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Protocol Violation or Incident

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Overview

Federal regulations require that changes in the conduct of an IRB-approved research study receive prior IRB review and approval. When *changes to the protocol are necessary to immediately eliminate or reduce an apparent hazard to the safety of research participants or others*, those changes may be initiated without prior IRB approval, but must be reported to the IRB/HRPP within 10 working days of initiation.

Protocol violations are changes in the conduct of a IRB-approved research protocol that are under the investigator's control and made without prior IRB approval. *Incidents* are any problematic or unanticipated events that are not protocol violations and that may adversely impact on the study participants or the conduct of the study. You must report all **major** study-related protocol violations and incidents to the IRB/HRPP.

The IRB reviews these reports to determine whether an event meets the definition of an unanticipated problem involving risk to participants or others (UP) and/or an instance of serious or continuing noncompliance (SCNC).

What, When and How to Report

See the **Post-Approval Reporting Requirements Summary Sheet**^[1] for one-page summary of the information below.

Use the Reporting Requirements chart below to determine which violations, incidents and immediate protocol changes need to be reported and how/when to submit the report.

Reporting requirements chart

Contact the IRB at 415-476-1814 or IRB@ucsf.edu ^[2] and speak with the QIU Analyst of the day with questions.

Note: The SF VA Medical Center (SFVAMC) ^[3] has a shorter timeline (5 days) and different definitions than UCSF for reporting certain categories of post-approval events. See the SFVAMC guidance page ^[3] and VHA Handbook 1058.01 ^[4] for specific examples.

Type of Event	When to Report	Reporting Form
Major Violation including, but not limited to incorrect intervention given, enrollment of ineligible participant, key safety procedure/lab not done or done outside window.	Within 10 working days of awareness	iRIS Protocol Violation/Incident Report Form
Immediate Protocol Change to Protect Participant Safety	Within 10 working days of occurrence	iRIS Protocol Violation/Incident Report Form

Major Incident including, but not limited to problem with consent or recruitment process, significant complaint or concern, lapse in study approval, loss of adequate resources, potential breach of confidentiality of confidentiality.

Potential breaches of privacy or confidentiality:

Within 48 hours of awareness

Other Major Incidents:
Within 10 working days
of awareness

iRIS Protocol
Violation/Incident
Report Form

Reporting Reminders:

Submit follow-up reports for unresolved events

If the event is unresolved at the time of initial reporting, a follow-up report generally is required.

Remove subject identifiers from reports/attachments

Do not include subject names or other direct identifiers on the Protocol Violation/Incident Report Form or attachments.

Complete violation/incident info sections during Continuing Review

When submitting the Continuing Review Form, complete the sections regarding reportable protocol violation and incidents.

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

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

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 IRB Study Assistant

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

2. Start a new Protocol Violation/Incident Report Form, or copy an older form

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 Protocol Violation/Incident Report 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.

What Are Protocol Violations?

Protocol violations are any unapproved changes, deviations or departures from the study design or procedures of a research project that are under the investigator's control and that have not been reviewed and approved by the IRB. Protocol violations are divided into two categories: major (reportable) or minor (non-reportable).

Major (reportable) protocol violations are any unapproved changes in the research study design and/or procedures that are within the investigator's control and not in accordance with the IRB-approved protocol that may affect the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Report all major violations to the HRPP/IRB using the Protocol Violation/Incident Report Form in iRIS.

Criteria for defining

HRPP criteria for defining major violations include any of the following:

1. The violation has harmed, or posed a significant or substantive risk of harm, to the research participant.
2. The violation resulted in a change to the participant's clinical or emotional condition or status.
3. The violation has damaged the scientific completeness or soundness of the data collected for the study.
4. The violation is evidence of willful or knowing misconduct on the part of the investigator(s).
5. The violation involves serious or continuing noncompliance with federal, state or local regulations.

Examples

Examples include, but are not limited to:

1. Enrolling participants who did not meet the eligibility requirements.
2. Failing to obtain informed consent prior to any study-specific tests/procedures.

3. Failing to follow protocol procedures that specifically relate to the primary safety or efficacy endpoints of the study.

Minor (non-reportable) protocol violations (also known as protocol deviations) are any unapproved changes in the research study design and/or procedures that are within the investigator's control and not in accordance with the IRB-approved protocol that **do not have a major impact** on either the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

Do **not report** minor protocol violations to the IRB/HRPP, but document them in the study files.

Criteria for defining

HRPP criteria for minor violations include all of the following:

1. The violation did not harm or pose a significant risk of substantive harm to the research participant, and
2. The violation did not result in a change to the participant's clinical or emotional condition or status, and
3. The violation did not damage the completeness, accuracy and reliability of the data collected for the study, and
4. The violation did not result from willful or knowing misconduct on the part of the investigator(s).

Examples

Examples of minor protocol violations include, but are not limited to:

1. Routine safety lab work for a participant without new clinical concerns and a history of previously normal lab values is inadvertently omitted at a study visit or performed outside the protocol-defined window. The lab will be performed at the next opportunity and is expected to remain within normal limits.
2. Investigators miss giving a study required self-administered quality of life questionnaire to a participant.

What are not considered to be protocol violations? Changes, deviations or departures from the study design or procedures that are due to a study participant's non-adherence are not considered to be protocol violations. However, you should document study participant non-adherence to the study design and/or procedures in the research records and report this to the IRB/HRPP as an incident if the event(s) adversely impacts the study participant's safety or well-being, or if a pattern of protocol departures indicate a need for changes in the protocol or informed consent document(s).

Examples

1. Study participant did not return for a scheduled study visit.
2. Participant refused a blood draw.

What Are Incidents?

Major (reportable) incidents are any problematic or unanticipated events involving the conduct of the study or participant participation that may occur during the course of the research project. Report all major incidents to the HRPP/IRB.

