

4.12. Research Monitoring

Separate from the IRB Quality Assurance Coordinator (see Section 2.8.1.1.1), the CHS has the authority to appoint one or more individuals to observe the consent process and/or the research and to report back to the CHS with any findings. The CHS shall appoint such an individual whenever it determines, based on information available (such as reports of adverse events or unanticipated problems involving risks to participants or others, deficiencies noted in the CHS office files, reports or complaints from study personnel or participants, media or scholarly reports of research activity) that monitoring is in the best interests of the participants and/or integrity of the study. The CHS also may request that an Investigator design an instrument to document the understanding of consent by a (potential) research participant. The CHS may request that this documentation be provided for its review at any time during the study.

4.13. International or Off-Site Research and Knowledge of the Local Research Context

The CHS is required to have knowledge of the local research context, whether domestic or international, (<http://www.hhs.gov/ohrp/humansubjects/guidance/local.htm>) in order to provide a thorough review, to understand particular risks and benefits of the study population, and the relevance, customs and cultural significance of study procedures to the community in which the research is taking place. All sites are required to have a local IRB or Independent Ethics Committee (IEC) approval. When federal funds are supporting the research, the local IRB or IEC must have a FederalWide Assurance of compliance with OHRP.

In the event that non-federal funds are supporting the research, IRB or IEC approval is still required, unless there is no such board at the site where the research is taking place. While some less populated communities may not have such a board, most communities have a structure (council or local leader) in place that approves the activities of that community. In addition to the approval of this committee or person, a letter of support from the local site (such as a school principal or superintendent, or a clinic director) where the research activities will be taking place should be obtained by the Investigator and provided to the CHS. The letter should include information pertaining to the appropriateness of the study to the local community, any required changes to the study, and a review and approval of the consent document, whenever possible. Letters not provided in English must be translated into English for CHS review and a Translation Attestation Form (Appendix 18a) signed by the Investigator must accompany the letter.

Depending on the research or the risks (or level of risks) to participants and the support from the local community, the CHS may also request that someone (other than the Investigator) with special knowledge of the setting either review a particular protocol, or attend a convened CHS meeting to provide the CHS with recommendations based on his/her expertise. This person must be familiar with the customs, practices, or standards of care (and language, whenever possible) where the research will be taking place.

5. Continuing Review of Research

Research projects must be reviewed at least annually (unless otherwise specified on the ROA) and before the study expiration date (also on the ROA), if the research is ongoing. Research projects are considered ongoing until analyses of data are complete and file closure has been confirmed in writing by the CHS office. Specifically, this means that continuing review must occur as long as the research remains active for long term follow-up of participants, even when the research is permanently closed to the enrollment of new participants and even though all participants have completed all research-related interventions. Additionally, continuing review still must occur even when the only remaining research activities are limited to collection of private identifiable data.

The HIRBERT database sends automatic reminders via email to Investigators 75, 45, and 15 days in advance of the study expiration date. Notifications contain a warning to prepare to stop study activities if the project is not re-approved by the expiration date. On the day the study expires, a final email is sent which states that all study activities must stop immediately.

Continuing review of research must be substantive and meaningful. Toward that end, when a completed Continuing Review Application (Appendix 31) is received at the CHS office, the application is logged into the HIRBERT database, screened by CHS Staff for completeness, and ordinarily pre-reviewed by (and in the same manner) the CHS staff member who had been responsible for the project when it was initially submitted to the CHS.

5.1. Required Continuation Submission Documentation

In addition to the requirements indicated throughout the Continuing Review Application, the following materials (if applicable) also must be submitted for continuing CHS review:

- Data Safety Monitoring Board (DSMB) reports, or adverse/unanticipated event reports with resolution from the institution where the research is taking place.
- Competing/non-competing grant submissions/annual/progress reports to funders.
- Copies of publications or abstracts resulting from the research.
- IRB approvals from any other reviewing IRB.
- Consent form(s) currently being used to enroll participants. Any revisions to the existing consent form or significant new findings that may relate to the participant's willingness to continue participation should be included in a new/revised consent form for CHS approval. If consent forms have been translated into languages other than English, a current copy of the translated version, as well as back-translations into English by an independent party, also must be submitted for CHS review.
- Requests for amendments of any modifications sought to the research project (such as the addition or removal of research personnel, changes in study design or study population, addition or subtraction of the number of participants to be enrolled in the study, additions or changes to recruitment or other research materials) and any supporting materials (such as revised protocols and/or revised CHS applications).

