

STANDARD OPERATING PROCEDURE ADDENDUM

Reporting and Review of Unanticipated Problems Involving Risks to Participants or Others

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 and IRB policies, this policy 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.

A. Definitions

1. 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.
2. Serious adverse event: Any event temporally associated with the participant's participation in research that meets any of the following criteria:
 - a. Results in death;
 - b. Is life-threatening (places the participant at immediate risk of death from the event as it occurred);
 - c. Requires inpatient hospitalization or prolongation of existing hospitalization;
 - d. Results in a persistent or significant disability/incapacity;
 - e. Results in a congenital anomaly/birth defect;
 - f. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the participant'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); or
 - g. Results in a severely debilitating situation for the participant, such as psychological distress, financial hardship or damaging impact on social standing or employability.
3. 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).)

4. Expected adverse event: Any adverse event that does not meet the definition of an unexpected adverse event.
5. 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.
6. 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.
7. 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.
8. External events: Adverse events experienced by participants enrolled in multicenter clinical trials by investigators at sites other than the site(s) over which the IRB has jurisdiction.
9. Unanticipated problems involving risks to participants or others (unanticipated problems): Any incident, experience or outcome that meets all of the following criteria:
 - a. 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;
 - b. Related or possibly related to a participant's participation in the research; and
 - c. 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.

B. IRB Reporting Requirements

1. Investigators are required to promptly report the following problems to the IRB:
 - a. 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.
 - b. Information that indicates a change to the risks or potential benefits of the research. For example:
 - i. 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.
 - ii. 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.

- c. Breach of confidentiality.
 - d. Event (other than B.1.a above) that requires prompt reporting according to the protocol or the sponsor.
 - e. Suspensions for any reasons other than planned suspensions for interim analyses, including sponsor-imposed suspension for risk.
 - f. Accidental or unintentional deviations to the IRB-approved protocol that involved risks or has the potential to recur;
 - g. Emergency protocol deviations taken without prior IRB review to eliminate apparent immediate hazard to research participants;
 - h. Complaints of participants that indicate unanticipated risk or which cannot be resolved by the research staff;
 - i. U.S. Food and Drug Administration Form 483 or findings from audits performed by other governing regulatory agencies (or authority); and
 - j. Any report provided to investigators for audits performed by an agency external to study sponsors or their authorized representatives.
2. Investigators must submit problems requiring prompt reporting to the IRB in accordance with the following timelines:
- a. 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 problem.
 - b. 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.
 - c. External problems that require prompt reporting are to be reported within 30 days of their receipt by the PSU/HMC principal investigator.
 - d. The problems listed above in B.1 require reporting to the IRB regardless of whether they occur during the study, after study completion or after participant withdrawal or completion.
3. Reports of problems requiring prompt reporting must include the following:
- a. 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;
 - b. For internal and external adverse events, a "Problem Accumulative Tracking Log"; and
 - c. Any associated materials, if any.
 - i. 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.

- ii. For external adverse events, the associated materials should include the sponsor's safety report form.
4. Investigators must submit problems and events that do not require prompt reporting according to the following reporting requirements.
 - a. 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.
 - b. 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.
 - c. For 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".
 - d. External adverse events that are unexpected and unrelated and those that are expected do not need to be reported to the IRB. These external event reports are reviewed 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.
 - e. Accidental or unintentional deviations to the IRB-approved protocol that do not involve risks to participants or do not have the potential to recur do not need to be reported to the IRB. A "Protocol Deviation Report Form", listing the protocol deviation that does not meet the IRB's reporting requirements, may be submitted to the IRB if required by the sponsor or requested by the IRB.
5. The Penn State College of Medicine (COM) IRB will no longer review individual adverse event reports related to Phase 3 Cancer Therapy Evaluation Program (CTEP)-sponsored multicenter trials that are submitted by cooperative groups to the COM investigators. The COM IRB will review the Data and Safety Monitoring Board (DSMB) report and the study report at time of continuing review. Investigators will be required to provide the most current DSMB report and study report with the Continuing Progress Report. IRB review of each study for continuation will be dependent upon receipt of the DSMB report and study report.

