Office for Human Research Protections (OHRP)

Department of Health and Human Services (HHS)

Guidance on Reporting and Reviewing Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others

Date: [DRAFT - October 11, 2005]

Target Audience: Institutional review boards (IRBs), investigators, and HHS funding agencies that may be responsible for review, conduct, or oversight of human subjects research conducted or supported by HHS.

Scope: This document provides guidance about HHS regulations for the protection of human research subjects (45 CFR part 46) related to the review and reporting of (a) adverse events, and (b) unanticipated problems involving risks to subjects or others (hereinafter referred to as unanticipated problems). In particular, OHRP offers guidance on the following topics:

X. What should written IRB procedures include with respect to reporting unanticipated problems?

NOTE: For some HHS-conducted or -supported research, the Food and Drug Administration (FDA) and the HHS agency conducting or supporting the research (e.g., the National Institutes of Health [NIH]) may have separate regulatory and policy requirements regarding the reporting of unanticipated problems and adverse events. Anyone needing guidance on the reporting requirements of FDA or other HHS agencies should contact these agencies directly. Furthermore, investigators and IRBs should be cognizant of any applicable State and local laws and regulations related to unanticipated problems and adverse events experienced by research subjects, as well as foreign national legal requirements for research conducted outside the United States. OHRP recommends that investigators and IRBs consult with their institutional general counsel for guidance regarding applicable State, local, and international laws and regulations that may be pertinent to reporting adverse events and unanticipated problems.

Regulatory Background:

HHS regulations for the protection of human subjects (45 CFR part 46, hereinafter referred to as the HHS regulations) contain five specific requirements relevant to the review and reporting of adverse events and unanticipated problems:

(1) Institutions engaged in human subjects research conducted or supported by HHS must have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and any supporting department or agency head of (a) any unanticipated problem involving risks to subjects or others; (b) any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval. 45 CFR 46.103(b)(5).

(2) For research covered by an assurance approved for federalwide use by OHRP, HHS regulations at 45 CFR 46.103(a) require that institutions report promptly to OHRP the events referenced in HHS regulations at 45 CFR 46.103(b)(5).

(3) In order to approve research conducted or supported by HHS, the IRB must determine, among other things, that:

(a) Risks to subjects are minimized (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subject for diagnostic or treatment purposes. 45 CFR 46.111(a)(1).

(b) Risks to subjects 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. 45 CFR 46.111(a)(2).

(c) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects. 45 CFR 46.111(a)(6).

(4) An IRB must conduct continuing review of research conducted or supported by HHS at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research. 45 CFR 46.109(e).

(5) An IRB must have authority to suspend or terminate approval of research conducted or supported by HHS that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval must include a statement of the reasons for the IRB's action and must be reported promptly to the investigator, appropriate institutional officials, and any sponsoring department or agency head. 45 CFR 46.113.

Guidance:

I. What are adverse events?

In OHRP's experience, most IRBs and investigators understand the scope and meaning of the term "adverse event" in the research context, but lack a clear understanding of OHRP's expectations for what, when, and to whom adverse events need to be reported, given the requirements of the HHS regulations.

The HHS regulations do not define or use the term *adverse event*, nor do they require that all such events be reported to the IRB or any other entity. There is no common definition of the term *adverse event* across government and non-government entities (see Appendix A for examples of definitions of adverse events and other related terms). Some definitions of *adverse event* are very broad and include any untoward or undesirable event experienced by a human subject, regardless of whether the event is expected or related to the subject's involvement in the research. Other definitions of this term are more limited in scope; for example, they may be limited to untoward or undesirable effects of a drug or device, to life-threatening adverse experiences, or to those injuries related only to a subject's involvement in research.

In general, for the purposes of this guidance document, OHRP considers adverse events to be defined in very broad terms and to include any event meeting the criteria for any of the sample definitions provided in Appendix A. Note that just because an event meets the criteria for any definition provided in Appendix A, it does not mean that the event must be reported under the HHS regulations to the IRB, appropriate institutional officials, the supporting agency, or OHRP.

Adverse events occur most commonly in the context of biomedical research, although on occasion, adverse events can occur in the context of social and behavioral research.

Adverse events may be the result of:

(a) the interventions and interactions used in the research;
(b) the collection of identifiable private information in the research;
(c) an underlying disease, disorder, or condition of the subject; and/or
(d) other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

In general, adverse events that are at least partially the result of (a) or (b) would be considered related to the research, whereas adverse events solely related to (c) or (d) would be considered unrelated to the research.

For the purposes of this guidance, OHRP considers the terms *expected* and *anticipated* (and the terms *unanticipated* and *unexpected*) to be synonymous. An *expected adverse event* is an event previously known or anticipated to result from:

(a) the interventions and interactions used in the research;
(b) the collection of identifiable private information under the research;
(c) an underlying disease, disorder, or condition of the human subject; and/or
(d) other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

For example, neutropenia and opportunistic infections frequently are adverse events expected to result from chemotherapy administered to subjects participating in an oncology clinical trial.

An *unexpected adverse event* is an adverse event not previously known or anticipated to result from:

(a) the interventions and interactions used in the research;
(b) the collection of identifiable private information under the research;
(c) an underlying disease, disorder, or condition of the human subject; and/or
(d) other circumstances unrelated to the research or any an underlying disease, disorder, or condition of the subject.

An assessment of the significance and expectedness of a particular adverse event or group of adverse events also needs to account for the level of severity and frequency of the adverse events occurring in the subject population (see section III below for further discussion of these concepts).

