

**Policy Number: 57**

**Title: Unanticipated Problems Involving Risks to Subjects or Others**

**Date of Last Revision: July 6, 2006**

## **I. General Overview**

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 the 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; and (ii) any suspension or termination of IRB approval [45 CFR 46 103(b)(5)].

The Food and Drug Administration (FDA) requires that institutions follow “written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of: (1) any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or (3) any suspension or termination of IRB approval” (21 CFR 56.108(b)].

## **II. Definition**

**Unanticipated Problem:** An event that is not expected given the nature of the research procedures and the subject population being studied, and places subjects or others at greater risk or harm/discomfort related to the research than was previously known or recognized.

## **III. Policies**

- A. The principal investigator is responsible and required to submit to the IRB all reports of unanticipated problems involving risk to subjects or others that occur during the course of the research.
1. Investigators must self-report to the IRB any identified unanticipated problems within ten working days of the problem or discovery of the problem.
  2. Other outside parties (sponsor, research staff, co-investigator, subjects) may also report to the IRB any unanticipated problems related to the research.

3. Information regarding unanticipated problems may also be contained in materials submitted to the IRB for review. This includes but is not limited to continuation and addendum applications, quality assurance audit reports, and reports of adverse events, protocol violations, noncompliance and incidents.
- B. The unanticipated event report should include the following information:
1. Description of the unanticipated event
  2. Explanation of how the unanticipated problem occurred and was discovered
  3. Description of any, risks to human subjects or others or if there is a potential for risk to occur
  4. Proposed action plan to avoid similar reoccurrence in the future
- C. This policy addresses unanticipated problems that are not related to adverse events.
1. Please refer to *UCLA Policy on Adverse Event Reporting* for the reporting of an unanticipated problem that is related to adverse event.
  2. Unanticipated problems may include but are not limited to events that pose social and psychological risk, breach of confidentiality, or invasion of privacy.
- D. All unanticipated problems reported to the IRB will be reviewed by the IRB and the IRB will determine what action and/or recommendation, if any, will be presented to the investigator.
- E. Any unanticipated problems involving risks to subjects or others will be reported to the appropriate federal agencies, institutional officials, and study sponsor as determined by the IRB.

#### **IV. Procedures**

- A. Immediately upon receipt of the report of an unanticipated problem involving risk to subjects or others, the IRB staff will direct the initial review to the IRB Chair/Vice Chair.
1. The IRB Chair/Vice Chair will determine if the unanticipated problem requires no further action (i.e. no risk to subjects or others), or
  2. The IRB Chair/Vice Chair will determine whether the reported unanticipated problem requires additional review by a convened IRB meeting.
  3. If the unanticipated problem is to be reviewed by full Committee, the review will be scheduled for the next scheduled meeting of the appropriate IRB.

4. If the unanticipated problem is of the nature that the safety, rights and welfare of subjects are at immediate risk, the IRB Chair/Vice Chair will contact the PI in order to establish an interim measure to be taken to protect the subjects. The decision will be provided to the IRB at the following meeting.
  5. If the unanticipated problem involves a noncompliance issue, potential protocol violation, or is identified upon review of a subject complaint, the review will proceed as described by the appropriate policy (see *UCLA Policies on Noncompliance, Protocol Violations, and Subject Complaints*).
- B. The IRB Chair/Vice Chair may request additional information from the principal investigator regarding the unanticipated problem prior to presentation at the next IRB meeting, in order to provide the convened Board with sufficient information to evaluate the issue.
- C. Review materials available to the Chair/Vice Chair include all study documents submitted to the IRB. The study file includes but is not limited to the following items: study protocol, IRB application, current approval notice, current approved informed consent document, correspondence between study sponsor and principal investigator, investigator brochure (if applicable), and other pertinent documents.
- D. Review by a convened IRB meeting (full Committee review).
1. The report of the unanticipated problem and appropriate review materials are distributed to the primary reviewer(s) and Committee members approximately one week prior to the meeting.
  2. Appropriate review materials may include but are not limited to the following: investigator's correspondence, study protocol, IRB application, current approval notice, current approved informed consent document, correspondence between study sponsor and principal investigator, investigator brochure (if applicable), and other pertinent documents. The entire IRB study file is available for review by IRB members upon request.
  3. The IRB may request additional information from the principal investigator regarding the unanticipated problem in order to facilitate an adequate review before a final determination is made.
  4. An action determination may be made by the IRB. This may include one or more determinations, but is not limited to the following:
    - a. **No further action required.**

- b. **IRB recommended corrective action plan.** Such actions will be appropriate to the nature and degree of the problem and may include but is not limited to the following: educational intervention for the investigator and support staff, status reports and consent monitoring. Staff will notify the investigator of the IRB's corrective action plan to avoid reoccurrence in the future. The Chair/Vice Chair will review and approve the correspondence prior to investigator notification. Upon receipt of the investigator's response, staff will prepare an evaluation of the response to include any regulatory or administrative guidance for the Chair/Vice Chair or IRB. The process may repeat until the response is ready for approval.

