UPIRHSOs, AEs, SAEs

Understanding the Difference & Knowing When and to Whom to Report

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Adverse Event

Any untoward or unfavorable medical occurrence in a human subject

- This includes any abnormal sign, 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.

- AEs include both physical and psychological harms
Serious Adverse Event

Any adverse event temporally associated with the subject’s participation in research that meets any of the following criteria:

- results in death
- is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect
- may require medical or surgical intervention to prevent one of the other outcomes listed in this definition
Unanticipated Problem Involving Risks to Human Subjects or Others (UPIRHSO)

Any incident, experience, or outcome that meets all the following criteria:

- Unexpected
- Related or possibly related
- Increases risk of harm

- OHRP

- Unexpected
- Serious
- Implications for the conduct of the study

- FDA
## UPIRHSO

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OHRP Definition of “Unexpected”

- The nature, severity, or frequency of the event is not consistent with risks outlined in the protocol, IB, package insert, or informed consent document (ICD)

- Event is not consistent with the expected progression of subject’s underlying disease, disorder, or risk for the event
FDA Definition of “Unexpected”

- Not previously identified in nature, severity, or degree of incidence in the investigational plan or application

- Any adverse experience, the specificity or severity of which is not consistent with the current investigator brochure (IB)
Related or Possibly Related

- There is a reasonable possibility that the incident, experience or outcome may have been caused by, or probably caused by, the procedures involved in the research

- The USF HRPP extends this definition to a minimum of 30-days post administration of the test article or intervention
Increased Risk of harm

- 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.
Some SAEs/AEs are UPIRHSOs.

Many SAEs/AEs are NOT UPIRHSOs and do not require immediate reporting to the IRB.

Anticipated events are those risks that have already been identified in the IRB-approved protocol, IB and/or the informed consent document.
Adverse Events

UPIRHSOs
USF IRB Reporting Requirements

- UPIRHSOs must be submitted to the IRB immediately upon the investigator becoming aware of the event.

- SAEs that do not meet the definition of UPIRHSOs do not require prompt reporting and should be reported at the time of Continuing Review.

- Sponsor reporting requirements may differ from those of the IRB, but all sponsors should be provided with the USF HRPP Policy 212 outlining our requirements.
Examples of UPIRHSOs

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure or is uncommon in the study population.

- An AE or SAE that is described or addressed in the IB, protocol, or informed consent document, but occurs at a specificity or severity that is inconsistent with prior observations.
Examples of UPIRHSOs

- AEs that are commonly associated with the underlying disease process being studied (e.g., deaths in cancer trial), or that are otherwise common in the study population independent of drug exposure (e.g., cardiovascular events in elderly population) that occur at higher rate in the drug treatment group compared to the control arm.

- Breaches in confidentiality, including the loss of data on a computer or any electronic device which holds private or confidential information, or which places the participant or others at risk.
Examples of UPIRHSOs (cont’d)

- Laboratory or medication errors that may involve risk to subject or others

- Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol

- Incarceration of a participant when enrolled in a study not approved under Subpart C provisions

- Allegations of noncompliance
Summary

- SAEs that do not meet the definition of an UPIRHSO do not need to be reported to the USF IRB immediately, but should be included in your application for continuing review.

- Investigators should continue to meet their obligations to report events to the sponsor, the Food and Drug Administration (FDA), and the data safety monitor, as applicable.

- If an event impacts the rights, safety, or welfare of subjects, report it to the IRB promptly.

- If an event is serious enough that you feel it must be reported to the FDA, Sponsor, or DSMB, report it to the IRB promptly.

- When in doubt, contact the IRB.
Common Audit Findings in Research and How to Avoid Them
Top 5 Most Common Audit Findings

1. Incomplete Informed Consent Documentation
2. Incomplete Determination and Documentation of eligibility criteria
3. Incomplete Adverse Event Review and Reporting
4. Non-Adherence to the IRB approved Protocol
5. Incomplete Regulatory Documentation
Incomplete Informed Consent Documentation

- ICD incomplete
  - Missing dates
  - Missing signatures
  - Missing initials or check marks (contraception, storage etc.)
  - Markings, cross outs, corrections
  - No source documentation of consent process
- Wrong version of ICD used
- Unstamped version of ICD used
Recommendations

- Remove extra old copies of ICDs from your files, except the one in your regulatory binder.

- Double check the ICD version before giving it to the subject (dates and watermark)

- Document everything you do

- Check the completed ICD prior to giving the subject a copy. Line through errors and initial and date any corrections.
Incomplete Determination and Documentation of Eligibility Criteria

- Unable to verify subject met eligibility criteria
  - Missing assessments (procedures, labs) needed to assess eligibility

- Missing PI determinations on eligibility (life expectancy, grading pre-existing conditions)

- Records of eligibility kept in multiple locations
Recommendations

- Create checklist with eligibility criteria and time frame the tests are needed. Include results and dates.

- Have a process for the PI to review inclusion/exclusion criteria prior to initiation of study procedures.

- Prove the subject is eligible and document the proof in the subject’s study file.
Incomplete Adverse Event Review and Reporting

- AEs noted in medical record not captured on CRFs or in study chart
- AEs not followed to resolution
- AEs not reviewed by PI in a timely fashion
- AEs not reported appropriately
Recommendations

- Have *Investigators* assess AEs for severity and causality in real time and document.

- Begin each study visit with a review of AEs. F/U on past events.

- Know reporting requirements in your clinical trial agreement, to your IRB, to your sponsor, and to federal agencies, if applicable.
Non-Adherence to the IRB approved Protocol

- Implementing revisions to the protocol without first obtaining IRB approval
- Clinical tests not performed as specified in the protocol
- Visits out of protocol-specified window
- Follow up visits not completed as specified in protocol
Recommendations

- Secure prospective IRB approval for any changes.
- Review study calendar.
  - Tests or assessments may differ from SOC. (checklists)
  - Same as in body of protocol?
- Use notes to file (NTF) to document deviations. Report serious deviations to the IRB promptly, non-serious at continuing review.
Incomplete Regulatory Documentation

- Missing or out-of-date delegation of authority log
- Incomplete or outdated CVs, professional licenses, training documentation
- Outdated lab certificates
Recommendations

- Maintain delegation of authority log, update as you go

- Schedule date to review regulatory file for outdated licenses and CVs
  - Be sure to collect these from new members of the study team as they are added
  - Check dates of CAP and CLIA as well