IRB Policy 18: Reporting of Unanticipated Problems & Events

Revision Date: March 27, 2009, revised 11/19/09, revised 6/11/10, revised January 27, 2011, revised January 17, 2012, revised 9/17/15, revised October 22, 2020, revised March 2, 2021

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 all investigators engaged in the conduct of human subjects research report all problems, events, and information that require prompt reporting to the IRB within ten (10) calendar days of identification of the problem. Federal regulations [45 CFR 46.103(b)(5) and 21 CFR 56.108(b)(1)] require the organization to ensure prompt reporting of any unanticipated problems involving risk to subjects or others to the IRB, regulatory agencies, and institutional officials. Problems, reports, or other information reported to the IRB will be reviewed to determine whether it is an unanticipated problem involving risks to subjects or others. Based upon such reports the IRB will consider corrective actions or substantive changes, as necessary, in order to protect the safety, welfare, and rights of subjects or others.

The purpose of this document is to describe the requirements for reporting UPIRTSOs and other events to the IRB. The investigator is responsible for tracking all adverse events, incidents, experiences, complaints, or outcomes that are possibly related to the research. Events that do not require prompt reporting should be included in summary form at annual continuing review or administrative check-in.

II. Pertinent Definitions

A. Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO): Any event or information possibly related to the research that was unforeseen and indicates that the research procedures, approved by the IRB and carried out as expected, caused harm (including physical, psychological, economic, or social harm) to participants or others, or indicates that participants or others are at increased risk of harm than was previously known or recognized.

B. Adverse Event: Any unfavorable or unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.

C. **Serious Adverse Event:** Any adverse event that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, or other medical events, based upon appropriate medical judgment, that may jeopardize the patient or subject and may require medical, surgical, behavioral, or other intervention to prevent one of the outcomes listed in this definition.

D. **Unanticipated or unexpected event:** Any problem, event, information occurring that is new or where the nature, severity, or frequency is not consistent with either (1) the procedures involved in the research that are described the approved protocol, investigator brochure, or consent document and other relevant sources of information, such as product labeling and package inserts; or (2) the expected natural progression of any underlying disease, disorder, or condition.

E. **Possibly related:** In the opinion of the PI, the incident, experience, or outcome may be reasonably associated with the procedures involved in the research.

F. **Serious Problem:** Any event, problem, or information, including research information security, that may reasonably be regarded as presenting a genuine risk of substantive harm to the safety, rights, or welfare of human research subjects, research personnel, or others, including their rights to privacy and confidentiality of identifiable private information; or substantively compromising the HRPP or research information security program.

G. **Internal:** Any occurrence involving subjects enrolled in a study approved by the ETSU IRBs and directed by a PI affiliated with ETSU or the JHQVAMC.

H. **External:** Any occurrence involving subjects enrolled in a multi-site, collaborative study that are not under the purview of the ETSU IRBs.

I. **Prompt Reporting:** Events must be reported to the IRB within 10 business days using the appropriate report xform; for VA, reporting must occur within 5 business days.

III. Reportable Events

The following events must be promptly reported to the IRB:

- An unexpected harmful or unfavorable occurrence to participants or others that possibly relates to the research protocol (injuries, side events, psychological events, dosing errors)
- A serious adverse event or problem that are unexpected and probably related to the research procedures, interventions, or treatment
- An unforeseen development that potentially increases the likelihood of harm to subjects or others
- Any new information that indicates a change to the risks, safety, or benefits of the research

- Any deviation from the protocol taken without IRB approval to eliminate apparent immediate hazard to a research participant
- Any subject complaint that indicates an unanticipated problem or that cannot be resolved by the research staff
- Any problem reflecting a deficiency that substantially compromises the effectiveness of the institution's human research protection or human research oversight programs

The following are examples of events that require prompt reporting:

- A local subject death possibly related to the research.
- Incarceration of a subject for research not previously approved to enroll prisoners.
- Sponsor imposed suspension of research.
- A publication from another study that shows the risks, or potential benefits, of your study may be different than what was initially considered by the IRB.
- A data and safety monitoring report that indicates the frequency or magnitude of harm or benefits may be different than what was initially considered by the IRB.
- A black box warning (or VA PBM Safety Alert) for any drug or device used in your research study.
- A problem involving data storage, privacy, or confidentiality.
- An accidental or unintentional change to the IRB-approved procedures that increases the potential for harm to subjects or others.
- For VA studies, the VA requires immediate reporting of the loss, unauthorized use, disclosure, transmission, removal, theft, or destruction of VA research-related PHI or confidential information stored on portable media such as laptops or personal computers.

