IRB Approval of Research with Stipulations

SOP 114.2
Revised: December 18, 2015

Purpose and Scope

This Standard Operating Procedure (SOP) documents the procedures related to Approvals with Stipulations.

This SOP is written to comply with applicable federal regulations including:

- U.S. Department of Health and Human Services (DHHS) 45 CFR Part 46 (Common Rule);
- U.S. Food and Drug Administration (FDA) 21 CFR Part 56; and
- “Guidance on IRB Approval of Research with Conditions” (DHHS November 10, 2010).

This SOP is also written to comply with:

- UH Federalwide Assurance (FWA00003526).

This SOP applies to all research undergoing initial or continuing review by any of the IRBs operating under the auspices of UH. It also applies to IRB review of proposed modifications to an IRB-approved protocol.

Background

Under federal regulation the IRB has the authority to approve or disapprove applications for initial or continuing protocol review or changes to previously approved research. The IRB can also defer (or table) a decision to approve or disapprove research pending further review of the study and any clarifying information or new or modified study documents provided by the Principal Investigator (PI).

Further, the IRB has regulatory authority to approve the research with conditions that must be satisfied before full IRB approval of the proposed research can be secured. The UH HSP refers to such approvals as “approvals with stipulations,” which is the focus of this SOP.

Definitions

Federal regulations require that the IRB or expedited reviewer must determine that all of the requirements for approval under 45 C.F.R. 46 and 21 C.F.R. 50 are satisfied before IRB approval can be granted. If the IRB cannot make all the determinations, as appropriate to the study, federal regulations do not permit the IRB to approve the research. Such research must be disapproved, deferred or approved with stipulations until changes are made that satisfy all of these approval criteria, as applicable.

- **Disapproval**: When the study does not meet the approval criteria (1.1 through 1.5 above and 1.6, 1.7 and/or 1.8 as appropriate) or when changes required for a study to meet these criteria

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are so substantial that major changes to the design, methods and/or informed consent sections of the protocol will be necessary, the IRB should disapprove the study.

- **Deferral**: When clarification(s) or additional documentation is required to determine whether a study meets the approval criteria (1.1 through 1.5 above and 1.6, 1.7 and/or 1.8 as appropriate), the IRB should defer the study pending receipt of the required information/ documentation from the PI.

  Following are examples of conditions/requests that would require a "Deferral":

  1. Provide a justification for randomizing subjects to the placebo arm of the study.
  2. Clarify whether minors will be enrolled in the research and, if so, describe additional safeguards that will be provided to protect them.
  3. Provide a description of procedures that the control group will undergo.
  4. Provide a consent form for the teachers who will be asked to participate in the study.
  5. Provide a plan for monitoring the safety of subjects.

- **Approval with Stipulations**: A determination of "approval with stipulations" is permissible under federal regulations when the IRB required the PI to:

  1. Make specific changes to the research protocol or consent form(s),
  2. Verify specific assumptions or understandings on the part of the IRB regarding how the research will be conducted, or
  3. Submit additional documents (e.g., certificate of ethics training)…

     …<u>such that, based on the assumption that the stipulations are satisfied, the IRB is able to make all of the determinations (1.1 through 1.5 above and 1.6, 1.7 and/or 1.8 as appropriate) required to approve the study</u>.

  Following are examples of conditions/ requests that could be required under an "Approval with Stipulations":

  1. Remove the placebo arm of the study.
  2. Verify the IRB's understanding that no minors will be enrolled in the study.
  3. Provide additional detail on how the prisoners' privacy will be protected.
  4. Verify the IRB's assumption that the procedures that the control subjects will undergo are the same as those for experimental subjects.
  5. In the consent form, under "Risks," add "headache" and "nausea."
  6. Remove the description of compensation for participation in the research from the "Benefits" section of the consent form, and place it under the "Voluntary Participation"
  7. In the protocol, explain in greater detail how the confidentiality of identifiable private information about participants will be protected.

Procedures

I. When proposed research is approved with stipulations, the IRB will identify the individual(s) who are authorized to review the PI's response and determine whether it satisfies the IRB's requirements.
   a. The individual(s) may be the IRB Chair, the primary reviewer, another member of the IRB, or the HSP staff.

