

**UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER
INSTITUTIONAL REVIEW BOARD
REPORTING UNANTICIPATED PROBLEMS INCLUDING ADVERSE
EVENTS**

I. PURPOSE

To specify the procedures for reporting unanticipated problems, including adverse events, that occur in studies approved by the University of Tennessee Health Science Center Institutional Review Board.

II. SCOPE

This SOP applies to all investigators performing research approved by UTHSC IRB.

Personnel responsible:

IRB administrative staff, IRB members, and investigators.

III. BACKGROUND

The federal regulations for the protection of human subjects specify that institutions engaged in research with human subjects must have written procedures for ensuring prompt reporting to the IRB, institutional officials, and any supporting department or agency of any unanticipated problems, including adverse events, involving risks to subjects or others. Unanticipated problems, including adverse events, are considered reportable to the IRB when they involve occurrences that are unexpected, related to or possibly related to study activities, and significant enough to suggest that the research may place subjects or others at a greater risk of harm than was previously known or recognized. Adverse events, which involve untoward or unfavorable medical occurrences in human subjects, are the most common type of unanticipated problem reportable to IRBs. Adverse events should be considered unanticipated problems **only if** they would have implications for the conduct of the study, requiring a significant safety-related change in the protocol, informed consent disclosure or investigator's brochure (e.g., revision of inclusion/exclusion criteria or a new monitoring requirement).

While most unanticipated problems reported to the IRB involve adverse physical or psychological events that may be related to study interventions, other types of incidents, experiences, or outcomes that occur during the conduct of human subjects research may also constitute unanticipated problems. Some

unanticipated problems may involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs. These unanticipated problems may be reportable to the IRB even when they do not result in any actual harm to subjects. For example, unintended disclosure of confidential research data represents an unanticipated problem that is not an adverse event. Even if the breach of confidentiality does not result in harm to subjects, it may necessitate re-consideration by the IRB of the study procedures used to protect the confidentiality of the research data.

Reports of unanticipated problems are utilized by the IRB to determine whether the risk-benefit ratio for the study, study procedures, and the previously approved informed consent process/document remain acceptable. In some cases, unanticipated problems warrant substantive changes to assure that the rights and welfare of subjects continue to be adequately protected. Changes that may be necessitated by unanticipated problems include, but are not limited to: modification of inclusion/exclusion criteria; implementation of additional monitoring procedures; suspension of enrollment of new subjects; suspension of research procedures in currently enrolled subjects; changes in procedures for protecting the confidentiality of research data; modification of consent documents to acknowledge newly identified risks; and provision of new risk information to previously enrolled subjects.

The procedures described below address only the obligations of investigators to report unanticipated problems to the IRB. By contrast, investigators conducting FDA-regulated drug/biologic studies have a much broader obligation for reporting to study sponsors all serious adverse events, even if they are not unanticipated problems. Similarly, sponsors of drug/biologic studies must provide the FDA with a summary of all serious adverse events in their annual reports. However, these additional reporting requirements of investigators and sponsors do not apply to communication with the IRB, which must only be informed regarding unanticipated problems that have occurred in the conduct of a study.

In accordance with:

For studies approved under the revised Common Rule:
45 CFR 46.108(a)(4); and

For studies approved under the Pre-2018 Common Rule:
[45 CFR 46.103\(b\)\(5\)](#); and

For FDA-regulated studies:

21 CFR 56.108(b)(1); 21 CFR 312.32; 21 CFR 312.53(c)(1)(vii); 21 CFR 312.64; 21 CFR 312.66; and 21 CFR 812.3(s)

Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events: OHRP Guidance (2007)
<http://www.hhs.gov/ohrp/policy/advevtguid.html>

Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (Video)
http://www.youtube.com/watch?v=hsUS0k3Ie_g&list=PL5965CB14C2506914

FDA Guidance for Clinical Investigators, Sponsors and IRBs: Adverse Event Reporting to IRBs – Improving Human Subject Protection (January 2009)
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079753.pdf>

Compliance with this policy also requires compliance with state or local laws or regulations that provide additional protections for human subjects.

IV. DEFINITIONS

Unanticipated Problem involving risks to subjects or others: Any incident, experience, or outcome that meets ALL of the following criteria:

- (1) it is unexpected (in terms of nature, severity, or frequency) given (a) the research interventions that are described in the protocol-related documents, such as the IRB- approved research protocol, investigator’s brochure/package inserts, and informed consent document; and (b) the characteristics of the subject population being studied (e.g., the expected natural progression of any underlying disease, disorder, or condition of the subject and the subject’s predisposing risk factor profile for the adverse event);
[**Note:** adverse events listed in the investigator’s brochure would, by definition, not be considered unexpected, unless it has been determined that they are occurring at a higher frequency than the investigator’s brochure indicates];
- (2) it is clearly related or there is a reasonable possibility that it is related to the research intervention or procedures (in this document, *reasonable possibility* means there is evidence to suggest a causal relationship between the adverse event, incident, experience or outcome and the research intervention or procedures involved in the research, other than a mere temporal association); and
- (3) it suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the

research than was previously known or recognized.

Adverse Event (adverse effect, adverse experience, unanticipated problems, or unanticipated adverse device effect): Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

External Adverse Event: From the perspective of one particular institution engaged in a multicenter clinical trial, *external adverse events* are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial.

Internal Adverse Event: From the perspective of one particular institution engaged in a multicenter clinical trial, *internal adverse events* are those adverse events experienced by subjects enrolled by the investigator(s) at that institution. In the context of a single-center clinical trial, all adverse events would be considered *internal adverse events*.

