Adverse Event or Safety Information

What, When and How to Report AEs

See thePost-Approval Reporting Requirements Summary Sheet[2] for one-page summary of the information below.

Federal regulations from OHRP [3] require the IRB to ensure that investigators promptly report "any unanticipated problems [UPs] involving risk to subjects or others." The FDA, study sponsors and institutional policy include similar, but not identical, reporting requirements. The

IRB/HRPP reviews the reports [4] and determines whether they meet the institutional definition of a UP, among other things.

The Post-Approval Reporting Requirements chart below describes which adverse events (AEs), other events and safety information updates need to be reported to the IRB/HRPP and how/when to submit the report.

Reporting requirements chart

Contact the IRB [5] at 415-476-1814 or IRB@ucsf.edu [6]and speak with the QIU Analyst of the day with questions. See the Protocol Violation or Incident [7] page for info on reporting for these types of events.

Type of Event	When to Report*	Reporting Form
*The SF VA Medical Center (SFVAMC) has has a shorter timeline and different definitions than UCSF for reporting certain categories of post-approval events. See the SFVAMC guidance page [8] and VHA Handbook 1058.01 [9] for specific examples.		
Adverse Events		
Internal (on-site) adverse event that PI determines to be 1. Definitely, probably or possibly related AND 2. Serious or unexpected	Within **5 working days** of UCSF PI awareness **Internal, related deaths and life-threatening events:** Report **immediately**	iRIS Adverse Event Reporting Form
External (off-site) adverse event that UCSF PI determines • changes the study risks or benefits, OR • necessitates modification to the IRB-approved consent document(s), and/or the IRB-approved application/protocol	Within **10 working days** of UCSF PI awareness	iRIS Adverse Event Reporting Form
Other Types of Events or Safety Information		

Audit or Monitoring Report with significant findings DSMB/DMC Report Hold on Study Activities due to unexpected risk or required by any oversight entity e.g. UCSF, FDA, OHRP Updated Investigator Brochure	Within **10 working days** of awareness	iRIS Reporting Form
Other Safety Information or Publication Pharmacy Packet Inserts	**Change** to risk language - within **10 working days** of awareness **No change** to risk language - **reporting not required**	iRIS Reporting Form

Reporting Reminders:

Submit follow-up reports for unresolved AEs

If an internal (on-site) AE is noted as ?unresolved? at the time of initial reporting, a follow-up report is required if the AE does not resolve as expected, or if the AE results in a chronic condition or death.

Remove subject identifiers from reports/attachments

Do not include subject names or other direct identifiers on the AE Reporting Form or attachments.

Complete AE/safety info sections during Continuing Review

When submitting the Continuing Review Form, complete the sections regarding reportable AEs and other safety information.

Remember outside reporting requirements to sponsors, FDA, NIH, etc.

Investigators may have AE reporting requirements (e.g., to an industry sponsor, the FDA or the NIH) in addition to HRPP reporting requirements. It is the investigator?s responsibility to know and comply with these additional requirements.

Inform participants about significant new findings ? the level of urgency determines how to communicate the info

Participants must be informed about significant new findings developed during the course of research that may affect willingness to participate. See the Modification [10] page for more details on how to provide this info to current study participants.

The level of urgency will determine how the information is communicated to participants:

For emergency situations [11]: If participants should be informed immediately, contact participants first and then call the IRB [5] for guidance on how to proceed with a modification [12] and/or follow up for the participants. This option should only be used when there is a certain emergency. For example, the researcher has just received notice that a drug is contaminated and not safe for consumption. The contact of each participant should be documented in the research record.

All other findings that do not constitute an emergency should be submitted to the IRB for review with the required modification.

For urgent situations: If new findings do not suggest an emergency, but nevertheless require timely changes to the approved research, call the IRB [5] to request urgent review. While significant new findings will generally need to be ultimately reviewed by full committee, a need to inform previous, current or soon-to-be-enrolled participants in a timely manner can often be processed by the IRB on the same day. Document all urgent contact with participants in the research record.

