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	Title: Unanticipated Problems Involving Risks to Subjects	Effective Date: 9/8/2006 Revised: 2/25/2013

I. PURPOSE

To describe the procedures for processing reports of potential unanticipated problems involving risks to participants or others submitted to the IRB.

II. POLICY STATEMENT

Principal Investigators are required to immediately submit to the IRB any unanticipated problems involving risk to human subjects or others. The notification to the IRB must occur no later than 2 weeks from the time of identification of the unanticipated problem.

III. SCOPE

These policies and procedures apply to all investigators, investigative team members, IRB staff and members, and institutional official.

IV. DEFINITIONS

Adverse Event (AE): 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 encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although, they can occur in the context of social and behavioral research.


For the purposes of this SOP the term Adverse Event includes Adverse Device Effects.

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

External (Off-Site) 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 (On-Site) Adverse Events: Adverse events experienced by subjects enrolled by the investigator(s) at CHOP or a CHOP-related site.

Related to Participation: Adverse events at least partially caused by participation in the research. Relatedness is assessed using the following terms: *Definitely related*, *Probably related*, *Possibly related*, *Unlikely to be related* or *Unrelated*. Possibly related means there is a reasonable possibility that the adverse event may have been caused by the procedures involved in the research. **In this document, related to the research means at least possibly related.**

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Serious Adverse Event (SAE): Any adverse event that meets any of the following conditions:


- (1) results in death;
- (2) is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- (3) requires inpatient hospitalization or prolongation of existing hospitalization; (hospitalization for a protocol-specified activity or for an elective, pre-planned procedure is not considered an SAE.)
- (4) results in persistent or significant disability/incapacity;
- (5) results in a congenital anomaly or a birth defect; or
- (6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (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).

Unanticipated Problem (general term) or Unanticipated Problems Involving Risks to Subjects or Others: 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 a subject's participation 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) related to the research than was previously known or recognized.

Unexpected Adverse Events: Any adverse event occurring in one or more subjects 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,

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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.

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 (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

V. PROCEDURES

A. Assessment of Potential Unanticipated Problems

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it promptly to the IRB.


1. Assessments of adverse events are described in Section B;
2. Assessments of unanticipated problems that are not adverse events are described in Section C.

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).

B. 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 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.

1. Assessment of whether an adverse event is unexpected.

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2. Assessment of whether an unanticipated problem is related to the research.
 - (a) Unanticipated problems and adverse events may be caused by one or more of the following: (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.
 - (b) Unanticipated problems and adverse events that are determined to be at least partially caused by one or more procedures involved in the research activity are considered related to participation in the research, whereas adverse events determined to be solely caused by a subject's underlying disease or other circumstances unrelated to the research are considered unrelated to participation in the research.

C. Unanticipated Events that are not Adverse Events and Require Reporting

Events that expose research subjects or others to a risk of physical, social or psychological harm, which is greater than the risk to subjects that was previously known or recognized, should be promptly reported when they warrant a change in the research protocol, the informed consent process, the informed consent document or other protective action is required to protect the rights and welfare of research participants or others.

Examples of unanticipated problems that are not adverse events that require reporting to the IRB due to their serious nature and relatedness to the research include:


1. Breach of privacy or confidentiality, including lost or stolen confidential information that might involve risk to that individual or others;
2. Receipt of the wrong dose of a study medication without evidence of harm;
3. Contaminated study drug (put subjects at risk of harm);
4. Publication in the literature, safety monitoring report, including a Data and Safety Monitoring Report, interim result, or other finding that indicates an unexpected change to the risk - benefit assessment;
5. Accidental or unintentional change to the IRB-approved protocol that involves risks or has the potential to recur;
6. Complaint from a subject or family member that indicates an unanticipated problem;
7. Laboratory or medication errors that may involve risk to that individual or others;

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8. Change in FDA labeling because of adverse consequences or withdrawal from marketing of a drug, device, or biologic used in a research protocol;
9. Disqualification or suspension of an investigator;
10. Sponsor imposed suspension of the study or study enrollment for risk;
11. Change in the status of a subject that might affect their eligibility to remain in the study, require their withdrawal from the study or require the IRB to re-review the research in order to make determinations that adequate protections are in place to protect vulnerable populations. Examples include:
 - (a) Incarceration within a penal institution or detention facility;
 - (b) Pregnancy at any time during participation in a research study;
 - (c) Transfer of a child from their parents/guardians to foster care (ward of the state).
12. Other events that are unanticipated and indicate the potential for increased risk of harm to subjects or others.
13. Potential non-compliance with CHOP research policies, federal research regulations or State laws controlling the conduct of research must be reported in accordance with the IRB's Non-Compliance Policy (SOP 901)

D. Reporting Unanticipated Problems Involving Risks to Subjects or Others to the IRB

1. All internal (at CHOP) unanticipated problems that are both serious (including SAEs) and related (at least possibly related) to the research procedures must be reported promptly to the IRB. Investigators must report these events in accordance with the following timeline:
 - (a) Those events that are either life-threatening or which result in death must be reported to the IRB via telephone, fax or email, within one business day of discovery. The full report must be submitted to the IRB within 48 hours of initial notification.
 - (b) Events that are not life-threatening and do not result in death, must be reported to the IRB within 7 business days of discovery.
2. A full report comprises the following materials and must be completed and submitted in accordance with the time requirements listed above:
 - (a) SAE report pathway in the eIRB electronic IRB management system;


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- (1) Information such as a summary of the event, the cooperating center, or drug company reports should be attached and submitted when applicable.
- (2) The information included in the SAE report can be abbreviated when supplemental materials (below) are available.
 - (b) The case-report form pages prepared for the study sponsor must be attached (when applicable);
 - (c) MedWatch or CIOMS form must be attached (when available);
3. In addition to their reporting responsibilities to the CHOP IRB, investigators must meet the reporting requirements of the study sponsor, the monitoring entity, coordinating center, applicable regulatory agencies (NIH, FDA, etc.) and those of the CTRC (if applicable).
4. All reports of external (at sites other than CHOP) unanticipated problems including SAE reports that are both serious and related to the research procedures must be reported to the IRB within 7 days of receipt of the report from the study sponsor. External reports that do not meet the criteria for an unanticipated problem do not need to be forwarded to the IRB.

