

Unanticipated Problems or Adverse Events	
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1. PURPOSE

Federal regulations require that IRBs have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and any supporting department or agency head for unanticipated problems involving risks to subjects or others. This document describes the institutional expectations and obligations of investigators to report unanticipated problems involving risks to subjects or others and certain types of adverse events. HHS Guidance issued on 1/15/2007 includes information on how reportable adverse events and unanticipated problems are defined and identified and what procedures for review and reporting will be followed.

2. DEFINITIONS

- 2.1. *Unanticipated problem involving risks to participants or others, referred to throughout this document as an “unanticipated problem”*, as defined by UCOP, involves risk to subjects or others and is an incident, experience, or outcome that meets **all** of the following criteria:
- 1) unexpected (in term 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 (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.
- 2.2. *Unexpected adverse event*, means 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.
- 2.3. *Adverse event*, means 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

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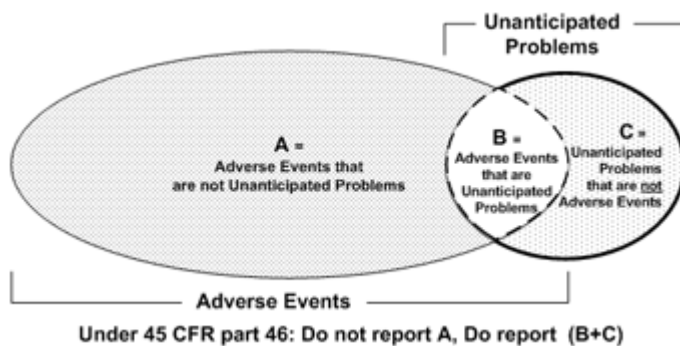
events may be physical or psychological in nature (for example, severe anxiety or psychological distress).

- 2.4. *Possibly related to the research*, means there is a reasonable possibility that the problem, event, incident, experience or outcome may have been caused by the procedures involved in the research.
- 2.5. *Serious adverse event*, means 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 persistent or significant disability/incapacity;
 - 5) Results in 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 intervention to prevent one of the other outcomes listed in this definition (for example, the development of a drug dependency or drug abuse or physical or psychological harm to oneself or others)

3. POLICY and PROCEDURE

- 3.1. Unanticipated problems or adverse events must be reported to the IRB if they are: 1) unexpected; 2) related or possibly related to participation in the study; **and** 3) suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized.
- 3.2. Based on such reports, the IRB will consider corrective actions or substantive changes in order to protect the rights, safety, and welfare of the subjects or others.
- 3.3. Although the IRB only requires immediate reporting of unanticipated problems or adverse events as defined above, the investigator is responsible for tracking all adverse events and/or unanticipated problems in the research study and submitting a progress report to the IRB.
- 3.4. **Identifying Reportable Unanticipated Problems or Adverse Events**
- 3.4.1. The IRB will utilize OHRP guidelines to determine what unanticipated problems and/or adverse events must be reported under 45 CFR 46 and/or other federal regulations as applicable. The Venn diagram below summarizes the general relationship between adverse events and unanticipated problems that the IRB will use when making its determination:

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3.4.2. This diagram illustrates three key points:

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

3.4.3. To determine whether an adverse event is an unanticipated problem, the following questions should be considered:

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

3.4.4. If the answer to **all three questions above** is *yes*, then the adverse event is an unanticipated problem.

3.5. Reporting Requirements

3.5.1. The lead faculty investigator or faculty advisor must promptly report to the IRB all unanticipated problems or adverse events: (NOTE: When in doubt, if there is a possibility that the event is related to the study intervention or procedures, the event should be reported to the IRB).

- a) *Unanticipated problems, or adverse events* as defined in Section 2, that occur under the oversight of any entities or investigators using the UCSB IRB as the IRB of record for that study.
- b) *Subject deaths*, that occur, that the investigator has determined to be (a) unexpected and (b) related or possibly related to the research.
- c) *Adverse events*, or series of adverse events, external reports, or safety findings that constitute unanticipated problems.

