

Reporting Unanticipated Problems and Adverse Events

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Adverse Events

Definitions

- **Adverse Event.** An Adverse Event (AE) is defined as any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article.

Adverse Events

- Adverse events can be
 - Serious or non-serious
 - Expected or unexpected
 - Related, possibly related or not related to the research
 - Local or external

Definitions

- **Serious Adverse Event.** A Serious Adverse Event (SAE) is defined as
 - death
 - a life threatening experience
 - hospitalization (for a person not already hospitalized); prolongation of hospitalization (for a patient already hospitalized)
 - persistent or significant disability or incapacity
 - congenital anomaly and/or birth defects
 - an event that jeopardizes the subject and may require medical or surgical treatment to prevent one of the preceding outcomes.

Definitions

- **Unexpected AE** is an event that is 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; or (b) the characteristics of the subject population being studied

Definitions

- **Related AE** is one for which there is reasonable information (e.g., strong temporal relationship, clinical indication) that the AE may have been at least partially caused by the procedures involved in the research (e.g., the use of the drug, device, or intervention).
- **Possibly Related AE** means there is a reasonable possibility that the adverse event, incident, experience, or outcome may have been caused by the procedures involved in the research (e.g., the use of the drug, device, or intervention); however, there is insufficient information to determine the likelihood of this possibility.

Definitions

- **Internal Adverse Event** is when the adverse event or incident is experienced by subjects enrolled by the investigator(s) at their institution (example: USUHS).
- **External Adverse Event** is when the adverse event or incident is experienced by subjects enrolled by investigators at other institutions engaged in a multi-center study.

Unanticipated Problems

Unanticipated Problems

- IRB regulations:
 - HHS: 45 CFR 46
 - FDA: 21 CFR 56, 21 CFR 312
- Investigators are required to report promptly “to the IRB... all *unanticipated problems involving risks to human subjects or others,*” including adverse events that should be considered *unanticipated problems* (§§ 46.103(b)(5), 56.108(b)(1), 312.53(c)(1)(vii), and 312.66).

Unanticipated Problems

Unanticipated Problems involving risk to subjects or others (UAPs), include any incident, experience, or outcome that meets **ALL** of the following criteria:

- **Unexpected**
- **Related or possibly related** to participation in the research
- Suggests that the research places subjects or others at a **greater risk of harm** (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

Unanticipated Problems

- Not all Unanticipated Problems are Adverse Events
 - Determined by risk of harm, not actual harm
 - Lost laptop
 - New risk in literature

Reporting

Reporting

- Reporting requirements are detailed in USUHS Instruction 3201 “**The Use of Human Subjects in Research at the Uniformed Services University of the Health Sciences (USUHS)**”

Reporting

- All AEs must be reported to the USUHS IRB
 - All fatalities (internal or external, expected or unexpected) related or possibly related to participation in the research must be reported within 48 hours
 - All other AEs must be reported either within 2 weeks (10 working days) or at continuing review

Reporting – Internal AEs

- Internal AEs that are either not serious and have been described on the informed consent or serious but definitely unrelated to the research can be reported at continuing review.
- All other non-fatal internal AEs must be reported within 2 weeks (10 working days).

Reporting – External AEs

- External AEs that are non-fatal, serious, unexpected and related or possibly related to participation in the research must be reported within 2 weeks (10 working days).
- All other non-fatal external AEs must be reported at continuing review.

Reporting – UAPs

- Local unanticipated problems involving breach of confidentiality or HIPAA violation should be reported within 2 weeks (10 working days).
- External unanticipated problems involving breach of confidentiality or HIPAA violation should be reported at continuing review.

Reporting – Other AEs

- Any other adverse events in the PI's opinion that may jeopardize the subject's health, confidentiality or well-being should be reported by the PI to the IRB within 2 weeks (10 working days).

Non-DoD Research

Guidance

■ FDA

- Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs- Improving Human Subject Protection

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf>

■ HHS

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

<http://www.hhs.gov/ohrp/policy/advevntguid.html>

Guidance

- FDA regulations require investigators to report adverse events to sponsors and sponsors to report adverse events to the FDA.
- The phrase “adverse events” does not appear in the IRB regulations.
- “Adverse events” are not an IRB issue!
- Only AEs and IND Safety Reports that meet the definition of UAPs should be reported to the IRB.