

Policy Number: 19

Title: Reporting Unanticipated Problems Involving Risk to Participants or Others

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Policy:

It is the policy of the UC Irvine (UCI) Institutional Review Board (IRB) to require reporting of unanticipated problems involving risk to participants or others. Additional reporting requirements are as follows:

I. Unanticipated Problems

- A. The phrase “unanticipated problems involving risks to subjects or others” is found but not defined in the HHS regulations at 45 CFR part 46. The Office for Human Research Protections (OHRP) considers unanticipated problems, in general, to include any 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 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** (in this guidance document, 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.**
- B. Food and Drug Administration (FDA) guidance is consistent with OHRP. The FDA states that an adverse event observed during the conduct of a study should be considered an unanticipated problem involving risk to human subjects, and reported to the IRB, only if it were unexpected, serious and would have implications for the conduct of the study.

II. Reporting of Unanticipated Problems

- A. **All unanticipated problems must be reported to the UCI IRB as follows:**
 - 1. **Where the event occurred at UCI for a single-site study.**
 - 2. **Where UCI is the IRB of record for a multi-site study, and the unanticipated problem occurred at a site relying on UCI IRB;**
 - 3. **Where the event occurred at a UCI site, but UCI is *not* the IRB of record and is relying on a non-UCI IRB.**
- B. UCI considers both OHRP and FDA guidance when assessing whether an event constitutes an unanticipated problem.
- C. Unanticipated problems must be submitted to the IRB via Reportable Events promptly - within 5 business days upon the Lead Researcher’s (LRs) knowledge of the event.

- D. In cases where the LR initially determined that an adverse event was not reportable, but either the Sponsor and/or Data Safety Monitoring Board (DSMB) upgrades the event to an unanticipated problem, a Reportable Event must be submitted within 5 business days of the LR learning of the Sponsor and/or DSMB's assessment of the event.
- E. In certain cases, the reports of serious and/or continuing non-compliance that are Unanticipated Problems may come from sources other than via reportable events such as phone call or an email from a participant, a family member, the IRB committee member, Whistleblower Office, UCI Health Affairs Compliance Officer etc. In such case the goals of the IRB, in general is to investigate and manage issues of potential noncompliance for subject safety, developing corrective and preventative action plans and reporting the serious or continuing noncompliance. (See policy #52.)
- F. Where an external IRB is the IRB of record, all unanticipated problems that occur at UCI must be reported to the UCI IRB. UCI will work in partnership with the reviewing IRB to investigate the matter for the purpose of (continued) human subject protection.

III. **Mechanism to Report: UP Reporting System**

- A. Reportable Events is a web-based module. It is accessible via the OR/HRP website 24 hours per day, seven days per week.
- B. The LR provides the following information:
 - 1. A description of the unanticipated problem;
 - 2. The date the event/problem occurred;
 - 3. The date the LR became aware of the event/problems;
 - 4. Identification of the drug, biologic, medical device, treatment or intervention;
 - 5. Explanation of the treatment provided to the participant;
 - 6. Outcome or anticipated outcome; and
 - 7. Status of the individual's participation in the study.
- C. The LR also attaches any associated materials such as redacted medical record notations or safety reports to the Reportable Events form.
- D. When IRB-approved documents (e.g., IRB Application; informed consent document) must be revised, the Investigator is required to submit an electronic Amendment request.
- E. If an unanticipated problem is unresolved at the time of initial reporting, a follow-up report must be submitted if the event or problem is not resolved as expected or if the event/problem results in a chronic condition or death.
- F. The LR is responsible for the accurate documentation, investigation, recordkeeping and follow-up of events or problems, including Safety Reports (SRs) received by the FDA or by a drug/device manufacturer.

IV. **Confirmation of an Unanticipated Problem**

- A. The IRB Chair or, if necessary, the full Committee, will review the Reportable Event to confirm whether the event/problem represents an unanticipated problem involving risk to participants or others.
 - 1. Where UCI is not the IRB of record, and the event occurred at UCI, the IRB Chair or, if necessary, the full Committee reserves the right to (also) review the UP report to ensure the protection of human subjects.

