9.0 Protocol Deviations

9.1 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 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.

9.2 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 protocol deviations.

9.3 Protocol Deviations

A protocol deviation is any change or alteration from the procedures stated in the study protocol, consent document, recruitment process, and/or study materials (e.g. questionnaires) approved by the IRB. Protocol deviation is a general term and includes 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 considered either non-serious or serious non-compliance. See Policy 10.0 – Non-Compliance.

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.

9.4 Protocol Violation

The Common Rule and the FDA regulations do not define this term. For the purpose of this policy a violation will be referred to as a deviation.

9.5 Participant Initiated Deviations and Investigator Initiated Deviations

9.5.1 Participant Initiated Deviations

Participant initiated deviations are due to a study participant's non-adherence to the protocol. Participant initiated deviations can be considered major or minor deviations depending on whether the event impacts safety. Participant initiated deviations only need to be reported to the IRB if the event impacts participant safety, or if a pattern of protocol departure indicates a need for a change in the protocol or informed consent documents. This is left to the investigator's discretion. Regardless of whether the deviation is considered major or minor the deviation should be recorded in the participant record. See 9.6 and 9.7 for specific reporting time frame.

9.5.2 Investigator Initiated Deviations

Investigator initiated deviations are the result of the investigator, research staff or other party involved in the conduct of the research intentionally or unintentionally deviating from the approved protocol. Investigator initiated deviations can be considered major or minor depending on whether the deviation has an impact on subject safety, may alter the risks to subjects or may affect the participant's willingness to participate in the study. All investigator initiated deviations should be reported to the IRB. See 9.6 and 9.7 for specific reporting time frame.

9.6 Major Protocol Deviation

A major protocol deviation 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 deviations 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.

9.6.1 Reporting Time Frame of Major Protocol Deviation

All major protocol deviations, no matter whether participant initiated or investigator initiated, must be reported by the investigator to the IRB within seven (7) working days of learning of the deviation. 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 deviation (e.g., sponsor or their agent during a monitoring visit), the investigator is responsible for reporting it to the IRB.

9.7 Minor Protocol Deviation

A minor protocol deviation 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.

9.7.1 Reporting Time Frame of Investigator-Initiated Minor Protocol Deviations

A minor investigator initiated deviation should be reported to the IRB not more than fourteen (14) working days after the PI first learns of the event.

9.7.2 Reporting Time Frame of Participant-Initiated Minor Protocol Deviations

A minor participant initiated deviation does not need to be reported; however, the participant record should have a record of the deviation.

9.8 IRB Review Process

9.8.1 Protocol Deviations

The IRB Chair or designee will review all the deviation and determine whether it should be reviewed via expedited or requires convened IRB review. All major protocol deviations should be summarized in the appropriate section of the continuing review form.

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

All protocol deviations should be reported to the research sponsor or funding agency in a timely fashion and according to that company's or agency's policy.

9.8.2 Full Board Review of Deviations

For protocol deviations that require fully convened IRB review, the assigned IRB reviewer will document the determinations and outcomes. 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 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 deviation constitutes an instance of serious or continuing non-compliance. If the protocol deviation 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 7-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 deviation. 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.

Pennington Biomedical Research Center investigators are not required to report protocol deviations 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.

9.8.3 Expedited Review of Protocol Deviations

If the deviation qualifies for an expedited review, the IRB Chair or designated reviewer will document their determination and the determination/outcome 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 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.

9.9 Examples of Deviations

Participant-Initiated Deviations

This list of examples is intended as a guide and is not exhaustive.

Major Participant Initiated Deviations Examples	**Minor Participant Initiated Deviations Examples**

• Participant discontinued study meds
• Participant misses visits involving study drug
• Participant did not disclose metal and had MRI
	• Participant misses visits due to following:
	  ○ Inclement weather
	  ○ Employment change
	  ○ Rescheduling for other reasons that do not involve safety and do not compromise the integrity of the data
	  ○ Procedures not completed at participant's request
	• Testing outside of protocol timeframe due to the following:
	  ○ Inclement weather
	  ○ Time and burden
	  ○ Rescheduling for other reasons that do not involve safety and do not compromise the integrity of the data

Investigator-Initiated Deviations

This list of examples is intended as a guide and is not exhaustive.

Major Investigator Initiated Deviations Examples	Minor Investigator Initiated Deviations Examples

• There should be no deviation from inclusion/exclusion criteria.
• Breach of human participants protection regulations
  ○ Failure to obtain informed consent prior to initiation of study –related procedures
  ○ Inadequate or improper informed consent procedures (including no documentation of informed consent process)
  ○ Performing tests or procedures beyond those anticipated in the protocol unless performed to rule out a medical condition
  ○ Falsifying research or medical records
  ○ Working under an expired professional license or certification
  ○ Breach of confidentiality/privacy
  ○ Inappropriate destruction of study records
  ○ Failure to report a serious adverse event to the IRB and/or sponsor
  ○ Enrollment of a participant after IRB-approval of study has expired
	• Missing original signed and dated consent form (only a photocopy available)
	• Outdated/expired consent form, as long as there has been no impact on participant safety
	• Missing pages from executed consent form
	• Failure to follow the approved study procedure, that in the opinion of the Principal Investigator, does not affect the participant safety or data integrity:
	  ○ Study procedures conducted out of sequence
	  ○ Omitting an IRB approved research activity on a protocol (e.g. mailing out or collecting QOL surveys, evaluating or documenting performance status), unless the omission could affect safety
	  ○ Failure to perform a required lab test that does not affect participant safety.