SLHS HRPP Guidance on Protocol Deviations

What is a protocol deviation?

The term "protocol deviation" is not defined by either DHHS human subjects regulations (45 CFR 46) or FDA human subjects regulations (21 CFR 50).

The Saint Luke's HRPP defines a protocol deviation as: any change, divergence, or departure from the study design or procedures of a research protocol that is under the Investigator's control and that has not been approved by the IRB. Upon discovery, the Principal Investigator is responsible for reporting protocol deviations to the IRB using the standard reporting form.

See the Reportable Event Diagram below.

Unplanned Protocol Deviations

Protocol deviations are not usually anticipated and those that result in harm or have the potential for harm are considered Unanticipated Problems involving risk to subjects or others. Below is a framework to help Investigators and study teams distinguish between those protocol deviations that require prompt reporting and those that don't.

Minor Deviations

Deviations that do not require prompt reporting can occur frequently during a research study. Although these are protocol deviations, they usually cause no harm and have no potential to cause harm to the research subject or others. Such deviations can be submitted to the IRB at the time of continuing review when continuing reviews are required. When continuing reviews are not required, they should be tracked and documented internally by the Investigators/study team but are not required to be submitted to the IRB.

Examples of Minor Deviations that can be reported at Continuing Review:

- Subjects may fail to show up for a scheduled study visit
- Difficulty obtaining all the required blood samples at the specified times for a PK study
- Minor errors in data entry that don't affect the overall data analysis or conclusions of the study
- Dates are missing or incorrect on an informed consent form, but the consent process itself was followed correctly
- Modifications to recruitment materials that don't materially alter the information presented to potential participants
- Over-enrollment of the locally IRB-approved number of subjects in the following circumstances:
    - **Minimal risk studies**, regardless of percentage over-enrolled;
    - **Greater than minimal risk studies**, **if:**

- The total over-enrollment is **less than or equal to 25%** of the locally approved target ***and***
    1. The total number of over-enrolled participants is **no more than 3 participants**, ***or***
    2. In studies with **≤10 participants**, the over-enrollment does **not exceed 1 additional participant**, unless there is a compelling justification.

Major Deviations

Deviations that do require prompt reporting, on the other hand, are typically events that cause or could cause harm to subjects or others or that impact the fidelity of the research. They require prompt reporting as Reportable Events (as they may constitute Unanticipated Problems*).

Examples of Deviations **that do require prompt reporting**:

- Produce actual harm to a participant or others (an AE)
- Have the potential to produce harm to a subject
- Result in the enrollment of an ineligible subject
- Cause a subject to be withdrawn from the study
- Prevent the subject from being evaluable for the study's primary endpoint
- Improper handling or disclosure of PHI (privacy violation)
- Over-enrollment on greater than minimal risk studies where:
    - The over-enrollment exceeds 25% or
    - More than 3 additional participants are enrolled or
    - Over-enrollment occurs without a clear justification or plan for managing increased risk, burden, or data integrity.

Please note that the IRB generally requires the Investigator to propose corrective and preventative actions to correct the deviation and prevent future recurrences. The corrective/preventative actions need to include specific steps taken by the Principal Investigator (who is responsible for the conduct and oversight of the study) to correct the situation and ensure compliance with the IRB-approved research plan going forward.

Planned Protocol Deviations

A one-time amendment to a protocol is sometimes referred to as a planned protocol deviation. Some of the protocol modifications proposed as part of a one-time amendment (planned protocol deviation) are relatively minor - e.g., changes to study visit windows to accommodate subjects' schedules, obtaining a second blood sample after loss of a prior sample - while others are major and involve modifications to the inclusion or exclusion criteria or other study procedures.

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Both the study sponsor and the IRB need to approve a one-time amendment prior to implementing the change. If the investigator anticipates that the circumstance is likely to arise again, then the protocol should be amended to add sufficient flexibility to avoid the need for additional one-time amendments.

What are the requirements for a one-time amendment (planned protocol deviation)?

All changes to an IRB-approved research plan require prospective IRB review and approval.

