

Guidance and Procedures Number: 57

Title: Post-Approval Reporting Requirements for Investigators: Reporting of Unanticipated Problems, Including Adverse Events as well as Protocol Violations, Deviations and Incidents and the Reporting of Updated Study Safety Information

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I. General Overview

Both The Department of Health and Human Services (DHHS) and the Food and Drug Administration require institutions to have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (1) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this guidance or the requirements or determinations of the IRB; and (2) any suspension or termination of IRB approval (45 CFR 46 103(b)(5) and 21 CFR 56.108(b)).

Unanticipated problems involving risk to subjects or others generally will require consideration of substantive modification to the research protocol, informed consent documents, or other corrective actions to protect the safety, welfare, or rights of subject or others. The expertise of the UCLA investigator is relied upon to make an initial assessment and determine the relationship of the reported event to the research activity and to determine if the event warrants a change to the protocol to minimize risks to human subjects and/or a change to the informed consent document to better inform subjects of the potential risks and the procedures needed to minimize such risks. The IRB will review the investigator's assessment and either accept this assessment or ask for changes.

This guidance document

- Provides definitions and examples of the different types of post approval events and information that may be used to determine if an event is an unanticipated problem,
- Describes the requirements and time frames for investigators to prepare and submit post approval reports to the IRB,
- Outlines the IRB review processes and procedures for assessing these reports so that the IRB may make determinations regarding risks, potential benefits, the adequacy of the consent documents, the provision of updated information to subjects, and the safeguards that are in place to protect human subjects.

II. Definitions

Adverse Event: Any untoward or unfavorable medical occurrence in a human subject (physical or psychological harm) temporally associated with the subject's participation in the research (whether or not related to participation in the research).

Deviation: Any intended or unintended variance or exception from the IRB approved protocol. This term, though sometimes used interchangeably with the term "violation," is most often used when the variance is intended for the safety of one or more research participants or an unintended change that is not considered as serious as a violation.

External Adverse Event or Outcome: An event or outcome that is experienced by subjects enrolled at study site(s) (e.g. multicenter clinical trial) under the jurisdiction of other IRBs.

Incident: An undesirable and unintended, although not necessarily unexpected, event or outcome involving any aspect of the research study.

Internal Adverse Event or Outcome: An event or outcome that is experienced by subjects enrolled at study site(s) under the jurisdiction of the UCLA IRB (IRB of record).

Noncompliance: Failure to comply with federal regulations, state laws, University policies, and/or the policies, requirements or determinations of the Institutional Review Board, or provisions of the approved research study.

Related (possibly related): In the opinion of the UCLA investigator there is a reasonable possibility that the event or outcome may have been caused by the procedures involved in the research

Serious Adverse Event: Any adverse event that may result in the following: death; is life threatening (places subject at immediate risk of death from the event as it occurred); a required or prolonged hospitalization, persistent or significant disability/incapacity; congenital anomaly/birth defect; or may require medical or surgical intervention to prevent one of the other outcomes previously listed in this definition. The occurrence of a serious adverse event suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

Unanticipated Problem: An event or outcome that meets the following criteria: 1) unexpected; 2) related or possibly related to participation in the research; and 3) subjects or others are placed at a greater risk of harm than was previously known or recognized.

Unexpected: The nature, specificity, severity or frequency of the event or outcome is not accurately reflected in the protocol-related documents, such as the IRB approved research protocol, informed consent document, and investigator brochure; and characteristics of the subject population being studied.

Unexpected Adverse Event: Any adverse event where the nature, specificity or frequency of the event is *not* consistent with either: 1) the known or foreseeable risk associated with the procedures involved in the research that are described in the protocol-related documents (IRB approved protocol, informed consent document, investigator brochure), and relevant sources of information (product labeling/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.

Violation: Any intended or unintended variance, exception or deviation from the IRB approved protocol. This term though sometimes used interchangeably with “deviation” is often though not necessarily considered a more serious variance from an approved protocol than a deviation and is not normally used when the variance is made intentionally to eliminate an immediate hazard to one or more research participants.