3.5.2. The regulations under 45 CFR 46 require “prompt” reporting of unanticipated problems, but do not define prompt. This IRB will follow guidelines for prompt reporting recommended by the OHRP guidance on this topic:

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- 1) Unanticipated problems that are serious adverse events must be reported to the IRB. Reports should be submitted **within 1 week** of the investigator becoming aware of the event.
 - 2) Any other unanticipated problem should be reported to the IRB **within 2 weeks** of the investigator becoming aware of the problem.
 - 3) All unanticipated problems that are also considered serious adverse events under 3.4.4 above, should be reported to the appropriate institutional officials, the supporting agency head, and OHRP **within one month** of the IRB's receipt of the report of the problem from the investigator.
- 3.5.3. In some instances, the requirements for prompt reporting may be met by submitting a preliminary report to the IRB and other officials/agencies involved, with a formal 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 IRB Chair, Research Integrity Director (or designee), investigator, or IO, and/or others involved as appropriate. The primary consideration in making these judgments will be the need to take timely action to prevent avoidable harm to other subjects.
- 3.6. Timeline Requirements:**
- 3.6.1. If the unanticipated problem is a serious adverse event that occurred at a UCSB research location and was reviewed by the UCSB IRB, it must be reported to the IRB promptly. It should be reported within no more than 1 week (7 calendar days) of recognition/notification of the event. The lead faculty investigator or faculty advisor is responsible for ensuring that the reporting is done. A follow-up written report must be submitted to the HS Office within 2 weeks (14 calendar days) unless the investigator has submitted in writing a request for an extension to gather more information regarding the problem.
 - 3.6.2. If the unanticipated problem or serious adverse event occurred at an external site as part of a multi-site research project or sub-award project, it must be reported to the Reviewing IRB and prime grantee institution as applicable. The report should also be submitted to the UCSB IRB within one month (30 calendar days) of recognition/notification of the event.
 - 3.6.3. Any other unanticipated problem should be reported to the IRB within 2 weeks (14 calendar days) of the investigator becoming aware of the problem. All other events should be documents and included in the continuing renewal application.
 - 3.6.4. For purposes of reporting, the investigator may submit the report to the IRB Staff in the HS Office, Research Integrity Director, or IRB Chair initially.
- 3.7. Reporting may be required by other organizations (such as the sponsor) and also must be reported by the investigator in a timely manner. Reporting to the IRB does not constitute a report to the sponsor or department, and vice-versa. The Research Integrity Office will work with the investigator(s) to ensure proper reporting requirements (e.g., notification to sponsor) are met. The Research Integrity Director/designee is responsible for reporting to

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OHRP as required and reporting to the Institutional Official. The Research Integrity Director/designee will utilize guidelines for reporting incidents described by OHRP.

3.8. **Reporting Procedures:**

The lead faculty investigator or faculty advisor is responsible for assessing and documenting unanticipated problems and serious adverse events and reporting to the IRB, as required by this Policy and Procedure, regardless of who observed or became aware of the event.

- 3.8.1. If the lead faculty investigator or faculty advisor is unavailable, a co-investigator can fulfill these requirements to meet the reporting timeline.
- 3.8.2. In the absence of above aforementioned, a professional researcher, post-doc, graduate or undergraduate student member of the research team must contact the HS Office for direction.
- 3.8.3. In instances where a graduate or undergraduate researcher suspects an unanticipated problem or serious adverse event, 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 with regard to reporting to the IRB.

3.9. The investigator should use their judgment when determining whether an event is considered reportable. If in doubt, the investigator should contact the HS Office for guidance.

What to include in the report to the IRB:

- 3.10. Include a brief description of the unanticipated complication or adverse event including:
 - What has occurred?
 - When did it happen?
 - Where did it happen? (some university projects occur off-campus)
 - Did the event appear to be directly related, indirectly related, or unrelated to the research?
- 3.11. For purposes of confidentiality, subject's names should not be included or identified in the event report to the IRB.
- 3.12. These reporting requirements apply to all studies that are open with the IRB. However, if any serious adverse events, unanticipated problems involving risks to subjects or other, or other unexpected non-serious events occur after the approval period closed and it appears that a relationship may exist between the event and the research, the investigator is strongly encouraged to report the event to the IRB.
- 3.13. **Special Considerations**
 - 3.13.1. Investigators should be aware that there are many types of unanticipated problems which might be associated with subjects' participation in research studies, including:
 - d) *Serious negative social, legal, or economic consequences resulting from participation in a study.* Situations may occur, especially in field-based studies, where a subject's confidentiality may inadvertently be compromised

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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).

- e) *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 instances these reactions may be transitory, occasionally reactions may, in the judgment of the investigator, suggest the need for professional counseling or intervention (e.g., suicidal ideation).
- f) *Data security breach resulting in a loss of participant confidentiality and/or personally identifiable information or protected health information.* Sometimes a laptop may be lost or stolen or data may be compromised resulting from unauthorized access (i.e., “hacked”) to the data. ***Any data security breach that results in disclosure of sensitive data, personally identifiable information and/or protected health information must immediately be reported to the Reviewing IRB.*** Data is considered “sensitive” when disclosure of identifying information could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation.

