

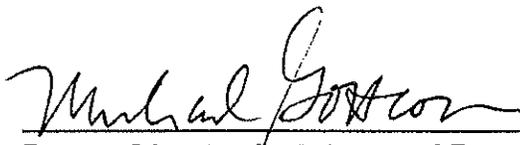
**HRPP STANDARD OPERATING PROCEDURE/POLICY APPROVAL &
IMPLEMENTATION**

OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

SOP Number: 9

SOP Title: CONTINUING REVIEW BY THE CONVENEED IRB

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

Approval:  2/17/17
Deputy Director for Intramural Research Date

Revision Implementation Date: 2-17-2017

Materials Superseded: SOP 9 (ver. 3) dated 3-8-2016
SOP 9 (ver. 2) dated 10-23-2013
SOP 9 (ver. 1) dated 6-27-2013

SOP 9 - CONTINUING REVIEW BY THE CONVENEED IRB

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SOP 9 - CONTINUING REVIEW BY THE CONVENEED IRB

9.1 PURPOSE

This Standard Operation Procedure (SOP) describes the policies and procedures for Continuing Review (CR) by the convened Institutional Review Board (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** below), NIH IRBs shall conduct CR of human subjects research at intervals appropriate to the degree of risk, but not less than once per year.

When conducting CR, 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 CR

- A. NIH IRBs conduct CR 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 CR as it does for Initial Review (IR) of 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). Note that the IRB’s CR for a protocol that’s remaining research activities include data analysis only may be performed as expedited review using an abbreviated process (**see 9.6.1 below**).

- B. CR occurs at intervals appropriate to the degree of risk, but not less frequently than once a year. The IRB must set the frequency for CR 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 CR 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. CR of research must be substantive and meaningful. At CR, 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 Principal Investigator (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 CR

- A. CR 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 (see **9.6.1** below for a discussion regarding the expedited continuing review process for ongoing data analysis); 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 CR; therefore, failure by the PI to ensure timely IRB review and approval is a serious matter that could lead to suspension and possibly termination of the study (see **9.12** and **9.13** below and SOP 11 - Suspensions and Terminations of IRB Approval and Administrative Holds) 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 CR SUBMISSION

- A. CR and approval must be completed by midnight on the date on which IRB approval of the research study would expire (the “expiration date”). See **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 CR 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 CR materials too far in advance of the CR expiration date but with enough time prior 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 CR except when the research satisfies expedited CR category 8(c) authorized by 45 CFR 46.110 (see **9.6.1** below): procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110

1. A completed “NIH Intramural Clinical Research Protocol Continuing Review Application” using the designated IRB submission system.
2. The current IRB-approved, 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 (submitted in the designated IRB system). For more information, see SOP 11A - Closure of an IRB-approved protocol.
5. The IC-approved Cumulative Inclusion Enrollment Report (CIER), (see SOP 13 - Recruitment, Selection and Compensation of Research Subjects).
6. Any data and safety monitoring reports for the last review period, such as Data and Safety Monitoring Board (DSMB) or Committee (DSMC) reports, as applicable (see SOP 17 - Data and Safety Monitoring).
7. Most recent Annual Report to the FDA (e.g. IND annual Report), as applicable (see SOP 15A - Research Regulated by the Food and Drug Administration (FDA): Information and Policies Specific to Research Involving Investigational New Drugs (Including Biological Products)).
8. Amendments to the protocol may accompany the CR submission but must be reviewed and approved separately. The separate vote approving the amendment must be documented in the Minutes of the IRB consistent with the requirements of SOP 4 - Human Research Protection Program (HRPP) Documentation and Records.
9. 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 CR 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 CR, it should be reported to the IRB at the time that it becomes known, and summarized at the time of CR.
- g. A summary of any research-related complaints from subjects.

9.6.1 EXPEDITED CONTINUING REVIEW SUBMISSION REQUIREMENTS WHEN THE PROTOCOL ACTIVITIES ARE LIMITED TO DATA ANALYSIS ONLY

This section applies only to expedited CR submission requirements when protocol activities are limited to data analysis.

In its "Guidance on IRB Continuing Review of Research", OHRP notes that the process for CR of research under expedited review category 8(c) can be accomplished through a simple, abbreviated process.

Under expedited review category 8(c) (see **References** below), an IRB may use an expedited review procedure to conduct CR when the only remaining human subjects research activity is the analysis of data that includes identifiable private information, and the IRB chair (or designee) determines that the research involves no more than minimal risk. This can be accomplished in a simple, abbreviated process provided that the CR submission to the IRB and must include statements that:

- A. No subjects were enrolled during the previous twelve months
- B. All subjects have completed all protocol visits or otherwise have withdrawn from the study
- C. No new data are being collected
- D. During the previous 12-month review period, there have been no adverse events, unanticipated problems, deviations, breaches of confidentiality, and no loss of specimens or data or other protocol-related problem that otherwise requires reporting to the IRB at the time of continuing review.
- E. 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 CR, it should be reported to the IRB at the time that it becomes known, and summarized at the time of CR.
- F. The IRB may require additional information by stipulation.

