8.0 Unanticipated Problems Involving Risks to Subjects or Others

8.1 Policy

Pennington Biomedical Research Center complies with DHHS and FDA regulations which state that institutions must have written policies on reporting unanticipated problems involving risks to subjects or others (as defined below) to the IRB, institutional officials and relevant federal agencies and departments.

The following procedures describe how unanticipated problems involving risk to subjects or others are handled in research under the purview of the Pennington Biomedical Research Center IRB.

8.2 Definitions

Unanticipated Problem Involving Risks to Participants or Others: means any incident, experience, outcome, or new information where all three elements exist:

1. Is 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;
2. Is related or possibly related to participation in the research, and
3. Indicates that subjects or others are at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unexpected Incident: an event or occurrence that is not expected or regarded as unlikely to happen, involves no more than minimal risk to participants or others and does not meet the standard of unanticipated problems involving risks to participants or others.

Unanticipated Adverse Device Effect: Any serious adverse effect on health or safety or any life-threatening problem or death caused by (or associated with) a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application; any other unanticipated, serious problem associated with a device that relates to the rights, safety or welfare of subjects.

Adverse Event (AE): is any untoward physical or psychological occurrence in a human subject participating in research, including any abnormal sign (e.g., abnormal physical exam or laboratory finding, symptoms or disease associated with the research or the use of a medical investigational test article), symptom, or disease, temporally

associated with the subject's participation in the research. An adverse event does not necessarily have to have a causal relationship with the research, or any risk associated with the research or the research intervention, or the assessment.

Expected Adverse Event: Any event that does not meet the definition of unexpected adverse event.

External (non-local) Adverse Events: Adverse events experienced by subjects enrolled by Investigators at other institutions engaged in a multi-center clinical trial, or a different ongoing clinical trial involving the same intervention.

Internal (local) Adverse Events: Adverse events experienced by subjects enrolled by the Investigator(s) at Pennington or Pennington-related site.

Serious Adverse Event (SAE): An adverse event that is fatal or life-threatening, permanently disabling, requires or prolongs hospitalization or results in significant disability, congenital anomaly or birth defect.

Unexpected Adverse Event: means the incident, experience or outcome is not expected (in terms of nature, severity, or frequency) given the research procedures that are described in the protocol-related documents, such as the IRB approved research protocol and informed consent documents; and the characteristics of the subject population being studied; or are consistent with either:

1. the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable Investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
2. the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

Others: means individuals other than research participants (e.g., Investigators, research assistants, students, the public, etc.).

Related (or "Possibly Related"): means that there is a reasonable possibility that the event, incident, experience or outcome may have been caused by the procedures involved in the research, underlying disease, disorder, or condition of the subject, or other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject. OHRP 7/15/2007 Guidelines

Unrelated: Unassociated or without a timely relationship; evidence exists that an outcome is definitely related to a cause other than the event in question.

8.3 Procedures

All unanticipated problems should be reported regardless of whether they occur during the study, after study completion, or after participant withdrawal or completion. The type of information that must be submitted in a report to the IRB is outlined in the Unanticipated Problem Reporting xForm in IRBManager.

8.3.1 Potential Unanticipated Problems: Adverse Events

In order for an adverse event to meet the definition of an unanticipated problem involving risk to subjects or others, the adverse event must meet the following conditions. It must be *unexpected*, it must be *related or possibly to the research*, and it must suggest that subjects are at greater risk than was previously known or recognized. The Investigator must determine that these conditions are met before reporting the event to the IRB. If the Investigator determines that the incident, experience, or outcome represents an unanticipated problem, a report must be forwarded promptly (see section 8.4) to the IRB. [CFR 46.108(a)(3)(iii)]

Some of the AEs experienced by subjects enrolled in research studies will meet the criteria for unanticipated problems involving risks to subjects or others and so must be reported promptly to the IRB. However, the vast majority of adverse events, both SAEs and non-serious AEs, occurring in the context of research, are expected in light of the known toxicities and side effects of the research procedures or are expected due to the natural history of subjects' underlying diseases and conditions. Thus, most individual AEs do not represent unanticipated problems subject to the reporting requirements outlined in the federal regulations at 45 CFR 46.103(b) (5) and 21 CFR 56.108(b) (1)

8.3.2 Examples of Events that Require Prompt Reporting

1. Internal adverse events that are unexpected, and related or possibly related to the research and that indicate there are new or increased risks to subjects or others;
2. External adverse events that have been determined to be unanticipated problems involving risks to participants or others;
3. Unanticipated adverse device effects that are serious and caused by, or associated with, the device;
4. Changes made to the approved research protocol or plan without IRB approval in order to eliminate apparent immediate harm or hazard to subjects or others;

