

Human Research Protection Program Policies & Procedures



Unanticipated Problems and Adverse Events

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Background

The Common Rule and FDA regulations require that unanticipated problems involving risks to subjects or others be promptly reported by the IRB to the federal agencies overseeing the research. Most adverse events occurring in the context of research are expected in light of the known toxicities and side effects of the research procedures or are due to the natural history of subjects' underlying diseases or conditions. Therefore, the majority of adverse events do not represent unanticipated problems which are reportable by the PI to the IRB and subsequently by the IRB to appropriate federal agencies.

I. Scope

This policy defines unanticipated problems and adverse events and establishes the reporting process and timeline.

II. Responsible Parties

- A. Principal Investigator (PI)
- B. Institutional Review Board (IRB)
- C. Central Monitor

III. Policy

- A. PIs are required to promptly submit written reports of events to the IRB that represent potential unanticipated problems involving risks to subjects or others.
- B. Meaningful review and management of adverse events and potential unanticipated problems is dependent on adequate and appropriate safety monitoring.

IV. Procedure

A. Responsibilities

1. Principal Investigators – It is the PI's responsibility to analyze and review all adverse events (AEs) and potential Unanticipated Problem (UPs) that occur in studies on which he/she is the PI, determine if an AE is a potential UP, determine the appropriate action to be taken in response to these events, and appropriately report potential UPs to the IRB. In the case of an On Protocol event in a Non-OHSU subject, the determination of whether the AE represents a UP lies with the central monitor.
2. Institutional Review Board – It is the IRB's responsibility to review the reports, determine if modifications are needed in response to a reported event, determine whether a reported event is an Unanticipated Problem, and to report Unanticipated Problems occurring at OHSU to, as applicable, the Federalwide Assurance (FWA) signatory official, any supporting department or agency head, OHRP, and/or FDA. The OHSU IRB's reporting obligations may be delegated to a central monitor or another IRB.
3. Central Monitor - It is the Central Monitor's responsibility to analyze and review applicable On Protocol events for Non-OHSU subjects and Off Protocol events

using the same drug or agent, determine if the AEs are UPs, and report the UPs to the PI for subsequent reporting to the PIs IRB. If OHSU is serving as a coordinating center, then the PI of the coordinating center is responsible for this determination via an approved monitoring plan.

B. Reportable Adverse Event Analysis

1. In order for the PI (or the Central Monitor) to determine whether a particular AE is “unanticipated” and also considered reportable as a potential UP, the following should be taken into account:
 - The description of known or foreseeable adverse events and risks in the IRB-approved research protocol, any applicable investigator brochure, the current IRB-approved consent form, and other relevant sources of information.
 - Any underlying disease or conditions of the subject experiencing the adverse event.
 - A careful assessment of whether the adverse event is related or possibly related to the subject's participation in the study.
2. The UP analysis charts and/or the UP Decision Tree should be used to help make this determination. The charts provide guidance on determining when an event is expected and related as well as when to report events that occur outside of OHSU or on different protocols.
3. Any event that is rare in the absence of drug exposure, such as agranulocytosis, hepatic necrosis, or Stevens-Johnson syndrome, should always be reported to the IRB.

C. When to Report

1. All potential UPs, including AEs that meet the definition of a potential UP as determined by the PI or the Central Monitor, unless otherwise determined by the reviewing IRB, must be reported by the PI to the IRB as soon as possible, and within the following time frames:
 - Deaths and potentially life-threatening events must be reported within seven (7) calendar days after the PI learns of the event. If any of these SAEs requires a change (as determined by the PI or the IRB) to the protocol or consent form, the PI must make those changes promptly and submit the revised documents to the OHSU IRB.
 - All other potential UPs must be reported within fifteen (15) calendar days. If the event requires changes (as determined by the PI or the IRB) to the protocol or consent form, the PI must make those changes promptly and submit the revised documents to the IRB.
2. A brief summary of UPs as well as a brief summary of all adverse events must be submitted with the continuing review using the IRB template “Annual Event Summary” Form located on the IRB website.
3. The IRB reserves the right to request a report or additional information at any time.

D. How to Report

1. Reports are made through the eIRB, which will ask for the following information.
2. Reports of potential UPs, including AEs that meet the definition of a potential UP, must include the following information:
 - Study Information: Title, PI, IRB#, Sponsor/award #, IND/IDE#
 - Number of subjects enrolled to date and currently actively involved in research procedures.
 - Date of potential UP, Date notified of potential UP
 - Classification of the Experience Type: On protocol UP for OHSU Subjects, On protocol UP for Non-OHSU subjects, Off protocol UP (using same drug or agent), or Other Unanticipated Problem
 - Participant ID, if applicable

- Description of event
- Agent involved if applicable (for example, drug, device, placebo)
- Relationship of the agent or research procedures to the potential UP.
- Basis for UP determination: Investigator's analysis as to why the event may represent a "problem" for the study and why it is "unanticipated". For instances of increased frequency or severity, it must state how the frequency or severity diverges from the expected.
- Response Plan. Description of proposed actions, including modifications, to be taken by investigators in response to the event.

