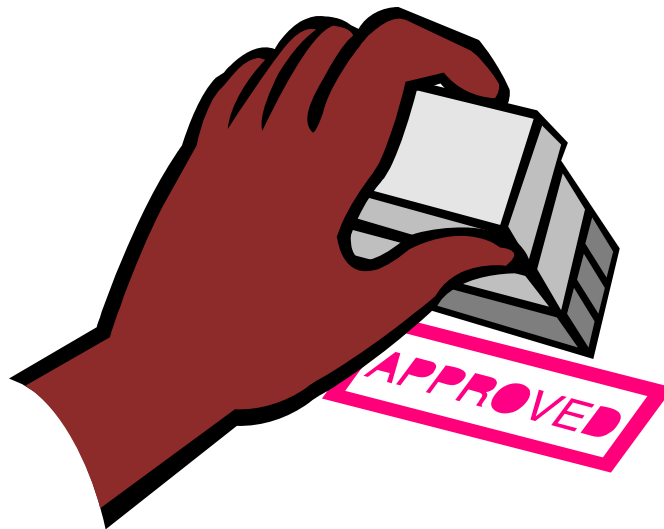




**ETSU**

*Your Study Is Approved*



NOW WHAT?



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 booklet 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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## Complying with Continuation Request

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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. 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. 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, e-mail (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 Expedited Reviewers 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 are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- ⇒ Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
- ⇒ Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
- ⇒ Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by [§46.116](#).
- ⇒ Informed consent will be appropriately documented, in accordance with, and to the extent required by [§46.117](#).
- ⇒ When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- ⇒ When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

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.

### **Source Verification**

When conducting continuing review, the IRB is responsible for determining which studies need verification from sources other than the investigator that no material changes in the research have occurred since the previous IRB review [21 CFR 56.108(a)(2)]. The need for additional verification will be determined by the IRB on a case-by-case basis according to the following criteria. Source verification will be required when:

- ⇒ Investigator is providing inconsistent information that can not be resolved
- ⇒ The IRB doubts the investigator's veracity
- ⇒ IRB doubts that the investigator has sufficient relevant knowledge
- ⇒ IRB perceives that investigator is intentionally not providing necessary information

If a reviewer determines the need for source verification for an expedited study, the continuation review must be referred to the full board.

If the IRB determines that a need for source verification exists, the IRB may request an independent assessment. This scope and extent of this assessment will be determined by the IRB on a case-by-case basis. Sources for information could include site visits conducted by authorized personnel, literature searches, or a directed audit. The IRB has the authority to observe or have a third party observe the consent process and the research [45CFR46.109(e)].

### **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:

1. Enrollment update
2. Adverse events
3. Data and Safety Monitoring Reports
4. Any unanticipated problems involving risk to participants or others
5. Audits
6. Any protocol changes (amendments or modifications)
7. Any change in risk/benefit ratio
8. Any complaints received from participants
9. Any participant withdrawals and reasons for withdrawals
10. Any interim findings
11. Any progress reports
12. Any multi-center reports, if applicable
13. Any recent relevant literature
14. Any protocol violations and /or deviations
15. 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.

### **Project 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, 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. (SEE EXCEPTION ON PAGE 10)

### **Study Closure**

The IRB requires that all investigators notify the 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 it is done.**

### **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.

If the study is approved pending requested changes, IRB approval is not given until the requested changes are received and approved. **The approval period is not extended.**

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.

**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.

## REPORTING 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. Modifications may include, but are not limited to, protocol amendments, changes in the number of subjects, changes in the informed consent, etc. 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. IRB members with a conflict of interest may provide information requested by the IRB, but may not participate in the deliberation or vote of the IRB on the involved modification.

### **Reconsenting/Notification of Participants**

If the modification warrants changes to the informed consent document, the investigator must address whether the information needs to be communicated to currently or previously enrolled participants, and if so, how it will be communicated. 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 determination 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)
2. Revision of phone number(s)

### **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
- ⇒ Deletion or decrease in tests performed as part of safety evaluations
- ⇒ The addition of serious unexpected adverse events or other significant risks to the ICD
- ⇒ Changes, which, in the opinion of the IRB Chair or his/her Designee, do not meet the definition of a minor modification
- ⇒ Any change that increases the risk of the study

### **Exempt Research**

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.

### **VA Studies**

Modifications must also be submitted to the VA R&D Office, if the study involves VA patients, VA staff, VA resources, time or equipment. Any change in authorized prescribers of the investigational drug requires the submission of a revised 10-9012.

### **Changes in Study Sites or Investigators**

Changes in study sites, investigators or revisions in study staff must also be reported to the IRB. These may require a cover letter, a revised Form 103, or, as applicable, a revised protocol. In the case of a change in the principal investigator, if at all possible, the letter should be signed by the investigator who holds the approval. The newly assigned investigator of a full review study however, must show proof of having obtained required education and submit a current CV for the purpose of assessment of qualifications. If the PI is unknown to the IRB, the PI must also attend a convened IRB meeting.

