

THE IRB REVIEW

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THE OFFICE FOR THE PROTECTION FOR HUMAN RESEARCH SUBJECTS (OPHRS)

After Approval Overview

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The federal regulations governing research that involves human subjects probably affect the work of more faculty, staff, and students at ETSU and the VA than any other research compliance requirement. At the same time, the provisions of those regulations and the system of review that they mandate are complex. The ways in which we can interact with human beings in the course of research are so varied that to standardize procedures for every possible encounter would be at best difficult, if not impossible.

To the researcher meeting the system of review for the first time, the regulations and procedures, and the language they use, may seem foreign and complicated. Therefore, the Office for the Protection of Human Research Subjects, the East Tennessee State University Institutional Review Board (ETSU IRB - Non-medical) and the East Tennessee State University / James H. Quillen Veterans Affairs Institutional Review Board (ETSU/VA IRB - Medical) have produced this newsletter in the hope of addressing some of the most frequently asked, broad questions on the subject of conducting human subject research. After reviewing the material, please contact the Office for the Protection of Human Research Subjects should you require further assistance. As gatekeepers for the protection of potential research participants and partners in research, it is our desire to provide the researcher maximum assistance within the framework of the review system provided by institutional policies, state and local laws, federate mandates, and best practices in applied research ethics and human subject research.

This is just an overview. For more details, consult the IRB Policies & Procedures and/or the Investigator's Handbook.

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A. Continuation Review

Complying with Continuation Request

The Department of Health and Human Services (DHHS), the Food and Drug Administration, East Tennessee State University and the James H. Quillen Veterans Affairs Medical Center, under the DHHS Regulations, Title 45 Code of Federal Regulations Part 46 (45 CFR 46), require at 46.109(e), that “an IRB shall conduct continuing review covered by this policy at intervals appropriate to the degree of risk, but not less than once per year...” of all projects involving human subjects. The policy of both the East Tennessee State University Campus Institutional Review Board (ETSU IRB) and the East Tennessee State University/ Veterans Affairs Institutional Review Board (ETSU/VA IRB) is to conduct continuing review of all research proposals at intervals appropriate to the degree of risk, but not less than once per year [21 CFR 56.108(a)(1), 56.109(f) and 45 CFR 46.109(e)]. Continuing review is substantive and meaningful, and of sufficient depth and frequency to ensure the continued protection of the rights and welfare of research participants. No IRB member may participate in the continuing review of any protocol in which they have a conflicting interest, except to provide information requested by the IRB.

Procedures for Continuing Review

- ⇒ As a courtesy, the IRB Coordinator will forward a letter to the Principal Investigator (PI) requesting submission of a completed Application for Continuing Review (Form 107). The template letter will clearly state the protocol number, Study title, current approval date, study status at last review, the date of expiration of approval, scheduled meeting date, the version date of latest approved informed consent, and the deadline for submission of completed packet. The letter will be forwarded approximately 4 weeks prior to the submission deadline, which will be approximately 8 weeks prior to the project expiration deadline. In addition, a second notice will be forwarded to the PI's attention if a response is not received from the first notice by the listed deadline. If a response is not received by the deadline, a Warning Letter is faxed and mailed to the PI and the Department/Chair.
- ⇒ Upon receipt of Principal Investigator's written response to the IRB Office, the Continuing Review packet will be checked by the IRB Coordinator for completeness
- ⇒ If the packet is not complete, i.e., unanswered questions or lack of required attachments, the IRB Coordinator will contact the PI per phone, email (or both) and request missing information. If there is no response within the week, packets that do not have sufficient information to enable meaningful review will be returned to the PI along with accompanying memo identifying the missing elements and requesting immediate response. The IRB Coordinator is responsible for maintaining progress of incomplete packets, and proceeding with appropriate notification of IRB.



Full Continuing Review

Studies initially reviewed by the full, convened IRB undergo continuing review by the full convened IRB with recorded vote on each study, unless the study has been modified such that it meets the federal guidelines to be eligible for reclassification for expedited continuing review. For full continuing review, the IRB reviews proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in the nonscientific areas (45 CFR 46.108(b)).

In conducting full continuing review, a Primary Reviewer System is utilized. Primary Reviewers are responsible for analyzing the protocol and the complete IRB application in detail and are authorized to discuss any unanswered questions with the investigators, associated researchers or consultants prior to or during the convened meeting.

