

Wayne State University Human Investigation Committee	
Subject	Amendments to Research Protocols and Informed Consent
Form Date	April 2009 (Rev. 7/11/10)
Approvals	Initial Review 07/13/03, General Counsel 11/19/06, Steering Committee 12/07/06, Administrative Review 02/28/07, Administrative Review 10/29/08, Office of General Counsel 11/07/08, Administrative approval 01/28/09, Administrative Approval 04/22/09, Administrative Approval 9/30/10.

Background

Under federal regulations [45 CFR 46.109, 38 CFR 16.109, and 21 CFR 56.109] the Institutional Review Board (IRB) is responsible for review of all revisions to an IRB-approved research protocol. Revisions range from a request to correct a simple typographical error in the consent form to a significant change in the study design. Researchers must be aware that all revisions must be approved by the IRB before implementation. The criteria for approval of all revisions made to an IRB approved research protocol are found at 45 CFR 46.111, 38 CFR 16.111, and 21 CFR 56.111.

Scope

Revisions to approved research protocols may be required as the research study proceeds. Revisions can be divided into two types: Minor revisions (involving no more than minimal risk) and substantive revisions (any modification that affects one or more of the regulatory criteria for the approval of research).

Definitions

Minimal Risk – The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Minor Modifications – A change that would not materially affect an assessment of the risks and benefits of the study, does not substantially change the specific aims or the design of the study, and all added procedures meet the applicability criteria and fall into one or more categories defined in the Expedited Review section of this HIC Policy/Procedure.

Substantive Modifications (revisions that are more than minor) – Any modification that affects one or more of the regulatory criteria for the approval of research. Examples of revisions that would be considered “substantive” include:

- increased risk to participants

- significant change in the study design
- revisions to the recruitment plan
- adding or revising eligibility criteria
- newly identified side effects or adverse events related to the study drug.

Substantive modifications must be reviewed by the full IRB. If there are substantial changes from the original approved version, the IRB may require submission of a new protocol.

Expedited Review – Minor changes in previously approved research during the period (of one year or less) for which approval is authorized can be reviewed by the HIC chair, IRB chair, or his/her designee to determine approval.

Full Board Review – When revisions are substantive (i.e., any modification that affects one or more of the regulatory criteria for the approval of the research), with increased risk to participants, or there is a significant change to the study design, the revisions must be submitted for review by the full IRB. Full IRB review of a properly submitted amendment requires review at a regularly scheduled meeting, by the IRB that originally reviewed the protocol, and a vote by the IRB members.

Scientific Review

All research involving human participants at the **John D. Dingell VA Medical Center (JDD VAMC)** must be reviewed and approved by the JDD VAMC Clinical Investigation Committee (CIC) before the amendment can be reviewed by the HIC/IRB. The CIC approval letter must accompany the amendment submission.

For research sponsored by the **Department of Defense**, substantive changes to approved research must undergo scientific review prior to IRB review. For further information, please see the HIC Policy, "Department of Defense Regulations."

HIC Policy

When a request for an amendment to an approved protocol is received in the HIC Office, the Human Investigation Committee (HIC) chairperson, IRB chair, or his/her designee will review the submission to determine the level of review required (i.e., expedited or full board review). All changes to an approved protocol, regardless of how minor, must be approved according to either the expedited or full board process as specified in the federal regulations (45 CFR 46). **Changes made to a protocol must not begin until IRB review and approval has been granted, except when necessary to eliminate immediate hazards to the participants** [VHA Handbook 1200.5(h)(16)]. Such changes must be reviewed by the IRB to ensure that they were consistent with protecting the participants' rights and welfare. See related HIC Policy/Procedures "Principal Investigator: Roles and Responsibilities", "Reporting Unexpected Problems, Suspensions and Terminations, and Serious and Continuing Non-Compliance and the Institutional Official's Responsibilities", "Investigational Drug Research" and "Research with Devices".

