

P&P: RR 408 Version No: 1.2 Effective Date: 5/5/2017	UNANTICIPATED PROBLEMS AND ADVERSE EVENTS	Supersedes: CPHS Policies and Procedures 10/1/2009
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1. BACKGROUND

This policy describes the obligation to report unanticipated problems involving risks to subjects or others (hereinafter referred to as “unanticipated problems”) and certain types of adverse events. This policy is based on U.S. Department of Health and Human Services Guidance issued 1/15/2007, and includes information on how reportable events will be defined/identified and what procedures for reviewing and reporting will be followed.

2. POLICY

Unanticipated problems (including the subset of adverse events that fall into this category), as defined by University of California, Office of the President and in section 3 of this document, must be reported to the Committee for Protection of Human Subjects (CPHS) . Based upon such reports CPHS will consider corrective actions or substantive changes, as necessary, in order to protect the safety, welfare, and rights of subjects or others.

Although CPHS only requires reporting unanticipated problems and adverse events as outlined by this policy, the Investigator is responsible for tracking *all adverse events, incidents, experiences, or outcomes that are unanticipated and related or possibly related, but do not suggest that the research places subjects or others at greater risk of harm.* Trends and frequencies of events that do not require immediate reporting should be reported to CPHS at the time of continuing review.

3. DEFINITIONS

3.1 *Unanticipated problem:*

An 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 CPHS-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, legal, or social harm) than was previously known or recognized.

3.2 *Possibly related to the research:*

There is a reasonable possibility that the problem, event, incident, experience or outcome may have been caused by the procedures involved in the research.

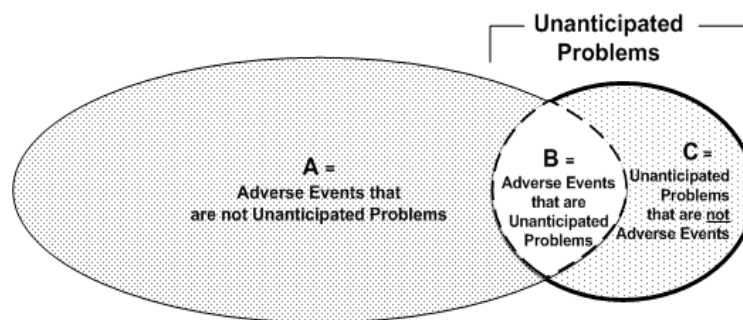
3.3 *Adverse event:*

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 may be physical or psychological in nature.

4. IDENTIFYING UNANTICIPATED PROBLEMS

- 4.1 CPHS will use Figure 1 and Office for Human Research Protection (OHRP) guidelines to determine what adverse event, incident, experience, or outcome constitutes an unanticipated problem that must be reported to CPHS.

Figure 1:



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

- 4.2 In addition to drug- and intervention- associated adverse events, other types of events, incidents, experiences, or outcomes might still meet the definition of an unanticipated problem. These include:
- (1) *Serious negative social, legal, or economic consequences resulting from participation in a study.* Situations sometimes occur, especially in field-based studies, where a subject's confidentiality may inadvertently be compromised that may result in serious negative social, legal or economic ramifications for the subject (e.g., serious loss of social status, loss of a job, interpersonal conflicts).
 - (2) *Serious psychological and/or emotional distress resulting from participation in a study.* Sometimes during the course of participating in a study, subjects may hear or experience something that causes them serious psychological or emotional distress. While, in many cases, these reactions are transitory, occasionally reactions may, in the judgment of the investigator, suggest the need for professional counseling or intervention (e.g., suicidal ideation).

5. REPORTING REQUIREMENTS AND PROCEDURES

- 5.1 The Principal Investigator must report promptly to CPHS:

- (1) Unanticipated problems, as defined in 3.1, if there is any possibility that the event is related to the study intervention or procedures, the event should be promptly reported.

