REPORTING UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

Key Points

- All unanticipated problems (UPs), and the subset of adverse events (AEs) that meet the definition of UPs, must be promptly reported to CPHS.
- **Reportable** UPs/AEs must meet **all three** of the following criteria***:**
  - **Unexpected (in nature, severity, or frequency)** *and*
  - **Related or possibly related to participation in research** *and*
  - **Suggest greater risk of harm**.

  ** See Section B below for definitions and examples.*
- **Reporting procedures**: Submit an initial report (via email, phone, or mail/delivery) to the OPHS Director within **seven** calendar days of the PI learning of the incident.
- Submit a report through **eProtocol** (Incident Report) within **fourteen** calendar days of learning of the incident.
- Once the Incident Report is submitted, CPHS will contact the PI if more information or clarification is needed. CPHS will assess whether any corrective actions/substantive protocol changes are needed and notify the PI of its determinations.

A. Introduction

Federal regulations require investigators to promptly notify the IRB of any incidents or outcomes that meet the definition of an "unanticipated problem involving risks to subjects or others." It is the responsibility of the Principal Investigator (PI) or Faculty Sponsor to make the initial determination of whether an incident meets this definition, and to promptly report the incident when warranted.

This guidance outlines the reporting responsibilities and review process for unanticipated problems and adverse events. As it may be difficult to determine whether an incident is reportable, investigators are encouraged to contact OPHS staff for assistance.

Note that while only certain incidents require prompt reporting, the PI is still responsible for *tracking* all adverse events, incidents, experiences, or outcomes that are unanticipated and related or possibly related to the research, but do not suggest that the research places subjects or others at greater risk of harm. These incidents that do not require prompt reporting must be included in the next continuing review application.

B. Important Definitions/Examples

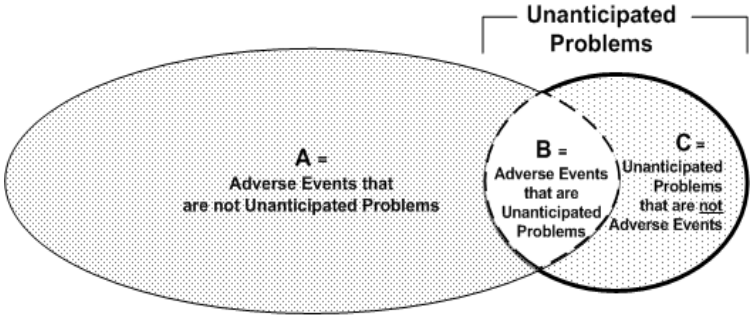
Unanticipated problem involving risks to subjects or others: Any incident, experience, or outcome that is:

(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 (i.e., a reasonable possibility exists that the problem, event, incident, experience, or outcome may have been caused by the procedures involved in the research study); **and**

(3) *suggests that the research places subjects or others at a greater risk of harm* (including physical, psychological, economic, legal, 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 (e.g., abnormal physical exam or laboratory finding), symptom or disease, temporally associated with the subject's participation in the research. Adverse events may also be psychological in nature. Adverse events may be expected or unexpected, and serious or not serious.



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

Examples of non-reportable incidents:

- A subject reports feeling dizzy during a blood draw. Dizziness is described as a risk associated with blood draw in the protocol and consent document.
- In a study involving magnetic resonance imaging (MRI), a subject becomes claustrophobic while in the MRI scanner. This is non-reportable as the protocol and consent document include that claustrophobia during an MRI scan may occur for some people.
- A student feels emotionally upset after completing self-assessment measures as part of a psychology study. The protocol and consent documents identify emotional upset/discomfort as a possible risk factor associated with the protocol and also include providing subjects with resources (e.g., student counseling center).

These are all AEs related or possibly related to participation in research, but not UPs because they are not unexpected given the research procedures and subject populations, and they do not suggest greater risk of harm than was previously known or recognized.

Examples of reportable incidents:

- A researcher conducts a clinical trial to compare the performance of experimental contact lenses with those already approved to market. A subject reports the onset of blurred vision while wearing the experimental lenses. Blurred vision was not described as a risk factor in the protocol or consent documents. *(AE that is also UP.)*
- A social-behavioral researcher conducts a focus group of school teachers to pilot test key messages designed to improve teaching staff morale in middle schools. While discussing the messages, two of the teacher subjects become engaged in an intense disagreement that culminates in physical aggression. *(This is an UP, but not an AE as it is not a medical occurrence.)*

- A pharmaceutical company initiates legal action against an institution participating in a multi-institutional clinical trial. As part of the discovery process, the PI receives a subpoena for the release of individually identifiable, sensitive subject data. *(Even though no actual harm has occurred, this is a reportable UP because subjects are at greater risk than previously known or recognized.)*

C. Reporting Responsibilities/What to Report

Prompt reporting is required only for those incidents that meet all three of the criteria defined above:

- Unexpected (in nature, severity, or frequency) and
- Related or possibly related to participation in research and
- Suggest greater risk of harm.

Other trends and events should be described in the continuing review application.

Keep in mind that harms may be physical, psychological, economic, legal, or social in nature. It is also possible that an unanticipated problem could include an experience or outcome that reveals an *increased risk* of harm from the research although no *actual* harm has occurred.

The PI is responsible for ensuring that student investigators and/or all members of the research team are familiar with these reporting requirements. It is recommended that each research team develop a protocol-specific plan for complying with the reporting requirements.

D. Reporting Timeframes

The initial incident report should be submitted to the OPHS Director within seven (7) calendar days of the PI learning of the incident.

- Email: ophs@berkeley.edu
- Phone: 510-642-7461
- Mail: Office for Protection of Human Subjects, 1608 Fourth Street, Suite 220, MC 5940, Berkeley CA 94710

The initial report must be followed by a report via eProtocol within fourteen (14) calendar days of the PI learning of the incident. (See instructions for submitting an Incident Report through eProtocol.)

E. CPHS Review and Actions

When an incident report is received, CPHS may ask the PI or other parties to provide additional information in order to ensure that the report is complete. CPHS will determine whether the incident meets the definition of *an unanticipated problem involving risks to subjects or others* and if any further action is necessary in order to protect research participants.

Possible CPHS actions may include, but are not limited to, the following:

- Modification of subject inclusion/exclusion criteria to mitigate newly-identified risks.
- Implementation of additional procedures for monitoring subjects.
- Modification of protocol/consent documents to include a description of newly-identified risks.
- Determination that already-enrolled subjects should be provided with information pertaining to newly identified risks.

- Suspension of enrollment of new subjects.
- Suspension of research procedures in currently enrolled subjects.
- Suspension of the entire study, or determination of approval for the entire study.
- Notification of the Institutional Official internally and/or outside agencies of the occurrence of unanticipated problems or serious adverse events according to the reporting requirements and guidelines of those pertinent agencies.

Note: The CPHS Chair has the authority to temporarily suspend research until such time as the full Committee can convene to review the report if the safety, rights, and/or welfare of subjects are jeopardized.

F. Additional Reading:

CPHS Policies and Procedures (RR408 – Adverse Events and Unanticipated Problems).