1. POLICY

This policy describes the obligation to report unanticipated problems involving risks to subjects or others (hereinafter referred to as "unanticipated problems") and certain types of adverse events. This policy is based on HHS Guidance issued 1/15/2007, and includes information on how reportable adverse events and unanticipated problems will be defined/identified and what procedures for reviewing and reporting will be followed.

Unanticipated problems or adverse events must be reported to the IRB if they are: 1) unexpected; 2) related or possibly related to participation in the study; **and** 3) suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized. Based upon such reports, the IRB will consider corrective actions or substantive changes in order to protect the safety, welfare, and rights of subjects or others (see Section 1.5 below).

Although the IRB only requires reporting unanticipated problems and adverse events as defined below, the Investigator is responsible for tracking *all adverse events and/or unanticipated problems* in the research study, including new physical and psychological symptoms. Trends and frequencies of adverse events that do not require immediate reporting should be reported to the IRB at the time of continuing review.

1.1 Definitions

1.1.1 *Unanticipated problem 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, legal, or social harm) related to the research than was previously known or recognized.

1.1.2 *Unexpected adverse event*

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, 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.

1.1.3 ***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. Adverse events may also be psychological in nature.

1.1.4 ***Possibly related to the research***

There is a reasonable possibility that the problem, event, incident, experience or outcome may have been caused by the procedures involved in the research.

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

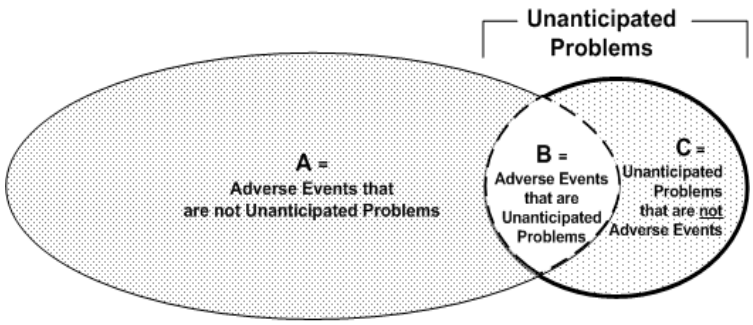
(1) results in death;
(2) is life-threatening (places the subject at immediate risk of death from the event as it occurred);
(3) requires inpatient hospitalization or prolongation of existing hospitalization;
(4) results in a persistent or significant disability/incapacity;
(5) results in a congenital anomaly/birth defect; or
(6) 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 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).

1.1.6 ***External adverse event*:** From the perspective of one particular institution engaged in a multicenter clinical trial, *external adverse events* are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial.

1.1.7 ***Internal adverse event*:** From the perspective of one particular institution engaged in a multicenter clinical trial, *internal adverse events* are those adverse events experienced by subjects enrolled by the investigator(s) at that institution. In the context of a single-center clinical trial, all adverse events would be considered *internal adverse events.*

1.2 Identifying Reportable Unanticipated Problems or Adverse Events

1.2.1. This IRB will utilize 1/15/2007 OHRP guidelines to determine what unanticipated problems and/or adverse events must be reported under 45 CFR 46, including a diagram provided to help explain the relationship between the two entities and make these determinations:



Under 45 CFR part 46: Do not report A; Report B and C.

1.3 Reporting Requirements and Procedures

1.3.1 The Lead Investigator must report promptly to the IRB all unanticipated problems and serious adverse events as defined above. [NOTE: When in doubt, if there is any possibility that the event is related to the study intervention or procedures, the event should be reported.]

1.3.2 Deaths MUST be reported to the IRB if they occur *within 30 days* of study intervention.

1.3.3 The regulations at 46.103(b)(5) require *prompt* reporting of unanticipated problems, but do not define *prompt*. This IRB will follow guidelines for prompt reporting recommended by the OHRP in its 1/15/2007 guidance on the topic:

(1) Unanticipated problems that are serious adverse events should be reported to the IRB within *1 week* of the investigator becoming aware of the event.

(2) Any other unanticipated problem should be reported to the IRB *within 2 weeks* of the investigator becoming aware of the problem.