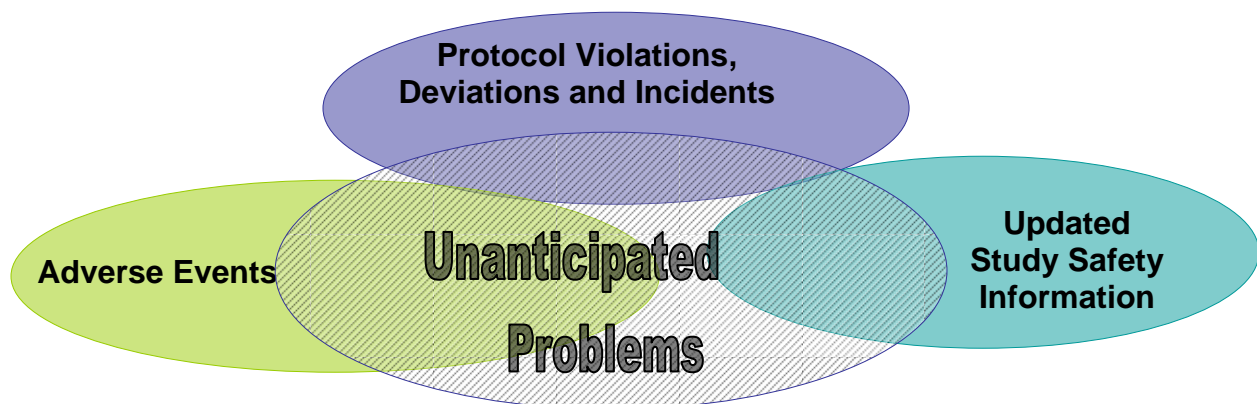
III. Policy

The Principal Investigator must submit to the IRB all post approval reports as defined and that meet the criteria described below within the proper timeframe, also described below. The IRB must review and determine the adequacy of the safeguards in place and make appropriate determinations regarding risks, potential benefits, the adequacy of the consent documents, the provision of updated information to subjects, and the safeguards that are in place to protect human subjects, including subject privacy and the confidentiality of data, are also outlined in light of these reports. The Principal Investigator must make any changes to the protocol or recruitment or consent documents as required by the IRB.

IV. PI Reporting Responsibilities

The Principal Investigator is responsible for submitting to the IRB ongoing reports of events that are unanticipated problems, and information regarding the conduct of the approved research. The expertise of the UCLA investigator is relied upon to make an initial assessment and determine the relationship of the event to the research activity and to determine if the event warrants a change to the protocol to minimize risks to human subjects and/or a change to the informed consent document to better inform subjects of the potential risks and the procedures needed to minimize such risks. The types of events and information to be reported to the IRB include but are not limited to those described below. Depending upon the Principal Investigator’s assessment of the event, the reports may be submitted separately or in conjunction with an amendment to the protocol or revisions to the recruitment or consent documents, or as part of the continuing review application.

Not all adverse events, violations, incidents or deviations are unanticipated problems. Examples are provided below of the types of events that do constitute unanticipated problems and, therefore, must be reported. There are also examples of events that need to be reported whether or not they are unanticipated problems. The diagram below provides a schematic of how to conceptualize post approval reporting requirements.



A. Reporting of Adverse Events

Adverse event reports should be reported to the IRB whether they occur during the course of the study, after study completion, or after subject withdrawal or completion if it affects the safety and welfare of either currently or previously enrolled subjects.