II. In general, research activities involving human subjects may not be initiated until the stipulations placed by the IRB have been satisfied and the approval becomes effective. However, the IRB may make specific determinations allowing certain aspects of the research, not affected by the stipulations, to commence while the response to stipulations is being developed or reviewed.
   a. For example, if the stipulations pertain to children as research participants, the IRB may determine that activities pertaining to adults may commence.

III. When the full IRB or expedited reviewer approves an IRB application with stipulations, the HSP staff will email a written notice of this action to the PI or the PI's designee within five (5) business days of the determination.
   a. The written notice will explain each of the IRB's stipulations in sufficient detail to enable the PI to fully understand the IRBs requirements.
   b. The written notice will explain that under an "approval with stipulations," proposed study activities, whether or not they are affected by the stipulations, cannot be initiated until the notice of full approval is received from the HSP.
   c. The IRB can allow certain activities proposed in the research application to commence if they are not related to the stipulations.
   d. Such determinations will be clearly spelled out in the letter to the PI and in the meeting minutes.

IV. Approvals with stipulations made by the IRB will be documented in the IRB meeting minutes and will include a comparable level of detail provided to the PI in the written notice.
   a. Meeting minutes will specify who is responsible for reviewing and accepting the PI's response.
   b. Approvals with stipulations made by an expedited reviewer will be documented on the expedited review coversheet or in an email(s) from the reviewer.
   c. This documentation will be maintained in the project file.

V. The PI should submit a written response to the IRB's stipulations within one month of receipt of the IRB's stipulation notice.
   a. The response must be signed by the PI or the PI's designee.
      i. An email from the PI or the PI's designee will be accepted in lieu of a signature.
   b. The response can be emailed to the UH HSP at uhirb@hawaii.edu.

VI. When an approval with stipulations applies to a ***continuing review (renewal)*** application or to a ***modification*** request, and IRB approval for the study expires prior to satisfaction of the stipulations and effective re-approval, study activities must stop.
   a. Study activities necessary to remove apparent immediate hazards to study participants may continue;
      i. The PI is required to immediately notify the IRB when study activities continue in order to remove an apparent immediate hazard.
         1. The PI must justify to the IRB the PI's decision to continue study activities.

VII. If the response to stipulations is not received within three months (90 days) following receipt of the stipulation notice issued by the IRB, the HSP will consider the application to have been withdrawn by the PI.
   a. If a response to stipulations is received after the three month deadline, it will be returned to the PI.
      i. In order to re-initiate the review process, the PI will be required to submit a new application for consideration by the IRB.

b. If the delinquent response relates to an application for continuing review and IRB approval has expired, the study will be closed and the PI will be so notified.

VIII. The response to stipulations will be reviewed by the IRB Chair, the HSP staff, the expedited reviewer, or another designated member(s) of the IRB.
a. Responses to minor stipulations can be reviewed and accepted by the designated HSP staff.

IX. Responses to stipulations can be accepted or not accepted. Either decision will be promptly communicated in writing to the PI.
a. When a response is accepted and the application is for initial or continuing review, the IRB communication will include the effective approval and expiration dates of the study.

X. At any time a response to IRB stipulations is accepted, the effective date of the approval will be the date on which the PI's final response was accepted as satisfactory.

XI. If a response is not accepted, the IRB notice will describe additional information required from the PI as a condition of approving the initial application.
a. The PI will have two months (60 days) to respond to the second request for information.

XII. When an application is withdrawn due to non-response by the PI, written notification will be provided to the PI.

XIII. To re-initiate the approval process, the PI must submit a new application for consideration by the IRB.

XIV. Copies of all substantive written communication between HSP and PIs pertaining to approvals with stipulations will be maintained in the study file.

Materials

- TMP 414 Initial Review – Approval with Stipulations – Full-Board
- TMP 420 Modification – Approval with Stipulations – Full- Board
- TMP 425 Continuing Review – Approval with Stipulations – Full-Board
- TMP 437 Initial Review – Letter Accepting Responses to Stipulations
- TMP 438 Continuing Review – Letter Accepting Responses to Stipulations
- TMP 439 Modification – Letter Accepting Responses to Stipulations

References

- The IRB has and follows written policies and procedures to conduct reviews by the convened IRB (**AAHRPP Element II.2.D.**).
    - Element II.2.D.1. – Initial Review
    - Element II.2.D.2. – Continuing Review
    - Element II.2.D.3. – Review of proposed modifications to previously approved research