



UNIVERSITY OF OREGON

**OFFICE FOR PROTECTION OF HUMAN SUBJECTS (OPHS)  
COMMITTEE FOR THE PROTECTION OF HUMAN SUBJECTS/  
INSTITUTIONAL REVIEW BOARD (CPHS/IRB)**

**Reporting Unanticipated Problems Unanticipated Problems Involving Risks  
to Subjects or Others and Adverse Events**

Department of Health and Human Services (HHS) <http://hhs.gov/ohrp/policy/AdvEvtGuid.htm>  
(January 15, 2007)

All investigators conducting research with human subjects are required to report unanticipated problems and adverse events to the Office for Protection of Human Subjects within 24 hours. A non-medical research adverse event can consist of an undesirable and unintended consequence of, or reaction to procedures or breach of confidentiality. In medical research, a headache following an activity which lowers the blood pressure or the development of blood clots associated with therapy. In either case, if new information becomes available, as a result of an unanticipated problem, the investigator is required to submit the new information for Committee review for possible inclusion in the consent form or additional consideration by the CPHS/IRB.

University of Oregon investigators who conduct human subject research are required to report unanticipated problems and adverse events to the Office for Protection of Human Subjects/CPHS/IRB. The Department of Health and Human Services (DHHS) requires institutions to have “written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and Department or Agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB.”[45 CFR 46.103 (b)(5)]

The CPHS/IRB relies on the expertise of the investigator to make an assessment and to determine the relationship of the unanticipated problem and adverse events to the research activity (procedure/ intervention) and whether the event warrants a change to the protocol to minimize risks and/or the informed consent form to better inform subjects of the potential risks and procedures to minimize such risks. Therefore, the reporting of adverse events is based upon the investigator’s assessment.

If the event is an unanticipated problem in the opinion of the investigator, the protocol and/or informed consent form requires modification. Examples: identification of a “new trend” (adverse event occurring with greater frequency than anticipated) or a change in the risk/benefit ratio. If the unanticipated problem results in a change in procedures or the consent form, the Amendment/Modification form (<http://humansubjects.uoregon.edu/>) needs to be completed in addition to the Unanticipated Problems and Adverse Event Report Form.

(2) All deaths regardless of relationship to the research activity. For deaths that occur in drug studies, report any death that occurs within 30 days of the last dose of study drug administered to the subject.

#### Timeline for Reporting:

(1) All deaths and life-threatening events must be reported within 24 hours after the discovery.

(2) Events that require protocol or informed consent form modification must be submitted within 3 business days after discovery. NOTE: The Amendment/Modification form needs to be completed in addition to the Unanticipated Problems and Adverse Event Report Form (<http://humansubjects.uoregon.edu/>).

#### **What are *unanticipated problems*?**

OPHS considers *unanticipated problems*, in general, to include 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.

OPHS recognizes that it may be difficult to determine whether a particular incident, experience, or outcome is unexpected and whether it is related or possibly related to participation in the research. OPHS notes that an incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

## What are *adverse events*?

The term *adverse event* in general is used very broadly and includes any event meeting the following definition:

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.

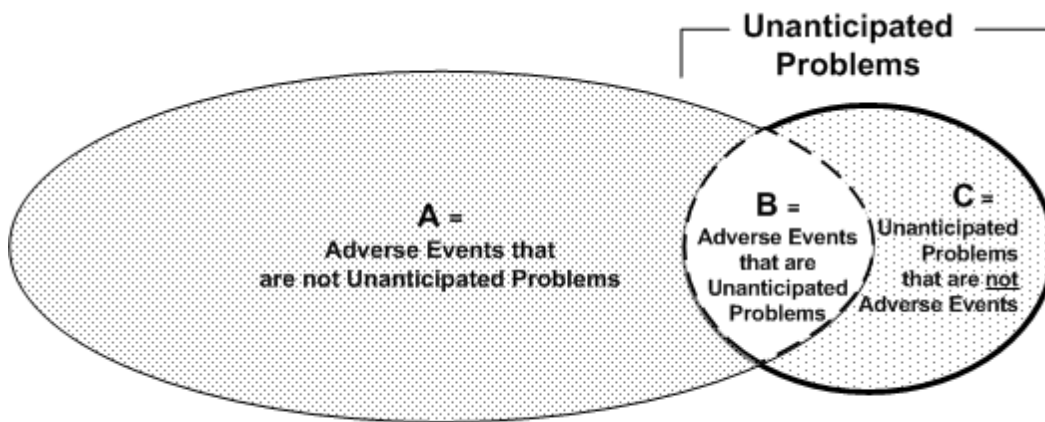
Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

In the context of multicenter clinical trials, adverse events can be characterized as either *internal adverse events* or *external adverse events*. 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, whereas *external adverse events* are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial. In the context of a single-center clinical trial, all adverse events would be considered *internal adverse events*.

