

9.0 Protocol Violations, Deviations, and Exceptions

9.1 Definitions

Protocol deviation(s): means a minor or administrative departure from the IRB-approved protocol procedures (e.g., the protocol, informed consent document, recruitment process or study materials) that was made without prior sponsor and IRB approval. It is an accidental or unintentional change to or non-compliance with the research protocol that neither:

- increases the risk or decreases the benefit;
- significantly affects the subject's rights, safety or welfare and/or the integrity of the research data.

Protocol exception: means a temporary protocol deviation that is pre-approved by the sponsor or funding agency, (and the FDA, if applicable, for investigational device studies) and the IRB prior to its implementation. Protocol exceptions are generally for a single subject (e.g., the patient/subject is allergic to one of the medications provided as supportive care) or, occasionally, a small group of subjects. The protocol exception is usually evaluated by both the sponsor or funding agency (and FDA, if applicable) and the IRB in order to determine that it does not increase the risk to the subject (s), or jeopardize the integrity of the research data. Documentation of sponsor (or FDA) pre-approval and IRB approval of the exception should be maintained in the investigator's research study file.

Protocol violation(s): means an accidental or unintentional change to, or non-compliance with the IRB-approved procedures (e.g., the protocol, informed consent document, recruitment process or study materials) without prior sponsor and IRB approval. Protocol violations generally increases risk and/or decrease the benefit; affect the subject's rights, safety or welfare and/or the integrity of the research data. This term is not defined by the Common Rule or FDA regulations.

9.2 Planned Changes to Research Protocol

With regard to planned changes to a research protocol, the most common occurs through the submission of a modification. Examples include an increase in subject number, changes in investigators or key personnel, a change to the funding source, changes in procedures and revised consent documents. These all involve planned changes through an amended protocol and are not protocol deviations themselves (although they may result from a protocol deviation).

Another type of planned change to the research is called a protocol exception, which is made for a single subject or a small group of subjects (see section 9.8 – Protocol Exception).

Another type of planned change to a protocol is a change made to eliminate apparent immediate harm to a subject. This type of change can be initiated without prior IRB approval, provided that subsequent IRB approval is obtained. These planned changes are a subset of protocol deviations.

9.3 Unplanned Changes to Research Protocol

The next category involves unplanned changes to a research protocol not otherwise approved by the IRB. Such unplanned changes are either protocol deviations or protocol violations. These unplanned changes may include changes of the IRB-approved research protocol, Good Clinical Practice (GCP) guidelines or regulatory standards.

9.4 Protocol Deviations

A protocol deviation is any change or alteration from the procedures stated in the study protocol, consent document, recruitment process, or study materials (e.g. questionnaires) originally approved by the IRB (but the change or alteration itself is not IRB approved). Protocol deviation is a general term and includes, protocol exceptions, changes made to avoid immediate harm to subjects, and protocol violations. [45 CFR §46.103 (b) (4) (iii), 21 CFR §56.108 (a) (4)]. Protocol deviations can be either major or minor. Protocol deviations can be examples of non-compliance, either non-serious or serious.

Repeated failure by an investigator to not report protocol deviations may be viewed as non-compliance with the federal regulations, the guidelines that govern ethical conduct of research and Pennington Biomedical Research Center IRB.

9.5 Protocol Violation

A protocol violation is a subset of protocol deviation. It is any planned or intended change or deviation from the IRB approved study protocol, consent document, recruitment process, or study materials that were not approved by the IRB prior to implementation. Generally, protocol violations occur after the subject is enrolled in the research. However, some protocol violations, such as deviations from the approved consent process, can occur before the subject is enrolled in the research. Protocol violations may be either major protocol violations or minor protocol violations, based on their relative severity.

9.6 Major Protocol Violation

A major protocol violation is a deviation that has an impact on subject safety, may substantially alter risks to subjects, may have an effect on the integrity of the study data, or may affect the subject's willingness to participate in the study. Major protocol

violations can vary in the degree of seriousness according to how the changes impact subject safety, the degree of non-compliance with federal regulations, state laws, the Pennington Biomedical Research Center's IRB and the degree of foreknowledge of the event.