5.2. CHS Office Processing of Continuing Review Submissions

The CHS staff member who previously reviewed the study materials (either initially or as part of the prior continuing review) will be responsible whenever possible, for seeing the continuation through the re-approval process. This staff person will communicate with the Investigator (or personnel designated by the Investigator) any requests for changes or additional documentation needed for a thorough review by the CHS (see Section 5.3), or CHS member (see Section 5.4).

Incomplete submissions (lacking requisite forms, signatures, or documentation) will not be placed on the CHS monthly agenda. However, should an Investigator exercise his/her discretion not to make recommended changes as a result of the pre-review, the submission will be placed on the agenda along with a memorandum regarding the issues of concern for the CHS' consideration in determining continuing approval.

5.3. Continuing Review by the Full Committee

The following materials are provided to all CHS members for review of study continuations at convened CHS meetings:

- Continuing Review Application
- The current consent document
- Any newly proposed consent document
- The initial application form, updated with any changes
- The last Continuing Review application (if applicable)
- A status report on the progress of the research (and progress reports for grants/contracts)
- New or competing and non-competing grants/contracts
- IRB approvals from other institutions (and applications, when applicable)
- Copies of amendment requests and approvals during the past review period
- Adverse or unanticipated event or DSMB reports (if applicable)
- HIPAA patient authorizations, or waivers/waiver requests
- Abstracts or publications resulting from the research
- Citations of current findings that might affect the risk: benefit balance of the study
- Communications with the Investigator (to/from CHS staff and/or Reviewer)
- Minutes from previous year reviews, if necessary

The CHS applies the same criteria for continuing approval of research projects as it does in the initial review (i.e., acceptable risks, potential benefits, informed consent, and safeguards for research participants). Review at a full CHS meeting is required for all research studies that were previously reviewed at a full CHS meeting unless the research qualifies for expedited review under categories 8 or 9 (see Section 4.9.2.2).

If possible, the same Reviewer who previously reviewed the proposal will be sent the continuation materials in order to maintain continuity. If the original Reviewer is no longer on the CHS or is otherwise unavailable, then another CHS member with similar knowledge and expertise in the field of the research (whenever possible) will be chosen. This system applies regardless of whether the proposal meets the criteria for review by the full CHS or qualifies for expedited review. If additional expertise is required, the CHS (Chair, Administrator, ORSP Director or IO) will determine the appropriate consultant for the review (see Section 3.3). If the

study involves prisoners or is adding prisoners to the study population, then the ad hoc prisoner representative will be a Reviewer along with another member of the Committee. While the Primary Reviewer is responsible for presenting the study at the meeting, all CHS members in attendance are expected to thoroughly review the materials sent to them for each study in order to discuss the protocol at the meeting.

In some circumstances, the CHS may request verification from others (such as a Department Chair, the study or site Coordinator, or the CHS QA Coordinator) that requested changes by the CHS have occurred, or that *no* material changes have occurred without appropriate and prior CHS review and approval. This may happen when there is suspected non-compliance with CHS determinations, either through communications with the Investigator or study personnel, or if the materials submitted to the CHS Office are inconsistent with the Continuing Review application.

For continuing reviews at full CHS meetings, the same criteria and procedures for initial review apply (see Section 4.10).

5.4. Continuing Review of Research Meeting Expedited Categories

Research eligible for an expedited review procedure (see Section 4.9) also may undergo continuing approval through the expedited review process (see Section 4.9). The CHS staff collects and reviews the documentation listed for review of continuations via full CHS meetings (see Section 5.3), then sends it to the CHS Chair or designated member for expedited review (Section 4.9). CHS member review criteria listed in Section 4.9.2.1, apply.

5.5. Lapse in Continuing Review Approval

Investigators are notified of study expiration dates starting 75 days prior to the expiration (see Section 5), and are encouraged to submit continuation materials two months in advance in order to avoid any lapse in approval. If there is a lapse in approval, the Investigator is automatically notified via email from the HIRBERT database that all study activities must cease until the continuation is reviewed and approved by the CHS (confirmed by a ROA; Appendices 32 and 33). The CHS staff will notify the Investigator's Department Chair and SPA representative if a study has expired to make sure that the research (and funding) has been/will be stopped.

Any lapse in approval is also handled under the non-compliance policy (see Section 14). There may be issues regarding current study participants continuing on study medications or scheduled events for participation and questions about notification of participants of the lapse in approval for the study. The CHS Chair or designee may allow current participants to continue in some or all research procedures when it finds an overriding safety concern or the ethical issues involved are such that it is in the best interest of individual participants to continue participating. The CHS will notify the investigator that new enrollment of participants may not occur after the expiration date of approval.

