Policy 25: Non-compliance

Effective Date: April 6, 2023

I. Summary Policy

It is 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) that investigators engaged in the conduct of human subjects research on behalf of ETSU or under the purview of the ETSU IRBs follow all applicable rules, regulations, and policies for the duration of the research. This policy addresses the process that the IRB follows to manage allegations and findings of non-compliance. All members of the research community are responsible for reporting to the ETSU IRB any concerns or allegations of potential noncompliance. Reports may come from any category of research reviewed and may include anyone involved, or not directly involved, in the research process/study. The IRB, as part of their oversight responsibilities (45 CFR 46.108(a)(4) and 21 CFR 108(b)(2)), must establish procedures for the evaluation of all non-compliance and the prompt reporting of any serious or continuing non-compliance with the federal regulations or institutional policies. The IRB also has the authority, and responsibility, to suspend or terminate approval of research not being conducted in accordance with IRB requirements or that has been associated with serious harm to subjects (45 CFR 46.113; and 21 CFR 56.113).

II. Definitions

A. Non-compliance: Failure to comply with applicable regulations, laws, agreements, policies, or the determinations or requirements of the IRB. Examples may include:

i. Failure to obtain IRB approval prior to initiating research activities;
ii. Failure to obtain or document the informed consent process, when required;
iii. Inadequate supervision;
iv. Failure to follow recommendations made by the IRB;
v. Failure to report adverse events or protocol deviations, as appropriate;
vi. Failure to provide ongoing progress reports, when required; or
vii. Failure to adhere to the approved protocol or implementing changes without prior IRB approval.

B. Serious Non-compliance: Non-compliance that any other reasonable Investigator would have foreseen as compromising the safety, rights, or welfare of a participant, research study staff, or others; or noncompliance that presents genuine risk of reputational harm to the institutions involved or to the institution's Human Research Protection Program. Examples may include:

i. Conducting non-exempt research without IRB approval;
ii. Enrollment of research subjects while study approval has lapsed;
iii. Enrollment of subjects that fail to meet the inclusion or exclusion criteria of the protocol, that in the opinion of the IRB Chair or convened IRB, increase the risk to the subject;

iv. Implementing unapproved protocol changes, that in the opinion of the IRB Chair or convened IRB, increase the potential for risks to participants or adversely affect their rights;
v. Serious protocol deviations that may place subjects at increased risk from the research;
vi. Failure to promptly report serious adverse events, unanticipated problems involving risks to subjects or others, or potentially serious or continuing noncompliance, as required by IRB policy;
vii. Providing false or intentionally misleading information to the IRB;
viii. Allowing unqualified or untrained personnel to perform research procedures or knowingly allowing personnel to engage in research activities that violate ethical standards or institutional or IRB policies; or
ix. Multiple issues suggesting lack of oversight, inaction, or carelessness such that subjects' right, safety, or welfare could be adversely affected or compromising the integrity of the Human Research Protection Program.

C. Continuing Non-compliance: A pattern of repeated actions, omissions, or instances taken by an Investigator that indicates a deficiency in the ability or willingness of an Investigator to comply with applicable federal regulations, laws, policies, agreements, or determinations or requirements of the IRB, or the prolonged persistence of noncompliance occurring after its identification, awareness, or implementation of a corrective action intended to effectively resolve the noncompliance.

D. Protocol Deviation: Any non-substantive alteration or modification to the IRB-approved protocol within the researchers' control but implemented without prospective IRB approval and does not have the potential to impact safety of participants or scientific validity of the protocol.

E. Protocol or Approved Protocol: The information included in the IRB approved submission form(s), including any attachments and information approved via subsequent amendments and annual reviews.

