

8. CONTINUING REVIEW

Institutional Review Board review is an ongoing process – not a one-time step. Regular reevaluation ensures that research is conducted responsibly. Even in responsibly conducted studies, a one-time review is inadequate, since risks can really be understood only after research has begun, and since the regulations for human subjects research are constantly being refined as the risks and benefits are better understood. Unexpected developments in a project can raise questions about the conduct of the research, and new findings can raise questions about the project.

8.1 Continuing Review

“Continuing review” refers to regularly scheduled complete reappraisals of a project. The goals of continuing review are to ensure that the risk/benefit ratio is still acceptable, that the measures taken to safeguard subjects are adequate, that the approved protocol is followed, and that the project reflects any changes that have been made in the regulations for human subjects research since the last approval.

The CPHS may require changes in protocol or revisions in the consent form if the study’s risks were originally underestimated, but the converse can also occur: the investigators and the CPHS may have underestimated the benefit to research subjects.

When Continuing Review is Required

The Department of Health and Human Services (DHHS) regulations 45 CFR 46, require that “an CPHS shall conduct continuing review covered by this policy at intervals appropriate to the degree of risk, but not less than once per year...” This continuing review must be substantive and meaningful. Research for exempt status applications will be reviewed every 5 years due to the reduced risk to human subjects.

The CPHS will determine a review interval for the research as appropriate to the degree of risk, but not greater than one year from the last date of CPHS approval. The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of CPHS approval. Therefore, continuing review and re-approval of the research must occur on or before the date when CPHS approval expires. If the research involves the following, the CPHS will review more often than annually:

- Previous suspensions of the researcher due to compliance, record-keeping or other concerns; and/or
- Any other situations for which the CPHS deems more frequent review appropriate.
- Research that involves adults unable to consent and the study is deemed greater than minimal risk.
- Research that includes children and is approved under 45 CFR 46.406(Subpart D).

The aforementioned research activities may also be used to determine if verification from sources other than the investigator is necessary to verify that no material changes have occurred since previous CPHS review.

A notice for renewal and a “continuing review form” are sent to the principal investigator approximately 60 days before the review date. The form should be completed and returned to the ORPCC office by the indicated deadline. The notice for student projects are sent to the faculty sponsor and this person is responsible for notifying the student and ensuring timely submission of the renewal form. The study expiration date is crucial for the continuation of the study. . If CPHS approval has expired, the PI must cease all research activities and may not enroll new subjects in the study after the expiration of the CPHS

approval. All data collection must stop and no funds may be spent (if the research is funded). However, if the IRB determines that an overriding safety concern and/or ethical issue is involved or that it is in the best interests of the individual subjects to continue participating in the research activities, the IRB may permit the subjects to continue in the study for the time required to complete the continuing review process.

A new application and review will be required to reinstate the study if it expires.

If the investigator does not respond, the IRB will classify the study as “inactive.”

If the study is complete, the investigator is asked to complete several portions of the continuing review form as a “final report” on the project.

Lapses of approval as outlined in the continuing review process are not reportable to OHRP under their federal guidelines.

What Forms to Complete

Continuing review requires that you complete the Continuing Review Form and attach a current consent form if subjects are currently being recruited. The form requires the following information:

- the number of subjects enrolled since the last review and the total number of subjects enrolled to date;
- breakdowns of the subject population by gender and other demographics;
- a summary of the results of the research to date, including
 - any unanticipated risks or adverse outcomes, and
 - any early indication that one of the treatments under study is significantly better or worse than others;
- any difficulties recruiting or retaining subjects, an explanation of the difficulties, and the number of subjects who withdrew from the study;
- changes in the last year that were approved and the dates they were approved;
- if currently recruiting subjects, a copy of the consent form currently in use (as most recently approved by the CPHS).

Incomplete forms will be returned, which may cause a delay in getting the study on the appropriate committee agenda.

Level of Review

A project usually merits the same level of review in continuing review as it received originally. Hence, most projects require full review. As in the initial review, the CPHS may require revisions in the protocol or the consent documents.

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The aforementioned research activities may also be subject to verification from sources other than the investigator that no material changes have occurred since previous CPHS review.

8.2 Making Changes in Research Protocols

A project approved by the CPHS must be executed according to the approved protocol. Any changes in subject population, recruitment plans, research procedures, study instruments, study sites, or major research personnel require prospective approval by the CPHS. Changes enacted without prior approval constitute protocol violations.