IV. PI Responsibilities for Reporting

This section describes the PI's responsibilities when assessing, documenting, reporting, and responding to adverse events.

A. PI Responsibilities

When an adverse event occurs, the PI is responsible for:

1. Eliminating apparent immediate hazards to subjects or others, which can be done before reporting the event to the IRB.
2. Documenting the details of the event in the study records including relevant outcomes related to the event.
3. Determining if the event meets the definition of a UPIRTSO and consulting with the IRB Chair for this determination, if needed.
4. Reporting any internal UPIRTSO to the IRB within 10 days (5 days for VA studies) of learning it using the appropriate report xform.

5. Reporting any other internal or external adverse events to the IRB in summary form at annual continuing review or administrative check-in using the appropriate xforms.
6. Monitoring subjects, as appropriate, to ensure their continued safety and welfare.
7. Modifying the study to incorporate appropriate protections or eliminate possible future harm related to the occurrence, and submit the appropriate xforms for IRB review.
8. Reporting the event to other entities, as appropriate, following their policies or requirement such as sponsors, VA R&D, data safety or site monitor(s), external site PIs, etc.

B. PI Reporting Criteria and Actions

Internal adverse events

When an internal adverse event occurs at sites where ETSU IRB serves as the IRB of record:

Upon becoming aware of an internal adverse event, PIs are required to immediately assess the event and determine whether the event is a UPIRTSO. The events details and PI's assessment including the rationale for the determination must be documented in the study records. PIs must evaluate each event by the following three criteria in order to make that determination.

1. Is the event unexpected?
2. Is the event possibly or definitely related to the research?
3. Does the event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized?

If the answer to all three questions is "yes," then the event meets the definition of a UPIRTSO and must be promptly reported to the IRB using the Unanticipated Problem Report xForm 109.

If all three questions are not answered "yes," then the event does not meet the definition of a UPIRTSO, and the event does not require prompt reporting. However, the PI responsible for documenting the event, the PI's assessment, determination and rationale that the event is not a UPIRTSO, and outcomes. All adverse events and protocol deviations are reportable to the IRB in summary format at the time of continuing review or administrative check-in. Refer to IRB Policy 11: Continuing Review.

External adverse events

When an external adverse event occurs at sites where ETSU IRB is not the IRB of record:

Upon becoming aware of an external adverse event that has been determined to be a UPIRTSO, the ETSU PI is required to document the event and its outcome in the study record including the external IRB's review of the event. External adverse events that are determined to be UPIRTSOs must be reported to the ETSU IRB in summary format at time of continuing review or administrative check-in.

Adverse events that do not meet the definition of a UPIRTSO occurring at external sites where ETSU IRB is not the IRB of record do not need to be reported to the ETSU IRB.

Follow-up Reports

Follow-up reports of an event may be submitted on a tracking log xform if the following are true:

1. The initial report of the event was submitted as a UPIRTSO on an Unanticipated Problem Report xForm
2. The local PI has determined that the follow-up information does not contribute meaningful new information

Reports of events occurring in studies that are completed and closed with the ETSU IRB should be reported if (1) the event is a UPIRTSO and (2) the PI determines that this event may affect risks to participants who have completed the study. The PI may consult with the ETSU IRB Director or Chair as needed for this assessment to determine if reporting is required.

C. Documentation

As stated above, PIs are responsible for documenting all adverse events and protocol deviations in the study record. Events that are determined by the PI not to be a UPIRTSO must be recorded in the study record along with the PIs rationale for the assessment. The unfounded classification of a serious adverse event as "anticipated" constitutes serious non-compliance with IRB policy. The PI is responsible for ensuring that the events are resolved as appropriate to eliminate future harm to subjects or others. All internal adverse events and protocol deviations must be reported to the ETSU IRB at time of continuing review or administrative check-in. PIs may utilize the tracking log xforms when prompt reporting is not required to submit the summary events to the IRB for review. The ETSU IRB will review the events to ensure adequate safety monitoring and determine if appropriate protections are in place for the welfare

of the subjects.