- B. Unanticipated problems involving risk to participants or others will be referred to the convened IRB Committee for further action.
 - C. The LR has the option to place some or all research activities on hold pending review by the convened IRB and/or until additional information can be provided to the Chair or the IRB to determine if a change in the risk-benefit profile has occurred or a change in the rights or welfare of the participants has occurred.
 - D. The IRB Chair or designee can determine that participants are at immediate risk of harm and there is insufficient time to wait for review by the convened IRB Committee, the Chair or designee may immediately place the study on "suspension". (See HRP Policy # 51.)
 - E. All IRB confirmations of unanticipated problems involving risks to participants or others must be reported to the LR, institutional officials, OHRP and the FDA (if applicable) as per federal regulations and per current policy.
- V. **Events/Problems that are not reportable to the UCI IRB**
- A. For protocols where UCI IRB serves as the IRB of record the following events/problems are not reportable to the UCI IRB:
 1. Protocol deviations that do not constitute an unanticipated problem involving risk to participants or others.
 2. Internal adverse events that do not constitute an unanticipated problem involving risk to participants or others.
 3. Safety reports that do not constitute an unanticipated problem involving risk to participants or others.
 4. Data safety monitoring reports that do not constitute an unanticipated problem involving risk to participants or others.
 5. Any other event or occurrence that, in the LR's assessment does not constitute an unanticipated problem involving risk to participants or others.
- VI. **All protocol deviations, internal adverse events, or safety reports whether reportable to the IRB or not as a possible unanticipated problem are to be maintained by the LR.**
- VII. **Other Reporting Requirements for the LR at Continuing Review**
- A. The IRB have access to all reported unanticipated problems during the last approval period as part of the continuing review process.
 - B. Independent safety monitoring reports or DSMB reports must be reviewed by the LR and submitted to the IRB at the time of continuing review.
- VIII. **Additional Reporting Requirements for Human Gene Transfer Research**
- A. Investigators involved in IRB-approved human gene transfer (a.k.a. "gene therapy") protocols have additional reporting responsibilities.
 1. In addition to submitting a Reportable Event to the UCI IRB, the LR must complete and submit an Office of Biotechnology Activities' (OBA) SAE report form when a subject on a gene transfer protocol experiences a hospitalization or a death. The form must be submitted to the UCI IRB, the UCI Institutional Biosafety Committee (IBC), NIH Office of Biotechnology Activities (OBA), OHRP, and FDA.

2. Failure to report SAEs related to gene transfer to the federal authorities can result in sanctions for the individual researcher and for the institution.

IX. Unanticipated Problems related to a Humanitarian Use Device (HUD)

- A. Whenever the physician or health care provider receives or otherwise becomes aware of information, from any source, that reasonably suggests that a HUD has or may have caused or contributed to the death or serious injury of a patient, the physician or health care provider must:
 1. Report such findings to the FDA and the IRB as soon as possible, but no later than 10 working days after the physician first learns of the event or problem. This reporting is in addition to, not a substitute for, FDA and/or manufacturer reporting requirements in accordance with 21 CFR 803.30.
 2. The Investigator must also promptly report any FDA action regarding the death or serious injury of a patient to the IRB.

References:

21 CFR 312.66

21 CFR 803.30

45 CFR 46.103(b)(5)

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

MedWatch – “What Is a Serious Adverse Event?”

OHRP Guidance Document, “Adverse Event Reporting Requirements,” January 11, 2001

OHRP Guidance Document, “Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events,” January 15, 2007

ICH-GCP: 3.3.8, 4.10.2

Procedure Number: 19.A

Title: Reporting Unanticipated Problems Involving Risk to Participants or Others

Procedure:

This procedure outlines the process for reporting unanticipated problems involving risk to participants or others.

I. LR Responsibilities

- A. The LR submits a Reportable Event as soon as possible, but no later than 5 working days after the LR first learns of the event/problem.
- B. The LR is responsible for the accurate documentation, investigation, and follow-up of all unanticipated problems.
- C. For clinical investigations, independent safety monitoring reports or DSMB reports must be reviewed by the LR and reported to the UCI IRB within 5 working days if the report constitutes an unanticipated problem or provided to the IRB at the time of continuing review.
- D. Relatedly, the Lead Researcher must notify the IRB of matters of (or potential matters of) serious and/or continuing non-compliance via Reportable Events as soon as possible, but no later than 5 working days after the LR first learns of the event/problem. (See Policy # 19.)