All adverse events should be reported as described below:

1. **Within 10 working days**, using either the External or Internal Adverse Event Reporting Form posted on the OPRS/Human Research website, any or all of the following should be reported:
 - a. Any adverse event, internally or externally occurring, that is an unanticipated problem, which meets the following criteria:
 - Unexpected,
 - Related or possibly related to the research, and
 - Places subjects or others at greater risk of harm than was previously known or recognized
 - b. Internal adverse events that are expected and related but indicate a higher frequency of occurrence or a higher level of severity (i.e., indicating a new trend) that was not previously known and/or described in the approved informed consent document or other protocol related documents.
 - c. Even if all subjects at the UCLA site have completed study participation, an external adverse event report that indicates a potential risk which requires notification of previously enrolled subjects (i.e., malignancy).
 - d. Any event that requires prompt reporting according to the IRB approved protocol.
2. **Within 2 working days**, using Internal Adverse Event Reporting Form posted on the OPRS/Human Research website:

Internal subject death that meet the following criteria; the death:

- Occurred in an interventional study (i.e., involving a drug, biologic, device procedure and/or behavioral interventions),
- Was unexpected ,and
- Was related or possibly related to research participation.

3. **At Continuing Review**, according to the directions in the Continuing Review application:

Internal subject deaths that meet the following criteria; the deaths:

- Occurred in an interventional study (i.e. involving a drug, biologic, device procedure and/or behavioral interventions),
- Were expected, and
- Were related or possibly related to research participation.

4. **Do not report** the following types of adverse events:

- a. External (off-site) adverse events that *do not* meet the criteria for submission as described above in Section IV.A.1.
- b. External (off-site) adverse event reports when all subjects at the UCLA site has completed study participation and the adverse events do not require that previously enrolled subject be notified.
- c. Internal (on-site) subject deaths occurring in non-interventional studies (i.e., surveys, interviews, or observation studies).

B. Reporting of Violations, Deviations, and Incidents

Violation, deviation, and incident reports should be reported to the IRB whether they occur during the course of the study, after study completion, or after subject withdrawal or completion if it affects the safety and welfare of subjects. However, the reporting timeframe is different depending on the criteria as defined below.

Examples of violations and deviations include, but are not limited to the following:

- any unintended or intended deviation from the IRB approved protocol that involves potential risks or has the potential to recur
- any emergent deviation from the IRB protocol made without prior IRB review to eliminate apparent immediate hazard to a research subject
- use of an expired or incorrect informed consent documents
- enrollment of subjects not eligible according to the IRB approved protocol
- any medication error involving dosing, administration and/or preparation of the study drug(s)
- any lapse in study approval where there is a continuation of research activities (i.e., recruitment, enrollment, procedures, data analysis)
- any identified noncompliance with federal regulations, state laws, University policies and/or requirements or determinations of the IRB or provisions of the approved research study
- any event that requires prompt reporting according to the protocol or the study sponsor.

Examples of incidents include, but are not limited to the following:

- any complaint of a study subject that indicates an unexpected risk or the complaint and cannot be resolved by the research staff
- any breach of confidentiality or privacy
- incarceration of a study subject in a medical study not approved to enroll prisoners
- loss of adequate resources to support continued research activities,
- an unexpected natural disaster, such as an earthquake, that destroys records or disrupts scheduling.

Any computer data security breach (i.e., lost or stolen computer/laptop and/or removable media used as storage devices, such as a flash drive or CD) on which personally identifiable information may have been or be acquired by an unauthorized person must be reported to your department's IT Compliance Coordinator. Please refer to [HRPP Guidance and Procedure #40: Data Security Guidelines](#) and [UCLA Policy #420: Notification of Breaches of Computerized Personal Information](#).

All violations and incidents should be reported as described below:

1. ***Within 10 working days***, using the Protocol Violation, Deviation or Incident Reporting Form posted on the OPRS/Human Research Protection Program website:

Any violation incident that is an unanticipated problem, which meets the following criteria:

- Unexpected,
- Related or possibly related to the research, and
- Places subjects or others at greater risk of harm than was previously known or recognized

2. ***Within 5 working days***, using the Protocol Violation, Deviation or Incident Reporting Form posted on the OPRS/Human Research Protection Program website:

Report any emergent variance from the approved IRB protocol that is made without prior IRB review in order to eliminate apparent immediate hazard to research subject.

3. ***At Continuing Review***, provide a list of the protocol violations, deviations and incidents that occurred during the previous year. A Protocol Violation, Deviation, or Incident Summary Log is available on the forms section of OPRS/Human Research Protection Program website for the convenience of the investigators. However, the use of this particular form is not required. What is required is a listing.

