

**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. Serious adverse events, as defined below, if they are unexpected and related or possibly related to study procedures, are *ipso facto* considered to be occurrences indicating that the research may involve greater risk of harm than previously known or recognized and, therefore, must be reported to the IRB.

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, including adverse events, to the IRB. Investigators conducting FDA-regulated studies incur additional obligations for reporting adverse events to study sponsors. Similarly, study sponsors have obligations for informing local investigators regarding the occurrence of adverse events at other study sites. These additional obligations of investigators and sponsors involve more extensive adverse event reporting requirements than those specified by the IRB.

**In accordance with:**

45CFR46.103(b)(5); 21CFR56.108(b)(1); 21CFR312.53(c)(1)(vii); and 21CFR312.66

OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events located at <http://www.hhs.gov/ohrp/policy/AdvEvtGuid.pdf>

FDA Draft Guidance for Clinical Investigators, Sponsors and IRBs on Adverse Event Reporting located at <http://www.fda.gov/OHRMS/DOCKETS/98fr/07d-0106-gdl0001.pdf>

#### IV. **DEFINITIONS**

**Unanticipated problem involving risks to subjects or others:** Any incident, experience, or outcome that meets all of the following criteria:

- (1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB- approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- (2) related or possibly related to a subject's participation in the research; and
- (3) 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:** 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*.

**Possibly related to the research:** There is a reasonable possibility that the adverse event, incident, experience or outcome may have been caused

by the procedures involved in the research.

**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).

**Unexpected adverse event:** Any adverse event occurring in one or more subjects in a research protocol, the nature, severity, or frequency of which is not consistent with either:

- (1) the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) 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 of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

## V. PROCEDURES

1. Reports of problems occurring in research studies, including adverse events at internal or external sites, should be submitted **only if** they are determined to be: unexpected; significant enough to suggest that subjects may be placed at greater risk of harm than previously known or recognized; and possibly, probably or clearly caused by the research intervention (rather than unrelated or unlikely related to the research intervention). Any serious adverse events, as defined above, if they

are unexpected and related or possibly related to study procedures, must be reported to the IRB. However, all serious adverse events, even if they are expected and/or not related to study procedures, must be reported for studies occurring at Methodist hospitals, including Lebonheur Children's Medical Center.

2. External adverse events (such as "IND Safety Reports" provided by the sponsor of the research) must be reported to the IRB within 10 working days of their receipt by the principal investigator.
3. Internal adverse events, other than deaths, 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 are unexpected and are possibly, probably, or clearly caused by the research intervention 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 Investigator will use the Report Local Adverse Event (Form 4a) to report internal adverse events. Information 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/or should be added to the informed consent disclosure. The Report External Adverse Event form (Form 4b) will be used to report unanticipated external adverse events. The Report Problem or Protocol Deviation form (Form 4c) must be used to report unanticipated problems other than adverse events. The Non-Reportable Adverse Events or Problems form (Form 4d) may be used to report problems for which reporting to the IRB is not required by IRB policy. The Methodist Hospital and Lebonheur Children's Adverse Event form (Form 4e) is used to report serious adverse events in those facilities.

7. The principal investigator will sign the report prior to submission to UTHSC IRB.
8. Upon receipt of a report of an unanticipated problem, including adverse events (Form 4), the administrative staff will stamp the date of receipt and the report will be recorded on the adverse event log (for placement on meeting agenda). The Form 4 and the study file are sent to the Chairman or designee for 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 DMC 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 Human Protections Administrator, the UTHSC Associate 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 OHRP.

14. All reportable adverse events will be placed on the agenda for review by the full Board.
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.