9.0 Protocol Deviations

Investigators are responsible for conducting human subjects research in compliance with all applicable federal and state regulations and the institution's HRPP policies and procedures. Federal Regulations require the IRB to review any proposed changes in approved research activities prior to their initiation (except when the change is necessary to eliminate apparent immediate hazards to the subject) [45 CFR 46.103(b) (4) (iii) and 21 CFR 56.108(a) (4)].

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, study materials (e.g. questionnaires) approved by the IRB and/or HRPP or Institutional policies. 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 – 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 Major Protocol Deviation

A major protocol deviation is a deviation that has the potential to impact subject safety or risk, to affect the integrity of the data or to 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 or risk, the effect on the integrity of the data, the effect on the subject's willingness to participate in the study, 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.

9.5.1 Reporting Time Frame of Major Protocol Deviation

All major protocol deviations must be reported by the investigator to the IRB within ten (10) 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.

9.6 Minor Protocol Deviation

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

9.6.1 Reporting Time Frame for Minor Protocol Deviations

All minor deviations should be reported by the investigator in a protocol-specific minor deviation log and submitted to the IRB at continuing review or IRB closure.

9.7 Investigator Responsibility

It is the responsibility of the Principal Investigator (PI) to determine whether a deviation from the IRB-approved protocol is major or minor and to ensure proper reporting to the IRB. When making the determination of whether the deviation is major or minor, the

Principal Investigator should consider whether the deviation negatively affected any of the following:

- The rights or welfare of the subject
- Risk benefit assessment
- The integrity of the data (the ability to draw conclusions from the study data)

The Principal Investigator is responsible for reviewing the Minor Deviation Log periodically to monitor compliance with the approved research. Frequent minor deviations of a similar nature should be reported to the IRB as a major deviation.

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 IRB Review Process

9.8.1 Protocol Deviations

The IRB Chair or designee will review the major deviation and determine whether immediate action is required before review at the convened IRB. All major protocol deviations must be summarized in the appropriate section of the continuing review form. Minor deviations must be included in a log at the time of continuing review or IRB closure.

Each protocol deviation reported to the IRB should discuss what measures have been put in place to prevent future recurrences 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 deviations. 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.

9.8.2 Review of Deviations

For studies reviewed under expedited review procedures, all major deviations will be reviewed by the convened IRB.

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 in the IRB minutes. The investigator will receive a notification of determination from the IRB. 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 deviation represents an unanticipated problem involving risks to participants or others (must be handled according to Policy 8 - Unanticipated Problems Involving Risks to Subjects 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 and/or study staff). 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 10-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.

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.

9.9 Examples of Deviations

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

Major Deviations Examples	Minor Deviations Examples
• Deviation from inclusion/exclusion criteria. • Changes necessary to eliminate apparent immediate hazards to the subject • 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 • 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 • Failure to perform a required lab test that, in the opinion of the PI, may affect subject safety or data integrity • Drug/study medication dispensing or dosing error • Study visit conducted outside of required timeframe that, in the opinion of the PI, may affect subject safety • Failure to follow safety monitoring plan • Participant discontinued study meds • Participant misses visits involving study drug • Participant did not disclose metal and had MRI	• 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: o Study procedures conducted out of sequence o 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 o Failure to perform a required lab test that does not affect participant safety. • Inappropriate documentation of informed consent, including o copy not given to the person signing the form o someone other than the subject dated the consent form • Over-enrollment • Participant misses visits due to following: o Inclement weather o Employment change o Rescheduling for other reasons that do not involve safety and do not compromise the integrity of the data o Procedures not completed at participant's request • Testing outside of protocol timeframe due to the following:

	o Inclement weather o Time and burden o Rescheduling for other reasons that do not involve safety and do not compromise the integrity of the data o Failure of subject to return study medication