Report any violation, deviation, or incident that does not meet the 10-day or 5-day reporting requirement as described in Sections IV.B.1 and IV.B.2 above.

C. Reporting of Updated Study Safety Information

Updated study safety information addresses the risks or potential benefits of the research and should be reported to the IRB whether the information described occurred during the course of the study, after study completion, or after subject withdrawal or completion if it affects the safety and welfare of subjects.

Examples of updated study safety information include, but are not limited to the following:

- Data Safety Monitoring Board (DSMB) report
- audit or monitoring report
- interim study results
- FDA Safety Alerts
- publication in the literature, or other findings
- revised Investigator's Brochure
- notification of sponsor-imposed suspension or termination of a study
- changes in the FDA labeling or withdrawal from marketing of a drug, biologic or device used in a research protocol
- any information that requires prompt reporting according to the protocol or the study sponsor.

Updated study safety information should be reported as described below:

1. ***Within 10 working days***, using the Updated Study Safety Information Reporting Form posted on the OPRS/Human Research Protection Program website.

Report any updated safety information that addresses the risk or potential benefit of the research as provided in the examples above.

2. ***Within 2 working days***, using the Updated Study Safety Reporting Form posted on the OPRS/Human Research Protection Program website.

Report any sponsor-imposed hold, suspension or termination of research.

V. IRB Responsibilities and Procedures

- A. The IRB is responsible for reviewing written reports of events and information, and determining if the reports meet the criteria of an unanticipated problem involving risk to subjects and others. The IRB must also evaluate the risks, potential benefits, the adequacy of the recruitment and consent documents, provision of updated information to subjects, and the safeguards that are in place to protect the safety and welfare of the human subjects, including subject privacy and the confidentiality of data. If any revisions are needed in the protocol, recruitment and/or consent documents, these revisions are to be communicated to the investigator.
- B. Upon receipt of the post-approval report forms (Adverse Event Reporting Form; Violation, Deviation, or Incident Reporting Form; and Updated Study Safety Information Reporting Form), the IRB staff will review the form(s) and material submitted for completeness. If the report is incomplete, the Principal Investigator will be contacted with a request for the missing information. Review will not proceed until the requested information is received.

If upon review by the IRB staff the submitted post-approval report form does not meet the submission criteria, review by the IRB Chair or Vice Chair will not proceed. The Principal Investigator will be notified by the IRB staff that the submission criteria was not met and educated regarding the required submission criteria.

- C. IRB staff will direct the post-approval report form and the review materials to the appropriate IRB Chair or Vice Chair for review. The review materials will include all study documents submitted to the IRB. Examples of study documents include but are not limited to the following: study protocol, IRB application, current approval notice, current approved informed consent document, correspondence between study sponsor and Principal Investigator, Investigator's Brochure (if applicable), and other pertinent documents.
 1. The IRB Chair/Vice Chair will review and evaluate the post-approval report form and other information provided to determine whether the risk-potential benefit profile of the study has changed.
 2. The IRB Chair/Vice Chair will evaluate the post-approval report form to determine whether the reported event or information meets the following criteria for an unanticipated problem involving risk to subjects or others. The criteria are as follows:
 - a. The event is unexpected;
 - b. The event is related or possibly related to participation in the research; and

- c. Subjects or others are placed at a greater risk of harm than was previously known or recognized.
- 3. If the IRB Chair/Vice Chair determines that the event does *not* meet the criteria for an unanticipated problem involving risk to subjects or others, no further action will be taken and the event will be considered *not* to represent an unanticipated problem. The report will be accepted and signed by the IRB Chair/Vice Chair.
- 4. If the IRB Chair/Vice Chair determines that the event meets the criteria for an unanticipated problem involving risk to subjects or to others or cannot make a definitive determination, the report will be forwarded to the Full Committee, and scheduled for the next meeting of the appropriate IRB.