Upon receipt of a request to amend an approved research protocol, the IRB will review the amendment and **approve it only** if it is determined that the following are true and/or the listed safeguards for the protection of human subjects are in place as follows:

- Risks to participants (physical, psychological, legal, economic, and social) are:

- minimized by using procedures that are consistent with sound research design and that do not necessarily expose participants to risk.
- minimized, when appropriate, by using procedures already being performed on the participants for diagnostic or treatment purposes.
- reasonable in relation to the potential benefits, if any, to participants and the importance of the knowledge that might be expected to result.
- If the research involves treatments or interventions, the research plan makes adequate provisions for monitoring the data to ensure the safety of participants.
- If the research involves vulnerable participants, that the protocol includes additional safeguards to protect their rights and welfare.
- The purpose of the research is specified.
- The setting in which the research will be conducted is identified.
- Whether prospective participants are vulnerable to coercion or undue influence.
- The inclusion/exclusion criteria are listed.
- Participant recruitment and enrollment procedures to ensure equitable selection are adequately stated.
- The influence of compensation (payments) to participants is addressed.
- The research plan makes adequate provisions to protect the (personal) privacy interests of participants.
- The investigator obtains the legally effective informed consent of the participant or the participant's legally authorized representative (LAR) (see the HIC Policy/Procedures "Informed Consent Process" and "Informed Consent Options" and Consent/Assent Template Requirements at www.hic.wayne.edu).

HIC Procedures

Submission Requirements for Expedited and Full Board Review:

Amendment requests for review of minor modifications can be submitted at any time. The Principal Investigator (PI) is responsible for completion of the Medical/Behavioral Amendment Form and is responsible for the accuracy of all information provided to the HIC for review.

Information and materials required for submission are as follows:

- Amendments must be submitted on a Medical/Behavioral Amendment Form. Only the current version of this form will be accepted; the form can be accessed on the HIC website.
- Revisions to a consent/assent/information sheet must have a revision date.

For all Veteran's Administration Medical Center (VAMC) amendments, a letter of approval from the Clinical Investigational Committee (VAMC CIC) must accompany the submission. If the amendment addresses an issue related to biosafety or radiation safety, the appropriate VAMC committee must first approve the amendment.

Specific instructions for submission of amendments can be found on the Medical/Behavioral Amendment Form.

Expedited Review:

Amendments which constitute minor changes to an approved research protocol/grant may meet the criteria for expedited review. Some examples of minor modifications are as follows:

- A change that would not materially affect an assessment of the risks and benefits of the study,
- A change that does not substantially alter the specific aims or design of the study,
- The addition of procedures that meet the applicability criteria and fall into one or more categories defined in "categories of research that may be reviewed by the IRB through an expedited review procedure." (45 CFR 46.110).
- A change that does not involve adding vulnerable subjects including children, prisoners, cognitively impaired, or mentally disabled participants.
- An increase or decrease in the proposed human research participant enrollment that is supported by a statistical justification.
- Administrative changes (e.g., contact information, the addition/deletion of key personnel and addition/deletion of study sites).
- Narrowing the range of inclusion criteria (e.g., lessening the risk to participants by excluding some participants previously allowed).
- Broadening the range of exclusion criteria (e.g., lessening the risk to participants by excluding some participants previously allowed).
- Alterations in oral forms of administration of a drug (e.g., table to capsule or liquid, providing the dose remains constant).
- Changing data collection points or amounts of data collected as long as it does not alter safety evaluations.
- An increase in safety monitoring resulting in more frequent visits or an increase in the length of hospital stay.
- Changes in compensation with proper justification.
- Changes to improve the clarity of statements or to correct typographical errors, provided that such a change does not alter the content or intent of the statement.
- The addition or deletion of qualified co-investigators or key personnel.
- The addition or deletion of study sites.
- Minor changes specifically requested by the IRB.

IRB Process for Expedited Review:

- Medical expedited amendments (i.e., minor changes that involve no more than minimal risk and minor changes in approved research per 45 CFR 46.110) are then routed to the HIC Chair or his/her designee for review. If the HIC Chair (primary reviewer for medical expedited amendments) feels that further scientific expertise is needed, he/she will request that the IRB Chair obtain an appropriate consult to review the submission.
- Behavioral expedited amendments (i.e., minor changes that involve no more than minimal risk and minor changes in approved research per 45 CFR 46.110) are then routed to the Behavioral IRB Chair or his/her designee for review.
- If the HIC Chair or Behavioral IRB Chairpersons are not available to do the initial review, his/her designee will review the amendments to ensure that they meet the criteria for expedited review, or whether they must be reviewed by the full board.

- Correspondence to the PI is generated based on the reviewer's comments.
- Response to requests for correction, clarification, etc., when received from the PI, is then directed back to the initial reviewer. Further requests may be required for which additional memos may be generated. If the amendment does not meet the criteria for expedited review, the PI is notified by either oral or written communication of the need for Full Board review and is requested to submit the appropriate copies (per directions on the Medical/Behavioral Amendment Form).
- Once approval of the amendment has been granted, a memorandum is generated within 7 to 10 business days) (See "Expedited Amendment Approval" letter template).
- Information regarding the amendment is entered into the Coeus database from which minutes are automatically generated.