E. Investigation and Evaluation of Reports of Unanticipated Problems

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

1. The report will be screened by the Director, HSR 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 be suspended or terminated in accordance with SOP 410.
2. Reports that do not meet these reporting criteria will be acknowledged and will be retained in the eIRB electronic management system.


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3. The investigator will receive notification, acknowledging receipt, and whether additional information, action, or reporting is required.

F. IRB Review and Determinations

When the Director, HSR determines that a reported event possibly constitutes an unanticipated problem involving risks to subjects or others, the event will be triaged to the Chair or Vice-Chair, CPHS for review. All materials submitted in the eIRB system will be available for review.


1. Chair or Vice-Chair may make a final determination as to whether the event meets the criteria for an unanticipated problem involving risks to subjects or others or forward the report to the convened IRB.
2. Those events that do not meet the criteria will be acknowledged and filed.
3. For events meeting the criteria for an unanticipated problem, the IRB, Chair or Vice-Chair may make multiple determinations. These include but are not limited to the following:
 - (a) Additional information is required to clarify the events or circumstances;
 - (b) No further IRB action is required;
 - (c) Recommend modification of the protocol including inclusion and exclusion criteria, the consent process, the consent document(s), the monitoring frequency, or other aspects of the safety management and reporting plan;
 - (d) Determine that the protocol should be suspended or terminated (SOP 410).
 - (e) Refer the report to the Office of Research Compliance and Regulatory Affairs for an internal investigation (audit) of the study.
 - (f) Require notification of participants;
 - (g) Require that enrolled subjects be provided with additional information (e.g., verbal information, written addendum, revised consent document). This will be required whenever the information may relate to the participants' willingness to continue participating;
 - (h) Determine that the incident may involve serious or continuing noncompliance (SOP 901);
 - (i) Require notification of investigators at other sites;
 - (j) Observe the process of informed consent;

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- (k) Refer concerns or findings to other parts of the organization that administer other policies, laws, and regulations.
- 4. The IRB, Chair or Vice-Chair will determine whether the research still meets the criteria for approval, whether risks to subjects have been minimized and are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result and whether additional action may be warranted by the IRB in order to protect current and prospective participants.
- 5. Applicable unanticipated problems involving risks to subjects or others will be reported in accordance with **SOP 907**.

G. Additional Investigator Responsibilities

Any proposed changes to the research study in response to an unanticipated problem must be reviewed and approved by the IRB before being implemented, except when necessary to eliminate apparent immediate hazard to subjects. (**IRB SOP 801**)

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VI. APPLICABLE REGULATIONS AND GUIDELINES


45 CFR 46.109, 45 CFR 46.113	21 CFR 56.109, 21 CFR 56.113
21 CFR 312.32	21 CFR 812.50
Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events. OHRP January 15, 2007	Guidance for Clinical Investigators, Sponsors and IRBs: Adverse Event Reporting – Improving Human Subject Protection. (FDA) January 2009 http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf

VII. REFERENCES TO OTHER APPLICABLE SOPS

SOP 403: Amendments and Reports of New Findings	SOP 801: Investigator Responsibilities
SOP 410: Suspensions and Terminations of Research	SOP 901: Non-Compliance with Human Subjects Research Policies
SOP 907: Reporting to Regulatory Agencies & Sponsors	

VIII. RESPONSIBILITIES

Title	Responsibility
Director, HSR	Director, HSR is responsible for establishing processes for IRB staff to triage the review of unanticipated problems involving risks to subjects or others.
Chair, CPHS	The Chair or Vice-Chair are responsible for initial review of possible unanticipated problems and for expedited review of unanticipated problems that do not involve more than minimal risk to subjects or others.

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Investigators	Investigators for IRB approved research are responsible for reporting potential unanticipated problems involving risks to subjects or others as outlined in the SOP 801 and in the Investigator Responsibilities information sheet. https://intranet.research.chop.edu/display/cmtirb/IRB+Policies+and+Procedures https://intranet.research.chop.edu/display/cmtirb/Investigator+Responsibilities
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IX. ATTACHMENTS


Reportable Events webpage contains a flowchart, frequently asked questions and links to OHRP and FDA guidance documents:

<https://intranet.research.chop.edu/display/cmtirb/Reportable+Events>

Reportable Events forms are contained within the eIRB application.

Investigator Responsibilities Information Sheet.

<https://intranet.research.chop.edu/display/cmtirb/IRB+Policies+and+Procedures>

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X. REVISIONS:

3-23-08: contains numerous revisions to align with OHRP's *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*; issued January 15, 2007 and feedback from AAHRPP after review of their review of CHOP's preliminary application.

1-30-09: updates the Applicable Regulations and Guidelines to reference the FDA's final Guidance document and to add the URL for accessing the OHRP and FDA Guidance documents.

6-10-10: updates include rewording definitions for clarity, the implementation of the eIRB electronic IRB management system and references new guidance information available on the IRB's website.

7-8-10: Revised to reflect AAHRPP's recommendations.

2-25-13: Revised to clarify the determinations the IRB Chair and convened committee may make.

XI. APPROVAL:

Director, Human Subjects Research

Date

Chair, Committees for the Protection of Human Subjects

Date