WCU
WEST CHESTER UNIVERSITY

UNIVERSITY POLICY

Reporting & Mitigating Unanticipated Problems & Adverse Events Policy

Accommodations for individuals with disabilities in accessing these policies are available upon request by emailing accessiblepolicy@wcupa.edu.

Purpose and Scope

This policy applies to all non-exempt human subjects research conducted at WCU, regardless of funding. It provides guidance on the federal regulation requirements for the protection of human research subjects at 45 CFR part 46 related to the review and reporting of (a) Unanticipated Problems involving risks to subjects or others (**hereinafter referred to as Unanticipated Problems**); and (b) Adverse Events. It is intended to help ensure that the review and reporting of Unanticipated Problems and Adverse Events occur in a timely, meaningful way so that human subjects can be better protected from avoidable harms while reducing unnecessary burden.

For Non-compliance see WCU Research Misconduct Policy.

Policy Statement

All instances of Unanticipated Problems and Adverse Events must be reported to the Institutional Review Board (IRB) and the Associate Provost for Research and Creative Activities.

Unanticipated Problems.

The phrase "unanticipated problems involving risks to subjects or others" is found but not defined in the Department of Health and Human Services regulations at 45 CFR part 46. The Office for Human Research Protections (OHRP) considers unanticipated problems, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

a. 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;
b. related or Possibly Related to participation in the research (in this guidance document, "Possibly Related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
c. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

The Office for Human Research Protections recognizes that it may be difficult to determine whether a particular incident, experience, or outcome is unexpected and whether it is related or Possibly Related to participation in the research. OHRP notes that an incident, experience, or outcome that meets the three (3) criteria set forth above generally will 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 subjects or others. Examples of corrective actions or substantive changes that might need to be considered in response to an Unanticipated Problem include:

- changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects;
- modification of inclusion or exclusion criteria to mitigate the newly identified risks;
- implementation of additional procedures for monitoring subjects;

- suspension of enrollment of new subjects;
- suspension of research procedures in currently enrolled 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.

As discussed below, only a small subset of Adverse Events occurring in human subjects participating in research will meet the three (3) criteria for an Unanticipated Problem.

Furthermore, there are other types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represent Unanticipated Problems but are not considered Adverse Events. For example, some Unanticipated Problems involve social or economic harm instead of the physical or psychological harm associated with Adverse Events. In other cases, Unanticipated Problems place subjects or others at increased risk of harm, but no harm occurs.

For guidance in determining if an event is an Adverse Event or an Unanticipated Problem see the OHRP website.

I. Adverse Events.

The HHS regulations at 45 CFR part 46 do not define or use the term Adverse Event, nor is there a common definition of this term across government and non-government entities. The term "Adverse Events" in general is used very broadly and includes any event meeting the following definition:

> Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of

Adverse Events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

Adverse Events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

In the context of multicenter clinical trials, Adverse Events can be characterized as either internal Adverse Events or external Adverse Events. 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, whereas external Adverse Events are those Adverse Events experienced by subjects enrolled by investigator(s) at other institutions engaged in the clinical trial. In the context of a single-center clinical trial, all Adverse Events would be considered internal Adverse Events.

In the case of an internal Adverse Event at a particular institution, an investigator at that institution typically becomes aware of the event directly from the subject, another collaborating investigator at the same institution, or the subject's healthcare provider. In the case of external Adverse Events, the investigators at all participating institutions learn of such events via reports that are distributed by the sponsor or coordinating center of the multicenter clinical trials. At many institutions, reports of external Adverse Events represent the majority of Adverse Event reports currently being submitted by investigators to IRBs.

II. Relationship between Unanticipated Problems and Adverse Events.

In OHRP's experience, most IRB members, investigators, and institutional officials 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 as

Unanticipated Problems, given the requirements of the HHS regulations at 45 CFR part 46.

There are three (3) key points to the general relationship between Adverse Events and Unanticipated Problems:

- The vast majority of Adverse Events occurring in human subjects are not Unanticipated Problems.
- A small proportion of Adverse Events are Unanticipated Problems.
- Unanticipated Problems include other incidents, experiences, and outcomes that are not Adverse Events.

The key question regarding a particular Adverse Event is whether it meets the three (3) required criteria 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 the Adverse Event related or Possibly Related to participation in the research?
3. Does the Adverse Event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized?

If the answer to all three (3) 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 46.103(a) and 46.103(b)(5).

III. Determining Whether the Adverse Event is Related or Possibly Related to the Research (C.b.).

Adverse Events may be caused by one or more of the following:

i. The procedures involved in the research;
ii. An underlying disease, disorder, or condition of the subject; or
iii. Other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

In general, Adverse Events that are determined to be at least partially caused by (i) would be considered related to participation in the research, whereas Adverse Events determined to be solely caused by (ii) or (iii) would be considered unrelated to participation in the research.

Determinations about the relatedness of Adverse Events to participation in research commonly result in probability statements that fall along a continuum between definitely related to the research and definitely unrelated to participation in the research. OHRP considers Possibly Related to participation in the research to be an important threshold for determining whether a particular Adverse Event represents an Unanticipated Problem.

OHRP recognizes that it may be difficult to determine whether a particular Adverse Event is related or Possibly 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 45 CFR part 46.103(a) and 46.103(b)(5)

IV. Determining Whether the Adverse Event Suggests that the Research Places Subjects or Others at a Greater Risk of Harm than was Previously Known or Recognized (C.c.).

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.

OHRP considers Adverse Events that are unexpected, related or Possibly Related to participation in research, and serious to be the most important subset of Adverse Events representing Unanticipated Problems because such events always suggest that the research places subjects 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 subjects.

V. IRB Responsibility.

West Chester University's Institutional Review Board (IRB) has 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 the IRB to exercise this important authority in a timely manner, they must be informed promptly of those Adverse Events that are unexpected, related or Possibly Related to participation in the research, and serious (45 CFR 46.103(b)(5)).

Definitions

Adverse Event – In general, this term is used very broadly and includes any event meeting the following definition:

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

Possibly Related – This term means there is a reasonable possibility that the Adverse Event may have been caused by the procedures involved in the research (modified from the definition of associated with use of the drug in FDA regulations at 21 CFR 312.32(a)).

Serious Adverse Event – This term refers to any Adverse Event that:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- 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).
  (Modified from the definition of serious adverse drug experience in FDA regulations at 21 CFR 312.32(a).)

Unanticipated Problems – In general, to include any incident, experience, or outcome that meets **all** of the following criteria:

- 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;
- Related or Possibly Related to participation in the research (in this guidance document, Possibly Related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

References

OHRP Reviewing and Reporting Unanticipated Problems

45 CFR 46

WCU Office of Research and Sponsored Programs Policies

Reviewed by: Associate Provost for Research and Creative Activities

Office of Labor Relations Review: Name and title

Policy Owner: Associate Provost for Research and Creative Activities; Office of Research and Sponsored Programs

Approved by:

Jeffery L. Osgood, Jr., Ph.D.
Executive Vice President and Provost (interim)

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