Appendices B and C provide a series of case examples of various types of adverse events (see additional discussion in section II below).

II. What are external adverse events versus internal adverse events?

OHRP is aware that many IRBs routinely receive a large volume of reports of individual adverse events experienced by subjects enrolled in multicenter clinical trials at sites other than the site(s) over which the IRB has jurisdiction. OHRP refers to these events as *external adverse events* throughout this guidance document. Although not required by the HHS regulations, the sponsors or coordinating centers of multicenter clinical trials frequently distribute reports of external adverse events to all principal investigators (PIs) at all study sites; these reports represent the majority of adverse event reports currently being submitted by investigators to IRBs.

Internal adverse events are those adverse events experienced by subjects enrolled at the site(s) under the IRB's jurisdiction for either multicenter or single-center research projects. In the case of an internal adverse event the PI typically becomes aware of the adverse event directly from the subject, another collaborating local investigator, or the subject's healthcare provider.

III. What are unanticipated problems, and how do they relate to adverse events?

The phrase "unanticipated problem involving risks to subjects or others" is found but not defined in the HHS regulations. OHRP considers unanticipated problems, in general, to include those events that (1) are not expected given the nature of the research procedures and the subject population being studied; and (2) suggest that the research places subjects or others at a greater risk of harm or discomfort related to the research than was previously known or recognized.

In OHRP's experience 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 due to the natural history of subjects' underlying diseases and conditions. Thus, most individual adverse events do not represent unanticipated problems, and therefore, do not need to be reported under the HHS regulations for the protection of human subjects. Appendix B provides examples of adverse events that are anticipated, do not represent unanticipated problems, and thus would not need to be reported under the HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

In OHRP's experience, a small proportion of adverse events occurring in research subjects do represent unanticipated problems that need to be reported under the HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5). Appendix C provides examples of such adverse events. This group of adverse events in general can be divided into the following three categories:

> (1) **Adverse events that are serious, unexpected, and related or possibly related to participation in the research.** In general, OHRP considers this category to be the most important group of adverse events that represents unanticipated problems. OHRP notes that IRBs must have authority to suspend or terminate approval of research that, among other things, has been associated with unexpected serious harm to subjects. 45 CFR

46.113. In order for IRBs to exercise this important authority in a timely manner they must be informed promptly of those adverse events that are serious, unexpected, and related or possibly related to participation in the research.

(2) **Serious adverse events that are expected in some subjects, but are determined to be occurring at a significantly higher frequency or severity than expected.** When monitoring a research study, an investigator, a DSMB/DMC, a sponsor, or another entity assigned responsibility for monitoring the research data under the IRB-approved protocol on occasion may detect that a particular type of serious adverse event is occurring in subjects with significantly greater frequency or severity than expected (see examples (3) and (4) in Appendix C).

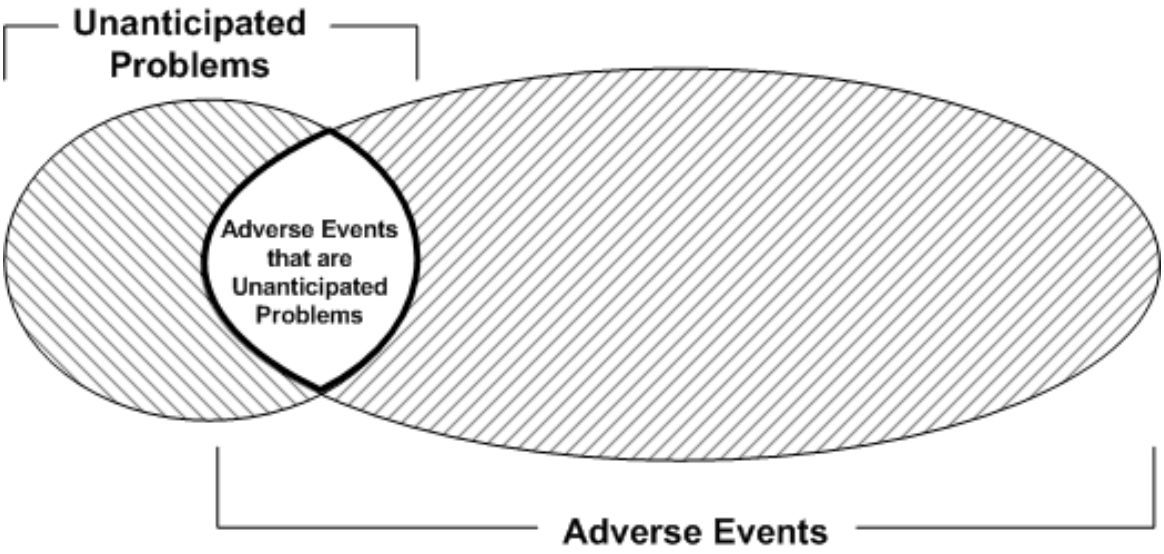
(3) **Other unexpected adverse events, regardless of severity, that may alter the IRB's analysis of the risk versus potential benefit of the research *and*, as a result, warrant consideration of substantive changes in the research protocol or informed consent process/document.** Examples of such events are provided in Appendix C (see examples (5) and (6)). Examples of substantive changes that might need to be considered in response to this category of adverse events include: modification of inclusion or exclusion criteria to mitigate the newly identified risks; implementation of additional monitoring procedures of subjects; termination of enrollment of new subjects; modification of informed consent documents to include a description of newly recognized risks; and provision of additional information about newly recognized risks to previously enrolled subjects.