Examples

Some examples of study-related incidents include, but are not limited to:

1. Receipt of a significant complaint or concern from a potential or enrolled study participant [5], such as a complaint/concern that may adversely impact the participant's safety, rights or welfare. Reminder: Investigators are obligated to make a good faith effort to resolve any study-related concern or complaint [5] they receive.
2. Inappropriate behavior of study participants and/or research personnel.
3. Problems during study recruitment or the informed consent process.
4. Problems with the study design in which a majority of participants have difficulty adhering to the study schedule of procedures.
5. Potential breach of study participant's privacy or confidentiality (see below).
6. Withdrawal or significant reduction in, resources necessary to adequately and safely conduct study activities.
7. Changes to the protocol to eliminate or reduce an apparent immediate hazard to the safety of research participants or others (see below).

Potential breaches of privacy or confidentiality: Report within 48 hours of awareness

Potential breaches of privacy [6] or confidentiality [6] of study participants' Protected Health Information (PHI) [7] are "major (reportable) incidents" that must be submitted to the IRB.

The review of these incidents is time sensitive: **Submit a Protocol Violation/Incident Report Form in iRIS within 48 hours of the PI's awareness of the potential breach.**

The IRB collaborates with the UCSF Privacy Office [8] to investigate these incidents to meet state and federal regulatory obligations. Investigations must be completed within a short time frame in order to avoid penalties and/or late reporting fines for the institution.

Some examples of major incidents involving privacy or confidentiality:

- Failure to properly execute a HIPAA Research Authorization Form [7] due to
 - Missing a participant's signature or date
 - Missing initials next to an information type in Section C that has been or will be accessed by the research team
 - Accessing items in Section B that are not approved for access or release by the participant
- Failing to obtain a properly executed consent form due to missing a participant's

signature or date

- Mailing, emailing or otherwise communicating identifiable study participant information to an unauthorized individual (e.g., incorrect participant, incorrect mailing address, incorrect e-mail address, etc.)
- Failing to redact identifiable study participant information sent to a study sponsor (only if the IRB Application and consent form require de-identification [6])

Change to eliminate or reduce an apparent immediate hazard to the safety of research participants or others

If you must implement changes to the protocol in order to eliminate or reduce an apparent immediate hazard to the safety of research participants or others, report such changes to the IRB within *10 working days* of initiating the changes in the study procedures. In the report, explain whether a modification [9] to the IRB Application/protocol and/or consent document(s) is necessary.

Reminder: Federal regulations require that you receive prior IRB approval [9] for other changes to your study ? even minor or sponsor-approved changes.

Example: You must immediately reduce the study drug dose or discontinue a study treatment based on new toxicity information from an interim Data Safety Monitoring Board review or a study sponsor report. In this case, a change in the approved study drug dose may be implemented immediately, with subsequent submission of a corresponding modification application.

You must also report any unanticipated problem involving potential risk to participants or others.

Minor (non-reportable) incidents are any events involving the conduct of the study or participant participation that may occur during the course of the research project but which is not problematic or involve significant potential to harm the participant(s) or others. Do not report minor incidents to the IRB/HRPP.

Example

Receipt, and subsequent resolution by the study team, of a participant complaint regarding late study payment.

IRB/HRPP Review and Definitions

The IRB/HRPP will review the Protocol Violation/Incident Report Form. 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 violation or incident or other related information.

Refer the violation or incident report (or other related information) to the IRB if it appears to meet the HRPP's institutional definition of an unanticipated problem (UP) involving risk to participants or others and/or an instance of serious or continuing noncompliance. The IRB may query you for additional information and will inform you if one of these determinations is made.

Report event to OHRP, appropriate University officials and study sponsors and FDA (for studies under FDA regulatory oversight) if a full IRB panel review determines that the event report is an UP or (after investigation) determines an instance of serious or continuing noncompliance [10].

Flag the report and monitor the study for additional violation or incident reports.

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 and/or serious or continuing noncompliance.

Definitions

Unanticipated problem 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.

Serious or continuing noncompliance

Noncompliance is defined as: failure to follow state or federal regulation, or the University policies, or the requirements of the VHA Handbook 1200.5, or determinations of the IRB for the protections of the rights and welfare of study participants.

Serious Noncompliance is defined as: failure to follow state or federal regulations or University policies or determinations of the IRB for the protection of the rights and welfare of study participants and that, in the judgment of the IRB, results in, or indicates a potential for a) a significant risk to enrolled or potential participants or others, or b) compromises the effectiveness of the UCSF HRPP or the University.

Continuing Noncompliance is defined as: a pattern of noncompliance that continues to occur after a report of noncompliance and a corrective action plan have been reviewed and approved by the IRB.

VA definitions

See VHA Handbook 1058.01 [4] and SFVAMC guidance [3].

Continuing Noncompliance: Continuing noncompliance is a persistent failure to adhere to the laws, regulations, or policies governing human research.

Serious Noncompliance: Serious noncompliance is a failure to adhere to the laws, regulations, or policies governing human research that may reasonably be regarded as:

- (1) Involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others; or
- (2) Substantively compromising the effectiveness of a facility's human research protection or human research oversight programs.

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.

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Links

- [1] <http://irb.ucsf.edu/sites/hrpp.ucsf.edu/files/post-approval-reporting-summary-sheet.pdf>
- [2] <mailto:IRB@ucsf.edu>
- [3] <http://irb.ucsf.edu/research-sfvamc>
- [4] http://www1.va.gov/vhapublications/ViewPublication.asp?pub_ID=3116
- [5] <http://irb.ucsf.edu/responding-and-reporting-research-related-concerns-and-complaints>
- [6] <http://irb.ucsf.edu/definitions>
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