C. IRB Process for Review and Handling Reported Problems

1. All reports are submitted to the ORP or HSPO.
2. Reports are evaluated by an IRB staff member for completeness.
 - a. If the report is incomplete, it is returned to the investigator with a request for the additional information.
 - b. The PSU/HMC investigator's assessment of external events must be provided or the report is considered to be incomplete and is returned to the investigator.
3. Complete reports are reviewed by an IRB Chair, Vice-chair or designated IRB member with appropriate expertise for initial review (IRB reviewer). The IRB reviewer is provided with the protocol file containing the IRB-approved protocol and consent form.
4. The IRB reviewer is responsible for determining whether the reported problem represents an unanticipated problem involving risks to participants or others as defined above. The PSU/HMC investigator's assessment of the event is reviewed and considered in this determination.

- a. If in the judgment of the IRB reviewer the problem is not an unanticipated problem involving risks to participants or others or that there is not enough information to make a determination, the report is documented as such, signed by the reviewer and filed in the IRB study file.
 - b. If the IRB reviewer is unable to determine if the event represents an unanticipated problem involving risks to participants or others, the report is referred for review by the IRB at a convened meeting as described below for unanticipated problems involving more than minimal risk.
5. If the IRB reviewer determines that the event is an unanticipated problem involving risks to participants or others, the IRB reviewer is responsible for determining and documenting on the review form whether the event involves more than minimal risk or not.
- a. Unanticipated problem reports that do not involve more than minimal risk are reviewed by the IRB reviewer using the expedited review procedure.
 - i. The IRB reviewer may take one or more of the following actions:
 - a. Accept the report and approve the proposed changes, if any, with no further action required;
 - b. Require additional information;
 - c. Require modifications to the protocol and/or consent form;
 - d. Require that participants currently on protocol be notified of the event;
 - e. Require that participants whose participation has ended be notified of the event; or
 - f. Any other actions deemed appropriate by the IRB reviewer.
 - ii. For a report of an accidental or unintentional deviation to the IRB-approved protocol that involves no more than minimal risk or has the potential to recur, the IRB reviewer also considers if the event represents serious or continuing non-compliance according to "SOP on the Handling of Allegations of Non Compliance".
 - iii. For a report of an emergency protocol deviation taken without prior IRB review, the IRB reviewer considers if the changes were consistent with the rights and welfare of participants.
 - iv. The IRB reviewer is responsible for documenting findings and actions.
 - v. An IRB Coordinator is responsible for communicating findings and actions to the Principal Investigator.
 - b. Unanticipated problems that involve more than minimal risk are referred for review by the IRB at a convened meeting.
 - i. If, in the judgment of the IRB reviewer, participants may be at immediate risk of harm and there is insufficient time to wait for review by the convened IRB, an IRB Chair, the Director of the Office for Research Protections, or the Director of the Human Subjects Protection Office is consulted. If the Chair or a Director determines that participants are at immediate risk of harm, the principal investigator will be required to suspend the study according to IRB policy for suspension or termination of research. (See the SOP on "Suspension or Termination of IRB Approved Research".)
 - ii. For reports that are sent to the convened IRB for review, the report is added to an IRB meeting agenda and is assigned to a primary reviewer by the IRB staff on the basis of the scientific expertise of the review.
 - iii. The primary reviewer and all other board members receive the following information:
 - a. The problem report form;
 - b. All supplemental materials attached to the report;
 - c. All tracking logs, if applicable;
 - d. The sponsor adverse event report form, if applicable