The IRB Chair/Vice Chair may request additional information from the Principal Investigator regarding the post-approval report prior to presentation at the next IRB meeting, in order to provide the convened Board with sufficient information to evaluate the issue.

- 5. If the post-approval report is of the nature that the safety, rights and welfare of subjects are at immediate risk, the IRB Chair/Vice Chair will contact the Principal Investigator 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.
- 6. If the post-approval report involves a matter of noncompliance, the review will also proceed as described by the appropriate policy (see [HRPP Policy #53: Noncompliance and Allegations of Noncompliance Regarding the Conduct of Human Subjects Research](#)).
- 7. If the Chair or Vice Chair is not available to review a post-approval report, a designated Committee member will be identified to review the report.

D. Review by a convened IRB meeting (Full Committee review).

- 1. The post-approval reports determined to be or possibly be an unanticipated problems involving risk to subjects or others along with the relevant additional review materials as described in D.2. below will be distributed to the primary reviewer(s) and Committee members approximately one week prior to the meeting.

Post-approval reports that are reported to the IRB in summary format will be reviewed at the time of continuation review.

- 2. Appropriate review materials may include but are not limited to the following: post-approval report, investigator's correspondence, study protocol, IRB application, current approval notice, current approved informed consent document, correspondence between study sponsor and principal investigator, investigator's 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 in order to facilitate a thorough review before a final determination is made.
- 4. The IRB will consider and make the following action determinations, which may include one or more action, but is not limited to the following:

- No further action required;
 - Accept and approve the Principal Investigator's corrective action plan;
 - Modification of the research protocol to minimize risk;
 - Modification of the interval at which continuing review is conducted appropriate to the degree of risk;
 - Modification of the recruitment or informed consent documents;
 - Requirement that current subjects re-consent to participation;
 - Notification of previously enrolled subjects of new information;
 - Notification of currently enrolled subjects of new information, as such information may relate to a subject's willingness to continue participation in the research;
 - Observation of the research or the consent process (i.e., use of a consent monitor);
 - Submission of more frequent progress or status reports to the IRB;
 - Educational intervention for the investigators and support staff;
 - Referral for on-site review by the HRPP Quality Improvement Program;
 - Referral to another University entity (i.e., institutional official, campus counsel, risk management);
 - Suspension of all or parts of the research (new enrollment, treatment, follow-up and data analysis) pending receipt of additional information from the Principal Investigator, including but not limited to a corrective action plan;
 - Termination of the research;
- E. The outcome and determinations made during the convened IRB meeting shall be documented in the correspondence to the principal investigator and the IRB meeting minutes.
- F. Written correspondence from the IRB regarding their final action determination will be forwarded to the Principal Investigator within ten working days of the IRB determination.
1. The HRPP senior staff will oversee and coordinate with the Chair all written correspondence from the IRB to the principal investigator.
 2. A copy of the IRB correspondence to the Principal Investigator will be forwarded to the Institutional Official and appropriate University departments within ten working days of the IRB's final determination.

VI. IRB Reporting Requirements

Unanticipated problems involving risks to subjects or others; any serious or continuing noncompliance; any suspension or termination of IRB approval; and the outcome of the IRB's actions are reportable to the appropriate federal department or agency head(s) and institutional official (45 CFR 46.103(b) (5) and 21 CFR 56.108(b)) and will be reported according to [HRPP Guidance and Procedure #60: IRB Reporting Procedures for Unanticipated Problems, Noncompliance, Suspension, or Termination.](#)

Regulations:

45 CFR 46.103(b) (5)
 45 CFR 46.103(a)
 45 CFR 46.111

45 CFR 46.116(b) (5)
21 CFR 50.25(b) (5)
21 CFR 56.108(b) (1)
21 CFR 312.32(a)
21 CFR 812.150(a)

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 Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (January 15, 2007)

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

FDA Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting – Improving Human Subject Protection (January 2009)

AAHRPP Tip Sheet: Unanticipated Problems Involving Risks to Participants or Others (May 24, 2007)

[UCLA Policy 420: Notification of Breaches of Computerized Personal Information.](#)