

Policy Number: 18

Title: IRB Continuing Review and Calculating the Expiration Date

Date of Last Revision: 08/07/07, 01/29/09, 08/30/10, 06/05/13, 04/21/15, 09/01/15, 03/03/16, 06/01/16, 02/28/18, 03/08/18, 01/24/19

Policy:

It is the policy of the UC Irvine (UCI) Institutional Review Board (IRB) that research activities be periodically reviewed at intervals appropriate to the degree of risk.

I. Types of Review

A. Review by Full Committee

1. Research protocols initially reviewed by the full convened IRB Committee are reviewed by the full Committee at continuing review unless the study has been modified such that it can be reclassified as eligible for expedited review, as defined in the Federal regulations (See IRB Policy 13).
2. Research activities that previously met criteria for exempt or expedited review may change such that full Committee review would be required. This change in review criteria is prompted at the time of continuing review or review of a modification.
3. When conducting continuing review at a full IRB Committee, only one Reviewer is required. The Reviewer receives a copy of the Continuing Protocol Application (CPA) including a description of any modifications previously approved by the IRB, the complete protocol narrative, informed consent documents, and any monitoring or audit reports conducted since the last review. The full, convened IRB Committee discusses the protocol and makes a determination with a recorded vote.

B. Expedited Review

1. When conducting research under an expedited review procedure, the IRB Committee Chair or designated IRB subcommittee or HRP Staff Reviewer conducts the review on behalf of the full IRB Committee.
2. Research protocols that were originally reviewed using expedited review procedures may receive continuing review on an expedited basis, unless previously met criteria has changed since the previous IRB review and approval.
3. Abbreviated CPA: Research protocols that are eligible for an extended IRB approval (e.g., no more than minimal risk, not subject to federal oversight and not subject to the UCI Conflict of Interest Oversight Committee (COIOC)) review will undergo an abbreviated version of the CPA. The abbreviated CPA prompts the LR to confirm currently registered information about the research, as well as the status of enrollment. The LR can upload any relevant documents that the study team may want reviewed as part of the CPA.
4. Research protocols that were originally reviewed by the full, convened IRB Committee but currently meet the following criteria may receive expedited review by the IRB Committee Chair or designated IRB subcommittee (excluding an HRP Staff Reviewer):
 - a. The research is permanently closed to the enrollment of new participants; and
 - b. All participants have completed all research-related interventions; and
 - c. The research remains active only for long-term follow-up of participants; or

- d. No participants have ever been enrolled at UCI and no additional risks have been identified; or
 - e. The remaining research activities are limited to data analysis.
- C. Exempt Research Activities
1. Exempt confirmation may be granted for no more than three (3) years. An abbreviated version of the CPA may be submitted to continue the research.

II. **IRB Continuing Review Criteria**

- A. Continuing review must be substantive and meaningful. The approval criteria for continuing review (including the abbreviated CPA) are the same as that for initial review (See IRB Policies 13 and 14 for details). Therefore, it is the responsibility of the IRB to determine that:
1. Risks to subjects continue to be minimized and reasonable in relation to the anticipated benefits;
 2. Selection of subjects continues to be equitable;
 3. Informed consent continues to be appropriately obtained and documented;
 4. There are significant new findings that might relate to participants' willingness to continue participation and whether they were/should be provided to participants;
 5. Adequate provisions for monitoring the data collected to ensure the safety of the subjects is provided, when appropriate;
 6. Adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data, is provided, when appropriate; and
 7. Appropriate safeguards for vulnerable populations are provided.
- B. The IRB will determine the need for verification from outside sources on a case-by-case basis and according to the following criteria:
1. Complex protocols involving unusual levels or types of risks to participants;
 2. Protocols conducted by Lead Researchers who previously have failed to comply with Federal regulations or the requirements or determinations of the IRB; and/or
 3. Protocols where concern about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources.
- C. To allow adequate time for IRB review and to avoid any unnecessary delays, the Lead Researcher (LR) submits an electronic CPA to the IRB preferably 60 days for full Committee and 30-45 days for Expedited or Exempt prior to the IRB expiration date. The CPA includes a status report on the progress of the research, including confirmation of or an explanation relating to the following:
1. The current status of enrollment;
 2. No changes have been made without prospective UCI IRB review and approval;
 3. There have been no Unanticipated Problems or subject complaints that require reporting to the UCI IRB;
 4. ClinicalTrials.gov registration status, as applicable;
 5. The maximum number of participants approved by the UCI IRB to be consented for the life of the study;
 6. The total number of participants consented since the previous IRB continuing approval;
 7. The total number of participants consented to participate to date (this figure includes any withdrawals by participant, LR or sponsor or screen failures – including the reasons for withdrawal);
 8. The total number of participants consented to participate to date breakdown by gender (if collected) and by age group (e.g., adults, minors);