The full IRB Committee is informed of the Primary Reviewer's findings at a convened meeting. Particular attention will be paid to the Risk/Benefit Ratio of the investigations and the adequacy of the Consent Forms in conveying the procedures, implications and full intent of each study. Problems identified by the Primary Reviewers or by other IRB members will be discussed and suggestions for any necessary changes will be agreed upon by the IRB.

After discussion, including an explanation of the important issues that were evaluated, the full, convened board makes its determination with a recorded vote. The PI is notified in writing of the Board's decision.

Expedited Continuing Review

Expedited continuing review may be conducted if the study was initially eligible for, and approved by, an expedited mechanism, with the following exception: if an amendment or continuing review indicates changes in the study so that it is now ineligible for expedited continuing review as noted with submission of modification/continuing review. The IRB is only permitted to use expedited review for the continuing review of research that involves solely one or more of the activities published at 63 FR 60364-60367. If the study is modified such that it fails to meet expedited criteria for review, the study will undergo full continuing review.

In limited circumstances described by expedited review categories (8) and (9) at 63 FR 60364-60367 addition, studies that were initially reviewed by the full convened board may undergo expedited continuing review if the certain criteria are met.

When conducting research under an expedited review procedure, the IRB Committee Chair or designated IRB Short Review Committee Member conducts the review on behalf of the full IRB Committee.

Exempt Studies

Studies that have been determined to meet exempt status do not undergo continuing review unless a change in the study renders it ineligible for exempt status per federal guidelines. Investigators are informed in the exempt status letter to inform the IRB of any change in the project prior to its implementation, and reclassification under expedited or full review would be determined at that time by the IRB Chair.

Please note that Closed to Accrual of New Subjects Still Requires Continuing Review.

Approval Criteria

Approval, both initial and continuing, must meet HHS regulations at 45 CFR 46.111, including determinations by the IRB regarding risks, potential benefits, informed consent and participant safeguards. Criteria for both initial and continuing review approval are the same and therefore, IRB continuing review must include a determination by the IRB that :

- ⇒ risks to subjects continue to be minimized
- ⇒ risks to subjects continue to be reasonable in relation to anticipated benefits
- ⇒ selection of subjects continues to be equitable
- ⇒ informed consent continues to be adequate, and appropriately obtained and documented;
- ⇒ where appropriate, the research plan continues to make adequate provision for monitoring the data collected to ensure the safety of subjects;
- ⇒ there continue to be adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data
- ⇒ appropriate safeguards continue to be included to protect vulnerable participants
- ⇒ current risk/benefit analysis based on study results

If interim changes in IRB policy have occurred such that the proposal submitted for continuing review would not be approved if the same study were an initial submission, the IRB does not approve the continuing review of that protocol.



Changes/New Information

The IRB is also responsible for ensuring that changes in approved research are promptly reported to, and approved by, the IRB [21 CFR 56.108(a)(3-4)]. Continuing review will include an IRB determination of whether new information or unanticipated risks have been discovered since the previous IRB review. Based on new information or unanticipated risk, the IRB has the authority to reconsider its approval, require modifications to the

study, and/or revise the continuing review timetable. Any significant new findings which may relate to the subject's willingness to continue participation should be provided to the subjects in accordance with 21 CFR 50.25.

Suspending/Terminating

The IRB is also responsible for suspending or terminating approval of research that is not being conducted in accordance with the IRB's requirements [21 CFR 56.108(b)(2) and 56.113]. The IRB, by regulation, has not only the authority but also the responsibility for taking appropriate steps including termination or suspension of approval of research that is not being conducted in accordance with the IRB's requirements.

