UPIRHSOs, AEs, SAEs

Understanding the Difference & Knowing When and to Whom to Report

Stacy Newalu, MPH, CCRC
Assistant Director for Regulatory Affairs
USF Division of Research Integrity & Compliance
813-974-7821
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, and are a subset of UPIRHSOs
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 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
### OHRP vs. FDA

<table>
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<td>Unexpected</td>
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<td>Related or Possibly Related</td>
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<td>Different or Greater Risk of Harm</td>
<td>Implications for the conduct of the study</td>
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OHRP Definition of “Unexpected”

- Unexpected (in terms of nature, severity, or frequency) given
  - the research procedures that are described in the protocol-related documents
    - IRB approved research protocol
    - informed consent document
  - the characteristics of the subject population being studied
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)
  - If an IB is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application
Related or Possibly Related

- There is a reasonable possibility that the incident, experience or outcome may have been reasonably regarded as 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 different or greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
Some SAE’s/AEs are UPIRHSO’s

Many SAE’s/AE’s are NOT UPIRHSO’s and do not require immediate reporting to the IRB.

Anticipated events are those reasonably foreseeable risks that have already been identified in the IRB-approved protocol, IB and/or 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
  - These include SAEs/AEs that qualify as UPIRHSOs
  - These include UPIRHSOs that are not SAEs/AEs
- Report via eIRB, AERS, or Information Report
USF IRB Reporting Requirements

- Events that do not meet the definition of UPIRHSO and therefore do not require prompt reporting
  - Should be reported at the time of Continuing Review
  - Excel Spreadsheet, Summary form, Chart form

- 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 investigator’s brochure, protocol, or informed consent documents, 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

- Laboratory or medication errors that may involve risk to that individual 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
Multi-Center Studies – External Reports

- SAEs, Safety Reports, MedWatch Reports, AE’s
- External Site (Non-USF/USF Affiliate)
- No Amendment to Protocol, ICD, IB Required
- Report to IRB in summary form at CR
- No change to Risk/Benefit Ratio

❖ If the event does require an amendment to the protocol, IB or informed consent, or changes the risk/benefit ratio, it should be reported to the IRB promptly.
Summary

- Events that do not meet the UPIRHSO criteria do not require submission to the USF IRB immediately, but should be included as information 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 participants safety, rights or welfare – report the IRB

- If an event is serious enough that you feel it must be reported to the FDA, Sponsor, DSMB – contact the IRB

- When in doubt – contact the IRB
Questions?

*Portions of this presentation were borrowed from All Children’s Hospital, St. Petersburg, FL*
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 date of signature
  - Missing witness (if applicable)
  - 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 ICD
- Double check the ICD version when giving it to the subject
- Document everything you do
- Check and re-check the completed ICD prior to giving the subject a copy
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 result and date

- 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 but 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 PI assess AEs in real time
  - Remind clinicians that this is research not standard of care so additional documentation is necessary
- Begin each study visit with a review of AEs so you remember to follow up on past events
  - If there is a lot of time between study visits, create a log for subjects to keep where they record when events occur and medications they take to treat them.
- Know your 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

- It is just as important to obtain IRB approval for an amendment as it is to have initial approval before beginning research activities.
- Tests or assessments may be required at frequencies that differ from routine care:
  - Make checklists for study visits.
- Read the protocol and compare the schedule of assessments with the study procedures outlined in the body of the protocol:
  - Seek clarification from sponsor/investigator as needed.
- Use notes to file to document reasons for deviations, report deviations to the IRB.
Incomplete Regulatory Documentation

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

- Begin new studies with a delegation of authority log that includes names of the study team
  - This is documentation that the PI has delegated specific responsibilities to members of the study team
  - When people leave or join the study, updated the log with their start and stop dates
- 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
Questions?