

Defining Unanticipated Problems
Involving Risks to Subjects or Others
(UPIRSO)

Difference between UPIRSO and SAE?

What is UPIRSO?

- A UPIRSO includes any adverse event, incident, experience, or outcome that meets **all** of the following criteria:
- **Unexpected** (in terms of nature, severity, or frequency) given:
 - the research procedures that are described in the protocol-related documents, such as the IRB approved research protocol and informed consent document; **and**
 - the characteristics of the subject population being studied.
 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-approved research protocol, any applicable investigator brochure, and the current IRB-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 subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.
- **Related or possibly related** to a subject's participation 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.

What is Serious Adverse Event (SAE)?

The following events are considered a serious adverse event and would place subjects at a greater risk of harm:

- *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).*

*****It is important to note that an event may not actually cause any physical, psychological, social, or economic harm to a research subject or another person, but nevertheless, meets the definition of a UPIRSO. In such cases, the UPIRSO still must be reported to the IRB.***

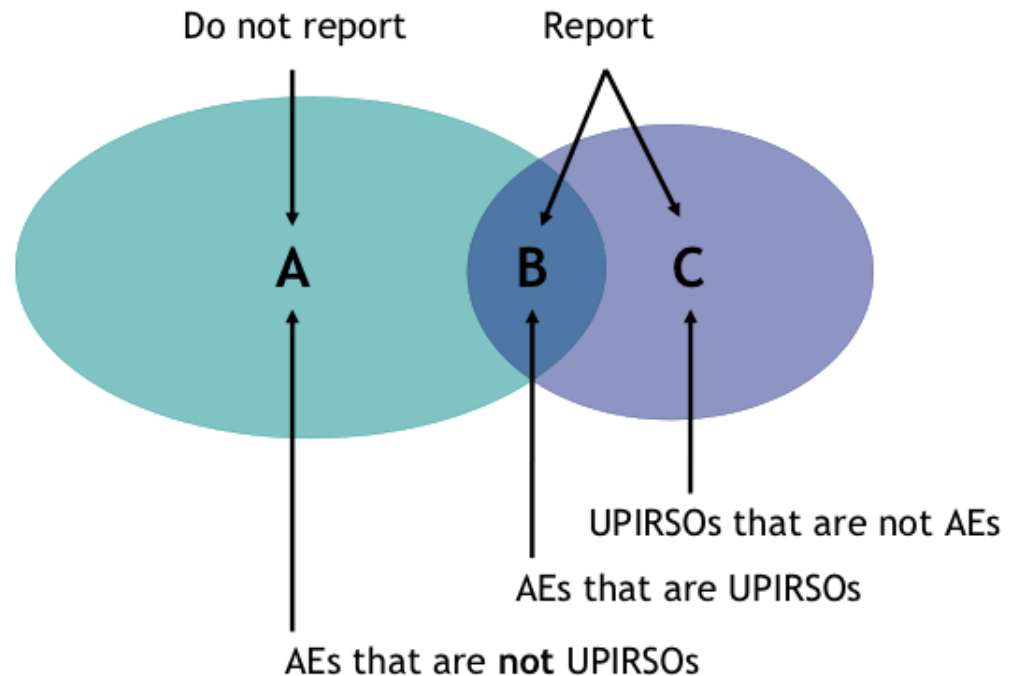
Difference between UPIRSO and AE?

UPIRSO

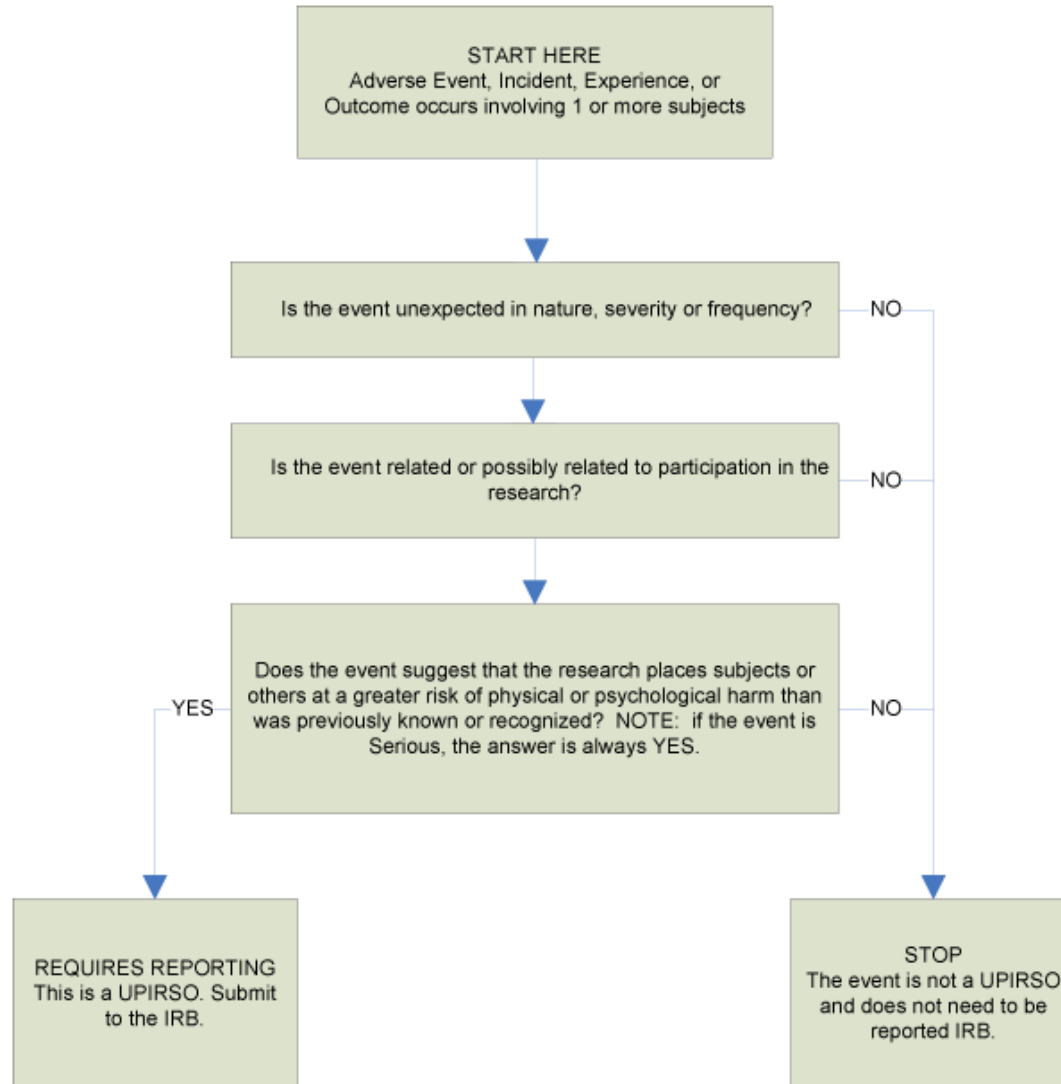
- UPIRSO is an unanticipated event and may involve the increased risk of harm—whether or not any actual harm occurred

