

# UPIRHSO

Unanticipated Problems Involving  
Risks to Human Subjects or Others



# AGENDA

- ① Regulatory Requirements
- ① Define UPIRHSOs, Adverse Events, and “Unexpected”
- ① Clarifying the Difference Between UPIRHSOs and AEs
- ① Reporting Requirements to USF IRB
- ① Examples of Reportable UPIRHSOs
- ① Q&A



# REGULATORY REQUIREMENTS

- ⦿ Federal regulations (45 CFR 46, and 21 CFR 56) require that institutions establish written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the federal department or agency head of any unanticipated problems involving risks to subjects or others (UPIRHSOs).
- ⦿ The FDA has separate regulations that require the prompt reporting of adverse events (or effects) from the investigators to the sponsor and from the sponsor to the FDA as well as to other clinical investigators using the same test article.

# USF HRPP POLICY

- ③ As the requirements are new, they are easy to misunderstand so study teams are unsure of what to report.
- ③ This presentation will review which UPIRHSOs should be reported to the USF IRB.
- ③ Please review USF HRPP Policy 212 for more information.

# OHRP DEFINITION OF UPIRHSO


- ③ **Unanticipated Problems Involving Risks to Human Subjects or Others (UPIRHSOs)** are defined as any incident, experience, or outcome that meets all 3 of the following criteria:
  - 1) Unexpected
  - 2) Related or Possibly Related
  - 3) Different or Greater Risk of Harm

# FDA DEFINITION OF UPIRHSO

- ① UPIRHSOs are defined by the FDA as any event that meets the following criteria:
  - 1) Unexpected
  - 2) Serious
  - 3) And would have implications for the conduct of the study (E.g. requiring a significant, and usually safety-related , change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, IC, or IB)
  
- ① An individual AE occurrence *ordinarily* does not meet these criteria

# OHRP DEFINITION OF “ UNEXPECTED ”

- ⊙ 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;



# 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); OR
- ⊙ 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

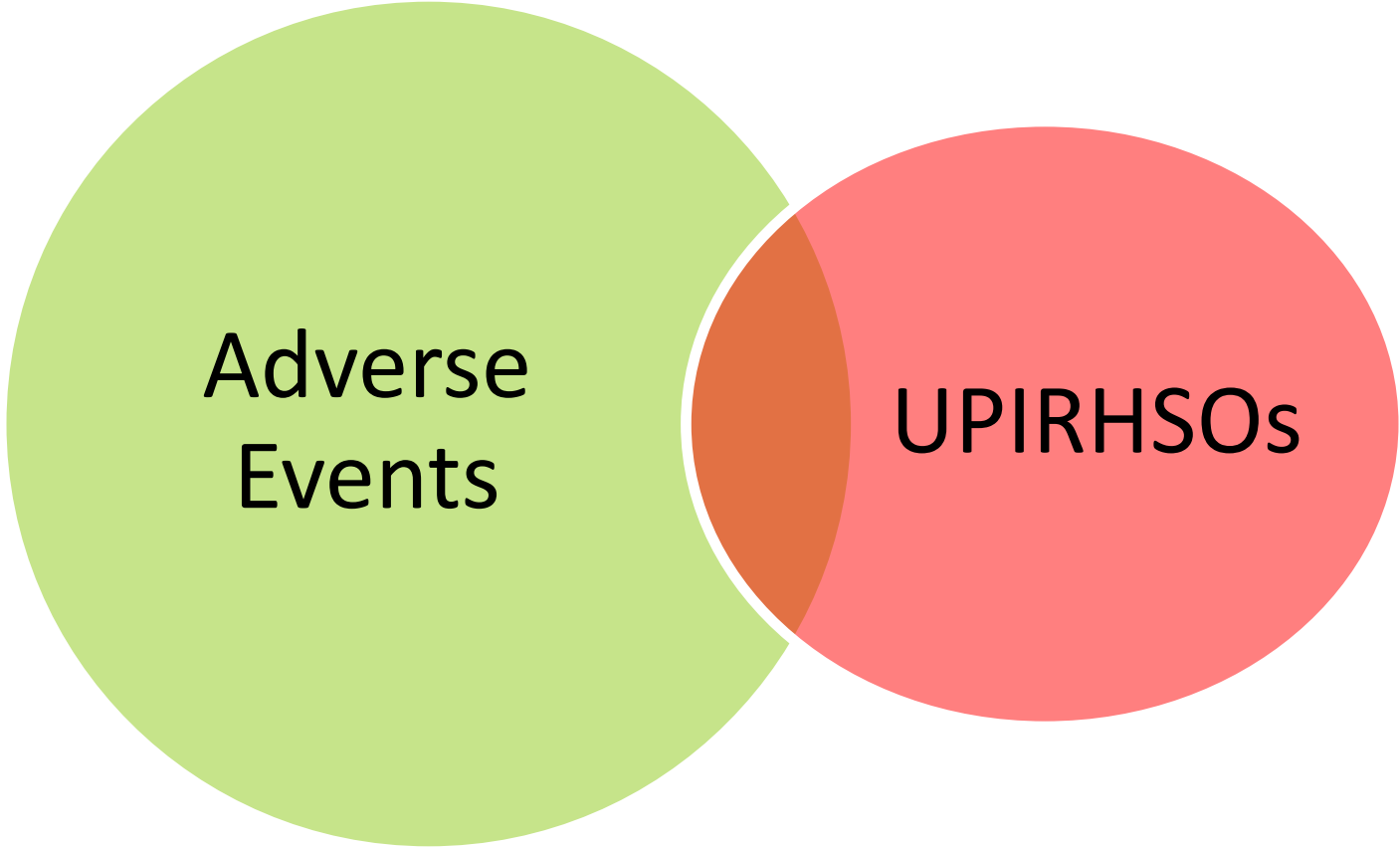
- © Suggests that the research protocol places subjects or others at a different or greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