Alternatively, the Chair/Vice Chair may determine that the response requires full Committee review. In this case, the response will be forwarded to the full Committee.

- c. **Submission of a corrective action plan by the principal investigator to avoid reoccurrence in the future.** Staff will notify the investigator of the IRB's corrective action plan to avoid reoccurrence in the future. The Chair/Vice Chair will review and approve the correspondence prior to investigator notification. Upon receipt of the investigator's response, staff will prepare an evaluation of the response to include any regulatory or administrative guidance for the Chair/Vice Chair or IRB. The process may repeat until the response is ready for approval.

Alternatively, the Chair/Vice Chair may determine that the response requires full Committee review. In this case, the response will be forwarded to the full Committee.

- d. **Modification to the research protocol.** Staff will notify the investigator of the IRB's request for a modification to the research protocol. The Chair/Vice Chair will review and approve the correspondence prior to investigator notification. Upon receipt of the investigator's response, staff will prepare an evaluation of the response to include any regulatory or administrative guidance for the Chair/Vice Chair or IRB. The process may repeat until the response is ready for approval.

Alternatively, the Chair/Vice Chair may determine that the response requires full Committee review. In this case, the response will be forwarded to the full Committee.

- e. **Modification of the informed consent document.** Staff will notify the investigator of the IRB's request for modification to the informed consent document. The Chair/Vice Chair will review and approve the correspondence prior to investigator notification. Upon receipt of the investigator's response, staff will prepare an evaluation of the response to include any regulatory or administrative guidance for the Chair/Vice Chair or IRB. The process may repeat until the response is ready for approval.

Alternatively, the Chair/Vice Chair may determine that the response requires full

Committee review. In this case, the response will be forwarded to the full Committee.

- f. **Notification of current and past subjects of new information.** Such information may relate to a current subject's willingness to continue participation in the research. Staff will notify the investigator of the IRB's request to inform current and past subjects of the new information. The Chair/Vice Chair will review and approve the correspondence prior to investigator notification. Upon receipt of the investigator's response, staff will prepare an evaluation of the response to include any regulatory or administrative guidance for the Chair/Vice Chair or IRB. The process may repeat until the response is ready for approval.

Alternatively, the Chair/Vice Chair may determine that the response requires full Committee review. In this case, the response will be forwarded to the full Committee.

- g. **Suspension of research – new enrollment, treatment and follow-up, data analysis.** Please see *UCLA Policy on Suspension and Termination of Research*.

Please note: actions c-f will require further review and approval by the IRB prior to implementation.

- E. The IRB will determine if the unanticipated problem or outcome of the IRB's decision is reportable to the appropriate federal agencies, institutional officials, study sponsor, and appropriate University department heads [45 CFR 46.103(b)(5) and 21 CFR 56.108(b)].
1. The IRB staff will oversee/coordinate all written correspondence from the IRB/OPRS to the principal investigator, federal agencies, institutional officials, study sponsor, and appropriate University departments and/or department heads.
    - a. Written correspondence from the IRB regarding final action determination will be forwarded to the principal investigator, and as determined by the IRB to institutional officials and appropriate University departments and/or department heads within ten working days of the IRB determination.
    - b. Written correspondence regarding the unanticipated problem involving risk to subjects and others from the Director of the Office of Protection of Research Subjects will be forwarded to the appropriate federal agencies, institutional officials, study sponsor, appropriate University departments and/or department heads, IRB Chair and principal investigator within ten working days of the IRB determination. Written correspondence will include but is not limited to the following:
      - i. Name of the institution.
      - ii. Title of the research project.
      - iii. Name of the principal investigator.
      - iv. IRB number and/or number of applicable federal award.

- v. Detailed description of the unanticipated problem.
- vi. Actions instituted to address the problem.

**Regulations:**

45 CFR 46.103(b)(5)(i)  
45 CFR 46.116(b)(5)  
21 CFR 50.25(b)(5)  
21 CFR 56.108(b)(1)

**References:**

U.S. Office for Human Research Protections' (OHRP, formerly OPRR) *Protecting Human Research Subjects Guidebook (1993)*.

OHRP Compliance Activities: Common Findings and Guidance #64, #66, #71, #72

OHRP Compliance Activities: Significant Findings and Concerns of Noncompliance, #49, #51

OHRP Guidance on Reporting Incidents to OHRP

OHRP Guidance on reporting and Reviewing Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others (Draft)

FDA Information Sheet Guidance to Sponsors, Clinical Investigators, IRBs: Continuing Review After Study Approval