Reasonable Possibility that the event is related to the research: There is evidence to suggest a causal relationship between the adverse event, incident, experience or outcome and the research intervention or procedures involved in the research, other than a mere temporal association.

Serious Adverse Event: Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- (1) results in death;
- (2) is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- (3) requires inpatient hospitalization or prolongation of existing hospitalization;
- (4) results in a persistent or significant disability/incapacity;
- (5) results in a congenital anomaly/birth defect; or
- (6) any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

V. PROCEDURES

1. Reports of problems occurring in research studies, including adverse events at internal or external sites, should be submitted **only if** they meet the definition of unanticipated problem, meaning that they are determined to be:
 - a. Unexpected (in terms of nature, severity, or frequency) given (a) the research interventions that are described in the protocol-related documents, such as the IRB-approved research protocol, investigator's brochure/package inserts, and informed consent document; and (b) the characteristics of the subject population being studied (e.g., the expected natural progression of any underlying disease, disorder, or condition of the subject and the subject's predisposing risk factor profile for the adverse event);
 - b. it is clearly related or there is a reasonable possibility that it is related to the research intervention or procedures; and
 - c. significant enough to suggest that subjects may be placed at greater risk of harm that previously known or recognized
2. **External adverse events** that meet all 3 reporting criteria (outlined in the definition of unanticipated problem above) must be reported to the IRB within 10 working days of their receipt by the principal investigator.
3. **Internal adverse events**, other than deaths, that meet all 3 reporting criteria (outlined in the definition of unanticipated problem above) must be reported by the principal investigator to the IRB within 5 working days of the time that the investigator or research staff member becomes aware of their occurrence.
4. **Deaths** occurring locally that meet all 3 reporting criteria (outlined in the definition of unanticipated problem above) must be reported by the principal investigator to the IRB within 24 hours of the time that the investigator or research staff member becomes aware of their occurrence.
5. **Unanticipated problems other than adverse events** must be reported by the principal investigator to the IRB within 5 working days of the time that the investigator or research staff member becomes aware of their occurrence.
6. The Principal Investigator will use the Form 4 to submit one of the following reports (via iMedRIS) for IRB review:
 - a. **Local Reportable Adverse Events or Other Unanticipated Problem-**
The report of an unanticipated problem, including an internal adverse event, should include the facts of the case, including subject identifier; adverse event or problem description; the event relationship to research

interventions; the degree of seriousness; whether the event was unexpected; date of injury; whether the intervention was stopped and if so, whether it was re-started; and whether the event provides new risk information that alters the risk-benefit assessment and whether the protocol procedures and/or informed consent disclosure should be modified.

- b. **External Reportable Adverse Events or Unanticipated Problem** – Report an unanticipated problem, including an external adverse event should include the facts of the case and whether the event provides new risk information that alters the risk-benefit assessment and whether the protocol procedures and/or informed consent disclosure should be modified
 - c. **Major Protocol Deviation/Violation** – See SOP: Protocol Waivers and Deviations.
 - d. **Protocol Waiver Request** – See SOP: Protocol Waivers and Deviations.
 - e. **Problem identified in an audit, inspection, or inquiry by a federal agency, or a study site or institution**
 - f. **Suspension or premature termination of the study by the sponsor, investigator, or institution**
 - g. **State medical board action**
 - h. **Loss of investigator’s credentials at an institution**
7. The principal investigator will apply his her/her electronic signature to the report prior to submission to UTHSC IRB.
8. Upon receipt of a Form 4, the administrative staff will electronically forward it to the Director or designee for review. Form 4s that are submitted for studies that occur at Methodist Healthcare facilities will also be forwarded to a Board member from Methodist to conduct an administrative review. Based on the review, a preliminary determination will be made about whether the event reported requires a revision of the protocol, the informed consent document/process, or other aspect of the study. If changes are determined to be necessary and represent more than minor revisions, then the changes must be reviewed and approved by the convened IRB.

9. The IRB has authority, under HHS regulations at 45CFR46.109(a), to require, as a condition of continued approval by the IRB, submission of more detailed information by the investigator, the sponsor, the study coordinating center, or Data Meeting Committee (or Data & Safety Monitoring Board) about any adverse event or other unanticipated problem occurring in a research protocol.
10. Any proposed changes to a study in response to an unanticipated problem must be reviewed and approved by the IRB before being implemented, except when necessary to eliminate apparent immediate hazards to subjects.
11. For multicenter studies, if the IRB proposes changes to the protocol or informed consent documents/process based on an adverse event report, in addition to any changes proposed by the study sponsor, coordinating center, or local investigator, the IRB will request that the local investigator discuss the proposed modifications with the study sponsor or coordinating center and submit a response or necessary modifications for review by the IRB.
12. If internally occurring unanticipated problems, including adverse events, necessitate changes in the study protocol or the informed consent process/document, then the IRB will notify the UTHSC Vice Chancellor for Research.
13. When internally occurring unanticipated problems, including adverse events, require suspension or termination of a research study, they will be reported by the Human Protections Administrator to the institution, supporting agency head (or designee) and, when federally funded, to OHRP.
14. All adverse events that are reportable as unanticipated problems will be placed on the agenda for review by the full Board and will be sent electronically to Board members before the Board meeting each applicable week when the agenda is finalized.
15. The investigator will be notified about whether the IRB considers the event reported to require a revision of the protocol, the informed consent document/process, or other aspect of the study, or about whether the IRB accepts any revisions proposed by the principal investigator. A copy of all correspondence / reports will be kept in the IRB files for the study.