9. A detailed description of the progress of the study, including a brief summary of any interim findings or trends, and plans for the next approval period;
 10. There is no new information relating to the circumstances of consent that may raise concern for subjects;
 11. All new findings that have developed since the last continuing review have been provided to subjects, as appropriate and applicable;
 12. The research team is using the most recently IRB approved consent documents;
 13. All signed consent documents are on file and available for inspection;
 14. Specificity if any subjects were enrolled using a non-English consent document, including the language in which the subject was consented;
 15. Any internal and/or external audits;
 16. Any recent relevant literature;
 17. Specificity if there has been a change in risk / benefit assessment;
 18. Any Data and Safety Monitoring reports;
 19. Current version of Investigator's Brochure;
 20. Specificity if there has been a change in the financial interests of researchers;
 21. Any other relevant information, especially that may impact the risk/benefit ratio (including multi-center reports or other progress reports);
 22. In addition, the LR may provide the following documentation:
 - b. Most recent Data Safety Monitoring Board report and/or most recent group-wide progress report, if available.
 - c. *DHHS-funded studies only* – latest version of the DHHS grant application.
 23. HRP staff will provide:
 - a. A copy of the current, IRB approved protocol narrative;
 - b. A copy of the current, IRB approved informed consent documents;
 - c. A summary of any Unanticipated Problems involving risks to participants or others that occurred over the last approval period.
 24. Informed Consent Documents (ICDs) - Review of the currently approved ICD must ensure that the information is still accurate and complete. Any significant new findings that may relate to the participant's willingness to continue participation should be provided to the participant in an updated ICD. Review of currently approved or proposed ICDs occur during the scheduled continuing review of research by the IRB, but may be done more frequently if new information becomes available.
- D. Modifications to Protocol may be submitted at Time of Continuing Review - Modifications or revisions to a research protocol may be submitted at the time of continuing review. The Committee will typically first review and approve the Continuing Protocol Application prior to reviewing the Modification request. Revisions must not be implemented by an Investigator prior to review and approval by the IRB.
- E. Seven-Year De Novo Review Requirement - In order to ensure that research protocols continue to meet current regulatory and institutional standards, *for protocols involving greater than minimal risk*, every seven years, protocols will be required to undergo a "Seven-Year De Novo Review."
1. The Lead Researcher and Administrative Contact listed on the protocol will receive an auto-generated seven-year reminder memo explaining the Seven-Year De Novo review requirement via email approximately 90 days prior to the expiration date.
 2. During the IRB's Seven-Year De Novo review(s), the IRB will require that all documents be incorporated into the current UCI templates. This may involve providing new information that has not been previously requested and therefore, not previously reviewed by the IRB.
 3. As with any review, studies are subject to meet all current regulatory requirements, UC/ UCI policies and procedures.

4. Protocols that do not require Seven-Year De Novo Review:
 - a) Research that involves no greater than minimal risk (e.g., protocols that underwent an expedited review)
 - b) Continuing review of greater than minimal risk research where:
 - (1) the research is permanently closed to the enrollment of new subjects;
 - (2) all subjects have completed all research-related interventions; and
 - (3) the research remains active only for long-term follow-up of subjects; or
 - c) Continuing review of greater than minimal risk research where the remaining research activities are limited to data analysis.

III. IRB Approval of Continuing Review

- A. The IRB conducts continuing review of all research proposals at intervals appropriate to the degree of risk.
 1. Full Committee Review. Research that meets the criteria for full Committee review is reviewed within one year of the date of the full, convened IRB meeting at which the research was approved (or required specific minor modifications).
 2. Expedited Review. Research that meets the criteria for expedited or exempt review is reviewed within one year of the date that approval was granted by the IRB Chair or designated IRB subcommittee – with the following exception.
 - a) Extended 3 Year IRB Approval
UCI's Federalwide Assurance (FWA# 00004071) allows some flexibility in applying human subjects federal regulations to non-federally supported research. As such, effective September 2012 the UCI's Human Research Protection Program will implement a procedure for granting IRB approval for up to 3 years. See Policy # 13.
 3. Exempt Review. Research that is confirmed exempt is registered for no more than three (3) years. A CPA may be submitted to continue the research.
- B. Research may be restricted, modified, or halted altogether based on continuing review by the IRB Committee. A determination of "minor revisions required" or "tabled for re-review" is given to all studies in which the IRB requests changes to current documents during Continuing Review. IRB approval is not granted until all requested changes to previously approved documents are completed by the Investigator, or by the HRP administrative staff, and reviewed and approved by the IRB. This does not extend the expiration period.
- C. Based on the IRB continuing review, previously imposed restrictions may be relaxed or additional restrictions may be imposed.