(3) All unanticipated problems should be reported to appropriate institutional officials (as outlined within this policy), the supporting agency head (or designee), and OHRP *within one month* of the IRB's receipt of the report of the problem from the investigator.

In some cases, the requirements for prompt reporting may be met by submitting a preliminary report to the IRB and other officials/agencies involved, with a follow-up report submitted at a later date when more information is available. Such determinations will be made on a case-by-case basis, with the IRB Chair, OPHS Director, investigator, institutional official(s) and/or others involved as appropriate. The primary consideration in making these judgments will be the need to take timely action to prevent avoidable harms to other subjects.

1.3.4 Timeline requirements:

A. If the unanticipated problem or serious adverse event occurred at a UCB research site, it must be reported to the IRB promptly, within no more than 1 week (7 calendar days) of recognition/ notification of the event. The Lead Investigator is responsible for ensuring that this reporting is done. The written report must be received by OPHS within 2 weeks (14 calendar days).

B. If the unanticipated problem or serious adverse event occurred at an external site as part of a multi-site research project, it must be reported to the IRB within one month (30 calendar days) of recognition/notification of the event.

C. Any other unanticipated problem should be reported to the IRB within 2 weeks (14 calendar days) of the investigator becoming aware of the problem.

1.3.5 The reporting requirements of other organizations (e.g. Sponsor, FDA) also must be completed and are not satisfied or precluded by submitting an unanticipated problem or serious adverse event report to the IRB. Likewise, submitting adverse event reports to other organizations (e.g., Sponsor, FDA) does not satisfy the reporting requirement to the IRB. The Director of OPHS is responsible for reporting to OHRP as required and reporting to the appropriate Institutional Official.

1.3.6 The Principal Investigator is responsible for assessing and documenting unanticipated problems and serious adverse events and reporting to the IRB, as required by this policy, regardless of who observed or became aware of the event.

A. In the absence of the Principal Investigator, a co-investigator can fulfill these requirements to meet the reporting timeline.

B. In the absence of either the Principal Investigator or a co-investigator project coordinator, a student member of the research team or other research personnel must contact the OPHS for direction.

C. In instances where a student (graduate or undergraduate) suspects an unanticipated problem or serious adverse event, it is expected that the faculty advisor will be immediately made aware of any suspicious event that occurs during the study. After consultation, a determination should be made as to reporting to the IRB.

1.3.7 The investigator should use his or her judgment when determining if an event is considered reportable. When in doubt, the investigator should contact the OPHS for guidance.

1.3.8 If an IRB-approved protocol includes more stringent reporting requirements, or if a Data and Safety Monitoring Board (DSMB) requires reporting events to the IRB, the more stringent requirements must be adhered to.

1.3.9 Any unanticipated problems or adverse events that do not meet the above reporting requirements may be reported at the time of continuing review and/or via independent Data and Safety Monitoring Board reports, if applicable.

1.3.10 For purposes of confidentiality, subject names must not be identified in the event report.

1.3.11 These requirements apply to studies that are open with the IRB. However, if any serious adverse events, unanticipated problems involving risk to subjects or others, or other unexpected non-serious events occur after the approval period and it appears that a relationship may exist between the event and the research, the Investigator is strongly encouraged to report the event to the IRB.

1.4 Special Considerations

In addition to drug- and intervention- associated adverse events, investigators should be aware that there are other types of unanticipated problems events which might be associated with subjects' participation in research studies. These include:

1.4.1 *Serious negative social, legal, or economic consequences resulting from participation in a study.* Situations sometimes occur, especially in field-based studies, where a subject's confidentiality may inadvertently be compromised that may result in serious negative social, legal or economic ramifications for the subject (e.g., serious loss of social status, loss of a job, interpersonal conflicts).

1.4.2 *Serious psychological and/or emotional distress resulting from participation in a study.* Sometimes during the course of participating in a study, subjects may hear or experience something that causes them serious psychological or emotional distress. While, in many cases, these reactions are transitory, occasionally reactions may, in the judgment of the investigator, suggest the need for professional counseling or intervention (e.g., suicidal ideation).