5.5.1. Investigator Reports for Lapsed Studies

Investigators who submit late continuing review applications must include with their application a report of non-compliance. The report must include a statement of why the application was not submitted on-time, what (if any) study procedures took place, and how many participants were engaged in research activities (or specimens/data analyzed) during the lapse in approval.

5.5.2. Review of Lapsed Approval of an Expedited Study

Lapses in continuing review of expedited studies may be reviewed and approved by a CHS member during the review of the study continuation, and do not require review at a convened CHS meeting. As with other expedited reviews, the Reviewer may request that the lapse be reviewed at a convened CHS meeting.

5.5.3. Review of Lapsed Approval for a Study Requiring Full-CHS Review

Lapses of continuing approval for studies requiring full CHS review are presented by the Primary Reviewer, along with the Investigator's report of non-compliance at the full CHS meeting. At the meeting there shall be two votes: one for the continuing approval of the research; and one for the use of any data collected during the period of lapsed approval. Both votes will be documented on the ROAs.

5.5.4. File Closure of Lapsed Studies

If a Continuing Review Application is not filed within three (3) months after expiration, the study will be closed by the CHS office and the Investigator notified in writing. The CHS staff will copy the Department Head and SPA representative on any letters indicating file closures or lapses in approval. SPA will notify any funding agencies or sponsors of closures or lapses in approval, as appropriate with the criteria/stipulations of the funding sponsor, and no funds will be expended for an expired study (see Section 17).

5.5.5. Reporting Study Lapses to OHRP and other Regulatory Agencies

A single lapse in continuing approval does not require reporting to institutional officials, OHRP or other regulatory agencies. However, continuous lapses in approval or serious issues of non-compliance with CHS, DHHS or FDA requirements do require notification to institutional officials, OHRP and other regulatory agencies (such as the FDA), as applicable. The serious and continuing nature of non-compliance is determined by the CHS, and notification schedules for non compliance are outlined in Section 14.

5.5.6. CHS Administrative Functions Resulting in Study Lapses

Studies that lapse due to CHS administrative error (i.e. materials were received in a timely manner, but the office did not review it in a timely manner) do not need a report of non-compliance, although all study activities must cease until re-approval by the CHS is confirmed by the ROA.

5.6. CHS Study and File Closure

Upon completion of a research project, meaning that all research activities are complete and data have been analyzed, the investigator must notify the CHS office that the study has ended and should be closed. A study may be closed using the File Closure Form (Appendix 34) and submitting all appropriate information and documentation listed on the form, including the Investigator's signature.

File closure may also be appropriate if the jurisdiction of IRB review has been transferred to another institution. Transfer of jurisdiction occurs when an Investigator leaves the Faculty of Medicine for another institution and will be conducting his or her research at that institution, or when his or her grant is administered through or transferred to another institution and no research activities are (or are no longer) taking place at HMS or HSDM facilities and Faculty of Medicine students are not the prime participants in the research study.

6. Amendments to Research Activity

6.1. Amendment Requests

If, after the initial approval of a research project, the Investigator wishes to amend or modify the study in any way (such as: changes to the study population, research personnel roster, recruitment, consent, inclusion/exclusion criteria, medications, devices or study procedures) the requested change(s) must be submitted on an Amendment Request form (Appendix 35) or a revised Personnel Roster form (Appendix 21), and preferably accompanied by a cover letter outlining the changes and the reasons for the them.

The most frequent example of non-compliance reviewed by the CHS is the implementation of study changes without prior CHS approval. *Any changes*, no matter how minor (minor changes include: a change that does not alter the risk:benefit analysis of the study, affect the safety of participants, include the addition of study procedures, interactions or interventions, alter in any way the scientific integrity of the study, or include a procedure or vulnerable population for which expedited review is not permissible), must be submitted to and approved by the CHS, documented by a ROA (Appendices 36 and 37), *prior to implementation* of the change(s).

The federal regulations specifically require the CHS to review proposed changes in research activity and to ensure that such changes are not initiated without CHS review and approval, except when necessary to eliminate apparent immediate hazards to the participant [45 CFR § 46.103(b)(4)(iii) and 21 CFR § 56.108(a)(4) (see Sections 10.3.3. and 12.6.1). As noted in Section 5.3, in some circumstances, the CHS may request verification from others (such as a Department Chair, the study or site Coordinator, or the CHS QA Coordinator) that requested changes by the CHS have occurred, or that *no* material changes have occurred without appropriate and prior CHS review and approval.

6.2. Required Materials for Amendment Requests