. This condition is among the protocol exclusion criteria. The study physician would like to keep Patient A on study.

Potential issues arising from this example:

1. If this is a sponsored study, the sponsor should be informed that a subject was enrolled who was ineligible. The sponsor must decide whether this person may continue on study.
2. If there are immediate health or safety issues that would require that this person remain on study (e.g drug is only available as part of the research and there may be consequences to abrupt withdrawal of drug, etc.), and the PI believes that remaining on study is in the best interest of the person, then to protect the safety of the subject that person should remain on study drug, if possible. This should be documented in the research file, the medical chart, and in an unanticipated problem report.
3. An unanticipated problem should be reported in any case as soon as possible. The IRB will consider whether to protect human subject(s), its recommendation would be that this subject should continue to be on study or that the subject should be taken off study, if the subject has not already been removed from the study.

Example #2:
Patient A is an otherwise-eligible 70 year old. The protocol inclusion criteria for this drug trial

states that persons ages 18-69 may be enrolled. The study physician feels that Patient A may benefit from the drug and would like to enroll the patient on the study. Patient A is coming to the hospital for a clinical care visit tomorrow. The PI wants to approach Patient A to participate in the study at that visit.

Potential issues arising from this example:

1. If this is a sponsored study, the sponsor should be queried as to whether an exception to eligibility criteria would be allowed. The sponsor must decide whether this person may be enrolled on study and if allowed, should provide documentation to the PI to that effect.
2. As this is a change to the approved research design, IRB approval should be requested prior to enrollment of this individual. As noted above, approval is needed whether this change applies only to this one individual or whether eligibility criteria are expanded for all future potential subjects.
3. It is unlikely that the IRB will be able to approve an amendment prior to the scheduled clinical care visit. The PI may wish to reschedule or explore other appointment options or opportunities with this patient.

I have a patient waiting to be enrolled, but I recently submitted an amendment to change the consent form. Can the IRB process that amendment quickly so that I can enroll this patient?

The IRB receives multiple requests for amendments to be processed more quickly due to patients waiting. Note that due to the volume of amendments requiring processing and the limited availability of IRB reviewers, the IRB cannot accommodate all requests for quicker processing. Note, too, that if an amendment qualifies for expedited review the IRB will likely expedite it regardless of whether or not expedited review was requested. If it does not qualify for expedited review, it will require review at the nearest convened meeting for which a reviewer is able to review it. If possible and upon request, the IRB may be able to review the amendment at an earlier meeting than the one for which deadline it was submitted. Please contact the IRB office for such a request. **Please copy the PI on all such requests.**

If a proposed change involves re-consenting of all subjects, it is unlikely that the amendment will receive expedited review.

If you have an IRB-approved consent form and enrollment has not been halted for safety or other concerns, you are free to enroll subjects using that approved consent form. If, however, in the PI's opinion a change described in an upcoming amendment is a change that potential subjects should be aware of due to safety or other concerns that might affect a subject's willingness to participate, the subject should not be enrolled until that person can be informed appropriately and with an approved consent form that adequately reflects approved study procedures.

Continuing Reviews and Amendments

I just had an amendment approved. Do I still need to submit a continuing review for that study?

Yes, if the study requires continuing review. Amendments deal with **changes** to the approved study. Approval of an amendment indicates specific approval of that change. Once approved, an amendment becomes a part of the approved study. On the other hand, a continuing review is a review of the **entire** study, including all amendments up to that date, to evaluate whether the study continues to meet all requirements for approval. If a continuing review is not approved prior to the study's expiration date, the study will expire.

Can I submit a continuing review and an amendment at the same time?

You can, although the submission of overlapping documents for both can be tricky. Remember that the continuing review is a review of the approved study and your submitted amendment has not yet been approved or may never be approved. If an amendment is approved after you have submitted your continuing review documents but before renewal approval, you may need to update your continuing review submission to reflect any changes made with the amendment. Conversely, if your consent form is revised during the time of continuing review, you may need to submit a revised consent form for any pending amendment to incorporate renewal changes with amendment changes to the consent form.

Especially with consent forms, be aware of whichever version is approved last. It becomes the approved version. Amendment changes are nullified if the renewal consent form, approved after the amendment, does not reflect the amendment changes. Another amendment must then be submitted to approve the revised consent form before it can be used.