9.7 PROCEDURES FOR CR BY THE CONVENEED 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 a preliminary review of the CR materials and present the findings at the convened IRB meeting (See SOP 7 - Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards (IRBs) for details). However, all IRB members should be provided with and are expected to review the materials described in **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 CR 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 7 - 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. UPs) 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 Memorandum of Progress for the status of enrollment and retention of subjects to assess the consistency with the recruitment plan in the protocol (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 CR 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 CR 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 CR at a convened meeting is discussed

and voted upon at the meeting and documented in the IRB Minutes (e.g., see SOP 4 - Human Research Protection Program (HRPP) Documentation and Records, SOP 7 - Requirements for the Conduct of Research Review at a Convened NIH Institutional Review Board (IRB) Meeting and SOP 2 - IRB Membership and Structure).

- F. The IRB votes separately on new amendments that accompany CRs (see **9.6.B.8** above).

9.8 IRB ACTIONS ON CRS

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

9.9 NOTIFYING THE PI ABOUT IRB ACTIONS

The IRB will notify the PI in writing of the IRB’s determination. See SOP 7 - Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards (IRBs) .

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 CR (EXPIRATION) DATE

- A. To determine the date of initial approval, see SOP 7 “Requirements for Expedited Review of Research by NIH Institutional Review Boards”.
- B. To determine the date of CR:
 - 1. Setting the date of the first CR:
 - a. For a study approved at IR 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 IR 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 CRs:
- 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 CR (see Section 9.12, below), **OR**
 - b. Fixed Anniversary Date: If the IRB conducts its CR 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, as long as the expiration date does not exceed 365 days-1 day (see item c below).
 - c. At the time of initial and CR, 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 CR APPLICATION FROM THE IRB

The OPS will extract required data from the CR Application and enter it into the NIH Intramural Research Program database. OPS will tabulate data from IC-approved Cumulative Inclusion Enrollment Report (CIER). Missing or incomplete information is resolved with the IRB office or the package is returned to the IRB. The IRB may forward any concerns to the PI for resolution (such as incorrect

CIERs); and return the corrected documents to OPS upon receipt.

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 CR Application and the updated watermarked consent/assent document(s) to the IRB office and the PI (see SOP 12 - Requirements for Informed Consent).

9.12 LAPSES AND IRB APPROVALS WITH STIPULATIONS

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, CR 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 CR date of the research.

9.12.2 LAPSE IN IRB APPROVAL

A lapse in IRB approval of research occurs ~~when~~ ^{ever} 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 an IRB has conducted continuing review but tabled or deferred the research and the expiration date passes, the research has lapsed.

When a lapse occurs, research activities (including recruitment, enrollment, consent, interventions, interactions, data collection and data/sample analysis) must stop. However, the IRB has authority to allow continuation of research for some or all previously-enrolled subjects 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 IRB APPROVAL WITH STIPULATIONS

An IRB has authority to approve research with stipulations. When research is approved at CR with stipulations, the PI generally has thirty days to respond to the stipulations. The thirty days is counted from the date the PI is notified of the stipulations. An IRB has discretion to give a PI more than thirty days to respond to stipulations, consistent with this policy.

Research is not considered to have lapsed if the research is approved with stipulations before the expiration date and final IRB approval is obtained no more than thirty days after the expiration. The research is considered lapsed if stipulations are not approved by the IRB within 30 days after the expiration date. If an IRB approval with stipulations crosses over the expiration date, PIs should respond quickly to these stipulations to avoid a lapsed protocol.

If an IRB approves a CR with stipulations that go beyond the expiration date, the IRB must document in minutes whether all research in that protocol may continue or whether any conditions must be satisfied before an investigator can continue particular research activities related to those conditions.¹ Furthermore the IRB must promptly inform OPS of the IRB decision to extend the expiration date on the existing consent document, and the IRB must inform OPS of the extended expiration date. The completed CR must be submitted to OPS by the extended expiration date or the protocol will lapse on that date.

9.12.4 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

¹ For example, 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. Likewise, if at the time of continuing review, the IRB requires that the investigator, within 30 days, (a) change the informed consent document to include a description of a newly identified risk, and (b) submit a written plan for informing currently enrolled subjects about the new risk, 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 informed consent document and verifies that the description of the new risk has been added." Alternatively, the IRB could stipulate that no further research activities involving human subjects (including activities of already enrolled subjects) may occur after the date of the IRB's continuing review until the investigator has submitted, and the designated IRB member has reviewed and accepted as satisfactory, the revised informed consent document and the written plan for informing currently enrolled subjects about the new risk.

this time period (aside from possible research performed in accordance with this policy in order to further a subject's best interest).

9.12.5 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 CR 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, IC CD and OHSRP that IRB approval has expired.

9.13.1 ACTIONS AT THE CLINICAL CENTER

In the event that the IRB has not approved the Continuing Review (with or without stipulations) by midnight on 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?CFRPart=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>