IRB Policy 11: Continuing Review
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I. Pertinent Definitions:

A. **Continuing Review:** periodic IRB review of ongoing research activities to ensure that the rights and welfare of human subjects are protected. Includes analysis of risk/benefit ratio, with special attention to whether new information or unanticipated risks have been discovered since the previous IRB review, and whether any new information regarding the risks and benefits should be provided to participants.
B. **Exempt Review:** Studies determined by the IRB to meet the exempt criteria as defined by the Federal regulations. Exempt studies do not require periodic review by the IRB unless a change in the project is planned.
C. **Expedited Review:** Studies determined by the IRB to meet the expedited criteria as defined by the Federal regulations.
D. **Not Less Than Once Per Year:** Current Federal regulations state that all research studies, with the exception of exempt proposals, must receive IRB continuing review at a minimum of once per year, with no exceptions or grace periods allowed. For studies subject to the 2018 Common Rule, this requirement changes as discussed in later sections of this policy.
E. **Full Continuing Reviews:** Studies reviewed by the full, convened IRB Committee with a recorded vote and corresponding minutes to document the discussion.

II. Summary Policy

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 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) and 56.109(f)]. Continuing review occurs as long as

- the research remains active for long-term follow-up of participants, even when the research is permanently closed to the enrollment of new participants and all participants have completed all research-related activities
- the remaining research activities include collection or analysis of private identifiable information

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.

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 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 under the 2018 Common Rule, 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. See Transition Procedure for details.

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

III. Review Category

A. Full continuing review

For studies under the 1991 Common Rule and FDA studies:
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. The IRB Chair reviews each study submitted for continuation review and selects the appropriate review process (review by convened board or expedited review).

For studies subject to the revised Common Rule:

Continuing review of studies (initially reviewed by the full convened IRB) by the IRB or an expedited reviewer is not required when:

• 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.

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. Consideration for the selection of Primary Reviewers to serve is based on area(s) of expertise in compliment to the research under review, term of IRB membership, dedication to continuing education and availability to accept new and continuing research proposals. The Chair or Vice Chair review each continuing review submission to determine which members have the relevant expertise to conduct an in-depth evaluation of the protocol. 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.

For continuing review of research that does not qualify for expedited review, all IRB members are responsible for reviewing:

1. Project Narrative or narrative section of the new protocol submission xform, which serves as protocol summary
2. Continuing Review/Study Closure Application (xForm 107), which serves as status report, and any attachments (complete documents as received from investigator).
3. Copy of the current approved informed consent document
4. Copy of any newly proposed consent document
5. Summary history of modifications reported to IRB and list of interim adverse events (if applicable)
6. Copy of any IRB (and if appropriate, VA) audits that have occurred in the period since the last review
7. For VA studies, Form 10-3203 for studies that are obtaining picture or video information from subjects.(not required if the information is embedded in the 10-1086)

For continuing review of research that does not qualify for expedited review, the primary reviewer(s) are responsible for reviewing:

1. Project Narrative or narrative section of the new protocol submission xform, which serves as protocol summary
2. Continuing Review/Study Closure Application (xForm 107), which serves as status report, and any attachments (complete documents as received from investigator).
3. Copy of the current approved informed consent document
4. Copy of any newly proposed consent document
5. Copy of current HIPAA Authorization document
6. Copy of the complete protocol, including any protocol modifications previously approved by the IRB
7. Summary history of modifications reported to IRB and list of interim adverse events (if applicable)
8. Copy of any IRB (and if appropriate, VA) audits that have occurred in the period since the last review
9. For VA studies, Form 10-3203 for studies that are obtaining picture or video information from subjects.(not required if the information is embedded in the 10-1086)

Upon request, any IRB member has access to the complete IRB protocol file and relevant IRB minutes prior to or during the convened IRB meeting. In addition,

any IRB member has access to additional information provided to individual reviewers.

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. Any controverted issues will be recorded in the minutes. This process allows the IRB to conduct a more substantive review and discussion at convened meetings.

Minutes of IRB meetings document separate deliberation, actions, and votes for each protocol undergoing continuing review by the convened board.

B. <u>Expedited continuing review</u>

For studies under the 1991 Common Rule and FDA studies:
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 following criteria are met:

1. The research presents no more than minimal risk to subjects (not applicable for category (8)(b)
2. The identification of the subjects or their responses will not reasonably place them at risk of criminal or civil liability or be damaging to their financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal (Not applicable for category (8)(b)
3. The research is not classified

4. The research falls into one or more of the following categories:

Category 8: Continuing review of research previously approved by the convened IRB as follows:

 (a) where **(i)** the research is permanently closed to the enrollment of new subjects,; **(ii)** all subjects have completed all research-related interventions,; **AND (iii)** the research remains active only for long-term follow-up of subjects; **OR**

 (b) Where no subjects have been enrolled and no additional risks have been identified; **OR**

 (c) Where the remaining research activities are limited to data analysis.

Category 9: Continuing review of research, not conducted under an investigational new drug (IND) application or investigational device exemption (IDE) where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

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. (any projects approved through expedited review initially)

When conducting research under an expedited review procedure, the IRB Committee Chair or designated IRB Expedited Reviewers conduct the review on behalf of the full IRB Committee. When performing continuing review by the expedited procedure, the IRB Chair or designated IRB Expedited Reviewers are responsible for reviewing all of the following documentation:

1. Project Narrative or narrative portion of the new protocol submission, which serves as protocol summary
2. Continuing Review, Study Closure Application (xForm 107), which serves as status report, and all attachments (completed documents as received from investigator)
3. Copy of the current approved informed consent document
4. Copy of any newly proposed consent document
5. Copy of current HIPAA Authorization document
6. Complete protocol, including any protocol modifications previously approved by the IRB
7. For VA studies, Form 10-3203 for studies that are obtaining picture or video information from subjects.(not required if the information is embedded in the 10-1086)

C. 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.

IV. Review Period

A. Determination of Appropriate Interval for Review:

For studies under the 1991 Common Rule and FDA studies:
The policy of ETSU IRB and ETSU/VA IRB is to determine appropriate continuing review interval for each review conducted by the IRB.