OHRP notes that categories (1) and (2) frequently warrant consideration of substantive changes as described for category (3).

To satisfy the regulatory requirement for reporting unanticipated problems, it is particularly important that institutions develop and implement written procedures for ensuring prompt reporting of these three subsets of adverse events to the IRB, appropriate institutional officials, the sponsoring agency head (or designee), and OHRP.

Finally, in addition to the three limited subsets of adverse events described above, there are other types of events that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. In other words, harm to a subject need not occur in order for an event to be an unanticipated problem. Appendix D provides examples of unanticipated problems that do not involve adverse events but must be reported under the HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

The following Venn diagram further illustrates the relationship between adverse events and unanticipated problems.



In summary, the diagram above is intended to illustrate that:

(1) the vast majority of adverse events occurring in human subjects do not represent unanticipated problems because most adverse events are expected in the context of known toxicities or side effects of the research procedures and/or are due to the natural history of subjects' underlying diseases and conditions;

(2) a small proportion of adverse events do represent unanticipated problems; and

(3) unanticipated problems include events that are not adverse events.

IV. How do you determine which adverse events are unanticipated problems that need to be reported under 45 CFR part 46?

To determine whether a particular adverse event is in the small proportion of adverse events that are also considered unanticipated problems, analysis of the event should take into account the following:

(1) The description of known or foreseeable adverse events and risks in the IRB-approved research protocol, any applicable investigator brochure, the current IRB-approved informed consent document, and other relevant sources of information, such as scientific literature, product labeling, and package inserts.

(2) Any underlying diseases or conditions of the subject experiencing the adverse event.

(3) A careful assessment of whether the adverse event is related or possibly related to subject's participation in the research study.

See appendices B and C for examples of adverse events that should and should not be categorized as unanticipated problems.

V. What should the IRB consider at the time of initial review with respect to adverse events?

Before research is approved and the first subject enrolled, the investigator(s) and the IRB should give appropriate consideration to the spectrum of adverse events that might occur in subjects.

In particular, in order to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111(a)(1), (2), and (6), the IRB needs to receive and review sufficient information regarding the risk profile of the proposed research study, including the type, probability, and expected level of severity of the potential adverse events that may result from the research. The investigator also should describe how the risks of the research will be minimized.

In addition, given the expected risks of the research, the IRB must ensure that the research includes, if appropriate, an adequate plan to monitor, among other things, adverse events and unanticipated problems that may occur in subjects enrolled in the research. 45 CFR 46.111(a)(6). In general, the IRB is not the appropriate entity to monitor research, nor do the HHS regulations require that the IRB conduct such monitoring. OHRP recommends that monitoring plans for research, if deemed appropriate, address the following:

(1) The type of data or events that are to be captured under the monitoring plan.

(2) Who will be responsible for monitoring the data collected, including data related to unanticipated problems and adverse events, and their respective roles (e.g., the investigators, the research sponsor, a coordinating or statistical center, an independent medical monitor, a DSMB/DMC, and/or some other entity). (OHRP notes that the IRB has authority to observe or have a third party observe the research. 45 CFR 46.109(e).)

(3) The time frames for reporting adverse events and unanticipated problems to the monitoring entity.

(4) The frequency of assessments of data or events captured by the monitoring plan.

(5) Definition of specific triggers or stopping rules that will dictate when some action is required.

(6) As appropriate, procedures for communicating to the IRB, the study sponsor, and other appropriate entities the outcome of the reviews by the monitoring entity.

The monitoring plan should be tailored to the nature, size, and complexity of the research protocol, the expected risks of the research, and the type of subject population being studied.

VI. How should reports of external adverse events, internal adverse events, and unanticipated problems be handled?

A. External adverse events

OHRP is aware that IRBs at many institutions routinely receive a large volume of reports of external adverse events experienced by subjects enrolled in multicenter clinical trials at sites other than the site(s) over which the IRB has jurisdiction. These external adverse event reports frequently represent the majority of adverse event reports submitted by investigators to IRBs.

As previously noted, because most individual adverse events do not appear to represent unanticipated problems, the vast majority of reports of external adverse events *do not need to be submitted* to the IRB, institutional officials, the supporting agency head, or OHRP under the HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5). Furthermore, reports of individual external adverse events seldom contain sufficient information to allow investigators or IRBs to make meaningful judgments about whether the adverse events alter IRB analysis of the risks and benefits of the research.

OHRP advises that it is neither useful nor necessary under the HHS regulations for reports of individual adverse events occurring in subjects enrolled in multicenter studies to be distributed routinely to investigators or IRBs at all institutions conducting the research. The IRBs at all these institutions are not appropriately situated or constituted to assess the significance of individual adverse events. Ideally, adverse events occurring in subjects enrolled in a multicenter study should be submitted for review and analysis to a central monitoring entity (e.g., a DSMB/DMC, a coordinating or statistical center, or the research sponsor) in accordance with a monitoring plan described in the IRB-approved protocol. Only when this central monitoring entity determines that a particular adverse event or series of adverse events represents an unanticipated problem should a report of the adverse event(s) be submitted to the PI and IRB at each institution. OHRP recommends that these reports to all sites include: (1) a clear explanation of why the adverse event or series of adverse events has been determined to be an unanticipated problem; and (2) a description of proposed actions to be taken by the investigators and/or IRB in response to the unanticipated problem (e.g., suspension of new subject enrollment, modification of the research protocol, and/or modification of the informed consent process).

