

## **PARTNERS HUMAN RESEARCH COMMITTEE ADVERSE EVENT REPORTING POLICY**

### **PURPOSE**

The purpose of this policy is to define the requirements for reporting adverse events to the Partners Human Research Committee (PHRC) and the time frame for reporting.

This policy is established to comply in part with the regulatory requirement in 45 CFR 46.103(b)(5) which states, “each IRB shall follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Department or Agency head of any unanticipated problems involving risks to subjects or others.” The Food and Drug Administration regulations include the same requirement [21 CFR 56.108(b)(1)].

Additionally, federal regulations 45 CFR 46.113 and 21 CFR 56.113 state, “IRBs shall have the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB’s requirements or has been associated with unexpected serious harm to subjects.” To exercise this important authority in a timely manner, IRBs must be informed promptly of those adverse events that are serious, unexpected, and related (or possibly related) to participation in the research. Possibly related means that the event is more likely than not related to participation in the research or, in other words, there is a >50% likelihood that the event is related to the research procedures. Therefore, once the research is approved by the PHRC, investigators covered by this policy are required to report adverse events to the PHRC, as described in this document.

In addition to this policy, the PHRC has established a policy on *Prompt Reporting of Unanticipated Problems Involving Risks to Subjects or Others* that specifically addresses unanticipated problems that are not adverse events.

### **SCOPE**

All investigators conducting non-exempt human research who rely on the PHRC for IRB review are subject to this policy. The adverse event reporting requirements outlined in this policy apply to both *internal* and *external* adverse events. *Internal adverse events* are those adverse events experienced by subjects enrolled in single center or multicenter studies at sites that rely upon the PHRC for IRB review. *External adverse events* are those adverse events experienced by subjects enrolled in studies at sites that do not rely on the PHRC for IRB review. These are typically safety reports submitted by sponsors to investigators participating in multicenter studies.

### **DEFINITIONS**

The definitions used in this policy come from OHRP’s Guidance on Unanticipated Problems and Adverse Events, dated January 15, 2007. The definition of reasonable possibility was added by the PHRC to provide investigators with additional guidance on reporting requirements.

**Adverse event:** Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

**Serious adverse event:** Any event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death;
- is life threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

**Non-serious adverse event:** Any event that does not meet the definition of a serious adverse event.

**Unexpected adverse event:** Any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is **not** 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.

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

**Possibly related to the research:** There is a *reasonable possibility* that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research (modified from the definition of *associated with use of the drug* in FDA regulations at 21 CFR 312.32(a)). A *reasonable possibility* is defined as more likely than not related to the research procedures or, in other words, there is a > 50% likelihood of the event having been caused by the procedures involved in the research.

## UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

Federal regulations require prompt reporting to the IRB of *any unanticipated problems involving risks to subjects or others*. The Office for Human Research Protections (OHRP) considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

- (1) 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) related or possibly related to participation in the research (possibly related means there is a *reasonable possibility* that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- (3) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some of the adverse events 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 PHRC. However, the vast majority of adverse events, both serious and non-serious, 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 adverse events 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).

For examples of adverse events that do not represent unanticipated problems and do not need to be reported under the HHS regulations at 45 CFR 46, refer to Appendix C of the OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events.

## ASSESSING ADVERSE EVENTS

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Adverse events are typically associated with physical or psychological, rather than social or economic harm. They occur most commonly in the context of biomedical research, although they can occur in the context of social and behavioral research. The principal investigator is responsible for assessing whether an internal adverse event is **unexpected** and **related** (or possibly related) to participation in the research and, when applicable, for promptly reporting adverse events to the PHRC.

When assessing whether an adverse event is **unexpected**, the investigator must consider whether the event is 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.

In general, adverse events are considered **unexpected** if they are not consistent with either the risks described in the protocol-related documents or the natural progression of the subject's underlying disease or condition.

