CHAPTER 7 – Continuing Review

For studies under the 1991 Common Rule and FDA studies, 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 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.

When the revised Common Rule goes into effect, for studies subject to the revised Common Rule: Continuing review by the IRB or an expedited reviewer is not required when:

• Research meets one or more categories of research that qualify for expedited review.

• Research has progressed to the point that it involves only one or both of the following:
  - Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
  - Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

The IRB or EC must justify the decision to conduct continuing review of research originally reviewed using the expedited procedure. When the IRB is not required to conduct continuing review, records will provide a rationale for any decisions to conduct continuing review of research otherwise eligible for review using the expedited procedure.

Continuing review is required when other applicable regulations require continuing review. All VA and FDA research requires continuing review as described in Policy 11.

The IRB may determine that continuing review is required when:

1. The research involves topics, procedures, or data that may be considered sensitive or controversial;

2. The research involves particularly vulnerable subjects or circumstances that increase subjects’ vulnerability;

3. An investigator has minimal experience in research or the research type, topic, or procedures; and/or
4. An investigator has a history of noncompliance
5. Other considerations as determined by the IRB

For expedited and full studies that do not require continuing review when the revised Common Rule goes into effect, an administrative check-in will be required to maintain oversight of open research studies. Review of this administrative check-in will be by IRB staff.

Continuing review is not required for research reviewed in accordance with the limited IRB review procedure described in § II.104(d)(2)(iii).

III. Review Category

Procedures for Continuing Review

⇒ As a courtesy, the electronic system will send an email to the Principal Investigator (PI) requesting submission of a completed application for continuing review. The template email will clearly state the protocol number, study title, the date of expiration of approval, and the deadline for submission of completed xForm 107.

⇒ The email will be sent approximately 4 weeks prior to the submission deadline, which will be approximately 8 weeks prior to the project expiration. If a response is not received by the deadline, a warning email is sent to the PI.

Investigator Responsibilities

It is the investigator’s responsibility to initiate an appropriate response, allowing sufficient time for the review and re-approval process to be completed before the current approval expires. Prior to the identified submission deadline, the PI will submit the following in response to the request email for continuing review application:

⇒ Completed Continuing Review/Study Closure Application (xForm 107). The Investigator’s signature on the Form 107 indicates his/her assurance that the information presented for continuing review is accurate and current.

⇒ Any required attachments as identified on the Continuing Review/Study Closure Application, including but not limited to applicable brief descriptions of summary events/reports

⇒ A copy of the current, IRB stamped, approved informed consent, (this will provide a verification that the investigator is using the current approved version)

⇒ A clean, unstamped copy of the identical informed consent to be stamped with the new continuing review approval dates. However, if a modification that changes the ICD is being submitted at the time of Continuing Review, the investigator must submit revised ICDs as indicated in the Modification Policy.

The Investigator ensures that the Continuing Review/Study Closure Application (xForm 107) is complete, answering all items as noted below and attaching necessary summary descriptive information:
⇒ Project status, IND information, population involved, enrollment update, including total number of consented participants, including screen failures/withdrawals, total multi-center enrollment if applicable, number of subjects consented by local PI since previous IRB review, number of male/female subjects, and number of participant withdrawals, any recruitment problems

⇒ Summary of project activities that have occurred since previous IRB review, including

  o Adverse events summary
  o Any Data and Safety Monitoring Reports
  o Any unanticipated problems involving risks to participants or others
  o Any protocol changes (amendments or modifications)
  o Any audits
  o Any change in risk/benefit ratio
  o Any complaints received from participants
  o Any participant withdrawals and reasons for withdrawals
  o Any interim findings
  o Any progress reports
  o Any multi-center reports, if applicable
  o Any recent relevant literature
  o Any protocol violations or deviations
  o Any other relevant information, especially information about risk

**Study Expiration:**
If study approval expires, the Investigator will cease all research activities as instructed in the Expiration Letter. Upon receipt of the Expiration Letter, the investigator will immediately notify the IRB Chair of any subjects currently active in the project who could be harmfully affected by expiration of the research. If follow-up of subjects for safety reasons is permitted/required by the IRB, the subjects will be so informed and any adverse events/outcomes should be reported to the IRB and sponsor.

**NO Grace Period**
For studies under the 1991 Common Rule and FDA studies, 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 expiration 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. Such expiration of IRB approval does not need to be reported to OHRP as a suspension of IRB approval under DHHS regulations.

If the IRB does not re-approve the research by the expiration date, the IRB approval expires. The PI, upon receipt of expiration letter, must immediately submit to the Chair a list of research participants that could be harmfully affected by expiration of the research.

**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.

**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 and the importance of knowledge
⇒ 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
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 subjects’ 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.

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 HHS 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.

Study Closure
The IRB requires that all investigators notify the IRB Coordinator, and VA R&D if applicable, in writing by using IRB xForm 107, when a study is completed.