- (2) An adverse event, a series of adverse events, external reports (e.g., IND Safety Reports), or safety findings (e.g., animal data, epidemiological data) that constitute unanticipated problems.
 - (3) Unanticipated problems occurring under the oversight of any entities or investigators that are using CPHS, UC Berkeley's Institutional Review Board (IRB), as the IRB of record.
 - (4) Any subject deaths that occur *within 30 days* of a study intervention that the Principal Investigator has determined to be (a) unexpected and (b) related or possibly related to the research.
- 5.2 The regulations at 46.103(b)(5) require *prompt* reporting of unanticipated problems, but do not define *prompt*. CPHS will be consistent with the guidelines for prompt reporting recommended by the OHRP by requiring that:
- (1) An initial report for all unanticipated problems must be submitted to CPHS within 1 week (7 calendar days) of the Principal Investigator becoming aware of the event.
 - (2) An eProtocol Incident Report must be submitted within 2 weeks (14 calendar days) of the Principal Investigator becoming aware of the event.
 - (3) All unanticipated problems will be reported to appropriate institutional officials (as outlined within this policy), the supporting agency head (or designee), and OHRP *within one month* of the CPHS' receipt of the report of the problem from the investigator.
 - (4) In some cases, the requirements for prompt reporting may be met by submitting a preliminary report to CPHS and other officials/agencies involved, with a follow-up report submitted at a later date when more information is available. Such determinations will be made on a case-by-case basis, with the CPHS Chair, Office for Protection of Human Subjects (OPHS) Director, investigator, institutional official(s) and/or others involved as appropriate. The primary consideration in making these judgments will be the need to take timely action to prevent avoidable harms to other subjects.
- 5.3 The Principal Investigator is responsible for assessing and documenting unanticipated problems and reporting to CPHS, as required by this policy, regardless of who observed or became aware of the event.
- (1) In the absence of the Principal Investigator, a co-investigator can fulfill these requirements to meet the reporting timeline.
 - (2) In the absence of either the Principal Investigator or a co-investigator project coordinator, a student member of the research team or other research personnel must contact OPHS for direction.
 - (3) In instances where a student (graduate or undergraduate) suspects an unanticipated problem, it is expected that the faculty advisor will be immediately made aware of any suspicious event that occurs during the study. After consultation, a determination should be made as to reporting to the CPHS.
 - (4) The investigator should use his or her judgment when determining if an event is considered reportable. When in doubt, the investigator should contact the OPHS for guidance.

- 5.4 For collaborative research, conducted under a reliance agreement (also known as UC Reliance, Inter-institutional Agreement, IRB Authorization Agreement), unanticipated problems should be reported to the IRB of Record.
- (1) When CPHS is the IRB of record, unanticipated problems must be reported according to 5.1–5.3 above. The UC Berkeley Principal Investigator is responsible for handling reports of unanticipated problems.
 - (2) When UC Berkeley is relying on the review of another IRB, unanticipated problems must be reported according to the policies and procedures of the IRB of Record. CPHS/OPHS will cooperate in investigations or follow-up, as needed.
- 5.5 The Director of OPHS is responsible for reporting Unanticipated Problems to OHRP and/or the Food and Drug Administration (FDA), as required, and for reporting to the appropriate Institutional Official (IO).
- 5.6 The investigator must fulfill the reporting requirements of other organizations (e.g., Sponsor, FDA), which are not satisfied nor precluded by submitting an unanticipated problem report to the CPHS. Likewise, submitting unanticipated problem or adverse event reports to other organizations (e.g., Sponsor, FDA) does not satisfy the reporting requirement to CPHS. The investigator must fulfill the reporting requirements of other organizations (e.g. Sponsor, FDA), which are not satisfied or precluded by submitting an unanticipated problem report to CPHS. Likewise, submitting adverse event reports to other organizations (e.g., Sponsor, FDA) does not satisfy the reporting requirement to CPHS.
- 5.7 If a CPHS-approved protocol includes more stringent reporting requirements, or if a Data and Safety Monitoring Board (DSMB) requires reporting events to CPHS, the more stringent requirements must be adhered to.
- 5.8 Any other incidents, outcomes, experiences, or adverse events that do not meet the definition of an unanticipated problem may be reported at the time of continuing review and/or via independent Data and Safety Monitoring Board reports, if applicable.
- 5.9 For purposes of confidentiality, subject names and identifiable information must not be included in the event report.
- 5.10 Requirements described in section 5 apply to studies that are open with CPHS. However, if any unanticipated problems occur after the approval period and it appears that a relationship may exist between the event and the research, the Investigator is strongly encouraged to report the event to CPHS.

