

## 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

**Adverse Event:** 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.

**Serious Adverse Event:** 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;

**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 questions.

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

- Is unexpected;
- Is related or possibly related to participation in the research, and
- 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.

**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.

## **8.3 Procedures**

### **8.3.1 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 [45 CFR 46.103(b)(5)].

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.

### 8.3.2 Problems to Report to the IRB

The following events may represent unanticipated problems involving risks to subjects or others and should be promptly reported to the IRB.

- Adverse device effects that are unanticipated
- Adverse events or injuries that are an increased risk of harm, unexpected and related
- Breach of confidentiality involving risks
- Data and Safety Monitoring Board (DSMB) report, interim analysis, or other oversight committee/monitoring report (Report information altering the risk/benefit profile.)
- Event requiring prompt reporting (Report only when required by the protocol, sponsor, or funding agency.)
- New information (Report information indicating an unexpected change in risks or potential benefits, e.g., literature/scientific report or other published finding.)
- Subject complaint (complaints indicating unanticipated risks or those that cannot be resolved by the research staff.)
- Unapproved change made to the research to eliminate an apparent immediate hazard
- Expected adverse events that have an unexpected increase in incidence or severity.
- Adverse events that involve new or increased risks.
- Other problem or finding (e.g., loss of study data, a subject becomes a prisoner while participating in research)
- New information that may affect adversely the safety of the participants or the conduct of the clinical trial. Any changes significantly affecting the conduct of the clinical trial or increasing the risk to participants.

Both internal events and external events that may represent unanticipated problems involving risks to subjects or others should be promptly reported.

### 8.3.3 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.

#### **8.3.4 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***

These should be reported within 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 there is a signal that is an unanticipated problem for the study. The 10 working days timer starts when the analysis or determination is made that there is an unanticipated problem, which may be more than 10 days past the adverse events that are some of the data points used in determining there is an unanticipated problem involving risks to subjects or others.

In device studies, the unanticipated adverse device event (UADE) evaluation by the sponsor must be reported by the sponsor to the IRB within 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 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 Expedited Review***

Event reports and accompanying information will be forwarded by IRB staff members to the IRB Chair or one of the experienced members with relevant expertise designated by the Chair for expedited review. Reviewers will have access to the complete protocol file, including previously reported events, for review. The Chair or designee will determine if the report raises new concerns about risks and will recommend further review by the convened IRB, as necessary, for a final determination. The IRB Chair may suspend or terminate approval of an investigator's research if necessary to assure the protection of research participants. The Chair will consider the rights and welfare of participants when suspending, terminating, or modifying research. If an unanticipated problem involving no more than a minimal risk to participants, the IRB Chair or designee will review the unanticipated problem, document the unanticipated problem and send the investigator an acknowledgement letter. The convened IRB will be notified at the next IRB meeting via the expedited report in the agenda and minutes.

### 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.

### 8.6 IRB Actions

1. If the IRB finds that the event is not an unanticipated problem, according to the definition in the policy, the IRB may recommend any of the following actions:
  - No action
  - Requiring modifications to the protocol
  - Revising the continuing review timetable
  - Modifying the consent process
  - Modifying the consent document
  - Providing additional information to 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
  - Other actions appropriate for the local context
2. 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
  - Providing additional information to 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
  - Referral to other organizational entities
  - Suspending the research
  - Terminating the research
  - Other actions appropriate for the local context
3. If a report suggests that participant safety is at risk, the IRB may immediately suspend or terminate the research. Any suspension or termination of research by the IRB must be promptly reported to OHRP and FDA (if FDA-regulated research). This should be done in writing.
4. 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 14 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).