In the case of an *internal adverse event* at a particular institution, an investigator at that institution typically becomes aware of the event directly from the subject, another collaborating investigator at the same institution, or the subject's healthcare provider. In the case of *external adverse events*, the investigators at all participating institutions learn of such events via reports that are distributed by the sponsor or coordinating center of the multicenter clinical trials. At many institutions, reports of external adverse events represent the majority of adverse event reports currently being submitted by investigators to IRBs.

## How do you determine which *adverse events* are *unanticipated problems*?

When, and to whom adverse events need to be reported as unanticipated problems. The following Venn diagram summarizes the general relationship between adverse events and unanticipated problems:



**Under 45 CFR part 46: Do not report A; Report B and C.**

The diagram illustrates three key points:

- The vast majority of adverse events occurring in human subjects are not unanticipated problems (area A).
- A small proportion of adverse events are unanticipated problems (area B).
- Unanticipated problems include other incidents, experiences, and outcomes that are not adverse events (area C).

The key question regarding a particular adverse event is whether it meets the three criteria described in [section I](#) and therefore represents an unanticipated problem. To determine whether an adverse event is an unanticipated problem, the following questions should be asked:

- Is the adverse event unexpected?
- Is the adverse event related or possibly related to participation in the research?
- Does the adverse event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized?

If the answer to **all three questions** is yes, then the adverse event is an unanticipated problem and must be reported to appropriate entities. The next three sub-sections discuss the assessment of these three questions.

### **A. Assessing whether an adverse event is *unexpected***

Any adverse event occurring in one or more subjects participating 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.

Examples of *unexpected* adverse events under this definition include the following:

- liver failure due to diffuse hepatic necrosis occurring in a subject without any underlying liver disease would be an unexpected adverse event (by virtue of its unexpected nature) if the protocol-related documents and other relevant sources of information did not identify liver disease as a potential adverse event;

In comparison, prolonged severe neutropenia and opportunistic infections occurring in subjects administered an experimental chemotherapy regimen as part of an oncology clinical trial would be examples of *expected* adverse events if the protocol-related documents described prolonged severe neutropenia and opportunistic infections as common risks for all subjects.

OPHS recognizes that it may be difficult to determine whether a particular adverse event is unexpected. For many studies, determining whether a particular adverse event is unexpected by virtue of an unexpectedly higher frequency can only be done through an analysis of appropriate data on all subjects enrolled in the research.

Thus, most individual adverse events do not meet the first criterion for an unanticipated problem and do not need to be reported under the regulations.

## APPENDIX A

### Definitions/Key Terms

#### Adverse Events

**Adverse event (AE):** 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 (SAE):*** 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).

***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.

***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.

## **Appendix B**

### **Examples of Unanticipated Problems that Do Not Involve Adverse Events and Need to be Reported Under the HHS Regulations at 45 CFR Part 46**

- (1) An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator's car on the way home from work. This is an unanticipated problem that must be reported because the incident was (a) unexpected (i.e., the investigators did not anticipate the theft); (b) related to participation in the research; and (c) placed the subjects at a greater risk of psychological and social harm from the breach in confidentiality of the study data than was previously known or recognized.
- (2) As a result of a processing error by a pharmacy technician, a subject enrolled in a multicenter clinical trial receives a dose of an experimental agent that is 10-times higher than the dose dictated by the IRB approved protocol. While the dosing error increased the risk of toxic manifestations of the experimental agent, the subject experienced no detectable harm or adverse effect after an appropriate period of careful observation. Nevertheless, this constitutes an unanticipated problem for the institution where the dosing error occurred that must be reported to the IRB, appropriate institutional officials, and OHRP because the incident was (a) unexpected; (b) related to participation in the research; and (c) placed subject at a greater risk of physical harm than was previously known or recognized.