For non-urgent situations: If significant new findings do not require urgent contact with previous, current or soon-to-be-enrolled participants, submit an AE report with the required major modification [12] within the required reporting period of the significant new findings. Participants must receive written notification [10] of clinically important late onset adverse events. The form and content of such notification must receive prior review by the IRB.

Submitting in iRIS

Follow these steps to submit the report. For additional assistance, read the quick guide called "Submitting Post-approval Forms" in the Help section of iRIS.

1. Open the study via the IRB Study Assistant

Go to **My Studies** under the IRB Study Assistant. Open the active study for which you want to submit the report.

2. Start a new Adverse Event Reporting Form or Reporting Form, or copy an older form

To determine when and which form to submit, review the guidance above. Click **Add New Form** to start a blank form. You can **copy a previous form** by selecting the form you want to copy and clicking Copy Form. The copied form will open automatically.

3. Submit the form

Anyone listed on the study can **sign off and submit** it.

4. If this form applies to more than one study, make a copy of it and submit it for additional studies

- Open the first study again and click on the Adverse Event Reporting Form or Reporting Form link.
- Click the "Apply to Multiple" icon next to the correct form.
- Check the boxes next to the studies for which you wish to submit this form. Click the "Save a Copy of the Selected Form" button.
- You will then need to open each of the studies you selected, open the copied form and submit the form.

Definitions and Types of AEs

Internal (on-site) adverse events

- AEs that occur in study participants who were enrolled through a UCSF or UCSF affiliated study site [13], or
- AEs that occur in a study under the direct supervision of a UCSF PI and for which the IRB of record.

External (off-site) adverse events

- AEs that occur in study participants who are not enrolled at a UCSF or affiliated study site. These AEs occur at sites that are under the oversight of another IRB.
- The PI typically receives notification of these events from the study sponsor and these AEs are usually referred to as Sponsor Safety Reports or Safety Memos.

Expected adverse event

An AE that may be reasonably anticipated to occur as a result of the study procedures or study participation and should thus be described in the research proposal, the informed consent document and Investigator?s Brochure (when applicable), or is part of the normal disease process or progression.

Unexpected adverse event

An adverse event is defined as being unexpected if the event exceeds the nature, severity or frequency described in the current IRB Application including the protocol, consent form and investigator brochure (when applicable). An unexpected AE also includes any AE that meets any of the following criteria:

- Results in subject withdrawal from study participation,
- Due to an overdose of study medication, or
- Due to a deviation from the IRB approved study protocol

Serious adverse event (SAE)

Any AE that results in any of the following outcomes:

- Death,
- Life-threatening adverse experience*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above,
- Event that changes the risk/benefit ratio of the study.

* A life-threatening adverse experience is any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Interventional research study

Any prospective, human research study that is designed to answer specific questions about the effects or impact of a particular biomedical or behavioral intervention, or are designed to answer specific questions about human physiology.

Hold on study accrual or other study activity

Various entities ? including the UCSF PI, the IRB/HRPP, a UCSF oversight entity such as the Cancer Center or CRS, the study sponsor, the SF VAMC, the FDA, etc. ? may place a hold on study accrual or other study activity. A hold is sometimes also called a ?suspension? or ?pause."

With one exception, any hold that is placed on study accrual or other activity is reportable to the IRB. The one exception occurs when the IRB Application and/or the sponsor?s protocol submitted to the IRB includes a planned hold on accrual/activity.

For instance, the IRB-approved protocol may indicate that after accrual of n subjects, accrual will cease until a safety analysis can be completed, after which accrual may re-start unless a safety issue is discovered. Thus, a planned hold and subsequent resumption of study accrual/activity need not be reported to the IRB as it has already been approved by the IRB. However, if a planned hold yields new safety information or any other unanticipated problem, or necessitates a change to the consent form or IRB Application, then it should be reported to the IRB.

VA Definitions

See the VHA Handbook 1058.01 [9] and SF VAMC guidance [14].

Serious AE (SAE): An SAE is an AE in human research that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly, or birth defect. An AE is also considered serious when medical, surgical, behavioral, social, or other intervention is needed to prevent such an outcome.

Unanticipated (Unexpected): The terms ?unanticipated? and ?unexpected? refer to an event or problem in VA research that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in protocol-related documents and the characteristics of the study population.