Researchers who plan a change must complete the Request for Revision form. The title should be that of the approved study and a description of the proposed changes should be written in lay language. Explain why the change is needed, describe any implications for subjects, and provide the appropriate revised consent documents. All requested changes should be highlighted in the submitted materials.

Absent and Exiting Principal Investigators

If a principal investigator on an approved project goes on sabbatical leave from the University, an interim PI must be appointed. The CPHS should be informed of this person's qualifications and the new PI should write to the CPHS accepting the responsibility for the treatment of subjects. If a researcher leaves the University permanently, the CPHS should be notified both of any interim investigators and of the final replacement. Otherwise, the study will be filed as "inactive."

How Changes are Reviewed

All requests for revisions are reviewed by the Chair or his or her designee. The Chair, or his/her designee, will provide approval if the changes are minor and do not alter the risks and benefits to the subjects, affect the equitable enrollment of subjects, or modify informed consent protections. Examples of minor changes include the substitution of one research instrument for a comparable one or the replacement of a co-investigator with an investigator with equivalent qualifications. If the requested modifications in research are not minor and represent a significant revision in the approved research or increase the risks to subjects, the Chair, or his/her designee will refer the request for revisions to the full CPHS for consideration at a convened meeting unless the amended research would qualify for expedited review.

Investigators are notified in writing of CPHS decisions on revisions. If a request for revision is not approved, the CPHS will provide the reasons for its decisions.

8.3 New Findings

Unanticipated Events

Unanticipated events are unexpected problems of a nature, severity, and frequency not described in the information provided to the CPHS or to participants. Examples include unexpected complications in a subject, missteps in the consent documentation, or breaches of confidentiality. Unanticipated events should be reported to the CPHS within 10 working days.

The report of the event should discuss:

- the facts of the case, including the date and a description of the subject;
- whether the event is related to the study's procedures or drugs or to the subject's underlying disease or condition;
- the steps that have been taken to address the problem;
- whether the event is likely to recur; and
- whether the event provides new information about the study's risks that should be conveyed to participants, in a revised consent form.

A study may be suspended to ensure subjects' safety. Reports of events occurring at other sites receive expedited review, but in some cases the full CPHS is involved. All events that occur at the University of Houston are reviewed at a full CPHS committee meeting.

Events at Other Institutions in a Multicenter Trial

If the project is a multicenter trial and the event occurred at another institution, the researcher must write to the CPHS, describing the nature of the event, its severity, the likelihood that it will occur at the University, and the implications for future subjects.

Death of a Research Subject

Researchers should alert the CPHS immediately to the death of any study subject, whether the death is believed to be related to the study or not.

New Risk/Benefit Findings

As a study progresses and the risks and benefits of participating in the study are better understood, researchers may find that the study must be stopped. For example, in some placebo-controlled trials, preliminary findings may give compelling evidence that a new treatment is efficacious. It then becomes unethical to continue giving placebos. (This occurs most frequently in multicenter trials in which a central statistical center receives and processes large volumes of data from several sites.)

In such cases, the investigator should write to the CPHS, describe the findings and the need to suspend the placebo portion of the study. If the CPHS agrees, the researcher should identify all subjects who

received a placebo and invite those subjects to continue in an “open label” study in which all subjects receive the study medication.

8.4 Keeping Records

Researchers should maintain a file of all documents concerning the use of human subjects in research for not less than five years after conclusion of the study. The file should include copies of all documents and include original paperwork whenever possible. The principal investigator’s records should mirror the CPHS’s records: where the CPHS holds an original, the principal investigator should hold a copy, and vice versa.

Researchers should have the following documents on file:

- a copy of the original application submitted to the CPHS, including the consent form and the research protocol;
- the original of the CPHS’s response;
- a copy of responses to CPHS contingencies or requests for additional information;
- the original notice of final approval;
- a copy of the “Certification of Approval” sent by the CPHS to any funding agencies;
- copies or originals of all other correspondence with the CPHS;
- copies of completed “Continuing Review” forms and attachments;
- the original notice of renewal of approval and certification, where applicable; and
- copies of any inspection or audit reports.

Original signed consent forms should be kept in a secure location separate from correspondence with the CPHS but readily available to inspectors. CPHS records are subject to inspection by federal authorities. Sanctions for incomplete or nonexistent records include suspension of funding, fines, exclusion from future funding, and suspension of laboratory access.