IRB Policy 11: Continuing Review
Revision Date: April 16, 2008, revised November 11, 2009, revised January 27, 2011, revised February 9, 2015, revised April 2, 2018, revised 9.14.18, revised October 18, 2019, revised October 22, 2020

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. **Administrative Check-in:** Periodic administrative review of ongoing research activities that do not require continuing review.
C. **Exempt Review:** Studies determined by the IRB Chair to meet the exempt criteria as defined by IRB Policy 7.
D. **Expedited Review:** Studies determined by the IRB to meet the expedited criteria whereby research is reviewed by one or more IRB members rather than the convened IRB.
E. **Full Board Review:** Studies reviewed by the convened IRB for research that does not qualify for exempt or expedited review.

II. Summary Policy

For studies approved in accordance with the 2018 Common Rule, research meeting the following criteria does not require continuing review, unless the IRB specifically documents that continuing review is required:

- Research reviewed in accordance with the limited IRB review procedure described in § ll.104(d)(2)(iii)
- Research that meets one or more categories of research that qualify for expedited review
- Research that has progressed to the point that it involves only data analysis or accessing follow-up data from procedures that subjects would undergo as part of clinical care

Continuing review of these studies will not occur unless subsequently required due to a modification making the study ineligible for the above criteria or as a corrective action deemed appropriate by the IRB. The IRB, at its discretion, may determine that research meeting the above criteria is required to undergo continuing review 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;
4. ETSU is the IRB of record for a multi-site, collaborative research study; and/or
5. An investigator has a history of noncompliance.

In such cases, when the IRB is not required to conduct continuing review, records will provide a rationale for any decision to conduct continuing review of research otherwise eligible for review using the expedited procedure.

For studies that do not require continuing review, an administrative check-in will be required to maintain oversight of open research studies. Review of the administrative check-in will be by IRB staff and will be documented in the study record.

For research meeting the following criteria, DHHS and FDA regulations require the IRB to perform continuing review of ongoing research at intervals appropriate to the potential risk to participants, but at least annually.

- Research that involves greater than minimal risk to subjects
- Research that is FDA-regulated
    - Involves a drug, or
    - Clinical investigation of a medical device
- Research that involves no greater than minimal risk to subjects and initially approved by the IRB prior to January 21, 2019 in accordance with pre-2018 Common Rule requirements

Continuing review occurs no less than annually 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. The criteria to grant continuing IRB approval are the same criteria required for initial IRB approval of the research (45 CFR 46.111 and 21 CFR 56.111).

For each initial or continuing review, the IRB will document the approval period in the approval letter with an expiration date specified. If the study does not require continuing review, no expiration date will be assigned, and the approval letter will inform the investigator of the administrative check-in date.

III. Level of Review

When continuing review is required, the following procedures will be followed depending on the level of review. The IRB Chair reviews each study submitted for continuing review and selects the appropriate review process (review by convened board or expedited review).

A. Full continuing review

Studies initially reviewed by the convened IRB undergo continuing review by the 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 determines and documents at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified; or
- One of the following criteria are met:
    - The research is permanently closed to the enrollment of new subjects; all subjects have completed all research-related interventions; and the research remains active only for long-term follow-up of subjects; or
    - No subjects have ever been enrolled and no additional risks have been identified at any site engaged in the research or any other relevant source; or
    - The remaining activities are limited to data analysis only.

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 as described in IRB Policy 9. For full continuing review of research, all IRB members are responsible for reviewing:

1. Project Narrative or Summary section of the new protocol submission xform
2. Continuing Review/Study Closure xForm 107, which serves as status report, and any attachments

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 reports (if applicable)
6. Copy of any audits that have occurred in the period since the last review

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 VA Research Consent Form) must also be reviewed.

