

Institutional Review Board
HUMAN SUBJECTS PROTECTION OFFICE

PENN STATE COLLEGE OF MEDICINE
PENN STATE MILTON S. HERSHEY MEDICAL CENTER

IRB Information Sheet

Reporting of Unanticipated Problems

The federal regulations require that organizations have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and appropriate federal officials of unanticipated problems involving risks to participants or others.

Consistent with these regulations, this information sheet outlines the problems that investigators are required to report promptly to the IRB in order to ensure prompt reporting of unanticipated problems involving risks to human participants or others.

Definitions:

- **Adverse Event:** Any untoward or unfavorable medical occurrence in a human participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice). Adverse events encompass both physical and psychological harms and can occur in the context of social and behavioral research.
- **Unexpected adverse event:** Any adverse event, occurring in one or more participants in a research protocol, the nature, severity or frequency of which is not consistent with either:
 - a. 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
 - b. The expected natural progression of any underlying disease, disorder or condition of the participant(s) experiencing the adverse event and the participant's predisposing risk factor profile for the adverse event.(Modified from the definition of unexpected adverse drug experience in FDA regulations at 21 CFR 312.32(a).)
- **Expected adverse event:** Any adverse event that does not meet the definition of an unexpected adverse event.
- **Possibly related to the research:** An event is related to the research if, in the opinion of the Penn State University (PSU) or Penn State Milton S. Hershey Medical Center (HMC) investigator, there is a reasonable possibility that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research (modified from the definition of *associated with use of the drug* in FDA regulations at 21 CFR 312.32(a)). A reasonable possibility is defined as more likely than not related to the research procedures or the collection of identifiable private information in the research.

- Unrelated to the research: An adverse event is unrelated to the research if, in the opinion of the PSU/HMC investigator, the adverse event is not related to the research.
- Internal events: Adverse events experienced by participants enrolled by the investigators at the site(s) under the IRB's jurisdiction for either multicenter or single-center research projects.
- External events: Adverse events experienced by participants enrolled in multicenter clinical trials at sites other than the site(s) over which the IRB has jurisdiction.
- Unanticipated problems involving risks to participants or others (unanticipated problems): Any incident, experience or outcome that meets all of the following criteria:
 - Unexpected (in terms of nature, severity, or frequency) given (1) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (2) the characteristics of the participant population being studied;
 - Related or possibly related to a participant's participation in the research; and
 - Suggests that the research places participants 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.

What types of problems must investigators report to the IRB?

Investigators are required to promptly report the following problems to the IRB.

1. Events that are (1) unexpected; (2) related or possibly related to the research as determined by the PSU/HMC principal investigator; and (3) involves increased or greater risk of harm to participant(s) or others than was previously known or approved by the IRB
2. Information that indicates a change to the risks or potential benefits of the research
For example:
 - a. An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB
 - b. A paper is published from another study that shows that the risks or potential benefits of the research may be different than initially presented to the IRB
3. Breaches of confidentiality
4. Events (other than adverse events listed above) that require prompt reporting according to the protocol or the sponsor
5. Suspensions for any reasons other than planned suspensions for interim analyses, including sponsor-imposed suspension for risk
6. Accidental or unintentional deviations to the IRB-approved protocol that involved risks or have the potential to recur
7. Emergency protocol deviations taken without prior IRB review to eliminate apparent immediate hazard to research participants
8. Complaints of participants that indicate unanticipated risk or which cannot be resolved by the research staff

What is the time frame for reporting these problems?

Investigators must report problems to the IRB according to the following timelines:

- Internal problems that require prompt reporting and are fatal or life-threatening must be reported to the IRB within one weekday of the principal investigator becoming aware of the event.
- All other internal problems that require prompt reporting must be reported within 5 weekdays of the principal investigator becoming aware of the event or problem.
- External problems that require prompt reporting are to be reported within 30 days of their receipt by the PSU/HMC principal investigator.

What must be included in the report to the IRB?

Reports to the IRB must include the following:

- A Problem Report Form, which includes identifying information (title of the research, name of principal investigator, IRB protocol number, name of the sponsor), and a description of the event;
- For internal and external adverse events, a Problem Accumulative Tracking Log; and
- Any associated materials, if any
 - For internal adverse events, the associated materials should include the following applicable materials: (1) reports sent to a sponsor about the event; (2) admission/discharge summaries; (3) relevant laboratory data; concomitant medications; and/or (4) medical record notations.
 - For external adverse events, the associated materials should include the sponsor's safety report form.

What should investigators do about problems that do not require prompt reporting to the IRB?

For problems that do not require prompt reporting, investigators should do the following:

- Internal adverse events that are unexpected and unrelated except for deaths do not need to be reported to the IRB. Unexpected and unrelated deaths are reported to the IRB at the time of continuing review on the Other Event/Problem Accumulative Tracking Log.
- Internal adverse events that are expected and unrelated except for deaths do not need to be reported to the IRB. Expected and unrelated deaths are reported to the IRB at the time of continuing review on the Other Event/Problem Accumulative Tracking Log.
- Internal adverse events that are expected and related which are consistent with the frequency and severity listed in the informed consent document, the principal investigator keeps a summary of these expected and related events that have occurred within the last approval period and submits the summary at the time of continuing review using the "Other Event/Problem Accumulative Tracking Log".
- External adverse event reports that do not require prompt reporting to the IRB, are reviewed, initialed and dated by the Principal Investigator and filed with the research regulatory documents. This record is to be made available to the IRB upon request. A Non Reportable External Event Form, listing the event codes for external adverse events that do not meet the IRB's reporting requirements, may be submitted to the IRB if required by the sponsor.

- Accidental or unintentional deviations to the IRB-approved protocol that involved no risks may be submitted to the IRB using the Protocol Deviation Report Form if required by the sponsor.

For additional help in determining the reporting requirements for adverse events, use the Internal and External Adverse Event Flow Sheets which are available on the IRB web site at:

<http://www.hmc.psu.edu/irb/forms/studies/index.htm>

For additional information see the on-line resources, including the Problem Report Form.

Internal Adverse Events HMC/COM Principal Investigator's Assessment