OHRP advises that institutional policies for handling reports of external adverse events that include the following actions would be one acceptable means of satisfying the HHS regulatory

requirements at 45 CFR 46.103(a) and 46.103(b)(5) (OHRP notes that institutions are free to develop alternative procedures that satisfy these regulatory requirements):

(1) The PI receives the report of the external adverse event from the study sponsor, a study coordinating or statistical center, a DSMB/DMC, or other central monitoring entity and only submits to the IRB reports of events that have been determined, preferably by the central monitoring entity, to represent an unanticipated problem based on the criteria presented in section III of this guidance. For any report of an external adverse event determined not to be an unanticipated problem, the PI maintains a copy of the external adverse event report and documentation of the basis for this determination. This record is to be made available to the IRB or OHRP on request.

(2) The PI provides the following information to the IRB when reporting an external adverse event determined to be an unanticipated problem:

(a) Appropriate identifying information, such as (i) the title of the research protocol; (ii) the PI's name; (iii) the IRB project number; (iv) the name of the supporting agency and the relevant award number; and (v) any relevant investigational new drug (IND) or investigational device exemption (IDE) number.

(b) A complete, detailed description of the external adverse event and the basis for determining that it represents an unanticipated problem.

(c) A description of any actions that have been taken or proposed by the study sponsor, the study coordinating site, any other monitoring entity (such as a DSMB/DMC), and/or the local PI in response to the unanticipated problem (e.g., suspension of new subject enrollment, modification of the research protocol, and/or modification of the informed consent information and/or process).

OHRP notes that reports of external adverse events submitted to the IRB should present the adverse event in the context of the entire multicenter study, if possible. In addition, the local PI should consult with the study sponsor or coordinating center regarding any changes to the protocol and/or informed consent documents independently proposed by the local PI.

(3) The IRB chairperson and/or other experienced member(s) designated by the IRB chairperson receives and reviews the report of the external adverse event(s) determined to be an unanticipated problem. Reports for which no modifications to the protocol or informed consent process/documents are needed, as determined by the IRB chairperson (or designee), may be: (i) filed in the IRB records without further review by the convened IRB or, (ii) at the discretion of the IRB chairperson (or designee) referred to the rest of

the IRB members for review and further action, as appropriate, at a convened meeting. If the central monitoring entity or the PI did not propose any modifications to the protocol or informed consent process/document, but the IRB chairperson (or designee) believes that modifications are needed in response to the external adverse event(s), the IRB chairperson (or designee) requests in writing that the PI discuss the proposed modifications with the study sponsor or coordinating center and submit a response or necessary modifications for review by the IRB. These modifications then are handled in accordance with paragraph 4(a) or 4(b) below.

OHRP notes that the IRB has authority, under HHS regulations at 45 CFR 46.109(a), to require submission of more detailed contextual information by the PI, the sponsor, the study coordinating center, or DSMB/DMC about any adverse event occurring in a research protocol as a condition of the continuation of the IRB's approval of the research.

(4) If the PI submits to the IRB a request for approval of modifications to the protocol and/or informed consent process/documents in response to the external adverse event, the IRB chairperson or other experienced member(s) designated by the IRB chairperson reviews the proposed modifications. If the IRB chairperson (or designee) determines that modifications in addition to those proposed by the PI are needed in response to the external adverse event, the IRB chairperson (or designee) requests in writing that the PI discuss the proposed additional modifications with the study sponsor or coordinating center and submit a response or the necessary additional modifications for review by the IRB.

(a) If all proposed modifications represent minor changes, the IRB chairperson (or designee) may review and, if appropriate, approve the modifications under an expedited review procedure (see HHS regulations at 45 CFR 46.110(b)). All IRB members are informed of the expedited approval in accordance with HHS regulations at 45 CFR 46.110(c) and the IRB's written procedures. The related report of the external adverse event may be: (i) filed in the IRB records without further review by the convened IRB or, (ii) at the discretion of the IRB chairperson (or designee), referred to the rest of the IRB members for review and further action, as appropriate, at a convened meeting.

(b) If any of the proposed modifications represent more than a minor change, or if the IRB chairperson (or designee) determines for any reason that he or she should not approve the proposed modifications under an expedited review procedure, the proposed modifications must be forwarded to the other IRB members for review at a convened meeting.

(5) The IRB submits a report of the external adverse event determined to be an unanticipated problem to appropriate institutional officials. These reports should include

the same type of information provided to the IRB by the PI, along with a summary of the actions taken by the IRB in response to the unanticipated problem.

OHRP notes that unanticipated problems occurring in research covered by an OHRP-approved assurance also must be reported to the supporting agency head (or designee) and OHRP. However, for multicenter research projects, only the institution at which the subject experienced an adverse event determined to be an unanticipated problem must report the event to the supporting agency head (or designee) and OHRP. Alternatively, the central monitoring entity may be designated to submit reports of unanticipated problems to the supporting agency head (or designee) and OHRP.

B.Internal adverse events

Internal adverse events are those events experienced by subjects enrolled at the site(s) under the IRB's jurisdiction. These adverse events can occur in the context of either multicenter research protocols or single-site research protocols. In contrast to external adverse events, which are reported to investigators by a study sponsor or coordinating center, a local PI typically becomes aware of an internal adverse event directly from the subject, another collaborating local investigator, or the subject's healthcare provider.