When assessing whether an adverse event is **related** (or possibly related) to participation in the research, the investigator must consider whether there is a reasonable possibility (i.e., more likely than not or >50% likelihood) that the adverse event may have been caused by:

- (1) the procedures involved in the research;
- (2) an underlying disease, disorder, or condition of the subject; or
- (3) other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

In general, adverse events are considered **related to participation in the research** if they are at least partially caused by the procedures involved in the research. Adverse events are considered **unrelated to participation in the research** if they are **solely** caused by the subject's disease or condition or by other circumstances unrelated to either the research or to the subject's condition.

For examples of adverse events that represent unanticipated problems and need to be reported under the HHS regulations at 45 CFR 46, refer to [Appendix D](#) of the OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events.

## **REQUIREMENTS FOR PROMPT REPORTING OF ADVERSE EVENTS TO THE PHRC**

During the period of IRB approval, individual reports of adverse events must be submitted to the PHRC, as outlined below. The requirements are also presented in a table appended to this policy.

### **I. Internal Adverse Events**

Internal adverse events are those adverse events experienced by subjects at sites that are relying on the PHRC for IRB review of the research. In the case of an internal adverse event the principal investigator typically becomes aware of the adverse event directly from the subject, co-investigator or other member of the study staff, or the subject's healthcare provider. Investigators are required to report to the PHRC any adverse events that are both **unexpected** and **related** (or possibly related), as follows:

#### **A. Serious Internal Adverse Events**

Any internal adverse event that is **serious, unexpected** and **related** (or possibly related, i.e., the event is more likely than not related or there is a >50% likelihood that the event is related) must be reported as soon as possible, but in no event later than 10 working days/14 calendar days of the date the investigator first becomes aware of the event.

**NOTE:** The PHRC may impose additional reporting requirements when it reviews the plan for data and safety monitoring described in the research protocol. For example, the PHRC may require investigators to report any internal serious adverse event that is **unexpected (regardless of the relationship to the study procedures)** or any internal serious adverse event that is **expected** to result from the study procedures when the Data and Safety Monitoring Plan (DSMP) does **NOT** include oversight by an independent individual or group of individuals, such as a Medical Monitor or a Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC).

## **B. Non-Serious Internal Adverse Events**

Any internal adverse event that is **unexpected** and **related** (or possibly related, i.e., the event is more likely than not related or there is a >50% likelihood that the event is related), but is **not serious** must be reported within 20 working days/30 calendar days of the date the investigator first becomes aware of the event.

For reporting purposes, investigators are asked to complete and submit the PHRC Internal Adverse Event Report Form. When, as a result of the event, changes are proposed to the research protocol and/or informed consent document, investigators are asked to complete and submit the PHRC Amendment Form together with the Adverse Event Report Form.

## **II. External Adverse Events**

External adverse events are those adverse events experienced by subjects enrolled at sites that are not relying on the PHRC for IRB review of the research. In the case of an external adverse event, the principal investigator typically becomes aware of the adverse event upon receipt of a report from the sponsor, coordinating center or other monitoring group, such as a Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC), or collaborating investigator at another site.

By regulation, sponsors are required to notify the FDA and all participating investigators of any adverse experience *associated with the use of the drug* that is both serious and unexpected or any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity. The FDA has defined *associated with the use of the drug* to mean that there is a reasonable possibility that the experience may have been caused by the drug; however the regulations do not define reasonable possibility. The regulatory requirements for reporting unanticipated adverse device effects to participating investigators are similar. Consequently sponsors notify investigators of any adverse event that the reporting investigator classifies as possibly related or that they classify as possibly related even when the sponsor's assessment indicates that the event was more likely

caused by progression of the subject's underlying disease, an intercurrent illness, or lack of drug effect.

The PHRC has defined a *reasonable possibility* of being related to the research procedures as more likely than not related or, in other words, there is a > 50% likelihood of the event having been caused by the procedures involved in the research. The PHRC requires that our participating investigators review the sponsor's safety report and report only those adverse events that, in their opinion, are more likely than not related to participation in the research.