F. Research Misconduct: Any fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.

G. Allegation of non-compliance: An unproven assertion of non-compliance.

H. Finding of Non-compliance: Non-compliance determined by the IRB to be true.

III. Reporting of Non-Compliance

Allegations of non-compliance can come from a number of different sources. Potential sources include investigators, members of the research team, study sponsors, regulatory bodies (OHRP, FDA), participants and their families, institutional personnel or committees, the media, the public, or anonymous sources. Additionally, the IRB can identify non-compliance during its review or audit of research studies. The identity of the source will be kept confidential to the extent possible unless they give permission to disclose their identity.

Research personnel are required to promptly report all non-compliance to the IRB within **5 working days** of becoming aware of the event. For VA studies, the written report of

noncompliance must also be made to the Associate Chief of Staff for Research (ACOS/R) within 5 working days. While the initial report can be made verbally to a member of the IRB or HRPP staff, the reporting party should submit written documentation to the IRB, including any supporting information from other sources (e.g. study sponsor, regulatory body, members of the research team, research subjects), involved in or having information related to the allegation of non-compliance (e.g. who, what, when, where, and why) and what actions were taken and will be taken to ensure subjects or others were not or are not harmed.

IV. Tracking and Reporting Protocol Deviations

The Principal Investigator is responsible for determining whether a protocol deviation meets the threshold for non-compliance that requires prompt reporting to the IRB. When making this determination, the Principal Investigator should consider whether the deviation negatively affected the rights, safety or welfare of the subject(s) or the scientific validity of the research. The Principal Investigator is responsible for establishing a tracking mechanism and ensuring proper documentation of all protocol deviations including, but not limited to, date of occurrence, date identified by the study team and by whom, detailed description of the deviation, the PI's assessment and rationale of the deviation, and the research team's response or resolution to said deviation. The protocol deviation log should be submitted to the IRB at the time of annual review (i.e., continuing review or admin check-in) or upon request (i.e., compliance review or audits) along with the PI's summary assessment. Examples of protocol deviations:

- Minimal over-enrollment for non-exempt studies
- Completing a study visit outside the protocol specified timeframe, when in the opinion of the PI, there are no safety implications
- Documentation deficiencies such as missing initials in the footer of the consent form or recording of the wrong date/missing time in the signature block
- Minor, non-substantive changes to study materials that do not alter the meaning or understanding of the materials such as correcting typos or moving text around

Unintentional or unavoidable deviations outside the reasonable control of the researchers do not constitute non-compliance. For example:

- A subject cannot attend a scheduled research visit and it results in the change in timing of procedures so long as there is not an adverse risk to participants
- An ineligible subject is enrolled due to misinformation provided to the researcher
- Changing the availability of the research or compensation when there is an overwhelming response to the research likely due to bots

The Principal Investigator should evaluate these sorts of events and determine the appropriate response. The research records should contain documentation and resolution of such events.

The Principal Investigator is responsible for monitoring their study(ies) for adherence to

the IRB approved protocol. The purpose of the monitoring is to identify any reportable events or concerning trends that may indicate a systematic issue in how the study is being conducted. A series of protocol deviations in a single study or set of studies would meet the threshold for prompt reporting of non-compliance to the IRB and possibly require immediate corrective action. If there is a question about whether a specific event requires prompt reporting, the PI is responsible for contacting the IRB for consultation.

V. Review of Protocol Deviations

During the annual review, the Principal Investigator is asked to submit a log and summary of any protocol deviations that occurred throughout the approval period. When a PI submits a summary of protocol deviations that do not require prompt reporting, the IRB Coordinator routes the submission to the appropriate IRB Chair for review. The log will be acknowledged by the IRB Chair, or designated reviewer. A copy of the log will be recorded in the study file, and PI will be notified in writing of the acknowledgement. Should the IRB Chair have concerns, additional information may be requested from the investigator prior to acknowledgement, or the matter may be referred for review as non-compliance. The investigator is notified in writing of the IRB Chair's assessment.