D. Study Modifications

PIs are responsible for ensuring that adverse events are resolved to eliminate potential harms to subjects or others and to avoid future events of the same nature. If in the opinion of the PI modifying the study is appropriate, a Modification xform should be submitted to the IRB for review and approval. The modification request should incorporate necessary revisions to the IRB-approved protocol, informed consent document, or other associated documents, as appropriate, to avoid future events that compromise subjects safety and welfare. Refer to Policy 10: Modifications.

V. IRB Review of Reports

When a PI submits a summary of internal events that do not require prompt reporting, the IRB Coordinator routes the submission to the appropriate IRB Chair for review. The tracking 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.

When an Unanticipated Problem Report xForm 109 is received by the ETSU IRB Office, the IRB Coordinator will route the written report to the appropriate IRB Chair immediately for priority review. The IRB Chair must determine and document whether any actions are warranted to eliminate apparent immediate hazards to subjects within 5 business days of the IRB receiving the written notification. If the Chair determines that there is the potential of immediate harm to participants, the Chair may immediately suspend the study pending the convened IRB review of the report and determination of any required actions. The investigator will be notified in writing if the Chair determines that actions are required to eliminate immediate harms to subjects or others, and the PI must respond in writing to confirm that appropriate actions were taken.

The Chair will perform an initial review and determine whether the event is a UPIRTSO by documenting on the Unanticipated Problem Report xForm whether the event is serious, unanticipated, and/or related or possibly related to the research.

If the Chair determines that the event is not a UPIRTSO, the xform is part of the study record, and the PI is notified in writing of the determination.

If the Chair determines that the event is probably a UPIRTSO, the Chair will refer the report to the convened IRB. The report will be added to the next agenda for the convened IRB. The Chair will select a Primary Unanticipated Problem (UP) Reviewer to complete the initial review and present recommendations to the committee. The UP Reviewer and IRB members will review:

- The Unanticipated Problem Report xForm 109 and attachments
- Narrative description of the project or new protocol submission xform
- Currently approved informed consent document(s)
- Previous reported events and tracking logs

If additional information is required in order to make a final determination concerning the event, the PI will receive such a request in writing from the Chair or convened IRB. The PI may be invited to attend the convened meeting to provide information requested by the IRB. The IRB will review the event and the preliminary determination/actions of the IRB Chair and must determine and document that:

a) The incident was serious and unanticipated and related to the research; or
b) There is insufficient information to determine whether the incident was serious and unanticipated and related to the research; or
c) The incident was not serious, and/or the incident was not unanticipated, and/or the incident was not related to the research.

The convened IRB will also determine any appropriate preventive or corrective actions. Examples of preventive/corrective actions or substantive changes that might need to be considered by the IRB in response to a UPIRTSO include:

a. Modification of inclusion or exclusion criteria to mitigate the newly identified risk
b. Implementation of additional procedures for monitoring subjects
c. Suspension of enrollment of new subjects
d. Suspension of research procedures in currently enrolled subjects
e. Modification of informed consent document(s) to include a description of newly recognized risks
a. Requirement of notification to participants that have completed study procedures
b. Reconsideration of study approval
c. Revision of the approval period
d. Termination of the research

The convened IRB may determine if any protocol or informed consent modifications are necessary. If information that may relate to subjects' willingness to continue to take part in the research is noted, the IRB will require notification of current participants. The IRB may require that the informed consent document(s) be revised to incorporate appropriate new information and that current participants be re-consented with the revised ICD. If modifications are required, the convened IRB must determine and document if re-consent of enrolled subjects is necessary, and if so, when such notification or re-consent must take place and how it must be documented.

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 others, or suspend/terminate IRB approval until such time that the safety of the participants can be assured.

The convened IRB review is recorded in the minutes and documented in the study record. The Principal Investigator will receive written notification of the IRB determination including any required actions within 30 days of the convened meeting.

The review determination for each Unanticipated Problem Report xform will be reported on the agenda of the next IRB meeting. If the IRB determines an event is a UPIRTSO, the reporting requirements outlined in IRB Policy 34 will be followed.

If the IRB makes additional determinations under its authority (e.g., serious noncompliance determination), any reporting requirements pertinent to such determinations must also be satisfied as outlined in IRB Policy 25.

