

**HRPP STANDARD OPERATING PROCEDURE/POLICY APPROVAL &
IMPLEMENTATION**

OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

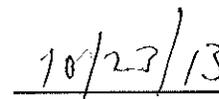
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SOP Title: CONTINUING REVIEW BY THE CONVENEED IRB

**Distribution: Scientific Directors; Clinical Directors; Clinical Investigators, IRB
Chairs, IRB Administrators, Protocol Navigators**

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SOP 9. CONTINUING REVIEW BY THE CONVENED IRB

9.1 PURPOSE

This SOP describes the policies and procedures for continuing review by the convened IRB. See SOP 7A “Requirements for Expedited Review of Research by NIH Institutional Review Boards” for policies and procedures for continuing review by the expedited process.

9.2 POLICY

Consistent with 45 CFR 46.109(e), and OHRP “Guidance on IRB Continuing Review of Research”, dated November 10, 2010, (see References), NIH IRBs shall conduct continuing review of human subjects research at intervals appropriate to the degree of risk, but not less than once per year.

When conducting continuing review, the IRB should start with the working presumption that the research, as previously approved, does satisfy all of the regulatory criteria. The IRB should focus on whether there is any new information provided by the investigator, or otherwise available to the IRB, that would alter the IRB’s prior determinations, particularly with respect to the IRB’s prior evaluation of the potential benefits or risks to the subjects. The IRB also should assess whether there is any new information that would necessitate revision of the protocol and/or the informed consent document.

9.3 REGULATORY REQUIREMENTS FOR CONTINUING REVIEW

- A. NIH IRBs conduct continuing review for each research study to ensure the continued protection of the rights and welfare of research subjects in accordance with 45 CFR 46.109(e) and, as applicable, 21 CFR 56.109(e). The IRB applies the same criteria for approval at the time of continuing review as it does for review of initial studies (see 45 CFR 46.111, SOP 7 “Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards (IRBs)”, and 21 CFR 56.111).
- B. Continuing review occurs at intervals appropriate to the degree of risk, but not less frequently than once a year. The IRB must set the frequency for continuing review based on its analysis of risk at the time

of initial (see SOP 7 “Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards (IRBs)”) and continuing review and may increase the frequency of review, i.e., if new information negatively impacts the risk/discomforts and benefits ratio, if the IRB is notified of a complaint or alleged non-compliance or for any other appropriate reason.

- C. Continuing review of research must be substantive and meaningful. At continuing review, the IRB will decide whether the research continues to meet the criteria for IRB approval as set forth in 45 CFR § 46.111.
- D. NIH IRBs will review information provided by the PI about the number and types of vulnerable subjects enrolled and determine whether the protections for vulnerable subjects continue to be adequate (see SOP 14A “Research Involving Vulnerable Subjects (General Considerations)”).

9.4 RESEARCH STUDIES WHICH REQUIRE CONTINUING REVIEW

- A. Continuing review and re-approval of all non-exempt research studies, including those approved by expedited review (See SOP 7A “Requirements for Expedited Review of Research by NIH Institutional Review Boards”), is required at least annually as long as the study remains active, e.g., human subjects are engaged. Active studies include all non-exempt IRB approved research when, for example:
 - 1. Recruitment of subjects has not yet begun.
 - 2. There is active recruitment and enrollment of subjects.
 - 3. The study is no longer recruiting, but research remains active for long-term follow-up.
 - 4. Subjects have completed all research-related activities and data analysis of private identifiable information is ongoing; or
 - 5. Research is under suspension or administrative hold (e.g., recruitment or enrollment of subjects is suspended see SOP 11 “Suspensions and Terminations of IRB Approval and Administrative Holds”).