VI. Receiving and Evaluating Reports of Non-compliance

IRB staff may receive reports of non-compliance verbally or in writing from a variety of sources and will obtain as much information as possible from the source and may solicit additional information to determine the validity of the report. The information will be summarized in a written report to be evaluated by the IRB Director. The totality of circumstances will be evaluated, and if it appears to be a one-time or isolated case that does not present additional risk with an appropriate corrective action plan in place, the IRB staff may acknowledge the report and resolve as needed with education and initiating a protocol modification. Documentation of the event and resolution will be prepared by the IRB staff, shared with the investigator, and placed in the study file.

Reports that appear to involve risks to participants, lack an appropriate corrective action plan, or are otherwise not appropriate for IRB staff resolution, will be routed for review by the appropriate committee chair. In cases involving serious harm to subjects or where it appears immediate action is needed, the IRB Chair and IO are notified immediately by the IRB staff. Other responsible parties (such as VA ACOS/R for VA studies) may be notified when appropriate to the specific incident. The IRB Chair and Institutional Official have authority to suspend the research in accordance with IRB Policy 26: Suspension. Suspension determinations will be reported in accordance with IRB Policy 34.

VII. IRB Review of Non-Compliance

The IRB Chair, or designee, in consultation with the IRB Director, conducts a

preliminary evaluation of the non-compliance report and other facts available to determine if the allegation appears to be true and involves non-compliance as defined in this policy. When needed, additional information is gathered from appropriate parties and others are consulted as needed (i.e., Privacy Officer, CISO, Legal Counsel, etc.). Once there is sufficient information available to evaluate the event, the IRB Chair conducts a preliminary review.

If the IRB Chair, or designee, determines that the non-compliance is clearly neither serious nor continuing, they may accept the report as presented or recommend a corrective action plan with documentation to be completed within 60 days of the initial report of noncompliance. The Chair or designee's decision will be reported to the IRB for acknowledgement at its next convened meeting, and if a VA study, the decision will be reported to the VA facility director, RCO, and ACOS/R within 5 days of the determination.

Subcommittee Review

If the IRB Chair, or designee, determines the non-compliance might be serious or continuing or is complex in nature, review of the incident may be referred to an ad hoc IRB Compliance Subcommittee. The subcommittee will consist of the IRB Chair or Vice Chair, at least two IRB members designated by the IRB Chair, and a VA IRB member representative, if it involves a VA study. Subcommittee members will be designated based on relevant expertise and availability. The subcommittee reviews the allegation(s) and related materials to ascertain whether the event constitutes serious and/or continuing noncompliance. The subcommittee, with support from the IRB staff, may obtain additional pertinent information from the IRB records, investigator, external consultants, or other appropriate parties. A for-cause audit may also be necessary to determine the nature and facts of the incident and could be initiated at the request of the IRB Chair, IO, or subcommittee in accordance with IRB Policy 24.

If the subcommittee determines the event to be neither serious nor continuing noncompliance, corrective actions to resolve the noncompliance are imposed by the subcommittee with documentation to be completed within 60 days of the initial report. Corrective action may include, but are not limited to:

- Acknowledgement with no further action required;
- Education or counseling with the PI regarding how to remain compliant in future incidents and clarification of IRB policy or requirements;
- Requiring additional human research protection or protocol specific training;
- Requiring submission of a modification or reportable event for IRB approval;
- Requiring the PI to create and submit a formal corrective and preventive action (CAPA) plan; and/or
- Directing post-approval monitoring visits or compliance reviews (in accordance with IRB Policy 24).

The subcommittee documents the fact finding, discussions, and determinations in a written report that is provided to the IRB Director and becomes part of the study record. The Chair of the ad hoc subcommittee reports the noncompliance event and outcome to

the next convened IRB for acknowledgement. The IRB staff communicates the outcome of the subcommittee review in writing to the investigator, and the original source, as appropriate.

If the subcommittee believes the event to be possibly serious or continuing noncompliance, the subcommittee ascertains all pertinent information and compiles a report for consideration by the convened IRB.