3.14. IRB Actions

- 3.14.1. An initial review of the unanticipated problem or adverse event will be conducted by IRB Staff or the Research Integrity Office in the event the IRB Chair/Designee is unavailable. The individual conducting the initial review is authorized to:
 - a) Perform an administrative review of the report. If an IRB staff member conducts the initial review, they will conduct the review report in consultation with the Research Integrity Director unless s/he is unavailable.
 - b) In consultation with the IRB Chair, an assessment will be made to determine whether the incident constitutes a reportable unanticipated problem and/or serious adverse event, and by whom it should be reviewed (e.g., the Chair only, a subcommittee, the convened IRB).
 - c) If the reportable event needs to be reviewed by the convened IRB, then it will be scheduled for review at the next regularly scheduled meeting, unless an emergency meeting is deemed necessary.
 - d) If warranted, temporary suspension of the research protocol may be initiated if the rights, safety, and welfare of the subjects are jeopardized until such time that the convened IRB can review the report.
- 3.14.2. In order to protect the ongoing safety of the research subjects due to the nature, severity, or frequency of the reported problem/event(s), the IRB make require the following actions:

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- a) Modification to the protocol of subject inclusion/exclusion criteria to mitigate the newly identified risks;
- b) Implementation of additional procedures for monitoring the research and subjects;
- c) Modification of the informed consent process and documents to include the newly identified risks;
- d) Provision of providing additional information to the previously enrolled subjects;
- e) Suspension of enrollment of new subjects;
- f) Suspension of research procedures in currently enrolled subjects;
- g) Suspension or termination of the entire study;
- h) Other actions not described above

3.14.3. If the unanticipated problem or adverse event results in an amendment of the research protocol and/or informed consent procedures/document, the amendment must be submitted to the IRB for review. If the changes are minor, they may be handled by expedited review procedures, unless specified by the IRB. If the changes are substantial, they must be reviewed and approved by the convened IRB. Any proposed changes in response to an unanticipated problem or adverse event must be reviewed and approved by the IRB before implementation, unless when implementation is necessary to eliminate apparent immediate hazards to subjects as described in HSC SOPs 017 and 018 (*Continuing Review and Amendments*).

3.14.4. If the unanticipated problem and serious adverse event results in a reporting requirement to OHRP, the Research Integrity Director/Designee will utilize the guidelines defined by OHRP for types of information to include in an incident report.

4. SCOPE

These policies and procedures apply to all human subject research submitted to the IRB.

5. RESPONSIBILITY

The IRB staff, Research Integrity Director or Designee, IRB Chair or members, are responsible for receiving reports of unanticipated problems and/or serious adverse events and initially evaluating the report.

The IRB Chair/Designee is responsible for reviewing all reports of unanticipated problems or serious adverse events and ensuring the appropriateness of IRB decisions and actions.

The Research Integrity Director or Designee is responsible for advising the IRB Chair on relevant institutional and regulatory requirements. The Director or Designee is also

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responsible for reporting unanticipated problems or serious adverse events to the IRB Chair, IRB, the IO, and/or outside agencies or others as needed and/or as required.

6. PROCESS OVERVIEW

- 6.1. Problems or adverse events that are unexpected, related or possibly relate to the study, and suggest that the research involves a greater risk of harm than was previously known must be reported to the IRB. The report should be submitted within 1 week (7 calendar days) of the lead investigator or faculty advisor learning of the incident. Initial reports may be made via phone, fax, email, mail, or in-person. However, investigators should submit an official report to the IRB within 2 weeks (14 calendar days) following the incident. If more time is required to submit the official report, the IRB must be notified of the request for an extension by the lead investigator or faculty advisor.
- 6.2. IRB staff may receive reports and must notify the IRB Chair/Designee or the Research Integrity Director or Designee if the former is unavailable.
- 6.3. IRB staff are responsible for ensuring that initial reports have been documented and are submitted to the IRB Chair for review.
- 6.4. The IRB Chair will review the initial report and may make an initial determination as to what action, if any, may be required to protect the rights, safety, and welfare of the subjects. If additional review is necessary, the IRB Chair can appoint a sub-committee to review the report, submit the report for the committee review at the next convened meeting, or convene an emergency meeting of the IRB.
- 6.5. The IRB staff will assist the IRB Chair in communicating the results of the review, discussion, and outcome to the investigator and other appropriate parties.
- 6.6. When appropriate, the Research Integrity Director, or designee, is responsible for reporting to the IO and working with the investigator to report to outside agencies as described in 3.5 above, the occurrence of unanticipated problems or serious adverse events, according to the reporting requirements and guidelines of the pertinent agencies.

References:

45 CFR 46 Regulations

UC Berkeley Guidelines and Policies

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

OHRP – Guidance on Reporting Incident to OHRP