- B. Federal regulations and NIH policy do not provide for exceptions to the

requirement for continuing review; therefore, failure by the Principal Investigator to ensure timely IRB review and approval is a serious matter that could lead to suspension and possibly termination of the study (see Sections 9.12 and 9.13 below) regarding what may occur when IRB approval expires. Continuing research activity on an expired study is considered non-compliant with HRPP policies and regulations and must be reported as described in SOP 16A “Allegations of Non-compliance with Requirements of the NIH Human Research Protection Program (HRPP)”.

9.5 TIMING OF THE CONTINUING REVIEW SUBMISSION

- A. Continuing review and approval must be completed by midnight on the date on which IRB approval of the research study would expire (the “expiration date”). See Section 9.10 below, for the explanation of how the expiration date is determined.
- B. It is the PI’s responsibility to ensure that the review and IRB re-approval of ongoing research is conducted before the expiration date.
- C. As a courtesy, the IRB office sends at least two separate reminders to the PI of the expiration date.

9.6 CONTINUING REVIEW SUBMISSION MATERIALS

An IRB staff member, or a designee, will review each IRB submission package to determine that each of the required items has been submitted.

- A. Timing: Investigators should not submit continuing review materials too far in advance of the continuing review expiration date but close enough to the expiration date to ensure time to respond, if needed, to any stipulations/conditions.
- B. Materials: The PI must submit the following materials for continuing review:
 - 1. A completed NIH Intramural Clinical Research Protocol Continuing Review Application (see Attachment 1 “Intramural Clinical Protocol Continuing Review Application Form”).

2. A dated protocol, if changed from the previous year, with version number, page numbers, and all amendments incorporated.
3. The current IRB-approved informed consent/assent document(s), unless enrollment is complete.
4. If the PI intends to close the study, an Intramural Clinical Protocol Study Closure Application (see Attachment 2 "Intramural Clinical Protocol Study Closure Application").
5. Amendments to the protocol may accompany the continuing review submission but must be reviewed and approved separately.
6. Aggregated summary reports, as follows (numbers a-e, below, are also referenced in SOP 16 "Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations" regarding event reporting duties):
 - a. All Unanticipated Problems (UPs).
 - b. All Protocol Deviations (except those expected Protocol Deviations granted a waiver in the protocol - unless it is also a UP).
 - c. All Unanticipated Adverse Device Effects (UADE)
 - d. All Adverse Events (AEs) (including expected AEs, except those specified in the protocol and approved by the IRB as not reportable, i.e., granted a waiver, unless it has been determined by the PI or IRB that they are also UPs).
 - e. While preparing the continuing review application, the PI must assess whether expected AEs are occurring at greater frequency or severity than previously expected. If this occurs, the aggregate information may also qualify as a UP and must be reported as such (See SOP 16 "Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations").

- f. Any information in the literature, or evolved from similar research, that might affect the IRB's analysis of risk/benefit for the protocol. If such information is obtained before the time of continuing review, it should be reported to the IRB at the time that it becomes known, and summarized at the time of continuing review.
 - g. A summary of any research-related complaints from subjects.
- C. Any additional requirements of the NIH Human Research Protection Program.

9.7 PROCEDURES FOR CONTINUING REVIEW BY THE CONVENED IRB

- A. An IRB staff member, or a designee, will review each IRB submission package to determine that each of the required items has been submitted.
- B. NIH IRBs may elect to assign primary (and possibly secondary) reviewer(s) to conduct an initial review of the continuing review materials and present the findings at the convened IRB meeting (See SOP 7B for details). However, all IRB members are provided with and are expected to review the materials described in Section 9.6 above prior to the convened IRB meeting. At the convened IRB meeting, the primary and, if applicable, the secondary reviewer leads the IRB through the criteria for approval, using the IRB's continuing review checklist, as applicable.
- C. The complete IRB file for the particular protocol will be available to IRB members before, during, and after the IRB meeting.
- D. IRB members or the primary and if applicable secondary reviewer, if applicable (see SOP 7B "Requirements for the Conduct of Research Review at a Convened NIH Institutional Review Board (IRB) Meeting"), will:
 - 1. Confirm that the current consent/assent is still accurate and complete.