OHRP again notes that because most individual adverse events do not appear to represent unanticipated problems, the vast majority of internal adverse events *do not need to be reported* individually to the IRB, institutional officials, the supporting agency head, or OHRP under the HHS regulations. As noted in section VIII below, OHRP recommends that a summary of adverse events be included in continuing review reports submitted to the IRB by investigators.

OHRP advises that institutional policies for handling reports of internal adverse events that include the following actions would be one acceptable means of satisfying the HHS regulatory requirements at 45 CFR 46.103(a) and 46.103(b)(5) (OHRP notes that institutions are free to develop alternative procedures that satisfy these regulatory requirements):

(1) The PI assesses whether the adverse event represents an unanticipated problem based on the criteria presented in section III above.

(a) If the PI determines that the adverse event represents an unanticipated problem, the PI reports it to the IRB, providing the same information noted in sub-section A(2) above for external adverse events. For multicenter research, the local PI should consult with the study sponsor or coordinating center regarding any changes to the protocol and/or informed consent documents being proposed by the local PI. The PI also must ensure that the adverse event is reported to a central or independent monitoring entity (e.g., a DSMB/DMC, independent medical monitor, coordinating site, and/or sponsor) if required under a monitoring

plan described in the IRB-approved protocol.

(b) If the PI determines that the adverse event is not an unanticipated problem, the PI only needs to ensure that the adverse event is reported to a central or independent monitoring entity (e.g., a DSMB/DMC, independent medical monitor, coordinating or statistical center, and/or study sponsor) if required under the monitoring plan described in the IRB-approved protocol. If the monitoring entity subsequently determines, in contrast to the PI's determination, that the adverse event does represent an unanticipated problem, procedures should be in place for the monitoring entity to communicate this determination to the PI, who then should report the unanticipated problem to the IRB, following the procedures outlined in A(2) above for external adverse events.

(2) The IRB handles the report of the internal adverse event determined to be an unanticipated problem using the same procedures described in A(3)-(5) above for external adverse events.

(3) Those internal adverse events determined to be unanticipated problems are reported to the supporting HHS agency head (or designee) and OHRP. Reporting to the supporting HHS agency head (or designee) and OHRP usually is accomplished by the IRB or another appropriate institutional official identified under the institution's written IRB procedures. These reports should include the same type of information provided to the IRB by the PI, along with a summary of the actions taken by the IRB and institutional officials in response to the unanticipated problem(s) (see OHRP's Guidance on Reporting Incidents to OHRP on the OHRP website at http://www.hhs.gov/ohrp/policy/incidreport_ohrp.html for more details).

C. Other unanticipated problems (not related to adverse events)

OHRP advises that for reporting and handling unanticipated problems that are not adverse events, institutional policies that parallel the same procedures as described in A and B above for adverse events would be one acceptable means of satisfying the HHS regulatory requirements at 45 CFR 46.103(a) and 46.103(b)(5) (OHRP notes that institutions are free to develop alternative procedures that satisfy these regulatory requirements). Examples of such unanticipated problems are provided in Appendix D.

VII. What is the appropriate time frame for reporting unanticipated problems to the IRB, appropriate institutional officials, the department or agency head (or designee), and OHRP?

The HHS regulations at 46.103(b)(5) require written procedures for ensuring "prompt" reporting of unanticipated problems to the IRB, appropriate institutional officials, any supporting

department or agency head (or designee), and OHRP (45 CFR 46.103(a)). The purpose of prompt reporting is to ensure that appropriate steps are taken in a timely manner to protect other subjects from avoidable harm. The regulations do not define *prompt*. In general, OHRP interprets *prompt* to be within a couple of weeks from the time a determination is made that an event represents an unanticipated problem. OHRP notes that the appropriate timeframe for satisfying the requirement for prompt reporting will vary depending on the specific nature of the unanticipated problem and the nature of the research associated with the problem. For example, an unanticipated problem that resulted in a subject's death or was potentially life-threatening generally should be reported to the IRB within a shorter timeframe than other unanticipated problems that were not life-threatening. OHRP further notes that, in some cases, one may fulfill the requirement for prompt reporting by submitting a preliminary report to the IRB, appropriate institutional officials, the department or agency head (or designee), and OHRP, with a follow-up report submitted at a later date when more information is available. Determining the appropriate timeframe for reporting a particular unanticipated problem requires careful judgment by persons knowledgeable about human subject protections. The primary consideration in making these judgments is the need to take timely action to prevent avoidable harms to other subjects.

VIII. What should the IRB consider at the time of continuing review with respect to adverse events and unanticipated problems?

For research conducted or supported by HHS that is not exempt, the IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. 45 CFR 46.109(e). At the time of continuing review, the IRB should ensure that the criteria for IRB approval under HHS regulations at 45 CFR 46.111 continue to be satisfied. In particular, the IRB needs to determine whether any new information has emerged, either from the research itself or from other sources, that could alter the IRB's previous determinations, particularly with respect to risk to subjects. Information regarding any unanticipated problems that have occurred since the previous IRB review in most cases will be pertinent to the IRB's determinations at the time of continuing review. It may also be appropriate for the IRB at the time of continuing review to confirm that any provisions under the previously approved protocol for monitoring study data to ensure safety of subjects have been implemented and are working.

OHRP recommends that, among other things, a summary of both adverse events and any unanticipated problems be included in continuing review reports submitted to the IRB by investigators (see OHRP Guidance on Continuing Review at http://www.hhs.gov/ohrp/humansubjects/guidance/contrev2002.htm). OHRP notes that the amount of detail provided in such a summary will vary depending on the type of research being conducted. In many cases, an appropriate summary would be a simple brief statement that there have been no unanticipated problems and that adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document, and/or any investigator brochure.