Written Progress Report

Routine IRB continuing review will include IRB review of a written progress report from the principal investigator. The written progress report will consist of a summary of project activities that have occurred since previous IRB review, including the following information:

- ⇒ Enrollment update
- ⇒ Adverse events
- ⇒ Data and Safety Monitoring Reports
- ⇒ Any unanticipated problems involving risk to participants or others
- ⇒ Audits
- ⇒ Any protocol changes (amendments or modifications)
- ⇒ Any change in risk/benefit ratio
- ⇒ Any complaints received from participants
- ⇒ Any participant withdrawals and reasons for withdrawals



- ⇒ Any interim findings
- ⇒ Any progress reports
- ⇒ Any multi-center reports, if applicable
- ⇒ Any recent relevant literature
- ⇒ Any protocol violations and /or deviations
- ⇒ Any other relevant information, especially information about risk associated with the research

Informed Consent

IRB continuing review will also include evaluation of the informed consent document currently in use. The currently approved informed consent, as well as any proposed informed consent document, will be reviewed to determine if the information provided continues to be accurate and complete, and to determine if any new information needs to be added. The informed consent document will also be reviewed to ensure that any significant new findings that may relate to the subject's willingness to continue participation are provided to the subject in accordance with DHHS regulations at 45 CFR 46.116(b)(5). Review of the informed consent document will take place not only at continuing review, but at other times when new information becomes available that needs to be communicated to participants.

Modifications

Amendments or revisions to a research protocol may be submitted at the time of continuing review. A Request for Modification Form and all appropriate documentation must accompany the Continuing Review Application (IRB Form 107) upon its submission. The modification is not implemented by an Investigator prior to review and approval by the IRB.

Study Closure

The IRB requires that all investigators notify the ETSU/VA IRB Coordinator, and VA R&D if applicable, in writing by using IRB Form 107, when a study is completed. **It is imperative that students doing research for their dissertation or thesis notify the IRB upon completion of the study by submitting a Form 107 as soon as the study is completed.**

No Grace Period

Per regulations, there is **no** grace period that allows the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of research must occur on or before the date when IRB approval expires. If any activity occurs or continues after the expiration date, the investigator is deemed to be out of compliance with both federal regulations and ETSU/VA policies. The IRB may restrict, require modifications, or terminate a research project based on continuing review by the IRB Committee. All studies in which the IRB requests changes to current documents are assigned a pending status. IRB approval is not given until the requested changes are received and approved. **The approval period is not extended.**

If continuing review and re-approval fails to occur by the continuing date specified by the IRB, all research activities must stop, unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions.

If the IRB does not re-approve the research by the expiration date, the IRB approval expires. The PI, upon receipt of an expiration letter, must immediately submit to the Chair a list of participants that could be harmfully affected by the expiration of the research. The IRB Chair, with appropriate consultation with (for VA) either the Chief of Staff (COS), or in his/her absence, the ACOS/R, or (for ETSU), the Vice Provost for Research (VPR), will determine if the subject(s) may continue in the research. If the ACOS/R or VPR is not a physician, they will designate a physician as a consultant. If the study is an FDA regulated study, the COS, ACOS/R or VPR and the IRB Chair will follow FDA requirements in 21 CFR 56.108(b)(2) and (3) in making their decision. The sponsoring agency or private sponsor will additionally be informed. In addition, the IRB Coordinator faxes a copy of expiration letter pertaining to VA Studies to the VA Administrative Officer (AO) on the date the letter is mailed/faxed to the PI.

B. Modifications

Requesting Changes

It is the policy of both the ETSU IRB and the ETSU/VA IRB to review all requests for modifications to any previously approved research study (including exempt studies) to determine if the change will alter the risk/benefit ratio of the study. A complete description of the modification must be received prior to review. All requested changes in the conduct of a study and/or changes to study documents must be approved by the IRB prior to implementation of that modification. The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects [21 CFR 56.108(a)(4)]. In such a case, the IRB will be promptly informed of the change following its implementation (within 10 working days) and will review the change to determine that it is consistent with ensuring the subject's continued welfare.

Reconsenting/Notification of Participants



If the modification warrants changes to the informed consent document, the investigator must address how the new information will be communicated to currently enrolled participants. This may be accomplished by using an addendum to the initial ICD or by re-consenting the subject using the modified ICD. While the investigator is responsible for making the initial decision regarding any necessary document changes, the IRB will make the final determination of whether the modification requires a change to the ICD or other study documents. The IRB will also make the final determination of the necessity of re-consenting of currently enrolled participants or notification of participants who have completed research interventions.

Minor Modifications

The initial request as to whether a modification alters risks to the participants is made by the Principal Investigator. The modification is received by the Coordinator and presented it to the Chair for his/her review. The Chair is responsible for evaluating the change in procedures and risks, and determining whether full IRB review of the modification is necessary. Proposed changes for previously approved research that are classified as minor modifications may be reviewed and approved in an expedited manner by the IRB Chair or, in the case of the Chair's absence or conflict of interest, his/her Designee.