Related AE or a Related Problem: A ?related? AE or a ?related? problem in VA research is an AE or problem that may reasonably be regarded as caused by, or probably caused by, the research (see 21 CFR 312.64).

Determining Cause

It is imperative that the investigator assess AE causality in terms of overall study participation and make an independent determination as to whether the AE was thought to be related to any study-related activity (i.e., study intervention, test article administration, study-related tests or procedures).

Use the following definitions to assess the AE relationship to study participation:

Definitely related

An AE is definitely related to study participation if it is clear that the event was caused by study participation. A definitely related event has a strong temporal relationship and an alternative cause is unlikely.

Probably related

An AE is probably related when there is a reasonable possibility that the event is likely to have been caused by study participation. The AE has a timely relationship to the study procedure(s) and follows a known pattern of response, but a potential alternative cause may be present.

Possibly related

An AE is possibly related when there is a reasonable possibility that the event might have been caused by study participation. A possibly related event may follow no known pattern of response and an alternative cause seems more likely. In other circumstances there may be significant uncertainty about the cause of the event, or a possible relationship to study participation cannot reasonably be ruled out.

Unrelated

The cause of the AE is known and the event is in no way related to any aspect of study participation. If there is any uncertainty regarding AE causality then the event must be assessed as possibly related to research participation and reported to the IRB as indicated. Often, the cause of an unrelated AE is disease progression.

Important Reminders:

- An AE may be unrelated to the experimental intervention, but nevertheless related to study participation.
    - ?Example: Study participation requires one or a series of IV drug infusions that would not otherwise be given as part of standard clinical care. A participant develops thrombophlebitis at the IV access site. This AE should be assessed as definitely related to research participation.
- Keep information involving AEs determined to be unrelated to research participation in the study files for follow up, documentation and reference.

What Not to Report to the IRB/HRPP

Do not submit the following items to the IRB/HRPP. Keep them in your study files and comply with outside reporting requirements (if/when applicable).

Sponsor IND/IDE safety reports not meeting reporting criteria

Do **not** submit non-reportable study sponsor IND/IDE safety reports to the IRB.

Note: The actual study sponsor safety reports should be kept in your study files unless the AE meets the IRB 10-working-day reporting criteria, in which case the IND or IDE Safety Report should be included with submission of the Adverse Event Reporting Form.

AEs unelated to research

Individual reports of internal (on-site) AEs determined to be unrelated to research participation should not be reported to the IRB. Instead, these events should be documented, referenced and retained in the PI?s study files for follow-up. The IRB no longer accepts AE Summary Log reports of AEs that do not meet the IRB reporting criteria.

IRB/HRPP Review of Adverse Event Reports

The IRB/HRPP will review the AE report and determine if a) the risk-benefit ratio continues to be acceptable, b) the research protocol and informed consent document accurately and completely present risk information, c) current subjects should be advised of newly identified risks and d) the event meets the definition of an Unanticipated Problem involving risk to participants or others.

Track the report using the Submission History feature in iRIS.

Possible subsequent actions may include the following

Acknowledge the report ? no letter is issued.

Request additional information about the adverse event or other safety information.

Refer the AE report (or other safety information) to the IRB if it appears to meet the institutional definition of an Unanticipated Problem (UP) involving risk to participants or others. The IRB may query you for additional information and will inform you if the UP determination is made.

Report the event to OHRP, appropriate University officials, study sponsors and FDA (for studies under FDA oversight) if a full IRB panel review determines that the event report or safety information is an UP.

Flag the report and monitor the study for additional AEs.

Require a modification to the study protocol and/or informed consent document.

Temporarily suspend enrollment and/or study treatment.

Permanently suspend or terminate approval of research that has been associated with unexpected serious harm to participants.

Definition: Unanticipated problem (UP) involving risk to participants or others

An unexpected, research-related event where the risk exceeds the nature, severity, or frequency described in the protocol, study consent form, Investigator?s Brochure or other study information previously reviewed and approved by the IRB.

Investigator Roles and Responsibilities

Develop a safety plan

Your initial IRB Application must include a plan for safety monitoring, reporting of AEs and/or unanticipated problems involving risks to subjects, descriptions of interim safety reviews, and the procedures for communicating these results to the IRB, study sponsor (when applicable) and federal regulatory authorities (when applicable).