IV. Expiration of IRB Approval

- A. There is no grace period extending the conduct of the research beyond the expiration date of IRB approval. The study expires at midnight of the date specified on the approval letter and the informed consent document.
- B. If the IRB does not re-approve the research by the specified expiration date, study activities must cease, pending re-approval of the research by the IRB.
- C. Once notified of the expiration, if the Investigator feels that stopping ongoing research-related interventions or interactions would jeopardize the rights or welfare of current subjects, the Investigator must immediately submit to the IRB Chair or IRB Vice-Chair or their designee(s) a request to continue to treat active subjects. The request must include an explanation of how discontinuing the research subjects from the protocol would cause harm.

- D. The IRB Chair or IRB Vice-Chair or their designee(s) review the request and allows individual subjects to continue participating in the research interventions or interactions only when the IRB determines that it is in their best interests. However any information collected during the lapse in approval may not be used for research.
- E. Enrollment of new subjects cannot occur after the expiration date.

References:

45 CFR 46.109(e)

45 CFR 46.110

OHRP Guidance on Continuing Review, July 11, 2002

21 CFR 56.109

21 CFR 50.25(b)(5)

Procedure Number 18.A

Title: Procedure for IRB Continuing Review

Procedure:

This procedure outlines the requirements for continuing review of previously approved human subjects research by the UC Irvine (UCI) Institutional Review Board (IRB).

I. Lead Researcher (LR) Responsibilities

- A. The LR completes the CPA.
 - 1. The Investigator verifies all pre-printed information contained within the CPA, submitting corrections as needed.
 - 2. The LR completes and electronically submits the CPA and all applicable documentation preferably 60 days for full Committee and 30-45 days for Expedited prior to the IRB expiration date to allow adequate time for IRB review and to avoid any unnecessary delays or lapse in approval.
- B. Continuing review of ongoing research is required until the criteria for study closure apply (See Policy 20). The study may be closed via the CPA.
- C. If a study expires, the LR will cease all research activities as instructed in the expiration notice. The LR should immediately submit a CPA with the required documentation to continue the research or notify the IRB of study closure.
- D. If stopping ongoing research-related interventions or interactions would jeopardize the rights or welfare of current subjects, the Investigator must immediately submit to the IRB Chair or Vice-Chair a request to continue to treat active subjects. The request must include an explanation of how discontinuing the research subjects from the protocol would cause harm.

II. IRB Committee Responsibilities

- A. Review Criteria
 - 1. All continuing review determinations are completed using the criteria found in 45 CFR 46.111 and 21 CFR 56.111 for approval of research. The Primary Reviewer documents the review of criteria using the "Reviewer's Checklist" and any other "Supplementary Reviewer's Checklist", as applicable.
 - 2. Research activities initially reviewed by the full IRB Committee are again reviewed by the full IRB Committee (See IRB Policy 14 and IRB Procedure 14.A), unless:
 - a. The study has been modified and is now eligible for expedited review as defined in the regulations (e.g., change in risk to minimal); or
 - b. The study meets one of the following expedited review criteria:
 - (1) The research is permanently closed to the enrollment of new participants; and
 - (2) All participants have completed all research-related interventions; and
 - (3) The research remains active only for long-term follow-up of participants; or
 - (4) No participants have ever been enrolled at any site and no additional risks have been identified; or
 - (5) The remaining research activities are limited to data analysis.
 - 3. Research activities that were originally reviewed using expedited criteria may receive continuing review on an expedited basis, unless the research activities no longer meet the expedited criteria for review and approval.
 - 4. Research activities that had previously met criteria for expedited review may change with the review and approval of modifications, such that full IRB Committee review

would be required at the time of continuing review (e.g., risk has changed to be greater than minimal).

