Unanticipated Events Reporting

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Background:

Federal Regulations [46.103(b)(5)(i) and 56.108(b)(1)] require that unanticipated problems involving risk to subjects or others be promptly reported to the IRB, appropriate institutional officials, and any supporting department or agency head and OHRP and/or FDA. Although the regulations do not define unanticipated problems, OHRP (2007) published guidance on unanticipated problems. Reportable events under FDA regulations include a subset of unanticipated problems (serious, unexpected and related adverse events).

For research at the VA, unanticipated problems involving risk to subjects or others and adverse events, the IRB will refer to the applicable requirements outlined in VHA Handbook 1058.01.

Q: What is considered an Unanticipated Problem?

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. The relationship is “more likely than not”: based on study interventions, the reporting investigator or the sponsor determines that a reasonable possibility exists that an outcome may have been caused or influenced by the study event in question (e.g., administration of a study drug); no plausible alternative cause/influence was present.

3. 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. Events that do not cause detectable harm or adverse effects to subjects or others may still represent unanticipated problems (OHRP Guidance, 2007).

Both risks to subjects and risks to other individuals (e.g., research personnel, subjects’ family members) are included in the concept of UPRs. Risks may reflect any type of potential harm (e.g., physical, psychological, social, economic). Other problems that are unanticipated and indicate that subjects or other are at increased risk, but that are not caused by research procedures may also be considered UPR.

Q: What is the difference between an Adverse Event and an Unanticipated Problem?

According OHRP guidance, an adverse event meets the definition of an unanticipated problem the following questions should be asked:

- Is the adverse event unexpected?
- Is the adverse event related or the relationship is “more likely than not.?”
- 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 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).

Q: What are some examples of an Unanticipated Problem?

Examples of unanticipated problems include but are not limited to:

- An adverse event to a local subject that was unexpected and related to the protocol, regardless of the severity of the event.
- More frequent or severe side effects than were anticipated as described in the protocol and consent form.
- Experiences or side effects of one or more subjects that were not described in the protocol or consent form.
- Any unapproved change or modification to an IRB approved protocol (deviation), intentional or unintentional, that places one or more subjects at risk or affects the integrity of study data.
- Changes to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a subject.
- Complaints that indicate unexpected risks, or complaint that cannot be resolved by the principal investigator.
- Malfunctioning of research equipment that results or could result in risk to subjects or others.
- Suspension of enrollment (by the investigator, sponsor) due to issues identified with the study that may involve risk to subjects.
- Events that require prompt reporting to the sponsor (i.e. pregnancy).
- Interim findings (data analysis and/or safety reports) and/or data safety monitoring reports that indicate an unexpected change to the risks or potential benefits of the research, in terms of severity or frequency.
- Publications in the literature that indicate new risks.
- Changes in product labeling indicating new risks.
- Breach of confidentiality (e.g. laptop containing identifiable private information is stolen or lost even if data files remain intact).
- Violations of applicable institutional (e.g. UF, VA) information security requirements.
- Loss of research data (e.g. paper records lost or destroyed; electronic records lost if hard drive crashes and data not backed up).
- Incorrect labeling, dosing, or dispensing of study medication or test article even if there is no indication of harm (e.g. randomization error).
- Unexpected disclosure of an event (e.g. child abuse) that requires reporting under state law and/or.
- Any unanticipated event that influences the risk-benefit of the research.

Q: How do I report Unanticipated Problems to the IRB?

If the PI of a study determines that an event may be an Unanticipated Problems that involves risks to subjects or others, they are reported via myIRB electronic submission under the type of event (e.g.
Regulatory Noncompliance, Protocol Deviation, or Adverse Event). You will be prompted to indicate if you feel the event is also an Unanticipated Problem.