Adverse Event (AE)

- “adverse event” ('AE') may be anticipated or unanticipated



Determining whether an event is a UPIRSO



Examples of UPIRSOs:

- Investigator finds out that the study involves a currently approved drug that may cause renal failure according to newly published literature. An interim analysis or safety monitoring report that indicates that frequency or magnitude of harms or benefits may be different than those initially presented to the IRB.
- The PI finds out that one of his subjects has become incarcerated. His project is not currently approved by the IRB to enroll prisoners.
- Investigator realizes subjects have been accidentally given study drug at a higher dose than was approved by the IRB. While no side effects were reported, the increase in dosage placed the subjects at potential risk of harm.
- A computer or other electronic device is stolen that contained identifiable subject information.
- 4 weeks into the study of a new asthma drug, the subject informs the research staff that she is pregnant although the pregnancy test done at screening had come back negative. Pregnancy is an exclusion factor in the study.
- A researcher has IRB approval to obtain written consent for a survey study to be conducted in women who live in a remote village in Ghana. Only after getting to the village does he realize that most of the women are unable to read or write in English. Since he is short on time and does not have ready access to computers, he chooses to obtain oral consent without first obtaining IRB approval.

Examples of events that are not adverse events, but are UPIRSOs

Example 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 consent document and IRB-approved protocol or NPSF did not anticipate the theft as an expected risk of participation); (b) the event was related to participation in the research; and (c) the event placed the subjects at a greater risk of psychological and social harm because of the breach in confidentiality of the study data.

Explanation

- The events described in the example were unexpected in nature, related to participation in the research, and resulted in new circumstances that increased the risk of harm to subjects.
- The unanticipated problems warranted 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.
- While these events may not have caused any detectable harm or adverse effect to subjects or others, they nevertheless represent unanticipated problems and should be promptly reported to the IRB, appropriate institutional officials, the supporting agency head and OHRP in accordance with HHS regulations.

Examples of events that are not adverse events, but are UPIRSOs

Example 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 ten times higher than the dose indicated in 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, 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.

Explanation

- The events described in the example were unexpected in nature, related to participation in the research, and resulted in new circumstances that increased the risk of harm to subjects.
- The unanticipated problems warranted 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.
- While these events may not have caused any detectable harm or adverse effect to subjects or others, they nevertheless represent unanticipated problems and should be promptly reported to the IRB, appropriate institutional officials, the supporting agency head and OHRP in accordance with HHS regulations.

Examples of events that are not adverse events, but are UPIRSOs

Example 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.

Explanation

- The events described in the example were unexpected in nature, related to participation in the research, and resulted in new circumstances that increased the risk of harm to subjects.
- The unanticipated problems warranted 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. In addition, this third example may have presented unanticipated risks to others (e.g., the sexual partners of the subjects) in addition to the subjects.
- While these events may not have caused any detectable harm or adverse effect to subjects or others, they nevertheless represent unanticipated problems and should be promptly reported to the IRB, appropriate institutional officials, the supporting agency head and OHRP in accordance with HHS regulations

UPIRSO Regulations:

FDA 21CFR56.108(b)

- Title **21**-Food and Drugs
- Part **56**-Institutional Review Board
- Sec **56.108** IRB functions and operations

In order to fulfill the requirements of these regulations, each IRB shall:

(b) Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the food and Drug Administration of: **(1) any unanticipated problems involving risks to human subjects or others;** (2) any instance of serious or continuing noncompliance with these regulations or the requirements of determinations of the IRB; or (3) any suspension or termination of IRB approval

UPIRSO Regulations:

HHS 45CFR46.103(b)(5)

- Title **45**-Public Welfare
- Part **46**-Protection of Human Subjects
- Sec **46.103** Assuring compliance with this policy-research conducted or supported by any Federal Department or Agency
- **b)**Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the department of agency head that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. Assurances applicable to federally supported or conducted research shall at a minimum include:
 - (5)** Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of **(i) any unanticipated problems involving risks to subject or others** or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB and **(ii) any suspension or termination of IRB approval**

UPRISO Regulations:

International of Conference on Harmonization (ICH) 4.11

4.11 Safety Reporting

4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).