5. In addition to the completed CPA and applicable continuing review documents submitted by the Investigator, the Reviewer and Committee Members receive a copy of the current IRB approved Protocol Narrative, current IRB approved Informed Consent documents, any supporting documentation such as a Sponsor's Protocol, Investigator's brochure, and copies of any monitoring reports conducted since the last review. All members have access to the protocol file and relevant minutes.
 6. Review of the currently approved consent document must assure that the information is still accurate and complete. Any significant new findings that may relate to the participant's willingness to continue participation is provided to the participant in an updated consent document. Review of currently approved or proposed consent documents must occur during the scheduled continuing review of research by the IRB, but may be done more frequently if new information becomes available.
- B. Continuing Review Approval Period
1. The IRB Committee approval period for Continuing Review is the same as initial Committee Review provided that the continuing review occurs annually.
 2. For research reviewed and approved by the full Committee at a convened meeting, the approval period starts on the date of the convened meeting. The expiration date (the last day the research is approved) is the last day of the approval period. (For example, if the IRB approves the research on April 12, 2005 for one year, the approval period is April 12, 2005-April 11, 2006.)
 3. For research that was determined by the full Committee to require minor modifications, the approval period begins on the date a Reviewer, usually the IRB Chair, verifies that the investigator has made the revisions requested by the full Committee. (For example, if the IRB determines that minor modifications are required on April 12, 2005 and approval is for one year period if a reviewer verifies the changes on April 27, 2005, the approval period is April 27, 2005-April 11, 2006.)
 4. In all cases the expiration date (the last day the research is approved) is the last day of the approval period. Research may be conducted on the expiration date, but may not be conducted after the expiration date without re-approval. (For example, if the approval period is April 27, 2005-April 11, 2006, the expiration date is April 11, 2006. Research must stop at midnight April 11, 2006 unless the Investigator received re-approval of the research.)
 5. Expedited Review: Research that meets the criteria for expedited review is approved for one year from the date approval is granted by the IRB Chair or designated IRB subcommittee, unless eligible for an extended three year approval.
- C. If the IRB determines that it needs verification from sources other than the Investigator that no material changes have occurred since the previous IRB review, the IRB may request an independent assessment of information or data provided in the renewal application.
1. The scope and extent of such an independent assessment is determined on a case-by-case basis.
 2. Sources for such outside information could include:
 - a. Compliance review from the HRP EQUIP team or designee;
 - b. Corroboration from School Deans, Department Chairs, Sponsors, other Clinical Research Organizations and other IRBs at collaborating institutions;
 - c. Copies of FDA audits;
 - d. Literature searches conducted by clinical librarians;
 - e. Reports from subjects or study staff; or
 - f. Directed audit at the direction of the IRB Committee or the HRP Executive

Director or designee.

3. Determining Appropriate Interval for Continuing Review - Appropriate continuing review intervals are addressed with each review conducted by the IRB. The following factors are taken into consideration when determining the appropriate review interval, but are not limited to:
 - a. Involvement of vulnerable populations;
 - b. Research conducted internationally;
 - c. Involvement of recombinant DNA or other types of gene transfer protocols;
 - d. Research for which participants would be exposed to additional risks, e.g. breach of confidentiality, phase I studies, disproportionate number or severity of unanticipated problems;
 - e. Previous Investigator Holds or Suspensions of the research due to compliance, record-keeping or other concerns; and/or
 - f. Recommendations from other Institutional committees.
- D. Expired Study
1. The IRB Chair and/or IRB Committee addresses on a case-by case basis, those instances where discontinuing intervention and interaction because of study expiration would seriously jeopardize the safety or well-being of an individual (e.g., discontinuing therapy may cause more harm to the participant or they may receive the same therapy off study).
- E. Calculating the "Date of IRB Expiration"
1. Approval at a convened IRB Committee meeting - The date of expiration is calculated from the date of the convened IRB Committee meeting. For example, if the committee meeting date is 2/01/2005, then the "Date of IRB Expiration" is 1/31/2006 (one year minus one day) for a 12 month review interval.
 2. Minor revisions required at a convened IRB Committee meeting - The date of expiration is calculated from the date of the convened IRB Committee meeting. It is not calculated from the date the Chairperson or his or her designee verifies and grants final approval. For example, if the committee approves pending changes on 2/01/2005 and the LR's response is reviewed by the Chair on 3/1/2005, then the "Date of IRB Expiration" is 1/31/2006 for a 12 month review interval (one year minus one day) and 7/31/2006 for a 6 month review interval (six months minus one day).
 3. Expedited review - Since there is no convened meeting in an expedited review, the "Date of IRB Expiration" will be calculated based on the review interval determined by the Chair or designee using the date that the initial IRB application or most recent Continuing Review Application was approved by the Chair or designee. For example, if the Chair requires minor revisions on 2/01/2005 and the LR's response is reviewed by the Chair on 3/1/2005, then the "Date of IRB Expiration" is 2/28/2006 for a 12 month review interval (one year minus one day).
 4. Modifications - The approval date of an amendment does not affect the calculation of the expiration date unless the Committee decreases the review interval.
 5. As noted in Policy # 34, HRP Staff will not stamp the date of IRB expiration on the Informed Consent Documents.