In addition, primary reviewers are responsible for reviewing the following items:

1. Copy of current HIPAA Authorization document
2. Copy of the complete protocol, including any protocol modifications previously approved by the IRB

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 committee is informed of the Primary Reviewer's findings at a convened meeting. With special attention to the analysis of risk/benefit ratio, 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. Problems identified by the Primary Reviewers or by other IRB members will be discussed, and suggestions for any necessary changes will be voted on by the IRB and recorded in the minutes. Any controverted issues will be recorded in the minutes.

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

B. Expedited continuing review

Generally, if research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, except in limited circumstances noted above and in accordance with expedited review categories (8) and (9) 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, 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; and
4. The research falls into one or more of the following categories:

   Expedited 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.

When conducting continuing review of research via expedited review, the IRB Chair, or designated expedited reviewer(s), conduct the review on behalf of the full IRB committee. When performing continuing review by the expedited procedure, the IRB Chair or designated expedited reviewer(s) 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 VA Research Consent Form)

The IRB Chair or designated expedited reviewer(s) complete the Expedited Reviewer xForm to determine whether the research meets the criteria allowing continuing review using the expedited procedure, and if so, whether the research continues to meet the criteria for approval.

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. Studies that have been granted exempt status may be required to undergo an administrative check-in by IRB staff to ensure that IRB records are current. Investigators will be informed of the administrative check-in date in their exempt status letter.

IV. Review Period

A. Determination of Appropriate Interval for Review:

When continuing review is conducted, the policy of ETSU IRB and ETSU/VA IRB is to determine the continuing review interval appropriate to the level of risk for each protocol, but not less than once per year. 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, even though the research activity may not begin until some time after the IRB has given approval.

In determining which studies require review more often than annually, the IRB 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. For a study approved by the convened board, the approval period starts on the date that the IRB conducts its final review of the study; that is, the date of IRB approval or the date the convened board approves the research pending minor modifications.

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 via expedited review requiring continuing review, the expiration date is calculated from the date the IRB Chair or designated IRB reviewer(s) issues 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 continuing review of a research project.

B. <u>No Grace Period</u>

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 applicable federal regulations and ETSU IRB Policy.

The IRB may require modifications, suspend, or terminate a research project based on continuing review by the IRB. 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 expiration 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)-(3) in making their decision. The sponsoring agency or private sponsor will additionally be informed. In addition, the IRB Coordinator provides a copy of expiration letters pertaining to VA studies to the VA Administrative Officer (AO) on the date the letter is communicated to the PI.

V. Continuing Review Determinations

A. Approval Criteria

Approval, both initial and continuing, must meet HHS regulations at 45 CFR 46.111 and (as applicable) FDA regulations at 21 CFR 56.111, 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
- Risks to subjects are reasonable in relation to anticipated benefits
- Selection of subjects is equitable
- Informed consent will be sought and appropriately documented, unless waived
- When research is more than minimal risk and involves an intervention, adequate provisions for monitoring the data

- When appropriate, adequate provisions to protect privacy and confidentiality

- Appropriate safeguards have been included to protect vulnerable 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.

The instructions above apply to studies that **do not** have a Certificate of Confidentiality. Refer to Policy 13, Section VIII.C. 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 may not approve the continuing review of that protocol and may require changes or request a new protocol submission to ensure the study meets the criteria for approval.

B. 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 the:

- Investigator is providing inconsistent information that cannot be resolved
- 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 continuing 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 [45 CFR 46.109(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 [45 CFR 46.108(3)(iii) and 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 period of approval. Any significant new findings which may relate to the subjects' willingness to continue participation should be provided to the subjects in accordance with applicable regulations [45 CFR 46.116(c)(5) and 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 or that has been associated with unexpected serious harm to subjects [45 CFR 46.113 or 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

IRB continuing review will include IRB review of a written progress report available on the Continuing Review 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. 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.

D. 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 when a study is completed by using either the IRB Continuing Review/Study Closure xForm 107 or Administrative Check-in xForm, as appropriate.

References:
45 CFR 46.109(e)
45 CFR 46.110
Continuing Review Guidance, OHRP, 2010
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)