



Recording, Assessment, and Reporting of Deviations Guidance to Investigators Participating in Clinical Research

1. Scope

This guidance is intended to support Perelman School of Medicine (PSOM) Principal Investigators of clinical trials under the purview of the UPenn IRB regarding the recording of deviations and exceptions of an approved protocol, and the reporting requirements to the Penn IRB and Sponsor (if applicable).

Specific Sponsor reporting instructions should be followed if those differ from this guidance.

2. Protocol Alteration Scenarios and Guidance for Addressing their Potential Impact

2.1. Identification

During the course of a trial, the Principal Investigator (PI) or their study team prospectively identify that specific elements of a protocol are unable to be met, or realize that protocol procedures/processes have not been followed.

The FDA defines *protocol deviations* as any change, divergence, or departure from the study design or procedures defined in the protocol.

It also defines *important protocol deviations* as a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. For example, important protocol deviations may include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial.

2.2. Documentation and Assessment

The PI and the study team should document **ALL SCENARIOS** where the protocol is not followed and provide, in particular:

- Who deviated from the protocol
- What was the deviation
- When did the deviation occur
- How did the deviation happen
- What is the impact of the deviation
- A root cause analysis of why the deviation occurred

The outcome of the assessment will determine the actions the PI and study team should take.

When the PI and/or study team becomes aware of a deviation from the approved protocol (whether minor, potentially impactful, substantial, etc.), the following **must occur** for each scenario:

- Assessment of what occurred with documented assessment and action plan
- Follow through on the action plan with any required documentation reviews of the scenario and any further action requested by any appropriate reviewing entity and/or sponsor
- Submission of any required revisions to address what occurred and the plan to avoid the occurrence again
- Evidence of any interactions to request consult on level of issue for what occurred and whether additional action/submission was required (i.e. if consult from the IRB is sought)

2.3. Reporting

2.3.1. Limited Impact Deviations

If the assessment is determined to be of limited impact (minor deviation), the documentation for this assessment and the outcome should be reported to the IRB at the time of continuing review. Reporting to the Sponsor should follow the same requirements unless otherwise specified by the Sponsor.

2.3.2. Important Protocol Deviations

If the assessment results in a determination that any of the following are potentially affected, the deviation would be considered of significant impact

- having the potential to adversely affect subject safety; OR
- increases risks to participants; OR
- adversely affects the integrity of the data; OR
- violates the rights and welfare of participants, OR
- affects the subject's willingness to participate in research.
- there is a potential for an overall impact on the research that should be shared with the IRB for consideration and development of next best steps to address it

These scenarios should be reported to the IRB following the real time reporting requirements (within 10 business days of discovery). Reporting to Sponsor should follow same requirements unless otherwise specified by the Sponsor.

Examples of important protocol deviations:

Below are some examples of the types of deviations that are generally considered important protocol deviations.

- Subjects who entered the study even though they did not satisfy the entry criteria;
- Subjects who developed withdrawal criteria during the study but were not withdrawn;
- Subjects who received the wrong treatment or incorrect dose;

- Subjects who received an excluded concomitant treatment.
- Failure to/late report of serious adverse events
- Procedures performed without or prior to consent, or procedures continued for a subject who has withdrawn consent
- Consent obtained by unauthorized staff/not listed on delegation log
- Failure to re-consent when new safety information has been identified
- Omitting/delaying a test or procedure that is required to ensure subject safety
- Conducting additional tests or procedures that have not been approved by the IRB
- Unintentional un-blinding of the subject or the research staff
- Use of recruitment advertisements not approved by the IRB
- Lack of payment to subjects (where applicable) or falsified insurance claims
- Privacy Breach
- A trend identified from the list of minor/limited impact deviations

The definition of important protocol deviations for a particular trial is determined in part by study design, the critical procedures, study data, subject protections described in the protocol, and the planned analyses of study data. The Sponsor may amend or add to the examples of important deviations provided in consideration of a trial's requirements.

Prospective revisions/alterations to the protocol that are known to be significant:

The PI and study team may encounter a situation where a potentially impactful protocol criteria or requirement should be altered or not followed for **one specific participant** if the participant stands to benefit from participation in the study or there is some other appropriate rationale for making this planned deviation (exception) for this one participant. In these cases,

- Sponsor approval must be obtained
- IRB approval must be obtained (this can be conducted via email if the timeline is pressing by providing the exception request form and any other supporting documentation via email to all three Director level personnel – Jessica Yoos (jessyoos@upenn.edu), Dave Heagerty (heagerty@upenn.edu) and Diane Pinder (pinder@upenn.edu).
- If approval is required from other ancillary review entities (i.e. Medical Monitor, Cancer Center, IND Sponsor, etc.) this must be obtained (and confirmed in the submission to the IRB or confirmed that approval has been sought and is pending).

The rationale for the exception should be documented in the request including a full description of the risks and benefits to the subject.

If the same revision/alteration continues to occur, a protocol amendment is required and should be submitted for approval as soon as possible.

3. Consequences of Protocol deviations

In order to minimize the additional workload associated with having to catalogue several minor deviations during the conduct of the study, and to avoid the potential significant implication of several minor deviations, a protocol revision should be considered.

- If a particular protocol requirement is found to be difficult to meet, the PI and the study team should query the study sponsor about whether a protocol revision should occur to remove/alter that protocol requirement.
- If a one-time exception request results in a determination that the protocol should be revised to avoid future exceptions of the same nature, the PI and study team should query the sponsor about making these revisions to the protocol.