2. Consider if new or additional risks have been identified (e.g. unanticipated problems) that would require changes to the research study protocol, consent form, review frequency, etc.
 3. Consider if any new information may impact subjects' willingness to continue participation.
 4. Review the cumulative number of subjects accrued by gender and ethnic/racial category(ies) (see SOP 13 "Recruitment, Selection and Compensation of Research Subjects").
 5. Verify that no material changes have been made since the previous IRB review or determine that independent verification is needed. In making this determination, the IRB takes into account the risk level of the research study; whether the PI has previously failed to comply with IRB requirements; when materials submitted for continuing review include unapproved modifications or inconsistent information, or when the IRB has been informed of non-compliance by other sources.
 6. Determine if new NIH policies necessitate changes in the study and/or consent. Changes that do not impact subject safety or welfare may be stipulated for completion prior to the next continuing review or within a stipulated timeframe.
 7. Determine that each of the elements of 45 CFR 46.111 is satisfied.
 8. If applicable, determine that the requirements of Subpart B (Pregnant Women, Fetuses, Neonates), C (Prisoners), D (Children) are met.
- E. Each study that is scheduled for continuing review at a convened meeting is discussed and voted upon at the meeting (See SOP 7B "Requirements for the Conduct of Research Review at a Convened NIH Institutional Review Board (IRB) Meeting"). These votes may be by show of hands or by written ballot, which may be secret and the vote of a simple majority (more than half) of the voting members who are present is required. Additional voting requirements include the following:
1. Each regular member, including the Chair and Vice Chair, and

each alternate who is substituting for a regular member, has one vote, unless recused.

2. The Chair and Vice Chair count towards the quorum, unless recused, and either vote or abstain from voting on all actions for which votes are taken. Chairs and Vice Chairs will recuse themselves, as appropriate, when conflicts of interest exist.
3. Consultants do not vote (see SOP 2 “IRB Membership and Structure” for use and selection of consultants).
4. A vote that is cast by an individual on behalf of an IRB member is permitted only when that individual is an appointed alternate for an IRB member or category of members (see SOP 2 “IRB Membership and Structure”).
5. If circumstances require members’ participation by telephone or video conference, approval of the IRB Chair must be obtained in advance. Members attending by telephone- or video- conference count towards the quorum and may vote only if (1) they have received all pertinent material prior to the meeting and (2) they can participate actively and equally in the discussion of the research study. The IRB minutes must document that these two conditions are met (see SOP 4 “Human Research Protection Program (HRPP) Documentation and Records”).
6. Members with a real or perceived conflict of interest may not participate in IRB deliberations and will be required to leave the room during the IRB discussion and vote. They may be asked to provide information prior to deliberations but cannot be included in the quorum. (See SOPs 7B “Requirements for the Conduct of Research Review at a Convened NIH Institutional Review Board (IRB) Meeting” and 21 “Conflict of Interest Requirements for Researchers and Research Staff”, for definitions and examples of conflict of interest).

F. The IRB votes separately on new amendments that accompany continuing reviews.

9.8 IRB ACTIONS ON CONTINUING REVIEWS

The types of action possible at continuing review are the same as for initial reviews (see SOP 7B “Requirements for the Conduct of Research Review at a Convened NIH Institutional Review Board (IRB) Meeting”).

9.9 NOTIFYING THE PRINCIPAL INVESTIGATOR ABOUT IRB ACTIONS

The IRB will notify the PI in writing of the IRB’s determination. See SOP 7B “Requirements for Expedited Review of Research by NIH Institutional Review Boards” which provides additional detail regarding the possible IRB determinations including the following:

- A. Unconditional Approval
- B. Approval with Stipulations – The IRB may approve research with stipulations (conditions).
 - 1. The IRB should be careful to specify whether any conditions need to be satisfied before an investigator can continue particular research activities related to those conditions. For example, if at the time of continuing review, the IRB requires the investigator to change the research protocol to include a specific new procedure for screening prospective subjects, the IRB could approve the research with the following condition: research activities involving currently enrolled subjects may continue, but no new subjects may be enrolled until a designated IRB member reviews a revised protocol and verifies that the protocol includes the new screening procedure. Suspension of subject enrollment at the time of continuing review would not be considered suspension of IRB approval.
 - 2. After the PI has submitted a response to the IRB-stipulated changes, the IRB Chair or another IRB member or group of IRB members with appropriate subject matter expertise or experience designated by the Chair may approve the PI’s response to the stipulations.
- C. Deferred-The protocol is not approved and the PI’s responses to stipulations/conditions require review by the convened IRB.
- D. Tabled-The IRB determines the protocol is not approved because the IRB does not have sufficient information

- E. Disapproval-The IRB determines that it cannot re-approve a study as submitted.

The IRB communication to the PI will also indicate the next expiration date. The correspondence also reminds the investigator that changes in research activity may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to subjects.

9.10 SETTING THE CONTINUING REVIEW (EXPIRATION) DATE

- A. To determine the date of initial approval, see SOP 7B “Requirements for Expedited Review of Research by NIH Institutional Review Boards”.

- B. To determine the date of continuing review:

- 1. Setting the date of the first continuing review:

- a. For a study approved at initial review by the convened IRB without stipulations/conditions, the approval period starts on the date the convened IRB approved the research.
 - b. For a study approved at initial review with stipulations/conditions, the approval period starts on the date the Chair or designee approves and signs off on the stipulations/conditions.
 - c. For a study initially approved by expedited review, the approval period begins on the date the IRB Chair or IRB member(s) designated by the Chair gave final approval to the study.

- 2. Setting the date of the second and subsequent continuing reviews:

- a. No Fixed Anniversary Date: The date of the last IRB approval (with or without stipulations/conditions) determines the latest permissible date of the next continuing review (see Section 9.12, below), **OR**

- b. Fixed Anniversary Date: If the IRB conducts its continuing review and approves the study for a year-long time period and approves the study (with or without stipulations/conditions) within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing review must occur.
- c. At the time of initial and continuing review, the IRB will make a determination regarding the frequency of review of the research studies. All studies will be reviewed by the IRB at intervals appropriate to the degree of risk but not less than once per year. In some circumstances, a shorter review interval (e.g. biannually, quarterly, or after accrual of a specific number of participants) may be required (see SOP 7 “Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards (IRBs)”). The meeting minutes will reflect the IRB’s determination regarding the frequency of review (see SOP 4 “Human Research Protection Program (HRPP) Documentation and Records”).

9.11 CC OFFICE OF PROTOCOL SERVICES (OPS) ACTIONS FOLLOWING RECEIPT OF THE CONTINUING REVIEW APPLICATION FROM THE IRB

The OPS will extract required data from the continuing review application and enter it into the NIH Intramural Research Program database. Missing or incomplete information is resolved with the IRB office or the package is returned to the IRB.

For research conducted at the NIH CC, the IRB-approved consent/assent document(s) are posted on the NIH Clinical Research Studies web page. OPS will apply the IRB approval date to the first page of the approved consent document. The period of approval for use of the consent document will be indicated on the last page of the form and will read “THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM “X DATE” (IRB approval date) through “Y DATE” (IRB approval expiration date)

Upon completion of these activities, OPS will provide a signed copy of the NIH Continuing Review Application and the updated watermarked consent/assent document(s) to the IRB office and the PI.

9.12 LAPSES: WHEN THE IRB DOES NOT RE-APPROVE RESEARCH BY THE EXPIRATION DATE

9.12.1 NO PROVISION FOR A GRACE PERIOD

The regulations and NIH policy make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of research with or without stipulations/conditions must occur by midnight of the date when IRB approval expires. The IRB Chair and staff do not have the authority to extend the continuing review date of the research. Note that when the IRB re-approves research with stipulations/conditions at the time of continuing review before the expiration date of the preceding IRB approval period, IRB approval does not lapse even if the investigator needs additional time – beyond the date on which the preceding IRB approval would have expired – to satisfy some or all of the IRB's stipulations/conditions.