Adverse events that occur in multicenter clinical trials are reviewed by the DSMB/DMC, the coordinating or statistical center, or the sponsor of the research as described in the monitoring plan in the IRB-approved protocol. The monitoring group is responsible for providing participating investigators with information about an individual or series of unexpected and related or possibly related adverse events and any changes to the research protocol and/or the informed consent document required by the monitoring group as a result of the event(s). Investigators, in turn, are responsible for reporting unexpected and related (or possibly related, i.e., more likely than not or >50% likelihood related) external adverse events to the PHRC, as follows:

#### **A. Serious External Adverse Events**

Any external adverse event that is **serious, unexpected** and **related** (or possibly related, i.e., the event is more likely than not related or there is a >50% likelihood that the event is related) to the research procedures must be reported within 10 working days/14 calendar days of the date the investigator first becomes aware of the event.

**NOTE:** When the research is no longer being conducted at sites that rely on the PHRC for IRB review, report only those adverse events that may impact the health, welfare or safety of subjects who were enrolled by sites that relied on the PHRC for IRB review. For example, submit reports of secondary malignancies or problems with implanted devices.

#### **B. Non-Serious External Adverse Events**

Any external adverse event that is **unexpected** and **related** (or possibly related, i.e., the event is more likely than not related or there is a >50% likelihood that the event is related) to the research procedures, but is **not serious** must be reported within 20 working days/30 calendar days after the date the investigator first becomes aware of the event.

For reporting purposes, investigators are asked to complete and submit the PHRC External Adverse Event Report Form. When, as a result of the event, changes are proposed to the research protocol and/or informed consent document, investigators are asked to complete and submit the PHRC Amendment Form together with the Adverse Event Report Form.

### **REQUIREMENTS FOR REPORTING ADVERSE EVENTS AT CONTINUING REVIEW**

At continuing review, the PHRC must ensure that the criteria for IRB approval under HHS regulations at 45 CFR 46.111 and, when applicable, FDA regulations at 21 CFR 56.111 continue to

be satisfied. Investigators will be asked to provide a summary of any unexpected and related adverse events as well as any other unanticipated problems that occurred since the last continuing review. The amount of detail provided in such a summary will vary depending on the type of research being conducted.

Additionally, investigators participating in multicenter clinical trials subject to monitoring by the sponsor, a coordinating or statistical center, or a DSMB/DMC will be asked to submit a copy of the current monitoring group report. Investigators responsible for monitoring their own investigator-initiated research will be asked to submit a report of all adverse events. The Partners Human Research Program (QI Program) has developed an adverse event log that can be used for this purpose. The adverse event log is available on the QI Program website.

#### Appendix I: Table of Adverse Event Reporting Requirements

##### Related Policies, Regulations, and References:

1. PHRC Policy on Reporting Unanticipated Problems Involving Risks to Subjects or Others
2. DHHS Regulations: 45 CFR 46.103(b)(5); 45 CFR 46.113
3. FDA Regulations: 21 CFR 56.108(b)(1); 21 CFR 56.113; 21 CFR 312.32(c)
4. Office for Human Research Protections (OHRP) Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 15, 2007.

## APPENDIX I

<b>ADVERSE EVENT REPORTING REQUIREMENTS</b>			
<b>Seriousness</b>	<b>Expectedness</b>	<b>Relationship</b>	<b>Time Frame</b>
Serious	Unexpected	Possibly, Probably, or Definitely Related	As soon as possible, but no later than 10 working days / 14 calendar days after the investigator is notified of the event.
Non-Serious	Unexpected	Possibly, Probably, or Definitely Related	As soon as possible, but no later than 20 working days / 30 calendar days after the investigator is notified of the event.
<p><b>Possibly related</b> means that the event is more likely than not related to participation in the research or, in other words, there is a &gt;50% likelihood that the event is related to the research procedures.</p>			
<p><b>NOTE: At the time of continuing review, investigators will be asked to summarize unexpected and related or possibly related adverse events that occurred since the last continuing review.</b></p>			