1.5 IRB Actions

1.5.1 Initial review of unanticipated problem or adverse event reports will be conducted by the IRB Chair (or his or her designee). The IRB Chair is authorized to take the following actions in response to any incident report:

A. Perform an administrative review of the report that includes assessing whether the incident constitutes a *reportable* unanticipated problem and/or adverse event, and by whom it should be reviewed (e.g., the Chair only, another IRB member, a subcommittee of the IRB, or the convened IRB).

B. If the latter, schedule the unanticipated problem or adverse event report for review by the full IRB at the next available regularly scheduled meeting.

C. If warranted, convene an emergency meeting of the full IRB to review the report.

D. If warranted, temporarily suspend research if the rights, safety, and welfare of subjects are jeopardized until such time that the full IRB can convene to review the report.

1.5.2 In order to protect the ongoing safety of research subjects due to the nature or frequency of reported problems/events, the IRB may require the following actions:

A. Modification of subject inclusion or exclusion criteria to mitigate the newly identified risks;

B. Implementation of additional procedures for monitoring subjects;

C. Modification of informed consent documents to include a description of newly recognized risks;

D. Provision of additional information about newly recognized risks to previously enrolled subjects;

E. Suspension of enrollment of new subjects;

F. Suspension of research procedures in currently enrolled subjects;

G. Suspension of the entire study; or

H. Termination of approval for the entire study.

1.5.3 If the unanticipated problem or adverse event results in an amendment of the research protocol and/or informed consent documents, an amendment application must also be submitted to the IRB. If the changes are minor they may be reviewed by expedited procedures. If the changes are more than minor, they must be reviewed and approved by the convened IRB. Any such proposed changes in response to an unanticipated problem or adverse event must be reviewed and approved by the IRB before being implemented, except when implementation is necessary to eliminate apparent immediate hazards to subjects. See RR 403-Continuing Review and RR 404-Amendment Requests.

2. SCOPE

These policies and procedures apply to all research submitted to the IRB.

3. RESPONSIBILITY

The IRB Chair or his or her designee is responsible for reviewing all reports of unanticipated problems or serious adverse events, and ensuring the appropriateness of all IRB decisions and actions.

The OPHS Director is responsible for advising the IRB Chair on relevant institutional and regulatory requirements.

The OPHS Director is responsible for reporting Unanticipated Problems or Serious Adverse Events to the IRB Chair, IRB, the IO, and/or outside agencies as needed.

4. PROCESS OVERVIEW

Unanticipated problems or adverse events that are unexpected, related or possibly related to the study, and suggest that the research involves a greater risk of harm than was previously known should be reported to the Director of the Office for Protection of Human Subjects as promptly as possible, and no later than within 1 week (7 calendar days) of the Lead Investigator learning of the incident. Initial reports may be made via phone, email, fax, mail/delivery, or during a site visit. However, Investigators are required to submit to CPHS an official report of the incident within 2 weeks (14 calendar days).

OPHS staff members may receive such reports and are responsible for informing the Director about them.

The Director, IRB Manager or IRB Administrator ensures that incoming reports have been recorded and forwarded to the IRB Chair or his or her designee for review.

The IRB Chair reviews the reports. He or she evaluates the incoming report and he or she determines what actions, if any, may be needed to protect the rights, safety, and welfare of research subjects due to the nature or frequency of the reported unanticipated problem or adverse event. If additional review is deemed necessary, the IRB Chair can schedule the adverse event report for review at the next regularly scheduled full IRB meeting or convene an emergency meeting of the full IRB.

OPHS staff members assist the IRB Chair in communicating the results of the review, discussion, and outcome to the Investigator and other appropriate parties.

As necessary, the Director is responsible for reporting to the IO internally and/or to outside agencies the occurrence of unanticipated problems or serious adverse events according to the reporting requirements and guidelines of these pertinent agencies.

5. APPLICABLE REGULATIONS AND GUIDELINES

45 CFR 46.103(a); 46.103(b)(5); 46.109(e); 46.111(a)(1), (a)(2), and (a)(6); 46.113
21 CFR 56.108(b)
21 CFR 812.46

OHRP – Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (January 2007)