9.12.2 LAPSE IN IRB APPROVAL

A lapse in IRB approval of research occurs whenever an investigator has failed to provide continuing review information to the IRB or the IRB has not conducted a continuing review and re-approved the research - with or without stipulations/conditions - by the expiration date of IRB approval. For instance, if a IRB has conducted continuing review but tabled or deferred the research and the expiration date passes, the research has lapsed. However, if the IRB conducted continuing review and approved the research subject to stipulations prior to the date of expiration, the research has not lapsed. In such circumstances, all research activities (including recruitment, enrollment, consent, interventions, interactions, and data collection) must stop unless one of the following IRB actions is taken and documented in the minutes:

The IRB may allow all or a subgroup of already-enrolled subjects to continue in a research project during the period when IRB approval has lapsed if the IRB finds that continuation is in the best interest of the subjects. For example, the IRB may find that research interventions hold prospect of direct benefit to subjects or, alternatively, withholding study interventions may pose increased risk for subjects. The IRB must document its approval for the continuation of research for these subjects.

9.12.3 REPORTING LAPSES TO OHRP

A lapse in IRB approval is not required to be reported to OHRP as a protocol suspension or termination so long as no human subjects research occurs during this time period (aside from possible research performed in accordance with this policy in order to further a subject's best interest).

9.12.4 LAPSES AS NONCOMPLIANCE

If the IRB notes a pattern of non-compliance with the requirements for continuing review, the IRB should determine whether this represents serious or continuing non-compliance that needs to be reported within NIH as described in SOP 16A "Allegations of Non-compliance with Requirements of the NIH Human Research Protection Program (HRPP)".

9.13 ACTIONS WHEN IRB APPROVAL LAPSES AND RESEARCH EXPIRES

When the IRB Office has not received the Continuing Review Application or if the protocol has not been re-approved (with or without stipulations/conditions) by its expiration date, the IRB will notify the PI that all human subjects research under that protocol must stop and notify the OPS, ICD and OHSRP that IRB approval has expired.

9.13.1 ACTIONS AT THE CLINICAL CENTER

For protocols conducted at the NIH Clinical Center, the OPS will deactivate the research study from the NIH Clinical Research Information System (CRIS) and remove the consent/assent documents from the CC website.

In the event that the IRB has received the application, but not approved the action by the expiration date, the OPS will deactivate the research study from the NIH Clinical Research Information System (CRIS) and remove the consent/assent document(s) from the CC website for studies conducted at the NIH Clinical Center.

9.13.2 ACTIONS AT OTHER SITES OTHER THAN THE CC WHEN AN NIH IRB IS THE IRB OF RECORD

For expired protocols conducted at sites other than/or in addition to the Clinical Center, the IRB office:

- A. Notifies the PI that human subjects research, consistent with the requirements outlined in Section 9.12.1 above, must cease, and
- B. Notifies OHSRP and the IC Clinical Director that the protocol has expired.

REFERENCES

- A. 45 CFR 46:
<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>
- B. 21 CFR 56:
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?C FRPart=56>
- C. OHRP “Guidance on IRB Continuing Review of Research”, dated 11/10/10: <http://www.hhs.gov/ohrp/policy/continuingreview2010.html>
- D. FDA “Guidance for IRBs, Clinical Investigators and Sponsors: IRB Continuing Review After Clinical Investigation Approval, February 2012: <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294558.pdf>

LIST OF ATTACHMENTS

- A. Attachment 1: Intramural Clinical Protocol Continuing Review Application Form*
- B. Attachment 2: Intramural Application Supplements*

* These will be posted at a later time.
DHHS/NIH/OD/OIR/OHSRP