6. IRB ACTIONS

- 6.1 Initial review of unanticipated problems through the eProtocol incident report will be conducted by the CPHS Chair (or his or her designee). The CPHS Chair is authorized to take the following actions in response to any incident report:
- (1) Perform an administrative review of the report that includes assessing whether the incident constitutes an unanticipated problem and by whom it should be reviewed (e.g., the Chair only, another CPHS member, a subcommittee of the CPHS, or the convened/full committee CPHS).

- (2) If full committee review is needed, assign the incident report for review at the next available regularly scheduled CPHS meeting.
 - (3) If warranted, convene an emergency meeting of the full committee CPHS to review the report.
 - (4) If warranted, temporarily suspend research if the rights, safety, and welfare of subjects are jeopardized until such time that the full committee CPHS can convene to review the report.
- 6.2 In order to protect the ongoing safety of research subjects due to the nature or frequency of reported problems/events, CPHS may require the following actions:
- (1) Modification of subject inclusion or exclusion criteria to mitigate the newly identified risks;
 - (2) Implementation of additional procedures for monitoring subjects;
 - (3) Modification of informed consent documents to include a description of newly recognized risks;
 - (4) Provision of additional information about newly recognized risks to previously enrolled subjects;
 - (5) Suspension of enrollment of new subjects;
 - (6) Suspension of research procedures in currently enrolled subjects;
 - (7) Suspension of the entire study; or
 - (8) Termination of approval for the entire study.
- 6.3 If the unanticipated problem results in an amendment of the research protocol and/or informed consent documents, an amendment application must also be submitted to CPHS. If the changes are minor they may be reviewed by expedited procedures. If the changes are more than minor, they must be reviewed and approved by the convened committee. Any such proposed changes in response to an unanticipated problem must be reviewed and approved by CPHS before being implemented, except when implementation is necessary to eliminate apparent immediate hazards to subjects. See RR 403-Continuing Review and RR 404-Amendment Requests.

7. SCOPE

These policies and procedures apply to all research submitted to CPHS/OPHS.

8. RESPONSIBILITY

The CPHS Chair or his or her designee is responsible for reviewing all reports of unanticipated problems and ensuring the appropriateness of all CPHS decisions and actions.

The OPHS Director is responsible for advising the CPHS Chair on relevant institutional and regulatory requirements.

The OPHS Director is responsible for reporting unanticipated problems to the CPHS Chair, CPHS, the IO, and/or outside agencies as needed.

9. PROCESS OVERVIEW

Unanticipated problems should be reported to the Director of OPHS as promptly as possible, within 1 week (7 calendar days) of the Principal Investigator learning of the incident. Initial reports may be made via phone, email, or mail/delivery, or in person. A formal Incident Report must be submitted in eProtocol within 2 weeks (14 calendar days) of the Principal Investigator learning of the incident.

OPHS staff members may receive such reports and are responsible for informing the Director about them.

The Director, Assistant Director, or IRB Administrator/Analyst ensures that incoming reports have been recorded and forwarded to the CPHS Chair or his or her designee for review.

The CPHS Chair reviews the reports. He or she evaluates the incoming report and he or she determines what actions, if any, may be needed to protect the rights, safety, and welfare of research subjects due to the nature or frequency of the reported unanticipated problem. If additional review is deemed necessary, the CPHS Chair can assign eProtocol incident report for review at the next regularly scheduled full committee CPHS meeting or convene an emergency meeting of the full committee.

OPHS staff members assist the CPHS Chair in communicating the results of the review, discussion, and outcome to the Investigator and other appropriate parties.

As necessary, the Director is responsible for reporting to the IO internally and/or to outside agencies the occurrence of unanticipated problems according to the reporting requirements and guidelines of these pertinent agencies.

10. APPLICABLE REGULATIONS AND GUIDELINES

45 CFR 46.103(a); 46.103(b)(5); 46.109(e); 46.111(a)(1), (a)(2), and (a)(6); 46.113

21 CFR 56.108(b)

21 CFR 312.32; 312.64

21 CFR 812.3(s); 812.46; 812.150

FDA – Adverse Event Reporting to IRBs – Improving Human Subject Protection

OHRP – Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (January 2007)