IX. What interactions should occur between IRBs and DSMBs/DMCs with regard to adverse events and unanticipated problems?

Whenever a DSMB/DMC determines during the course of its monitoring activities that an adverse event or series of adverse events represents an unanticipated problem, the DSMB/DMC or study sponsor should follow procedures for ensuring that this event is reported promptly to the PIs and IRBs at each participating study site. OHRP recommends that such procedures be described in a monitoring plan in the IRB-approved protocol.

OHRP also recommends that if the DSMB/DMC during its monitoring determines that adverse events are occurring at the expected frequency and severity level and has no concerns regarding the safety of human subjects, the DSMB/DMC or study sponsor submit a periodic report to that effect to the PI and IRB at each participating study site.

As previously noted, OHRP recommends that continuing review of research by the IRB include, among other things, consideration of adverse events, interim findings, and any recent literature that may be relevant to the research. OHRP recognizes that such information may not be readily available to local investigators participating in multicenter clinical trials or to their local IRBs. For multicenter clinical trials subject to oversight by a DSMB/DMC, IRBs conducting continuing review of research may rely on a current report from the DSMB/DMC indicating that it has reviewed study-wide adverse events, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB. OHRP recommends that such reports from the DMSB/DMC to the IRB indicate what information was reviewed by the DSMB/DMC, the date of its review, and a summary of its findings. For additional details about OHRP's guidance on continuing review, see the OHRP website at http://www.hhs.gov/ohrp/humansubjects/guidance/contrev2002.htm.

X. What should written IRB procedures include with respect to reporting unanticipated problems?

Written IRB procedures should provide a step-by-step description with key operational details for complying with the reporting requirements described in HHS regulations at 45 CFR 46.103(b)(5). Important operational details for the required reporting procedures should include:

(1) The type of information that is to be included in reports of unanticipated problems.

(2) A description of which office(s) or institutional official(s) is responsible for promptly reporting unanticipated problems to the IRB, appropriate institutional officials, any supporting department or agency heads (or designees), and OHRP.

(3) A description of the required time frame for accomplishing the reporting requirements for unanticipated problems.

(4) The range of the IRB's possible actions in response to reports of unanticipated problems.

OHRP notes that many institutions have written IRB procedures for reporting adverse events, but do not address specifically the reporting requirements for unanticipated problems. Such institutions should expand their written IRB procedures to include reporting requirements for unanticipated problems.

Appendix A
Examples of Definitions of Adverse Events and Similar Terms

(1) Any undesirable and unintended, although not necessarily unexpected, effect of the research occurring in human subjects as a result of (a) the interventions and interactions used in the research; or (b) the collection of identifiable private information under the research. [Adapted from the 1993 OPRR IRB Guidebook]

(2) Any occurrence of injury, dysfunction, disease, or abnormality of any organ or tissue that occurs in a human subject enrolled in a research protocol. Manifestations of an adverse event may include symptoms, physical exam abnormalities, diagnostic study abnormalities, and/or death. [Adapted from Walter Reed Army Medical Center – May 31, 2002 Policy for Reporting Adverse Events in Human Use Protocols]

(3) Any untoward medical occurrence in a human subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the product, whether or not considered related to the product. [Adapted from International Conference on Harmonization guideline E2A]

(4) Any untoward sign, result, event, misadventure, injury, dysfunction, adverse drug reaction, or other undesirable happening that involves any human subject regardless of whether it was listed in the informed consent document as an expected risk.[Adapted from Naval Medical Research Center's March 26, 2002 Principles and Policies for the Ethical Protection of Human Subjects from Research Risks, chapter 14, paragraph 3(a)]

(5) Any untoward physical or psychological occurrence in a human subject participating in research. An adverse event can be any unfavorable or unintended event including abnormal laboratory finding, symptom, or disease associated with 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. [Adapted from Veterans Health Administration Handbook 1200.5]

(6) An adverse drug experience as defined by FDA regulations at 21 CFR 314.80(a) - Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: an adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

(7) An adverse experience as defined by FDA regulations at 21 CFR 600.80(a) – Any adverse event associated with the use of a biological product in humans, whether or not considered

product related, including the following: an adverse event occurring in the course of the use of a biological product in professional practice; an adverse event occurring from overdose of the product whether accidental or intentional; an adverse event occurring from abuse of the product; an adverse event occurring from withdrawal of the product; and any failure of expected pharmacological action.

(8) A life-threatening adverse drug experience as defined by FDA regulations at 21 CFR 312.32 – Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

(9) A life-threatening adverse experience as defined by FDA regulations at 21 CFR 600.80(a) – Any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred, i.e., it does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

(10) A serious adverse drug experience as defined by FDA regulations at 21 CFR 310.305(b), 312.32(a), and 314.80(a) – Any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an 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.

(11) An unanticipated adverse device effect as defined by FDA regulations at 21 CFR 812.3(s) – 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.