Convened IRB Review

Review of the incident is referred to the convened IRB for review when:

- The event may involve serious and/or continuing noncompliance;
- There is uncertainty or disagreement about the level of noncompliance or appropriate CAPA plan;
- The investigator fails to cooperate with the fact finding or corrective actions imposed by IRB staff or the subcommittee;
- The IRB disagrees with the IRB staff or subcommittee's determination and resolution; or
- There are other factors contributing to the complexity or concern for subject safety.

A report prepared by the subcommittee describing the allegation of noncompliance, facts available, and relevant materials, are shared with all members of the IRB for review within 30 days of the initial allegation report. The PI is informed of the IRB's review and may be invited to attend the meeting to discuss the report with the convened IRB. The subcommittee Chair presents the findings and recommendations to the convened IRB. The IRB reviews the information available to determine if the event constitutes noncompliance that may be serious and/or continuing noncompliance and the appropriate CAPA plan. If the IRB needs additional information to make a determination, they may vote to defer the review until additional information is available.

VIII. IRB Review Outcomes

The convened IRB votes on the final determination of whether the noncompliance is serious and/or continuing and must consider the following actions during deliberation:

- Suspension (temporary halt of IRB approval or some activities)
- Termination of IRB approval/discontinuation of the research study(ies)
- Notification to current participants when such information might relate to participants' willingness to continue to take part in the research

In addition to the required considerations above, the IRB must approve or require changes to the proposed CAPA plan that may include a variety of actions, depending on the nature, seriousness, and outcome of the review. The corrective and preventive actions may include, but are not limited to:

- Education or counseling with the PI regarding how to remain compliant in future

incidents and clarification of IRB policy or requirements;
- Requiring additional human research protection or protocol specific training;
- Requiring submission of a modification for IRB approval;
- Increasing frequency of the annual check-in or continuing review;
- Requiring continuing review instead of administrative check-in;
- Directing post-approval monitoring visits or compliance reviews (in accordance with IRB Policy 24).
- Notifying past participants or providing additional information to current or past participants;
- Requiring re-consent of participants;
- Restricting the ability to serve as Principal Investigator on IRB protocols;
- Referral to the Research Integrity Officer if the event appears to constitute research misconduct;
- Referral to the Institutional Official, Dean, Department Head, Provost, or other appropriate official, for determining or imposing additional sanctions such as formal reprimands or limitations on research activity;
- Referral or notification to other individuals or entities (i.e., Legal Counsel, HIPAA Compliance, Internal Audit, etc.) for determining other appropriate institutional actions; or
- Other appropriate actions.

When appropriate, a reasonable timeframe for implementation of these actions should be established by the IRB. The convened IRB minutes will document the review, deliberation, and determination. The determination will be documented in writing and communicated to the Principal Investigator following the meeting. The investigator is expected to confirm receipt of the documentation within one week.

The convened board's determination may not be altered by a higher authority.

IX. Follow-up

The Principal Investigator is responsible for ensuring the corrective actions outlined in the final report are implemented in the timeframes established in the report. The IRB staff will track progress and report updates to the IRB Chair, and the IRB Chair will provide updates to the convened IRB as appropriate. The PI is responsible for timely response to all IRB inquiries, including noncompliance follow-up and progress reports. Failure to meet the conditions established in the report will result in additional review by the IRB for continuing noncompliance and possible termination or suspension of IRB approval.

The investigator may appeal the decision in accordance with IRB Policy 12: IRB Appeal Process.

X. Report of Findings

IRB Policy 34: Reporting is followed for reporting determinations of serious or continuing non-compliance.

References:
45 CFR 46.108(a)(4)
45 CFR 46.113
21 CFR 56.108(b)(2)
21 CFR 56.113
VHA Directive 1058.01, October 22, 2020

Revision History:

March 29, 2009, revised June 11, 2010, revised September 15, 2015, revised September 14, 2018, revised March 2, 2021