- e. The DSMB or safety report, if applicable;
 - f. A summary of the study;
 - g. Current, IRB-approved informed consent document(s) and revised informed consent document(s); and
 - h. Any other relevant materials.
- iv. The primary reviewer is responsible for an in-depth review of the report of the event and materials provided and completion of the reviewer form for problem reports. All other members are responsible for review of the report of the event and the consent form(s) in sufficient depth to vote at the meeting.
 - v. By majority vote of a quorum of the membership present at the convened meeting, the IRB determines if the reported problem represents an unanticipated problem involving risks to participants or others as defined above and may take one or more of the following actions:
 - a. Accept the report and approve the proposed changes, if any, with no further action required;
 - b. Require additional information;
 - c. Require modification to the protocol and/or informed consent document(s) for future participants ;
 - d. Require notification of current or past participants by phone, letter or addendum to the informed consent document;
 - e. Modify the continuing review schedule;
 - f. Require monitoring of the research or consent process;
 - g. Request a directed post-approval on-site review by the Quality Assurance Coordinator (COM) or Post-approval Reviewer (UP);
 - h. Suspend or terminate the research according to IRB SOP on "Suspension or Termination of IRB Approved Research";
 - i. Referral to legal counsel, risk management or the institutional official; and/or
 - j. Other appropriate action as determined by the IRB.
 - vi. For a report of an accidental or unintentional deviation to the IRB-approved protocol that involved risks or has the potential to recur, the IRB also considers if the event represents serious or continuing non-compliance according to "SOP on the Handling of Allegations of Non Compliance".
 - vii. For a report of an emergency protocol deviation taken without prior IRB review, the IRB considers if the changes were consistent with the rights and welfare of participants and determine if any additional follow-up action is warranted.
 - viii. The HSPO or ORP staff are responsible for recording the findings and actions of the IRB and, when relevant, the discussion of controverted issues and their resolution in the minutes of the meeting.
 - ix. The HSPO or ORP staff are responsible for notifying the principal investigator in writing of the findings and actions of the IRB.
- 6. The IRB submits a report of the events determined to be unanticipated problems involving risk to participants or others to appropriate institutional officials and entities according to IRB SOP on Reporting of Unanticipated Problems, Terminations, Suspensions, and Non-compliance.
 - 7. Investigators may appeal the IRB determinations regarding the report of an unanticipated problem involving risks to participants or others. In order to appeal an IRB decision, the investigator must submit his/her rationale or that of the sponsor and any supporting information. An appeal must be reviewed by the IRB that made the original decision.

D. IRB Process for Handling Reports that Do Not Require Prompt Reporting

1. Internal events submitted on the "Other Event/Problem Accumulative Tracking Log" at the time of continuing review are reviewed according to the IRB SOP's for Continuing Review.
2. Accidental or unintentional deviations to the IRB-approved protocol that do not involve risks are reviewed by a designated IRB reviewer. The PSU/HMC investigator's plan to prevent future occurrences is considered during the review.
 - a. If the report is incomplete, it is returned to the investigator with a request for the additional information.
 - b. If the IRB reviewer determines that the deviation involved risks or has the potential to recur, the deviation report is reviewed according to Section C of this policy.
 - c. Otherwise, the IRB reviewer stamps the form acknowledging receipt by the IRB office, signs, dates the form and returns a copy of the form to the investigator.
3. External events submitted to the IRB using the Non Reportable External Event Form are reviewed by designated IRB reviewer.
 - a. If the report is incomplete, it is returned to the investigator with a request for the additional information.
 - b. If the investigator indicates that any event meets the definition of a reportable problem, the IRB reviewer contacts the investigator to request that the investigator complete the "Problem Report Form" as required in Section B of this policy.
 - c. Otherwise, the IRB reviewer stamps the form acknowledging receipt by the IRB office, signs, dates the form and returns a copy of the form to the investigator.

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| Institutional Review Board The Pennsylvania State University Penn State College of Medicine Penn State Milton S. Hershey Medical Center | PENNSSTATE  |
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