The events described in the above examples were unexpected in nature, related to participation in the research, and resulted in new circumstances that increased the risk of harm to subjects. In all of these examples, the unanticipated problems warranted consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects. In each of these examples, while these events may not have caused any detectable harm or adverse effect to subjects or others, they nevertheless represent unanticipated problems and should be promptly reported to the IRB, appropriate institutional officials, the supporting agency head and OHRP in accordance with HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

## **Appendix C**

### **Examples of Adverse Events that Do Not Represent Unanticipated Problems and Do Not Need to be Reported under the HHS Regulations at 45 CFR Part 46**

- (1) A subject enrolled in a phase 3, randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of a new investigational anti-inflammatory agent for management of osteoarthritis develops severe abdominal pain and nausea one month after randomization. Subsequent medical evaluation reveals gastric ulcers. The IRB approved protocol and informed consent document for the study indicated that there was a 10% chance of developing mild to moderate gastritis and a 2% chance of developing gastric ulcers for subjects assigned to the active investigational agent. The investigator concludes that the subject's gastric ulcers resulted from the research intervention and withdraws the subject from the study. A review of data on all subjects enrolled so far reveals that the incidence of gastritis and gastric ulcer are within the expected frequency. This example is not an unanticipated problem because the occurrence of gastric ulcers – in terms of nature, severity, and frequency – was expected.
- (2) An investigator is conducting a psychology study evaluating the factors that affect reaction times in response to auditory stimuli. In order to perform the reaction time measurements, subjects are placed in a small, windowless soundproof booth and asked to wear headphones. The IRB approved protocol and informed consent document describe claustrophobic reactions as one of the risks of the research. The twentieth subject enrolled in the research experiences significant claustrophobia, resulting in the subject withdrawing from the research. This example is not an unanticipated problem because the occurrence of the claustrophobic reactions – in terms of nature, severity, and frequency – was expected.
- (3) An investigator performs prospective medical chart reviews to collect medical data on premature infants in a neonatal intensive care unit (NICU) for a research registry. An infant, about whom the investigator is collecting medical data for the registry, dies as the result of an infection that commonly occurs in the NICU setting. This example is not an unanticipated problem because the death of the subject is not related to participation in the research, but is most likely related to the infant's underlying medical condition.

**NOTE:** For purposes of illustration, the case examples provided above represent generally unambiguous examples of adverse events that are not unanticipated problems. OHRP recognizes that it may be difficult to determine whether a particular adverse event is unexpected and whether it is related or possibly related to participation in the research. In addition, the assessment of the relationship between the expected and actual frequency of a particular adverse event must take into account a number of factors including the uncertainty of the expected frequency estimates, the number and type of individuals enrolled in the study, and the number of subjects who have experienced the adverse event.

## Appendix D

### Examples of Adverse Events that Represent Unanticipated Problems and Need to be Reported Under the HHS Regulations at 45 CFR Part 46

- (1) Subjects with essential hypertension are enrolled in a phase 2, non-randomized clinical trial testing a new investigational antihypertensive drug. At the time the clinical trial is initiated, there is no documented evidence of gastroesophageal reflux disease (GERD) associated with the investigational drug, and the IRB approved protocol and informed consent document do not describe GERD as a risk of the research. Three of the first ten subjects are noted by the investigator to have severe GERD symptoms that began within one week of starting the investigational drug and resolved a few days after the drug was discontinued. The investigator determines that the GERD symptoms were most likely caused by the investigational drug and warrant modification of the informed consent document to include a description of GERD as a risk of the research. This is an example of an adverse event that, although not serious, represents an unanticipated problem that must be reported because it was (a) unexpected in nature; (b) possibly related to participation in the research; and (c) suggested that the research placed subjects at a greater risk of physical harm than was previously known or recognized.
- (2) A behavioral researcher conducts a study in college students that involves completion of a detailed survey asking questions about early childhood experiences. The research was judged to involve no more than minimal risk and was approved by the IRB chairperson under an expedited review procedure. During the completion of the survey, one student subject has a transient psychological reaction manifested by intense sadness and depressed mood that resolved without intervention after a few hours. The protocol and informed consent document for the research did not describe any risk of such negative psychological reactions. Upon further evaluation, the investigator determines that the subject's negative psychological reaction resulted from certain survey questions that triggered repressed memories of physical abuse as a child. The investigator had not expected that such reactions would be triggered by the survey questions. This is an example of an unanticipated problem that must be reported in the context of social and behavioral research because, although not serious, the adverse event was (a) unexpected; (b) related to participation in the research; and (c) suggested that the research places subjects at a greater risk of psychological harm than was previously known or recognized.

In all of these examples, the adverse events warranted consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects.

**NOTE:** For purposes of illustration, the case examples provided above represent generally unambiguous examples of adverse events that are unanticipated problems. OHRP recognizes that it may be difficult to determine whether a particular adverse event is unexpected and whether it is related or possibly related to participation in the research.

The flow chart below provides an algorithm for determining whether an adverse event represents an unanticipated problem that needs to be reported under HHS regulations at 45 CFR part 46.

**Algorithm for Determining Whether an Adverse Event is an Unanticipated Problem**