5. Any accidental or unintentional change to the approved research protocol or plan that placed subjects or others at an increased risk of harm regardless of whether there was actual harm to subjects or others or has the potential to recur;
6. Any event that requires prompt reporting according to the research protocol or investigational plan or the sponsor;
7. Breach of confidentiality or violation of HIPAA (e.g., lost or stolen laptop);
8. Any unanticipated untoward or unfavorable medical occurrence, including abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease that indicated the research places subjects at increased risk of physical or psychological harm than previously known or recognized;
9. Medication, procedural or laboratory error (e.g., errors in drug administration or dosing, surgical or other procedure, or testing of samples or test results) regardless of whether subjects experienced any harm;
10. Interim analysis, safety monitoring report, publication in the literature, or other finding that indicates an unexpected change to the risks or potential benefits of the research;
11. Change in FDA labeling (e.g., black box warning), withdrawal from market, manufacturer alert from the sponsor, or recall of an FDA-approved drug, device, or biologic used in the research;
12. Complaint by/on behalf of a subject that indicates an unanticipated risk or that cannot be resolved by the research staff;
13. Incarceration of a subject during participation in research that is not approved for involvement of prisoners as subjects;
14. Pregnancy of a subject during participation in research that is not approved for involvement of pregnant women as subjects (pregnant women may take part in research only when the IRB has approved the research on Subpart B;
15. Noncompliance with applicable regulations or requirements or determinations of the IRB identified by the research team or others (e.g., FDA Form 483 or Warning Letter) that indicates that the rights, welfare, or safety of subjects have been adversely affected;
16. Suspension or termination of the research, in whole or in part, based on information that indicates that the research places subjects at an increased risk of harm than previously known or recognized (e.g., FDA clinical hold);
17. Suspension or disqualification of an Investigator by FDA, sponsor, or others;
18. Scientific misconduct;
19. Any other problem that indicates that the research places subjects or others at an increased risk of harm or otherwise adversely affect the rights, welfare or safety of subjects or others.

8.3.3 Reporting

All adverse events must be reported to the sponsor. Federal guidelines do not require reporting adverse events to IRBs. They do require that Unanticipated Problems Involving Risks to Subjects or Others [21 CFR 56.108(b)] and Unanticipated Adverse Device Events [21 CFR 812.150(a) (1)] be reported to the IRB CFR 46.108(a)(3)(iii) or (4).

Some adverse events qualify as unanticipated problems that must be reported to the IRB; however, most adverse events do not. When Unanticipated Problems Involving Risks to Subjects or Others or Unanticipated Adverse Device Events are reported to the IRB, and the IRB agrees that they fall into these categories, then the IRB notifies the institution about these events, and the institution notifies FDA and OHRP (as applicable) that these unanticipated problems have occurred when the studies are under their oversight.

Generally, an analysis of adverse event(s) that are an increased risk of harm, related, and unexpected (all three) is the basis for concluding there is an unanticipated problem. These unanticipated problems must be reported to the IRB and usually require some change in the study (revised consent, protocol, or investigational brochure; stopping enrollment; terminating an arm of the study; etc.). These types of analyses are often done by Data Monitoring Committees or similar groups set up by the sponsor.

8.3.4 Local SAEs vs. External (non-local) SAEs / Medwatch Safety Reports

To maximize subject protection, when local adverse events occur that are in the judgment of the Investigator related + unexpected + increased risk of harm, these should be reported along with the Investigator opinion/analysis of whether this rises to the level of an unanticipated problem involving risks to subjects or others, and what if anything should change in the study.

To avoid taking valuable time away from more useful subject protection activities, do not report external adverse events unless there has been an analysis or a judgment made that a particular adverse event or events that are related + unexpected + increased risk of harm have created a signal that has been determined to be an unanticipated problem involving risks to subjects or others. Generally this will mean that something changes in the study (consent form, protocol, Investigator brochure, stop enrollment, one arm will be closed, etc.). This type of analysis is usually done by the sponsor or a Data Monitoring Committee. The local Principal Investigator will rarely have enough data or a denominator to make appropriate conclusions whether there is

a signal that rises to the level of an unanticipated problem involving risks to subjects or others.

8.3.5 Events Not Requiring Prompt Reporting

Potential risks and adverse events that may be reasonably anticipated (i.e., "expected") should be described in the informed consent form.

Potential risks and adverse events that may be reasonably anticipated (i.e., "expected") do not require prompt reporting to the IRB by Investigators and/or research staff. Below are other examples of events that do not require prompt reporting:

- Adverse device effects that are not an increased risk of harm, anticipated, or unrelated
- Adverse events or injuries that are not an increased risk of harm, expected, or unrelated
- Deaths not attributed to the research, e.g., from "natural causes," accidents, or underlying disease and the Investigator has ruled out any connection between the study procedures and the participant's death
- DSMB reports; interim analyses; or other reports, findings, or new information not altering the risk/benefit profile
- Subject complaints that were resolved or complaints not involving risks
- Problems or findings not involving risk (unless the Investigator or research staff member believes the information could affect participants' willingness to continue in the research).