E. IRB Review of Submitted Unanticipated Problems

1. The IRB chairperson and/or designee will review the potential UP report to determine if it is an unanticipated problem involving risks to subjects or others, and the appropriateness of the response plan, including any proposed modifications.
 - Proposed modifications which represent minor changes may be triaged for expedited review.
 - In the case of proposed modifications which represent more than a minor change or are otherwise not approvable under expedited review procedures, review will be referred to the full board for review and further action.
 - In all cases, the IRB Chairs reserve the right to refer any report or proposal to the full board.
2. If the response plan indicates that no modifications are proposed and the reviewer(s) agree, the report will be approved and no further action is needed.
3. If the reviewers believe that modifications are needed, either because no modifications were proposed in the response plan or because insufficient or incorrect modifications were proposed, the IRB chairperson or designee will request in writing that the PI discuss this with the central monitor, if applicable, and submit a response or the necessary modification(s). In situations where there is not a central monitor, the PI will be required to respond.
4. All reports of potential UPs will continue through appropriate IRB review procedures until the reports and any applicable modifications are approved or disapproved. As with any disapproval, the PI may appeal the decision.
5. The IRB has authority to require submission of more detailed contextual information by the PI, sponsor, and study coordinating center or DSMB/DMC about any adverse event or unanticipated problem.

V. Authority

45 CFR 46.103(b)(5) and 21 CFR 56.108(b) requires that Institutions engaged in human subjects research conducted or supported by HHS must have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and any supporting department or agency head of any unanticipated problem involving risks to subjects or others.

OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events.

<http://www.hhs.gov/ohrp/policy/AdvEvtGuid.htm>

FDA Draft Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting - Improving Human Subject Protection.

<http://www.fda.gov/cber/gdlns/advreport.htm>

VI. Definitions

Adverse Event (AE) – Any untoward or undesirable, although not necessarily unexpected, event experienced by a human subject that may be a result of:

- The interventions and interactions use in the research
- The collection of identifiable private information in the research
- An underlying disease, disorder, or condition of the subject ; and/or
- Other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

Anticipated – previously known or expected to result.

Central Monitor – Data Safety Monitoring Board (DSMB), Data Monitoring Committee (DMC), a coordinating or statistical center, the research sponsor or the PI (in certain cases).

Coordinating Center - A Coordinating Center is responsible for overall data management, monitoring and communication among all sites, and general oversight of conduct of the project.

Data Safety Monitoring Board (DSMB) or Committee (DMC) – An independent formal committee that is established specifically to monitor data throughout the life of a study to determine if it is appropriate, from both the scientific and ethical standpoint, to continue the study as planned. DSMBs/DSMCs are typically made up of individuals who have expertise in the field, experience in the conduct of clinical trials, and/or statistical knowledge, and who do not have any serious conflicts of interest, such as financial interests that could be substantially affected by the outcome of the trial, strong views on the relative merits of the interventions under study, or relationship with the sponsor or those in trial leadership positions that could be considered reasonably likely to affect their objectivity.

Data Safety Monitoring Plan (DSMP) – A plan which describes how the investigator plans to oversee the research participants' safety and welfare and how unanticipated problems and adverse events will be detected, characterized and reported. The intensity and frequency of monitoring should fit the expected risk level, complexity and size of the study.

Off Protocol AE – AE's that occur to an OHSU or a non-OHSU subject in one protocol that may influence the risks to subjects in another OHSU protocol (e.g., studies of the same drug/device but in a different protocol at OHSU or another site).

On Protocol AE – Non-OHSU subjects – AE's that are external to OHSU and occur to subjects in a multi-center study in which OHSU participates (e.g., multi-center NIH studies, industry-sponsored drug or device studies, etc.) but over which the OHSU IRB has no jurisdiction. The PIs are usually notified by the sponsors or a central monitor of the AEs.

On Protocol AE – OHSU subjects – AEs that occur to a subject in a study, both single site and multi-center, which has been reviewed and approved by an OHSU IRB. PIs usually become aware of these AE's directly from the subject, or a co-investigator or the subject's provider.

Reportable Adverse Event – AEs that qualify as potential unanticipated problems, which must be reported by the PI to the IRB, are categorized as follows:

- On Protocol Serious Adverse Events (SAEs) that are unexpected and related or possibly related to participation in the research.
- On Protocol SAEs or AEs that are expected in some subjects, are related or possibly related, but are determined to be occurring at a significantly higher frequency or severity than expected.
- On or Off Protocol Unexpected SAEs or AEs that are related or possibly related, regardless of severity, that may alter the IRB's analysis of the risk versus

potential benefit of the research and, as a result, warrant consideration of substantive changes in the research protocol or informed consent process/document.

- Other events that are On or Off Protocol and unexpected that may place subjects or others at a greater risk of harm or discomfort than was previously known or recognized. Harm to a subject need not have occurred.

Serious Adverse Event – Any AE that:

- Is fatal
- Is life-threatening
- Is persistent or significantly disabling or incapacitating
- Results in inpatient hospitalization or prolongation of hospitalization
- Results in psychological or emotional harm requiring treatment
- Creates a persistent or significant disability
- Causes a congenital anomaly or birth defect and/or
- Results in a significant medical incident (considered to be a serious study related event because, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.)

Unanticipated – not previously known or expected (including increases in severity or frequency).

Unanticipated Problems - 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 participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved 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) than was previously known or recognized.