

Appendix 2

**Determining which Adverse Events are Unanticipated Problems**

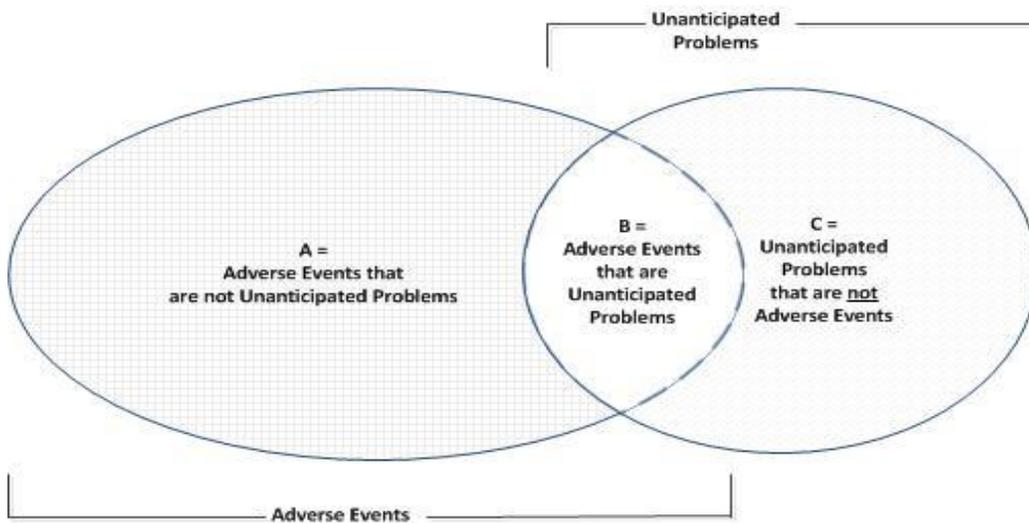
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The following Venn diagram summarizes the general relationship between adverse events and unanticipated problems:



**Under 45 CFR part 46: Do not Report A, Do report (B + C)**

The diagram illustrates three key points:

1. The vast majority of adverse events occurring in human participants are not unanticipated problems.
2. A small proportion of adverse events are unanticipated problems.
3. Unanticipated problems include other incidents, experiences, and outcomes that are not adverse events.

<sup>1</sup> Appendix B text modified from OHRP's Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, <http://www.hhs.gov/ohrp/policy/advevntguid.pdf>

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The key question regarding a particular adverse event is whether it meets the three criteria listed in the Unanticipated Problems definition and therefore represents an unanticipated problem. To determine whether an adverse event is an unanticipated problem, the following questions should be asked:

1. Is the adverse event unexpected?
2. Is there a reasonable possibility that the adverse event is related to participation in the research?
3. Does the adverse event suggest that the research places participants or others at a greater risk of harm than was previously known or recognized?

If the answer to **all three questions** is *yes*, then the adverse event is an unanticipated problem and must be reported to appropriate entities under the HHS regulations at 45 CFR 46. The next three sections discuss the assessment of these three questions.

**A. Assessing whether an adverse event is unexpected**

OHRP defines an *unexpected adverse event* as follows:

Any adverse event occurring in one or more persons participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either:

(1) the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol related documents, such as the IRB/EC-approved research protocol, any applicable investigator brochure, and the current IRB/EC-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 participant(s) experiencing the adverse event and the participant's predisposing risk factor profile for the adverse event. (Modified from the definition of *unexpected adverse drug experience* in FDA regulations at 21 CFR 312.32(a).)

It may be difficult to determine whether a particular adverse event is unexpected. Determining whether a particular adverse event is unexpected by virtue of an unexpectedly higher frequency can only be done through an analysis of appropriate data on all participants enrolled in the research.

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The vast majority of adverse events occurring in the context of research are *expected* in light of (1) the known toxicities and side effects of the research procedures; (2) the expected natural progression of participants' underlying diseases, disorders, and conditions; and (3) participants' predisposing risk factor profiles for the adverse events. Thus, most individual adverse events do not meet the first criterion for an unanticipated problem and do not need to be reported under the HHS regulations at 45 CFR 46.

**B. Assessing whether there is a reasonable possibility that an adverse event is related to participation in research**

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 participant; or
3. Other circumstances unrelated to the research or any underlying disease, disorder, or condition of the participant.

In general, adverse events that are determined to be at least partially caused by the procedures involved in the research would be considered related to participation in the research, whereas adverse events determined to be **solely** caused by the participants' underlying disease, disorder, or condition or other circumstances unrelated to the research or participants' underlying disease, disorder, or condition would be considered unrelated to participation in the research.

*Reasonable Possibility* is defined as follows:

There is evidence to suggest a causal relationship between the research procedures and the incident, experience, or outcome.

It may be difficult to determine whether there is a reasonable possibility that the adverse event is related to participation in the research. Many individual adverse events occurring in the context of research are not related to participation in the research and, therefore, do not meet the second criterion for an unanticipated problem and do not need to be reported under the HHS regulations at 45 CFR 46.

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**C. Assessing whether an adverse event suggests that the research places participants or others at a greater risk of harm than was previously known or recognized**

The first step in assessing whether an adverse event meets the third criterion for an unanticipated problem is to determine whether the adverse event is *serious*.

A *serious adverse event* is any adverse event that:

- (1) results in death;
- (2) is life-threatening (places the participant at immediate risk of death from the event as it occurred);
- (3) results in inpatient hospitalization or prolongation of existing hospitalization;
- (4) results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- (5) results in a congenital anomaly/birth defect; or
- (6) based upon appropriate medical judgment, may jeopardize the participant'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).

(Modified from the definition of serious adverse drug experience in FDA regulations at 21 CFR 312.32(a).)

Adverse events that are unexpected, present a reasonable possibility that the adverse event is related to participation in research, and *serious* are the most important subset of adverse events representing unanticipated problems because such events always suggest that the research places participants or others at a greater risk of physical or psychological harm than was previously known or recognized and routinely warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of participants.

IRBs/ECs have authority to suspend or terminate approval of research that, among other things, has been associated with unexpected serious harm to participants (45 CFR 46.113). In order for IRBs/ECs to exercise this important authority in a timely manner, they must be informed promptly of those adverse events that are unexpected, present a reasonable

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possibility that the adverse event is related to participation in the research, and serious (45 CFR 46.103(b)(5)).

However, other adverse events that are unexpected and present a reasonable possibility that the adverse event is related to participation in the research, but *not* serious, would also be unanticipated problems if they suggest that the research places participants or others at a greater risk of physical or psychological harm than was previously known or recognized. Again, such events routinely warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of participants or others.

The flow chart below provides an algorithm for determining whether an adverse event represents an unanticipated problem that needs to be reported under HHS regulations at 45 CFR 46.