All major protocol violations must be reported by the investigator to the IRB within five (5) working days of learning of the violation. If it is necessary to make a permanent change to the study procedures in order to avoid harm to other subjects, then a protocol modification should be submitted as soon as possible by the investigator. If appropriate to maintain safety of the subjects, new subject enrollment should be temporarily stopped by the investigator until the modification is approved.

No matter who discovers a major protocol violation (e.g., sponsor or their agent during a monitoring visit), the investigator is responsible for reporting it to the IRB.

9.7 Minor Protocol Violation

A minor protocol violation is one that does not impact subject safety, compromise the integrity of the study data, or affect the subject's willingness to participate in the study.

No matter who discovers a minor protocol violation (e.g., sponsor or their agent during a monitoring visit), the investigator is responsible for reporting it to the IRB.

All minor protocol violations do not require prompt reporting and should be reported by the investigator to the IRB within ten (10) working days (or no later than at the time of continuing review) of learning of the violation.

9.8 Protocol Exception

A protocol exception is a temporary protocol deviation that is reapproved by the sponsor or funding agency, (and, if applicable, the FDA for investigational device studies) and the IRB, prior to its implementation. Protocol exceptions are generally for a single subject or, occasionally, a small group of subjects.

Protocol exceptions must be submitted to IRB and granted approval prior to subject enrollment and implementation, except where necessary to eliminate apparent immediate hazards to the Human Subjects.

[DHHS 45 CFR §46.103(b)(4); FDA 21 CFR §56.108(a)(4); ICH 3.3.7].

The Protocol exception is usually evaluated by both the sponsor or funding agency (and the FDA, if applicable), and the IRB in order to determine that it does not increase the risk to the subject(s) or jeopardize the integrity of the research data. Documentation of sponsor (or FDA) pre-approval and IRB approval of the exception should be maintained

in the investigator's research records. If the research involves an investigational device, and the changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of the human subjects, FDA pre-approval is also required [21 CFR §812.150 (4)].

The investigator has ultimate responsibility for obtaining prior IRB approval for protocol exceptions. Repeated failure to obtain prospective IRB approval for protocol exceptions may be viewed as non-compliance with the federal regulations, the guidelines that govern ethical conduct of research, and Pennington Biomedical Research Center's IRB.

Example of Protocol Exceptions:

- Enrollment of a research subject who fails to meet all of the protocol eligibility criteria (e.g., the subject may have been evaluated for all other parameters, and it was determined that not meeting this inclusion criteria or laboratory screening value would not cause harm to the subject or alter the validity of the study)

9.9 IRB Review Process

9.9.1 Protocol Deviations

Protocol deviation is a general term and includes, protocol exceptions, changes made to avoid immediate harm to subjects, and protocol violations. Major protocol violations that occur in research that involves greater than minimal risk (originally reviewed and approved by the convened IRB) must be submitted for convened review. Major protocol violations that occur in research that involves minimal risk (originally reviewed and approved via expedited review procedures, or determined by the convened IRB to meet expedited review criteria) may be eligible for expedited review. The IRB Chair or designee will review the violation and determine whether it should be reviewed via expedited or requires convened IRB review. All major protocol violations that occurred since the initial or most recent continuing review should be summarized in the appropriate section of the continuing review form.

9.9.2 Major Protocol Violations

Each protocol violation report should discuss what measures have been put in place to prevent future re-occurrences of the same event. The investigator should also evaluate protocol violations for any trends or patterns that would require additional corrective actions or submission of a protocol modification to prevent future violations. Repeated violations of a similar nature may be a clear indication that a permanent change (i.e. a modification) to the study procedures is necessary. The IRB Chair or designated

reviewer will determine the level of review required (i.e. expedited review or full convened IRB review).

If the violation/deviation qualifies for an expedited review, the IRB Chair or designated reviewer will document their and the determination will be documented on the expedited review portion of the IRB minutes. The possible determinations the IRB Chair or designee reviewer may make about the event through expedited review are as follows:

- Acknowledged - no further information or action required
- Additional information required – additional information is needed in order to appropriately evaluate the event or changes to the research that are minor in nature are being required based upon the event;
- Refer for full board review – the IRB Chair or designated reviewer may determine the event is not eligible for expedited review.
- The deviation or violation appears to be serious or continuing non-compliance may be involved.
- The report represents an unanticipated problem involving risks to participants or others

Additional information or materials may also be requested. If there are safety issues or concerns related to the event, the IRB may make additional determinations as described below for convened review;

- Suspend IRB approval of the research; and refer events or concerns regarding the research for non-compliance (see 10.0 – Complaints and Non-Compliance) for review of non-compliance.