## Reporting of AE's and Unanticipated Problems

### 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.

### Summary Policy

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. Note: VA reporting requirements require immediate reporting of the loss or theft of VA research data/information or portable media such as laptops, or personal computers (see “VA Reporting of Loss or theft of VA research data/information” section on page 13)

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.

Reports of off-site events occurring in studies that are completed and closed at the local site should be reported if the event meets the IRB definition as detailed above AND the local PI judges that this event may affect risk to participants who have completed the study.

All problems/events that do not meet these criteria should be reported to the IRB in the summary form (table or spreadsheet) at the time of continuing review.

Follow-up reports of an off-site event may be submitted on a tracking log without an accompanying Form 109 if the following are true:

- ⇒ the initial report of the event was submitted as a UPIRTSO on a Form 109
- ⇒ the local PI has determined that the follow-up information does not contribute meaningful new information

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.

### **\*VA Reporting of Loss or Theft of VA research data/ information**

The loss or theft of VA research data/information or portable media such as laptops or personal computers must be immediately reported (as soon as it is discovered that there has been a loss) as follows:

1. Report the loss to security/ police officers IMMEDIATELY. If within a VA health care facility, notify the VA police. If the loss or theft occurs while on travel or at another institution, notify the security police officers at the institution (such as hotel security, university security, etc.) as well as the police in the jurisdiction where the event occurred.
2. Obtain the case number and the name and badge number of the investigating officer. If possible, a copy of the case report should be obtained.
3. Report the incident IMMEDIATELY to your immediate supervisor\*  
VA Privacy Officer at your facility \*  
VA Information Security Officer at your facility\*  
ACOS at your facility\*
4. Report the incident to the IRB using a Form 109 (Unanticipated Problem Involving Risks to Subjects or Others).

\* The name and contact information should always be readily available. Wallet cards that list the contact name and number of the James H. Quillen VA ACOS, the VAMC Privacy Officer and the VAMC Information Security Officer are available through the VA R&D office and the IRB Office.

### **IRB Responsibilities**

The IRB Coordinator will present the written report of the unanticipated event received from the investigator to the IRB Chair within 5 days. (\*SEE EXCEPTION ABOVE FOR VA STUDIES) The Chair will perform an initial review, and determine whether the event is an unanticipated problem involving risks to participants or others.

The Chair determines the action required based on his/her decision; if no, no further action; if yes, consider suspension and go to IRB. If the Chair determines that there is the potential of immediate harm to participants, the Chair may immediately suspend the study pending the IRB's receipt and review of the unanticipated problem and determination of any required actions

.f Chair says UPIRTSO, the report, with any attached documents, and the current approved informed consent, will be forwarded to the IRB Primary Unanticipated Problem (UP) Reviewer for initial review. The UP Reviewer, appointed by the IRB, will review all UPIRTSOs submitted and report findings and any recommendations for local ICD revisions to the IRB. In addition, all IRB members receive a copy of the Unanticipated Event Form (Form 109). If additional information is required in order to make a final determination concerning the event, the investigator will receive such a request in writing from the Chair/Board. The report will be added to the next agenda for the convened board. The IRB may reconsider study approval, require modifications to the study, revise the continuing review timetable, require notification of past participants, or require modification of the consent process or documents. The IRB may deem it necessary to directly audit the research site and medical records pertaining to the event, monitor the consent process, interview participants or witnesses, or suspend/withdraw IRB approval until such time that the safety of the participants can be assured. If information that may relate to subject's willingness to continue to take part in the research is noted, the IRB will require notification of current participants. The IRB may require that current participants be re-consented. The IRB may terminate the research.

Correspondence will be forwarded to the Principal Investigator as per the decision of the IRB following the completion of the review process.

The ETSU/VA IRB Chair is responsible for reviewing any report of a local death to determine if the death is unanticipated. For VA studies, if the Chair determines that the death is unanticipated, the ETSU/VA IRB Coordinator immediately forwards the Chair's written assessment to the VA AO. The VA AO is responsible for submitting the report to ORO within 24 hours of the Chair's determination that the death was unanticipated.

If the local site submits a tracking log for non-reportable events to satisfy sponsor requirements, the events/problems listed on the tracking log will be acknowledged by the IRB Chair, as indicated by his/her initials and date in the final column of the tracking log. A copy of the log will be filed with the study file, and the original returned to the investigator.

#### \*FOR VA STUDIES

If the IRB receives a report of a reported loss or theft of VA research data/information or portable media, the report will be immediately forwarded to the HRPP Director. The HRPP Director will immediately follow the reporting pathway outlined in the "VA Reporting of Loss or theft of VA research data/information" section on page 13".

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