University of California, San Diego
Human Research Protections Program
Institutional Review Board
Standard Operating Policies and Procedures

Section 3.12
Protocol Amendments

Policy

All modifications/changes in a project must be received and approved by the Institutional Review Board (IRB) ***before*** they are initiated except where necessary to eliminate apparent immediate hazard to the subject. Requests for approval of modifications/changes may be submitted at any time by the Principal Investigator (PI) during the active, approved period of a study.

The modification is reviewed by the IRB Chair or the IRB Chair's designee and a determination of whether convened IRB review is necessary is made.

A modification/change to a project may require a NEW application when the modification/change is to two or more of the following three items: a) the purpose of the study; b) the population involved in the study; or c) the procedures associated with the study.

Major modifications/changes are reviewed through a convened IRB review process. Examples of modifications considered to be major in nature include escalation in the drugs(s) dosage(s), the introduction of an additional drug(s); the addition of a new invasive procedure. Major modifications may impact on the risk/benefit ratio in the study. It is the investigator's responsibility to assess the degree of change in procedures and risks of the study.

Federal guidelines include that "An IRB may use the expedited review procedure to review…minor changes in previously approved research during the period (of one year or less) for which approval is authorized." [45 CFR 46.110(b)(2)]. The review will be carried out by the IRB Chair or his/her designee(s). If the Chair or designee believes that the "minor" modification is too substantive to receive this type of review, the submission will be referred for convened IRB review. Minor modifications that *may* receive expedited review include minor changes in recruitment materials/procedures; correction of typographical and grammatical errors or editorial revisions that do not change the meaning of the study document; change in compensation for participation if not considered to be coercive; addition of new study site; and translations of materials previously reviewed and approved by the IRB.

For protocols involving investigational drugs or devices, an amendment or protocol change intended to eliminate an apparent immediate risk or danger to participants may be implemented immediately provided the FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with 21 CFR 56.104(c). Any amendment provided under these circumstances must undergo convened IRB review at the earliest

opportunity. The review will also include a determination whether each change was consistent with ensuring the participants' continued welfare.

Changes in study sites, investigators, and/or key personnel must also be reported to the IRB. The submission requesting modifications/changes includes a cover letter, and may involve revised application Facesheets, revised Research Plan and consent documents or use the Cover Letter For Request Change/Modification--Key Personnel Changes Only form. In the case of a change in the PI, the cover letter should be signed by the investigator who holds the approval. In addition, a letter signed by the "new" PI should also be provided that indicates the "new" accepts the role of PI and the responsibilities associated with that role.

Process for Conducting Amendment Requests

When reviewing project amendments, the IRB will assess all of the same criteria for approval that were evaluated during initial review. When an amendment is reviewed at the IRB meeting, at least one IRB member is provided with and reviews the complete protocol. The e-IRB process involves conversion of documents to PDFs for electronic review so that all documentation is also made available to all members of the IRB when the meeting agendas are posted. Information is made available to other IRB members who wish to review the project or whose expert review is requested. The PI must submit the following materials to the HRPP office to request modifications/changes to an approved study:

1. A cover letter that contains the project number, title, name of principal investigator, and should specifically state that an amendment to the currently approved study is being requested. The cover letter should clearly detail what the modification is, why it is being requested, and any potential changes to risks to subjects, risk/benefit ratio, risk management procedures, etc. If revisions have been made to study documents, the cover letter must provide an outline of those revisions as well as why those revisions are being made. The cover letter must be provided over the PI's signature. It is strongly suggested that the Amendment Request Cover Letter form be used.
2. If a change is only being made to key personnel associated with the study, Cover Letter For Request Change/Modification--Key Personnel Changes Only can be used. This cover letter can be used for making changes to key personnel associated with the study only where those changes do not require revision of the consent/permission/assent form(s) and/or the change is not to the PI of the study. Revised Application Facesheets and Research Plan documents would not be required to be submitted until the next submission of either or both of these documents, when the revised document(s) would need to reflect the current personnel and appropriate information about those personnel.
2. Revised application Facesheets, if applicable. The revised Facesheets must be signed and dated by the PI. If a change in the study PI is being requested, revised application Facesheets reflecting the change in PI that is signed and dated by the incoming PI and Department Chair must be provided.
3. Revised Research Plan, if applicable. Two copies of a revised Research Plan are required. One copy must clearly and specifically highlight all the changes made to the document including additions and deletions by using the track changes function in Microsoft Word (or a similar function in other word processing software), and one clean copy of the document must be submitted.

4. Revised consent/permission/assent forms, if applicable. Two copies of the revised document(s) must be submitted. One copy must clearly and specifically highlight all the changes made to the document including additions and deletions by using the track changes function in Microsoft Word (or a similar function in other word processing software). Consent/permission/assent forms are stamped by the HRPP once they have been approved; therefore, the second copy submitted should be a clean copy of the revised consent/assent with a 2-inch by 2-inch "content free" space on the upper left-hand corner of the first page of the document and the lower right-hand corner on the remaining pages for appropriate placement of the IRB stamp-of-approval.
5. Additional information including updated Master Protocol, Investigator's Brochure, package insert, recruitment flyers, if applicable. Two copies must be provided, one that highlights the changes and one clean copy, as noted above.

The amendment request submission should contain sufficient information to permit determination of the current risk-benefit assessment based on study results. Special attention should be paid to determining whether new information or unanticipated risks were discovered. Any significant new findings that may relate to the subjects' willingness to continue participation should also be included.

All necessary information relevant to the assessment of the project's risks and benefits to study participants will be reviewed by the assigned IRB reviewer, or Chair or designee in the case of an expedited review.

Based on its review of the above information, the convened IRB determines for each approved research protocol whether the amendment is approved, requires modifications to secure approval, or is disapproved based on assessment of the amendment risks and benefits. The IRB may also require appropriate changes to the Research Plan and/or informed consent/assent forms content, frequency of continuing review, level of safety monitoring, and may determine whether the project requires verification from sources other than the investigator that no material changes have occurred since previous IRB review. The IRB will vote upon the recommendations made by the reviewers and will determine the frequency of review.

For expedited review, the Chair or designee will determine for each amendment request whether the amendment can be approved or requires modifications to secure approval based on assessment of the project's risks and benefits. Appropriate changes to the informed consent/assent form content and/or Research Plan may also be requested.

Applicable Regulations

21 CFR 50.25(b)(5)
21 CFR 56.108(a)(4)
21 CFR 56.108(b)(1)
21 CFR 56.109 (f)
21 CFR 56.110(b)
21 CFR 812.150(a)(6)
45 CFR 46.109(e)
OHRP Guidance: Continuing Review
Amendment Request Cover Letter form
Cover Letter for Request Change/Modification--Key Personnel Changes Only