For Protocol violations that require fully convened IRB review, the assigned IRB reviewer would document the determinations and outcomes will be reported on the IRB minutes. The potential determinations are as follows:

- No further action is required.
- Request additional information.
- The deviation or violation appears to be serious or continuing non-compliance may be involved.
- The report represents an unanticipated problem involving risks to participants or others
- Suspend IRB approval of the research
- Other (e.g., modify the protocol, observe informed consent process, alter continuing review timeline, require additional training of investigators). The reviewer must specify the action and document the determination.

For Federal reporting purposes the IRB will need to determine whether the protocol violation constitutes an instance of serious or continuing non-compliance. If the violation

is an event involving a change in the protocol to eliminate immediate hazard or harm to subjects, the IRB should ensure that the event was reported in the required 5-day period. Also, the IRB should make certain that the investigator implemented appropriate measures to alleviate or eliminate the harm to current and future subjects in the research.

The fully convened IRB discusses the event at the convened meeting and the IRB meeting minutes document the discussion and final determination of the convened IRB regarding the protocol violation. The documentation of review is placed in the IRB protocol file. Once a determination is made by the IRB, the investigator will receive a notification of determination from the IRB. If there are no issues with the protocol violations, the investigator will receive an Acknowledgement of Protocol Violation.

9.9.3 Minor Protocol Violations

Each protocol violation report should discuss what measures have been put in place to prevent future re-occurrences of the same event. The investigator should also evaluate protocol violations for any trends or patterns that would require additional corrective actions or submission of a protocol modification to prevent future violations. Repeated violations of a similar nature may be a clear indication that a permanent change (i.e. a modification) to the study procedures is necessary.

Minor protocol violations do not require prompt reporting and should be reported within (30) working days of the violation. All protocol violations should be reported to the research sponsor or funding agency in a timely fashion and according to that company's or agency's policy. All protocol violations should be documented in the investigator's research study files.

Pennington Biomedical Research Center investigators are not required to report protocol violations to the IRB that occur at other research sites in multi-center research trials. The investigator may have other reporting requirements such as reporting to Institutional Biosafety Committee, and/or other appropriate institutional entities that are not covered in this policy.

9.9.4 Protocol Exceptions

Investigators requesting a protocol exception must submit a protocol exception request to the IRB office with any supporting documentation. The protocol exception is processed within the IRB office. The submission is pre-reviewed for completeness and determines the level of review required.

Protocol exceptions can be reviewed either through expedited or convened procedures depending upon the type of research and nature of the exception request. If the

exception requires fully convened IRB review, the IRB staff schedules the protocol exception for an IRB meeting agenda. The pre-review and any subsequent IRB member review is documented.

The IRB members reviewing the protocol exception via expedited review procedures or the primary reviewers assigned to review the exception at a fully convened IRB meeting, as well as all members of the convened IRB, will have access to the full protocol file, which includes the current version of the research protocol. The possible determinations IRB members can make regarding exceptions include:

- Exception approved – no issues;
- Expedited review (as determined by IRB Chair or designee);
- Modifications required;
- Referred for fully convened IRB review;
- Disapproval (use only for fully convened IRB review);
- Deferral- further justification or information required (use only for fully convened IRB review);
- Deferred to institutional official or legal department (as determined by IRB Chair (or designee), or fully convened IRB).

For protocol exceptions reviewed via expedited review, the IRB reviewer documents their determination. If the protocol exceptions are reviewed at a convened IRB meeting, the primary reviewers document their initial determinations regarding the protocol exceptions on the review guide. The fully convened IRB discusses the event at the convened meeting and the IRB meeting minutes document the discussion and final determination of the fully convened IRB regarding the protocol exceptions. The documentation of review is placed in the IRB protocol file.

Once a determination is made by the IRB, the investigator will receive a notification of determination from the IRB.

Regulations & Guidelines: DHHS 45 CFR §46.103(b)(4)(iii); FDA 21 CFR §56.108(a)(4); 21 CFR §56.108(b); 21 CFR §812.150.