(12) An unexpected adverse drug experience as defined by FDA regulations at 21 CFR 312.32(a) – Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the

investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

Appendix B
Examples of Adverse Events that Do Not Represent Unanticipated Problems and Do Not Need to be Reported under the HHS Regulations

(1) A subject participating in a phase 3, randomized, double-blind, controlled clinical trial comparing the relative safety and efficacy of a new chemotherapy agent combined with the current standard chemotherapy regimen versus placebo combined with the current standard chemotherapy regimen for the management of multiple myeloma develops neutropenia and sepsis. The subject subsequently develops multi-organ failure and dies. Prolonged bone marrow suppression resulting in neutropenia and risk of life-threatening infections is a known complication of the chemotherapy regimens being tested in this clinical trial and these risks are described in the protocol and informed consent document. The investigators conclude that the subject's infection and death are directly related to the research interventions. A review of data on all subjects enrolled so far reveals that the incidence of severe neutropenia, infection, and death are within the expected frequency. This example is not an unanticipated problem because the risks of severe infections and death were anticipated.

(2) A subject enrolled in a phase 3, randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of a new investigational anti-inflammatory agent for management of osteoarthritis develops severe abdominal pain and nausea one month after randomization. Subsequent medical evaluation reveals gastric ulcers. The investigator breaks the blind on the subject's study group assignment and learns that the subject was assigned to receive the active investigational agent. The protocol and informed consent document for the study indicated that the there was a 10% chance of developing mild to moderate gastritis and a 2% chance of developing gastric ulcers for subjects assigned to the active investigational agent. The investigator concludes that the subject's gastric ulcers resulted from the research intervention and withdraws the subject from the study. A review of data on all subjects enrolled so far reveals that the incidence of gastritis and gastric ulcer are within the expected frequency. This example is not an unanticipated problem because the risk of gastric ulcers was anticipated.

(3) A subject is enrolled in a phase 3, randomized clinical trial evaluating the relative safety and efficacy of vascular stent placement versus carotid endarterectomy for the treatment of patients with severe carotid artery stenosis and recent transient ischemic attacks. The patient is assigned to the stent placement study group and undergoes stent placement in the right carotid artery. Immediately following the procedure, the patient suffers a severe ischemic stroke resulting in complete left-sided paralysis. The protocol and informed consent document for the study indicated that there was a 5-10% chance of stroke for both study groups. To date, 25 subjects have been enrolled in the clinical trial, and 2 have suffered a stroke shortly after undergoing the study intervention, including the current subject. The DSMB responsible for monitoring the study concludes that the subject's stroke resulted from the research intervention. This example is not an unanticipated problem because the risk of stroke was anticipated and the frequency at which strokes were occurring in subjects enrolled so far was at the expected level. (NOTE: The

assessment of the relationship between the expected and actual frequency of a particular adverse event must take into account a number of factors including the uncertainty of the expected frequency estimates, the number and type of individuals enrolled in the study, and the number of subjects who have experienced the adverse event. In many cases, making a definitive determination regarding whether the frequency of a particular event is within the expected range is not possible.)

(4) A subject with advanced renal cell carcinoma is enrolled in a study evaluating the effects of hypnosis for the management of chronic pain in cancer patients. During the subject's initial hypnosis session in the pain clinic, the subject suddenly develops acute chest pain and shortness of breath, followed by loss of consciousness. The subject suffers a cardiac arrest and dies. An autopsy reveals that the patient died from a massive pulmonary embolus, presumed related to his underlying renal cell carcinoma. The investigator concludes that the subject's death is unrelated to participation in the research. This example is not an unanticipated problem because the subject's pulmonary embolus and death were clearly attributable to causes other than the research interventions.

(5) An investigator is conducting a psychology study evaluating the factors that affect reaction times in response to auditory stimuli. In order to perform the reaction time measurements, subjects are placed in a small, windowless sound proof booth and asked to wear headphones. The research protocol and informed consent document describe claustrophobic reactions as one of the risks of the research. One subject enrolled in the research develops a severe anxiety reaction due to claustrophobia, resulting in the subject withdrawing from the research. This example is not an unanticipated problem because the risk of claustrophobic reactions was anticipated.

NOTE: For purposes of illustration, the case examples provided above represent generally clear-cut and unambiguous examples of adverse events that are not unanticipated problems. OHRP recognizes that it is not always clear whether a particular event is expected and whether an event is study-related.

Appendix C
Examples of Adverse Events that Represent Unanticipated Problems and Need to be Reported Under the HHS Regulations

(1) A subject with chronic gastroesophageal reflux disease enrolls in a randomized, placebo controlled, double-blind, phase 3 clinical trial evaluating a new investigational agent that blocks acid release in the stomach. Two weeks after being randomized and started on the study intervention the subject develops acute kidney failure as evidenced by an increase in serum creatinine from 1.0 mg/dl pre-randomization to 5.0 mg/dl. The known risk profile of the investigational agent does not include renal toxicity, and the informed consent document for the study does not identify kidney damage as a risk of the research. The investigator breaks the blind for the subject's study group assignment and learns that the subject was randomized to the active investigational agent. Evaluation of the subject reveals no other obvious cause for acute renal failure. The subject is taken off the investigational agent and managed as an outpatient, and the subject's renal function returns to normal two weeks later. The investigator concludes that the episode of acute renal failure probably was due to the investigational agent. This is an example of an unanticipated problem that must be reported because the risk of acute renal failure was unforeseen.

(2) A subject with seizures enrolls in a randomized, phase 3 clinical trial comparing a new investigational anti-seizure agent to a standard, FDA-approved anti-seizure medication. The subject is randomized to the group receiving the investigational agent. One month after enrollment, the subject is hospitalized with severe fatigue and on further evaluation is noted to have severe anemia (hematocrit decreased from 45% pre-randomization to 20%). Further hematologic evaluation suggests an immune-mediated hemolytic anemia. The known risk profile of the investigational agent does not include anemia, and the informed consent document for the study does not identify anemia as a risk of the research. The investigators determine that the hemolytic anemia is possibly due to the investigational agent. This is an example of an unanticipated problem that must be reported because the risk of hematologic toxicity was unforeseen.