Common examples include:

- Change in the inclusion or exclusion criteria (most require full-board review)
- Change in study procedures, including omission of a study procedure (most can be expedited)
- Change in the timing of study procedures such as a change to the procedure window (most can be expedited)
- Requests to continue the participation of a subject who has violated adherence requirements or who was enrolled incorrectly.

Emergency Planned Protocol Deviations

Emergency deviations occur when a departure from the protocol is required immediately to protect the life, physical well-being of a participant or to avoid an immediate hazard. In such cases, there is no time to prospectively seek approval from the IRB.

In this situation, the Principal Investigator may implement the departure from the protocol but must report it to the IRB as soon as possible (no later than 5 days after implementation). As part of the submission to the IRB, the Principal Investigator must provide rationale for why prior IRB approval was not possible.

Protocol Deviation FAQs

Are all Protocol Deviations reportable?

No, only Protocol Deviations attributable to the study team or sponsor; or attributable to a participant if the deviation results in a safety issue or increased risk of harm (e.g., missed safety labs, incorrect self-administered dose of study drug, participant or partner becomes pregnant when study involves potential risks to fetus).

Protocol deviations attributable to a participant that do **NOT** result in a safety issue or increased risk of harm (e.g., nonconsequential out of window visit) do not require reporting.

When and how should a PI report protocol deviations to the SLHS IRB and the sponsor?

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There are several types of protocol deviations recognized by the SLHS IRBs, and each type has a different IRB reporting requirement:

A. Emergency Deviations require reporting to the IRB promptly after they occur

The sponsor and the IRB of record must be notified as soon as possible, but not later than 5 days after the emergency situation occurred (21 CFR 812.150(a)(4))**. The PI must submit the deviation in iMedRIS as a reportable event application and include the rationale for why prior IRB approval was not possible. Deviations of this nature are always considered to be unanticipated problems involving risks to subjects or others.

** The reporting standard in 21 CFR 812.150(a)(4), which applies to studies involving Investigational Device Exemptions, shall apply broadly to all emergency deviations at SLHS.

B. Major, non-emergent deviations require approval by the IRB before they occur

Major, non-emergent deviations are planned deviations that represent a major change in the approved protocol. These deviations are changes that the IRB must approve before the proposed change is implemented.

> Examples include exceptions to eligibility criteria, exceptions to the form and manner of obtaining informed consent, and exceptions to the schedule of administration of an investigational product.

If a planned major, non-emergent deviation occurs without prior IRB approval, the event is non-compliance which must be reported promptly to the IRB. A PI's failure to report promptly any major, non-emergent deviation for which the PI did not obtain prior approval is itself an incident of non-compliance. Incidents of non-compliance will be managed in accordance with the SLHS HRPP Handbook.

C. Minor or administrative protocol deviations require reporting to the IRB at continuing review

Minor or administrative deviations are those which do not "affect the scientific soundness of the research plan or the rights, safety, or welfare of human subjects." A minor or administrative protocol deviation must be reported to the SLHS IRB at the time the continuing review application is submitted.

Examples include follow up visits occurring outside the protocol required time frame because of the participant's schedule, or blood samples being obtained at times close to but not precisely at the time points specified in the protocol.

What are the protocol deviation reporting requirements for commercially sponsored research?

Sponsored research agreements may require the PI to notify the sponsor of all unplanned deviations or departures from IRB approved protocol procedures. Sponsor reporting requirements for deviations may differ from SLHS IRB reporting requirements. It is the PI's responsibility to comply with the reporting requirements outlined in the signed agreement.
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Does the FDA Good Clinical Practice (GCP) Guidance affect reporting of deviations?

Many sponsors require investigators to follow Good Clinical Practice (GCP) guidelines. The GCP Guidance for Industry states:

"The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB…of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s))."
https://www.fda.gov/media/184745/download

If investigators have any questions regarding a sponsor's specific deviation reporting requirements, they should check with the sponsor and obtain clarification before the study enrollment begins.

**OHRP considers unanticipated problems, in general, to include any incident, experience, or outcome that meets all of the following criteria:*

- 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;
- 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
- 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.

FDA defines an unanticipated problem as: an event that is unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure).

Reportable Event Diagram

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