II. IRB Chair/Designated Committee Member Responsibilities

- A. All Reportable Events are provided to a Chair or a designated Committee Member for review either within 72 hours or during the weekly IRB Chair meeting, depending on the severity of the event/problem.
- B. The reviewer is provided:
 - 1. A copy of the report and all attachments; and
 - 2. The IRB Application file including the most recently approved protocol consent form and any other applicable documentation.
- C. The Chair reviews the materials to confirm whether the event represents an unanticipated problem.
 - 1. If the Chair cannot decide for each criterion, the event will be forwarded to the convened IRB Committee to make these decisions.
 - 2. If the Chair determines that the event meets all three criteria, then the event will be considered an unanticipated problem involving risk to participants or others and the event will be referred to the convened IRB Committee for further action. If participants are at immediate risk of harm and there is insufficient time to wait for review by the convened IRB, the Chair or designee can suspend the research. (See HRP Policy # 51.)
 - 3. If the Chair determines that the event does not meet one or more of the three criteria, then the event will be considered not to represent an unanticipated problem involving risk to participants or others. Documentation of this assessment will be maintained in the study file.

III. **IRB Committee Responsibilities**

- A. If the Chair confirms that the Reportable Event constitutes an unanticipated problem involving risk to participants or others, or when the determination is required by the IRB Committee, the UP report will be forwarded to the convened IRB Committee.
- B. Documentation for IRB review of unanticipated problems involving risk to participants or others, or possible unanticipated problem includes:
 - 1. All Committee members review:
 - a. The Reportable Event and all attachments;
 - b. Previously reported unanticipated problems;
 - c. The current IRB-approved Application and informed consent document(s); and
 - d. The Amendment Application, if applicable.
 - 2. The assigned member also reviews:
 - a. The sponsor's protocol, if applicable
 - b. The Investigator's Brochure, if applicable.
 - c. Data Safety Monitoring Charter, if applicable.
- C. The IRB may postpone a decision while awaiting additional information.
- D. If the IRB confirms that the event/problem meets all three criteria, then any of the following actions may be taken:
 - 1. The IRB may:
 - a. Accept the report with no changes;
 - b. Accept the report with changes to the risk/benefit profile, the protocol, or the informed consent documents (require submission of an Amendment);
 - c. Require notification/re-consenting of participants when such information might relate to the participants' willingness to continue participation in the research (the consent document or notification letter must be reviewed by the IRB prior to notification);
 - d. Require notification of past participants when such information might relate to long term risks (the notification letter must be reviewed by the IRB prior to notification);
 - e. Request further information from the LR or DSMB;
 - f. Increase the frequency of continuing review;
 - g. Impose additional monitoring requirements of the protocol, such as monitoring of the consent process;
 - h. Require additional training of the LR and research team;
 - i. Require notification of researchers at other sites;
 - j. Referral to other organizational entities;
 - k. Suspend the study per HRP Policy 51.
 - m. Terminate the study according to HRP Policy 51.
 - 2. The event will be reported according to HRP Policy 53.
 - 3. The IRB will consider whether the event represents serious or continuing non-compliance according to HRP Policy 52.
 - 4. In the case of changes to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant, the IRB will consider whether the changes were consistent with the rights and welfare of participants.
 - 5. If the IRB determines that the event does not meet one or more of the three criteria, then the event will be considered not to represent an unanticipated problem involving risks to participants or others.

IV. **IRB Administrator Responsibilities**

- A. The IRB Compliance Manager (EQUIP Team) monitors when potential UPs are reported to the IRB. The HRP staff works closely with the IRB Chair and IRB to manage potential UPs. When an UP may involve noncompliance the IRB Compliance Manager works closely with the IRB Chair and IRB to manage the potential UP. (See HRP Policy # 52.)
- B. All unanticipated problems reports made under HRP Policy 19 are provided to a Chair or a designated Committee Member for review either within 72 hours or during the weekly IRB Chair meeting, depending on the severity of the event/problem.
- C. Unanticipated problems involving risk to participants or others or where the IRB Chair is unable to confirm whether the event/problem qualifies as an unanticipated problem involving risk to participants or others are prepared for convened IRB Committee review. The Reportable Event is placed on the next convened Committee agenda, one IRB Reviewer is assigned, and the appropriate documents are included on the agenda for the Committee.
- D. Letters requesting information from the LR are drafted using an appropriate HRP memo template.
- E. Appropriate database entries are completed.