(3) The fifth subject enrolled in a phase 2, open-label, uncontrolled clinical study evaluating the safety and efficacy of a new oral agent administered daily for treatment of severe psoriasis unresponsive to FDA-approved treatments, develops severe hepatic failure complicated by encephalopathy one month after starting the oral agent. The known risk profile of the new oral agent prior to this event included mild elevation of liver enzymes on serum chemistry tests in 10% of subjects receiving the agent during previous clinical studies, but there was no other history of subjects developing clinically significant liver disease. The informed consent document for the study identifies mild liver injury as a risk of the research. The investigators identify no other etiology for the liver failure in this subject and attribute it to the study agent. This is an example of an unanticipated problem that must be reported because (a) although the risk of mild liver injury was foreseen, severe liver injury resulting in hepatic failure was

unforeseen; and (b) consideration of changes to the research protocol and the informed consent process is warranted.

(4) Subjects with coronary artery disease presenting with unstable angina are enrolled in a clinical trial evaluating the safety and efficacy of an investigational vascular stent. Based on prior studies in animals and humans, the investigators anticipate that up to 5% of subjects receiving the investigational stent will require emergency coronary artery bypass graft (CABG) surgery because of acute blockage of the stent that is unresponsive to non-surgical interventions. The risk of needing emergency CABG surgery is described in the informed consent document. After the first 20 subjects are enrolled in the study the investigators conduct an interim analysis and note that 10 subjects have needed to undergo emergency CABG surgery soon after placement of the investigational stent. The DSMB monitoring the clinical trial concludes that the rate at which subjects have needed to undergo CABG greatly exceeds the expected rate. This is an example of an unanticipated problem that must be reported because the investigators concluded that the frequency at which subjects have needed to undergo emergency CABG surgery was significantly higher than the expected frequency.

(5) Subjects with essential hypertension are enrolled in a phase 2, non-randomized clinical trial testing a new investigational antihypertensive drug. At the time the clinical trial is initiated, there is no documented evidence of gastroesophageal reflux disease (GERD) associated with the investigational drug, and the IRB-approved informed consent document does not describe GERD as a risk of the research. Three of the first ten subjects are noted by the PI to have severe GERD symptoms that began within one week of starting the investigational drug and resolved a few days after the drug was discontinued. The PI determines that the GERD symptoms were most likely caused by the investigational drug, may alter the IRB's risk:benefit assessment, and warrant modification of the informed consent document to include a description of GERD as a risk of the research. This is an example of an adverse event that, although not serious, represents an unanticipated problem because it altered the IRB's analysis of the risk versus potential benefit of the research and warranted consideration of substantive changes to the informed consent process/document.

(6) A behavioral researcher conducts a study in college students that involves completion of a detailed survey asking questions about early childhood experiences. The research was judged to involve no more than minimal risk and was approved by the IRB Chairperson under an expedited review procedure. During the completion of the survey, one student subject has a severe psychological reaction manifested by intense sadness, depressed mood, and suicidal ideation. The protocol and informed consent document for the research did not describe any risk of such negative psychological reactions. Upon further evaluation, the investigator determines that the subject's negative psychological reaction resulted from certain survey questions that triggered repressed memories of physical abuse as a child. The investigator had not anticipated that such reactions would be triggered by the survey questions. This is an example of an adverse event occurring in the context of social and behavioral research that was not anticipated because the

risk of the negative psychological reaction was not foreseen, and consideration of changes to the research survey and the informed consent process is warranted. It is therefore an unanticipated problem that must be reported.

NOTE: For purposes of illustration, the case examples provided above represent generally clear-cut and unambiguous examples of adverse events that are unanticipated problems. OHRP recognizes that it is not always clear whether a particular event is expected and whether an event is study-related.

Appendix D
Examples of Unanticipated Problems that Do Not Involve Adverse Events

(1) An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator's car on her way home from work. This is an unanticipated problem that must be reported because the investigators did not anticipate the theft and the subjects have been placed at significantly greater risk of harm from the breach in confidentiality of the study data.

(2) As a result of a processing error by a pharmacy technician, a subject enrolled in a clinical trial receives a dose of an experimental agent that is 10-times higher than the dose dictated by the IRB-approved protocol. While the dosing error increased the risk of toxic manifestations of the experimental agent, the subject experienced no detectable harm or adverse effect after an appropriate period of careful observation. Nevertheless, this constitutes an unanticipated problem that must be reported.

(3) Subjects with cancer are enrolled in a phase II clinical trial evaluating an investigational biologic product derived from human sera. After several subjects are enrolled and receive the investigational product, a study audit reveals that the investigational product administered to subjects was obtained from donors who were not appropriately screened and tested for several potential viral contaminants, including the Human Immunodeficiency Virus and the Hepatitis B virus. This constitutes an unanticipated problem that must be reported.

The events described in the above examples were unexpected and resulted in new circumstances that increased the risk of harm to subjects. In addition, the third example may have presented unanticipated risks to others (e.g., the sexual partners of the subjects) in addition to the subjects. In each of these examples, while these events may not have caused any detectable harm or adverse effect to subjects or others, they nevertheless represent unanticipated problems and should be promptly reported to the IRB, appropriate institutional officials, the sponsoring agency head and OHRP in accordance with HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).