In determining which studies require review more often than annually, the IRB or EC will consider:

(A) The nature of and any risks posed by the clinical investigation.
(B) The degree of uncertainty regarding the risks involved.
(C) The vulnerability of the participants.
(D) The experience of the clinical investigator in conducting clinical research.
(E) The IRB's previous experience with that researcher or sponsor (e.g., compliance history, previous problems with the researcher obtaining informed consent, prior complaints from participants about the researcher).
(F) The projected rate of enrollment.
(G) Whether the study involve novel therapies
(H) other reasons as determined by IRB

Each initial study reviewed by the convened board will identify the required interval for continuing review, and the minutes will reflect the recorded vote.

The Office for Human Research Protections (OHRP) interprets not less than once per year to mean review on or before the one-year anniversary date of the previous IRB review required by 45 CFR 46, even though the research activity may not begin until some time after the IRB has given approval.

The determination of date by which continuing review must occur will be made by evaluation of the date of the convened meeting at which IRB approval occurs and the review interval determined by the IRB.

The following serve as examples, using a determination by the IRB that a one-year interval is appropriate for a project's continuing review:

- Project A undergoes full review by the convened IRB on May 2, 2005 and is approved without revisions. Project A must undergo continuing review prior to May 2, 2006. Expiration date is May 1, 2006.

- Project B undergoes full review by the convened IRB on May 2, 2005 and is approved pending minor modifications that can be approved by the Chair. The requested modifications are received by the IRB Office on May 26, 2005, and are approved by the Chair on June 2, 2005. Project B must undergo continuing review by May 2, 2006. Expiration date is May 1, 2006.

For a study approved under expedited review, continuing review must occur within 1 year of the date the IRB Chair or IRB member(s) designated by the Chair gives final approval to the protocol.

The frequency of continuing review will be determined by the IRB and will be set at the time of initial review and at each subsequent review of a research project. For studies that require continuing review, the criteria listed above will be used to evaluate the frequency of continuing review.

B. 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.

If an investigator does not provide continuing review information to the IRB or the IRB has not approved a protocol by the expiration date, new enrollment of participants cannot occur.

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. 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. For VA studies, this determination must be made within 2 business days. 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 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 letters pertaining to VA studies to the VA Administrative Officer (AO) on the date the letter is mailed/faxed to the PI.

V. Continuing Review Determinations

A. Approval Criteria

For studies under the 1991 Common Rule and FDA studies:

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

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

> (1) Risks to subjects continue to be 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.
>
> (2) Risks to subjects continue to be 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.

(3) Selection of subjects continues to be 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.

(4) Informed consent will continue to be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.

(5) Informed consent will continue to be appropriately documented, in accordance with, and to the extent required by §46.117.

(6) When appropriate*, the research plan continues to make adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there continue to be adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

*When research is more than minimal risk and involves an intervention

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards continue to be included in the study to protect the rights and welfare of these subjects.

For VA studies,

- The patient's medical record must be flagged if the study has been determined to be more than minimal risk.

If the IRB determines and documents that the patient health record must be flagged in Computerized Patient Record System (CPRS) as participating in a research study, then the health record must identify the Researcher, as well as contact information for a member of the research team that would be available at all times, and contain information on the research study or identify where this information is available. The duration of flagging is the length of the duration of the individual's participation in the study.

Refer to Policy 13, Section VIIIC for instructions regarding studies that have a Certificate of Confidentiality.

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.

For studies subject to the revised Common Rule,

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized by: (a) by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk, and (b) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) 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.

(3) 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. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or or economically or educationally disadvantaged persons.

(4) 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, § __.116

(5) Informed consent will be appropriately documented or appropriately waived in accordance with § __.117.

(6) When appropriate*, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

*When research is more than minimal risk and involves an intervention; not applicable for expedited studies

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

B. <u>Source Verification</u>

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)].

C. 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.

D. 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.

VI. Continuing Review Process

A. Written Progress Report

For studies under the 1991 Common Rule and FDA studies:
Routine IRB continuing review will include IRB review of a progress report xform 107 from the principal investigator. The 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

B. 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.

C. Protocol Summary

The project narrative or narrative portion of the new protocol submission xform, which serves as the protocol summary, must contain the relevant information required to determine whether the proposed research continues to meet the criteria for approval.

D. Project Modifications

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

E. Cooperative Protocol Research Program (CPRP) Protocols.

For studies under the 1991 Common Rule and FDA studies:
As long as individually identifiable follow-up data are collected on participants enrolled in HHS-supported Cooperative Protocol Research Program (CPRP) protocols, continuing review is required. This remains true even after a protocol has been closed to enrollment at all sites and protocol-related intervention has been completed for all participants, even if research is limited to final data analysis.

VII. Study Closure

The IRB requires that all investigators notify the IRB by using IRB XForm 107, when a study is completed.

References:
45 CFR 46.109(e)
45 CFR 46.110
OHRP Guidance on Continuing Review, July 11, 2002
21 CFR 56.108(a)(1) and 56.109(f)]
FDA Information Sheets, Guidance for IRBs and Clinical Investigators, 1998 Update
21 CFR 56.108(a)(2)]