Related internal and external events involving risk but not meeting the prompt reporting requirements should be reported to the IRB in summary form at the time of continuing review. In lieu of a summary of external events, a current DSMB report can be submitted for research subject to oversight by a DSMB (or other monitoring entity).

External events that do not meet the reporting requirements (e.g., not related or not involving risk) and that are not relevant to the protection of participants at Pennington Biomedical Research Center should not be reported. Investigators should retain copies of all individual event reports on file.

8.4 Time Frame for Reporting Unanticipated Problems involving Risks to Subjects or Others

Unanticipated Problems involving risks to subjects or others should be reported within ten (10) working days of the Principal Investigator or research staff becoming aware of

the unanticipated problem. Most often an analysis is required of multiple adverse events to determine whether these met the criteria for an unanticipated problem for the study. The ten (10) working days timer starts when the analysis or determination is made that there is an unanticipated problem.

In device studies, the unanticipated adverse device event (UADE) evaluation by the sponsor must be reported by the sponsor to the IRB within ten (10) working days after the sponsor first receives notice of the UADE. If the UADE occurred at Pennington Biomedical Research Center, the Investigator must report it to the IRB and the sponsor within ten (10) working days.

Events resulting in temporary or permanent interruption of study activities by the Investigator or sponsor to avoid potential harm to subjects should be reported within 48 hours when possible.

8.5 Review Process

8.5.1 Initial Review

Once a report of a potential unanticipated problem is received in the IRB Office the following actions will occur:

- The report will be screened by the HRPP Director or designee in order to determine:
    a. Whether or not the events are possibly unanticipated problems and are related to the research and increase risks to subjects or others. If there are questions regarding the classification of the event, the Chair or designee will be contacted.
    b. Whether or not the currently enrolled or prospective subjects in the trial may be subject to immediate increased harm to their health, safety, or welfare. If a concern arises, the Chair or designee will be promptly contacted and if necessary, the protocol will be suspended or terminated to assure the protection of research participants in accordance with HRPP policy.
- Events that meet the Unanticipated Problems reporting criteria will be sent to the convened board for review. Events that are determined to be Unexpected Incidents involving no more than minimal risk to participants and others will require no further review and will be returned via IRB Manager.
- Reports meeting the criteria will undergo review by the convened IRB.
- The primary reviewer will review the event using the unanticipated problems primary reviewer form. IRB decisions will be communicated to the PI via correspondence in IRBManager.

8.5.2 Convened Review

Reports of events determined during screening or expedited IRB review to represent possible unanticipated problems involving risks to subjects or others will be forwarded to the IRB for convened review. Modifications proposed by the Investigator or IRB reviewer that represent more than minor changes will also be reviewed by the convened IRB. The Chair or other member with relevant expertise will serve as the primary reviewer. Copies of the reports, all other information provided by the Investigator, and current consent documents (or verbal scripts) with any proposed changes will be included in the review materials for each IRB member. Sections from the protocol, previous event reports and other relevant information or reference materials will also be included, as applicable. The complete protocol file will be available to any IRB member upon request prior to or during the convened IRB meeting.

The IRB will determine by convened review whether the event is an unanticipated problem involving risks to subjects or others and if further action is necessary. Action(s) will be based on the nature of the event, degree to which research participants are placed at risk, occurrence of previous problems, etc. The IRB will consider the rights and welfare of participants when suspending, terminating, or modifying research.

If the IRB finds that the event is an unanticipated problem, according to the definition in the policy, the IRB may recommend any of the following actions:

- Requiring modifications to the protocol
- Revising the continuing review timetable
- Modifying the consent process
- Modifying the consent document
- Notifying current participants (e.g. whenever the information may relate to the participant's willingness to continue participation)
- Providing additional information to past participants
- Requiring additional training of the Investigator and/or study staff
- Reconsidering approval
- Requirement that current participants re-consent to participation
- Monitoring of the research
- Monitoring of the consent process
- Referral to other organizational entities
- Suspending the research
- Terminating the research

If, after reviewing a report, the IRB finds that the event is an unanticipated problem or that suspension or termination of approval is warranted, the IRB will, within fifteen (15) working days of the determination:

- Notify the Investigator in writing of its findings.
- Report its findings and recommendations to the institutional official for further reporting to the appropriate federal officials (e.g., OHRP or FDA), for studies under their oversight (see Policy 11 - Reporting to Regulatory Agencies and Institutional Officials).

8.6 Investigator Responsibilities

- The Investigator must consider whether the Unanticipated Problem requires changes to the research protocol or informed consent process/document or other corrective actions are to protect the safety, welfare, or rights of subjects or others. However, any proposed changes must be reviewed and approved by the IRB before being implemented, except when necessary to eliminate apparent immediate hazard to subjects.
- Investigators are responsible for reporting all adverse events and unanticipated problems to the sponsor.