

Examples of
Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO)
[REF: 45CFR46.103.b.5, 21CFR56.108.b.1 and 21CFR812.3.s]

An unanticipated problem involving risks to subjects or others may include any event that was not expected given the nature of the research, the population under study and the approved procedures or protocol for conduct of the study. These problems involve risk to subjects or others (for example, research staff, family members, or others not directly involved in the research), and are related to the research intervention, research procedures, and/or conduct of the research study. The risks (including physical, financial, legal, social, emotional, psychological well being, subject privacy, or data confidentiality) may affect the rights, safety, or welfare of subjects or others.

Federal regulatory guidance published by the Office for Human Research Protection (OHRP) states that it considers *unanticipated problems*, in general, to include 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) related or possibly related to participation in the research (*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
- (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.

Examples from OHRP Guidance (Appendix B)
<http://www.hhs.gov/ohrp/policy/AdvEvtGuid.pdf>

(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 the way home from work. This is an unanticipated problem that must be reported because the incident was (a) unexpected (i.e., the investigators did not anticipate the theft); (b) related to participation in the research; and (c) placed the subjects at a greater risk of psychological and social harm from the breach in confidentiality of the study data than was previously known or recognized.

(2) As a result of a processing error by a pharmacy technician, a subject enrolled in a multicenter 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 for the institution where the dosing error occurred that

must be reported to the IRB, appropriate institutional officials, and OHRP because the incident was (a) unexpected; (b) related to participation in the research; and (c) placed subject at a greater risk of physical harm than was previously known or recognized.

(3) Subjects with cancer are enrolled in a phase 2 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 because the incident was (a) unexpected; (b) related to participation in the research; and (c) placed subjects and others at a greater risk of physical harm than was previously known or recognized.

Additional Examples of UPIRTSO reports:

- “Non-medical”
 - An interview subject begins to cry uncontrollably when asked about high school experiences.
 - Research team conducting interviews draws gunfire at field site.
 - Breach of confidentiality where one or more research records are inadvertently disclosed to persons who should not have had access to the information.

- “Medical” (note, in the UR system, “adverse events” such as new toxicities are reported as “Type 1”)
 - A subject in a study of diabetes grabs his chest and shows signs of a heart attack. In the emergency response, it is discovered that the CPR equipment wasn’t working.
 - After the administration of a reconstituted vaccine, it was discovered that the test vaccine was contaminated on the research unit because of faulty procedures.
 - Part-way through a study, it is discovered that the research procedures or test equipment gives an unexpected rate of false positives that required medical referrals, work-ups and expense.