Recognize and assess AEs

Investigators are responsible for the accurate documentation, causality assessment and follow-up of all definite, probable and possible study related AEs and safety-related information (such as sponsor or DSMB updates and holds on study activities due to safety concerns).

Evaluate the AE's impact on the study

- Evaluate an AE?s impact on the risk/benefit ratio of the study.
- Evaluate whether new information may affect participants? willingness to continue participation in the study, and if so, inform participants of new information according to a plan described to the HRPP.
- When appropriate make changes to the informed consent document and/or IRB Application/protocol resulting from an AE, and submit a modification [15] to the IRB for review and approval.
- When appropriate, ask subjects to sign an updated informed consent document describing new information.

Conduct timely and complete AE reporting

Investigators are required by law to inform the IRB and other entities (such as governmental or other sponsors) of any AE or other safety-related information in accordance with each entity?s regulations, policies and guidelines.

Submit Data Safety Monitoring Board (DSMB) reports

It is the investigator?s responsibility to submit any independent DSMB report to the IRB when it becomes available, as these events may require reassessment of the study protocol or consent documents.

Reassess safety plan, as needed

Prior to and at the time of continuing review it is the investigator?s responsibility to keep the IRB informed of any safety-related information or AEs that result in a **change to the risk/benefit ratio described in the currently approved IRB Application,** even if these events did not occur at UCSF.

Special AE Reporting Requirements

Research activities not involving drugs, biologics, procedures or devices

Use reasonable judgment to determine what constitutes an AE. Such events do not have to

be physical in nature. Attention must be paid to psychological, emotional, and social harm, and overall subject well-being. If in doubt, it is best to err on the side of reporting the event or contacting the IRB.

Human gene transfer research

In accordance with Appendix M-I-C-4 [16] of the NIH Guidelines [17], investigators who have received authorization from the FDA to initiate a human gene transfer protocol must immediately report in writing any SAE to the IRB, Biological Safety Committee (IBC) [18] and NIH Office of Biotechnology Activities (OBA) [17]. This should be followed by the submission of a written report to each group when additional pertinent information becomes available. Reports submitted to the NIH OBA may be sent by: email to oba@od.nih.gov [19]; by fax to (301) 496-9838; or by mail to the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, Maryland 20892-7985, Phone: (301) 496-9838.

When submitting reports to the OBA, use either a copy of the OBA Adverse Event Reporting Form [20] or another form that includes the required information on the event (as described in Appendix M [16]). Completed copies of the form submitted to OBA, as well as the IRB Adverse Event Report, should be submitted to the IRB and IBC.

Page last updated:
Oct 31, 2018

Links
[1] http://irb.ucsf.edu/#submitting
[2] http://irb.ucsf.edu/sites/hrpp.ucsf.edu/files/post-approval-reporting-summary-sheet.pdf
[3] http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.103
[4] http://irb.ucsf.edu/#review
[5] http://irb.ucsf.edu/contact-us
[6] mailto:IRB@ucsf.edu
[7] http://irb.ucsf.edu/protocol-violation-or-incident
[8] http://irb.ucsf.edu/research-sfvamc#considerations
[9] http://www1.va.gov/vhapublications/ViewPublication.asp?pub_ID=3116
[10] http://irb.ucsf.edu/node/201#continuing
[11] http://irb.ucsf.edu/node/201#approval
[12] http://irb.ucsf.edu/modification
[13] http://irb.ucsf.edu/ucsf-affiliated-institutions
[14] http://irb.ucsf.edu/research-sfvamc
[15] http://hrpp.ucsf.edu/modification
[16] http://osp.od.nih.gov/sites/default/files/NIH_Guidelines_0.pdf
[17] http://oba.od.nih.gov/oba/index.html
[18] http://www.research.ucsf.edu/rspc/techcomm.asp
[19] mailto:oba@od.nih.gov
[20] http://osp.od.nih.gov/office-biotechnology-activities/hgt-guidance-pis-and-trial-participants/template-

reporting-adverse-events-human-gene-transfer-trials