VI. Additional VA Requirements

VA researchers are expected to be familiar and comply with applicable VHA requirements. For VA studies, Investigators, VA Research Compliance Officers, and other members of the VA research community are required to report all problems involving, or suggesting, risks to subjects or others to the Associate Chief of Staff for Research (ACOS/R) as soon as possible but no later than five (5) business days after becoming aware of the problem.

For VA studies, the following are also considered serious unanticipated problems that require prompt reporting (in addition to Section III):

- Interruptions of participant enrollments or research activities due to concerns about safety or welfare of subjects, research staff, or others
- Any work-related injury to research staff, or others, that requires more than basic first aid, time away from work or restricted work activities, extended medical surveillance, or leads to serious complications
- Any sponsor analysis describing a safety problem for which action at the VA facility might be warranted

For VA studies, the following apply to a local research subject death that is both unanticipated and related to the research:

1. VA personnel, including WOC and IPA appointees, must ensure oral notification to the Institutional Review Board (IRB) and ACOS/R&D immediately (i.e., within one hour) upon becoming aware of any local research death that is both unanticipated and related or possibly related to the research.
2. VA personnel, including WOC and IPA appointees, must ensure written notification to the IRB within one (1) business day of becoming aware of the death.
3. The ACOS/R&D must alert the VAMC Facility Director and ORO by e-mail or telephone within one (1) business day after receiving such notification and provide relevant information as requested.

4. Within one (1) business day after receiving written notification of the death, the IRB Chair, or designated qualified IRB member, must determine and document whether any actions are warranted to eliminate apparent immediate hazards to subjects, and if so, initiate those actions.
5. The IRB must review the death and the determination of the IRB Chair, or qualified IRB member, at its next convened meeting and must determine and document within 30 days of the IRB review that (a) the death was both unanticipated and related or possibly related to the research; or (b) there is insufficient information to determine whether the death was both unanticipated and related or possibly related to the research; or (c) the death was not unanticipated and/or the death was not related to the research.
6. Regardless of the determination under paragraph above, the convened IRB must also determine and document whether any protocol or informed consent modifications are warranted. If modifications are warranted, the convened IRB must determine and document whether or not investigators must notify or solicit renewed/revised consent from previously enrolled subjects; and if so, when such notification or consent must take place and how it must be documented.
7. The IRB must notify the VA Facility Director, RCO, and the ACOS/R&D of its determinations under #5-6 within 5 business days of the determinations.
8. The VA Facility Director must report the determinations to ORO within 5 business days after receiving the IRB's notification.

For VA studies, when receiving a report of a suspension or termination of non-exempt VA research:

1. The convened IRB must review the suspension/termination at the earliest practicable opportunity, not to exceed 30 business days after notification, to determine whether it:
    a. Resulted from a local adverse event(s), apparent serious noncompliance, or other issue(s); or
    b. Requires local action (in addition to the suspension/termination) to ensure the safety, rights, or welfare of local human research subjects, personnel, or others or the effectiveness of the local HRPP.
2. If the IRB determines that either (a) or (b) above applies:
    a. The IRB must notify the VA Facility Director, ACOS/R, and R&D within 5 business days after the determination; and
    b. The VA Facility Director must report the suspension/termination to ORO within 5 business days after receiving the IRB's notification.

VA reporting requirements require immediate reporting of the loss, unauthorized use, disclosure, transmission, removal, theft, or destruction of VA research-related PHI or confidential information stored on portable media such as laptops or personal computers (in accordance with VHA Directive 1058.01, Section 11.a). For VA studies, notifications of information security incidents must be reviewed by the IRB at its earliest practicable convened meeting but not to exceed 30 business days from the date of notification. The convened IRB must determine:

a) Whether or not the incident constitutes a serious problem and

b) In conjunction with the ISO and/or PO, as applicable, whether and what remedial actions are warranted by the facility or the relevant investigator(s).

If the IRB determines that the incident constitutes a serious problem:

a) The IRB must notify the VA Facility Director and the ACOS/R&D within 5 business days after the determination.
b) The VA Facility Director must report the determination to ORO within 5 business days after receiving the committee's notification.

Refer to Policy 34 for VA reporting requirements.

References:

45 CFR 46.108, 46.104(a), 35.104(b)
21 CFR 56.108(b)(1)
VHA Directive 1058.01, October 22, 2020
Appendix A, Memo from Deputy Under Secretary for Health Operations and Management (DUSHOM) and Chief Research and Development Officer (CRADO), dated February 6, 2007
OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, dated January 15, 2007