Full Board Review:

Amendments containing substantive or major modifications (i.e., any modification that affects one or more of the regulatory criteria for the approval of research.) meet the criteria for full board review. The criteria for substantive modifications include::

- Broadening the range of inclusion criteria;
- Narrowing the range of exclusion criteria;
- Alterations in the dosage or route of administration of an administered drug;
- Extending substantially the duration of exposure to the test material or intervention;
- The deletion of laboratory tests, monitoring procedures, or study visits directed at the collection of information for safety evaluations;
- The addition of new, serious unexpected adverse events or other significant risks to the protocol, Investigator Brochure/packet insert and consent documents;
- Changes that, in the opinion of the HIC chair, IRB chair or his/her designee do not meet the criteria or intent of a minor modification.

The PI should provide written justification for the requested modification explaining how it will change the study, how it will affect the risks to study participants, and what safeguards will be implemented to protect study participants from the additional risks. If appropriate, the PI should provide references to support the modification. If the modification involves a change in the consent process, a revised consent form must be submitted for review by the full IRB.

IRB Process for Full Board Review:

- Medical full board amendments are routed to the HIC Chair or his/her designee for review. If the amendment does not meet the criteria for full board review, the amendment will receive expedited review (see "Amendments for Expedited Review" above).
- Behavioral full board amendments are routed to the Behavioral IRB Chair or his/her designee for review. If the amendment does not meet the criteria for full board review, the amendment will receive expedited review (see "Amendments for Expedited Review" above).
- Once determined that the amendment meets the criteria for full board review, the amendments to medical protocols are forwarded to the IRB that reviewed the initial protocol. The IRB Chair or his/her designee will then assign a primary and secondary reviewer. Whenever possible, the

HIC Chair, IRB Chair, or his/her designee assigns a reviewer with specific experience or knowledge of the protocol/science under review, specifically experience with the vulnerable population under review. Research involving prisoners is required to have the presence of the WSU Prisoner Advocate present at the meeting.

- When necessary, an outside consultant will be obtained by the IRB Chair in order to adequately review an amendment for full board review. The consultant will provide additional expertise for the full board review, but will not have a vote at the meeting.
- For research sponsored by the Department of Education – National Institute on Disability and Rehabilitation Research, a protocol that purposefully requires inclusion of children with disabilities or individuals with mental disabilities as research participants, the IRB must ensure the presence at the meeting of at least one person primarily concerned with the welfare of these research participants
- Amendments are distributed to the IRB members approximately one week in advance of the scheduled convened meeting to allow ample time for review. The primary and secondary reviewers will receive a complete copy of the amendment submission, including, if applicable, old and revised copies of the following:
 - MIC Medical/Behavioral Amendment Form
 - Advertising materials
 - Consent/Assent/Information Sheets
 - Educational materials to be distributed to potential participants
 - Full Research Proposal
 - Questionnaires/Surveys/Data collection tools
 - HIPAA Forms
 - Investigator's Brochure/Package Insert
 - Other items as deemed appropriate.

The IRB members at large will receive:

- HIC Medical/Behavioral Amendment Form
- If applicable, revised copies of:
 - Advertising materials
 - Consent/Assent/Information Sheets
 - HIPAA Forms
 - Educational materials to be distributed to potential participants
 - Questionnaires/Surveys (nonstandard forms)
 - Other items as deemed appropriate.
- A copy of the full application is available, upon request, to any IRB member for use during the course of discussion at a convened meeting.
- The primary and secondary reviewers will perform an in-depth review of all pertinent documentation. A full Board Reviewer Form will be completed for each amendment for use as a guide for the reviewer to present his/her findings to the full IRB Committee. All other members are provided material in enough depth to be prepared to discuss the information at the convened meeting.

- Following discussion and decision by the IRB regarding the outcome of the amendment under review, the primary and secondary reviewers will finalize the Full Board Reviewer Amendment Form.
- Correspondence may be forwarded to the PI via fax or e-mail, and is then sent via campus or U.S. mail within 7 to 10 business days.
- Response to requests for correction, clarification, etc., when received from the PI, is then directed back to the originating IRB Chair or his/her designee for review (see the HIC SOP entitled "Notification of IRB Decisions to Principal Investigator and PI Response Requirements" for details on the review and response process).
- All information regarding the review process is entered into the Coeus database from which minutes are automatically generated.