Examples of minor modifications may include, but are not limited to, the following:

1. Administrative changes, such as correction of typographical error(s) and/or revision of phone numbers

Non-Minor Modifications

When a modification is determined to be non-minor, the Chair or his/her designee serves as a primary reviewer. The IRB Committee receives a synopsis of the primary reviewer's findings at the convened meeting. The IRB must review and approve changes at a convened meeting* before changes can be implemented (*meeting at which a majority of the members are present, including at least one member whose primary concerns are non-scientific). At the Chair's discretion, the Principal Investigator may be required to present the non-minor modification to the convened board.

Examples of non-minor modifications may include, but are not limited to, the following:

- ⇒ Change in protocol procedures, such as increasing the number of times a test is performed or adding additional procedures

Exempt Studies

Any changes in an exempt study must be submitted to the IRB for approval prior to initiation of the change. The IRB Chair will determine if the modification renders the study ineligible for continuing exempt status; and if so, the modification will not be approved. The investigator will be notified in writing that he may withdraw the modification request and continue the study as previously determined to qualify under exemption guidelines or submit the study for appropriate review and approval through an expedited or full board review.

C. UPIRTSO

Reporting Unanticipated Problems Involving Risks to Subjects or Others

Pertinent Definitions:

- ⇒ **Unanticipated Problem:** Unanticipated problems /events are those that are NOT already described as potential risks in the consent form, NOT listed in the Investigator Brochure, or NOT part of an underlying disease.
- ⇒ **Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO):** Includes those events that (1) are not expected given the nature of the research procedures and the subject population being studied (2) suggest that the research places subjects or others at a greater risk of harm or discomfort related to the research than was previously known or recognized.

Federal regulations require the organization to ensure promptly reporting of “any unanticipated problems involving risk to subjects or others” to the IRB, regulatory agencies, and institutional officials. The ETSU/VA and ETSU IRB require investigators to promptly submit any problem or event that meets the following criteria to the IRB within 10 working days using the Form 109 (unanticipated problem report) signed by the PI. All problems/events that do not meet these criteria should be reported to the IRB in summary form (table or spreadsheet) at the time of continuing review.

Events to be reported include:

- a. any serious event, including on-site and off-site adverse events, injuries, side effects, deaths, or other problems, which in the opinion of the local PI, was unanticipated, involved risk to participants or others, and was possibly, probably or definitely related to the research.
- b. Any serious accidental or unintentional change to the IRB-approved protocol that involves risks or has the potential to recur
- c. Any deviation from the protocol taken without IRB approval to eliminate apparent immediate hazard to a research participant
- d. Any publication in the literature, safety monitoring report,(including Data and Safety Monitoring Reports), interim result, or other finding that indicates an unexpected change to the risk/benefit ratio of the research.
- e. Any breach in confidentiality that may involve risk to the participant or others
- f. Any complaint of a participant that indicates an unanticipated risk or that cannot be resolved by the research staff
- g. any local death, whether anticipated or not
- h. incarceration of a participant
- i. Any other serious and possibly related event which in the opinion of the investigator constitutes an unanticipated risk.

For more information on procedures to report AE's and unanticipated problems, see IRB Policy #18 at www.etsu.edu/irb.

The Office for the Protection for Human
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We're on the web
www.etsu.edu/irb

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July 2006

Sun	Mon	Tue	Wed	Thu	Fri	Sat
						1
2	3	4 ETSU Closed	5 Medical board Meeting	6 Campus Board Meeting	7	8
9	10 Deadline for Full submission for August Meeting	11	12	13	14 Campus packets go out to members	15
16	17	18	19	20	21 Medical packets go out to members	22
23	24	25	26	27	28	29
30	31					

Coming Up in July

- Process once a protocol is submitted to the IRB



Coming Up in August

- Recruitment/Ads/Payments



A Graduate Brochure with more detailed information is available on the IRB website.

IMPORTANT NOTE

As of May 1, 2006, the ETSU and ETSU/VA Institutional Review Board no longer accepts any old forms. When submitting an initial proposal or a proposal for continuation review, please check the IRB website for new Forms. Always obtain forms from the IRB website. Do not use older forms that you or someone else have previously saved.