III. HRP Staff Reviewers

- A. HRP Staff Reviewers are delegated the authority to conduct continuing review of minimal risk research protocols. Expedited continuing review applications are accepted on a rolling basis and are administratively reviewed by an HRP Staff Reviewer in consideration of the expiration date.

- B. Delegation is provided in the HRP Staff Reviewer Delegation of Authority document maintained on the HRP WIKI page – and signed by the IRB Chairs for A, B and C, as well as the Executive Director of Research Protections.
 - 1. An HRP Staff Reviewer is defined as follows:
 - a) **HRP STAFF REVIEWER:**
 - (1) **Tier 1:** Administrator or above, CIP or CCRP certified and appointed as IRB members or alternate members may review and approve transactions related to exempt and expedited level protocols. Exceptions are noted as applicable.
 - 2. An HRP Staff Reviewer (**Tier 1**) may review and approve expedited continuing review applications except under the following conditions:
 - a. Category 1: Clinical studies of drugs and medical devices
 - b. Category 9: Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified
 - c. Other FDA-regulated protocols (e.g., Humanitarian Use Device protocols)
 - d. Protocol involving serious or continuing noncompliance or Unanticipated Problem reported during last approval period
 - e. Increase in risk/decrease in benefit reported during last approval period
 - f. Review required more frequently than annually
 - g. Renewals with a positive disclosure of financial interest

IV. IRB Analyst or Higher Responsibilities

- A. Assuring Continuing Review Completion
 - 1. The Human Protocol System (HPS) database automatically sends the LR and Administrative Contact (AC) a reminder notice 90 days prior to the expiration date of the study for full committee studies and 60 days prior to the expiration date of the study for expedited studies.
 - 2. When the continuing IRB approval is not received prior to the study expiration date, HPS automatically sends a notice of study expiration to the LR and AC.
- B. The Analyst performs a pre-review of the documents submitted for completeness and to verify the type of continuing review in which the study is eligible.
- C. The Analyst provides the following for review:
 - 1. A copy of the current, IRB approved protocol narrative;
 - 2. A copy of the current, IRB approved informed consent documents; and
 - 3. A report of all reportable events/problems provided by the LR since initial IRB approval.
 - 4. A summary of any unanticipated problems involving risks to participants or others that occurred over the last approval period.
- D. The Analyst proceeds with preparing the continuing review documents accordingly.
 - 1. Studies requiring expedited continuing review are provided to the Chairperson or designated IRB subcommittee members or a HRP Staff Reviewer for review and approval.
 - 2. Studies requiring full IRB Committee review are assigned a Reviewer and placed on the next available Committee agenda.
- E. The IRB "Reviewer's Checklist" and any "Supplemental Reviewer's Checklists" are completed and signed by the Reviewer.
- F. Letters requesting reviewer revisions and approval letters are drafted using the

- appropriate template.
- G. Appropriate HPS database entries are completed.

V. **IRB Analyst Responsibilities**

- A. Upon notification of submission of the CPA, the Analyst imports the information into HPS, prints all submitted documents, and assures submission of the proper documents (e.g. a completed continuing protocol application, a copy of the most recently approved protocol narrative and informed consent documents.)
- B. The Analyst requests the IRB protocol file and places the new submitted documents in the IRB file. The Analyst will at times review expedited research. As such, the Analyst will either review the submission, or forward to HRP staff.
- C. Once the continuing approval is received, the Analyst:
 - 1. Electronically stamps the informed consent documents, copies original approval letter and all approved documents.
 - 2. Notifies the LR and Administrative Contact via email when the approval documents are available.
 - 3. Complete appropriate HPS database entry and collate the file.
 - 4. Returns the file to shelf for filing.

References:

IRB Policy 13, "IRB Review of Human Subjects Research – Expedited"

IRB Procedure 13.A, "Procedure for IRB Review of Human Subjects Research – Expedited"

IRB Policy 14, "IRB Review of Human Subjects Research - Full Committee"

IRB Procedure 14.A, "Procedure for IRB Review of Human Subjects Research - Full Committee"