# ADVERSE EVENT

- ⊙ Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), 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 includes both physical and psychological harms, and are a subset of UPIRHSOs

# SERIOUS ADVERSE EVENT

- ⦿ **Defined as 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; OR
  - ⦿ may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

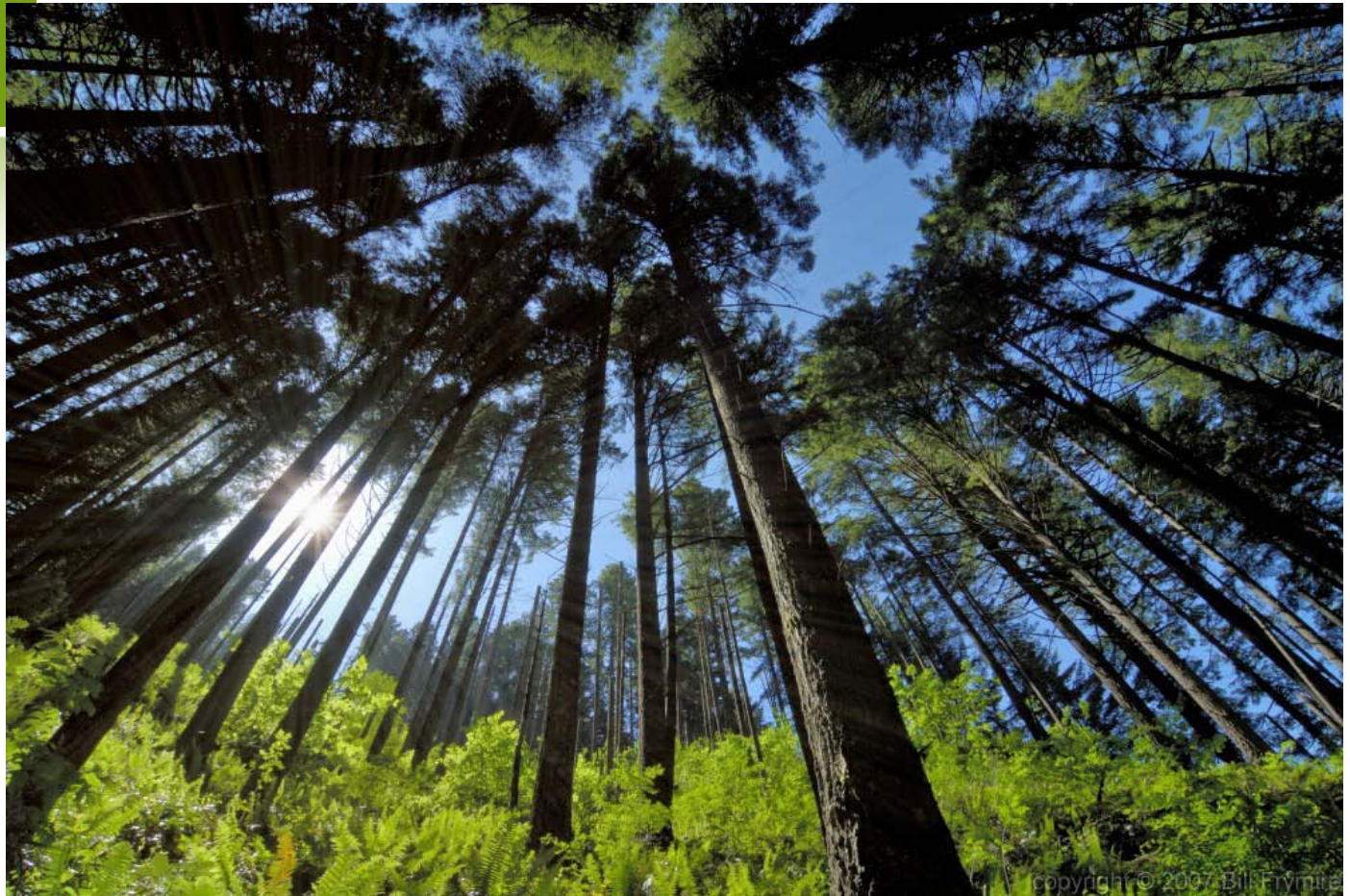


Adverse  
Events

UPIRHSOs

# PROBLEM

- ⊙ Most AE reports sent to the IRB are for risks that are already known to be associated with the research and therefore, should not be submitted.
- ⊙ Reports contain too little information to be meaningful.
- ⊙ IRBs are unable to serve as the DSMB for the study.



# BOTTOM LINE

- ③ While some adverse events are also unanticipated problems involving risks to human subjects or others, **most adverse events are anticipated risks of participation in a study and do not require reporting to the IRB.**
- ③ Anticipated events are those reasonably foreseeable risks that have already been identified in the IRB-approved protocol, IB and/or consent document.



# REPORTING REQUIREMENTS

- ◎ UPIRHSOs must be submitted to the IRB immediately upon the investigator becoming aware of the event
- ◎ This includes SAEs that qualify as UPIRHSOs
- ◎ An OHRP Flow Chart provides guidance for determining whether an adverse event represents a reportable UPIRHSO:  
<http://www.hhs.gov/ohrp/policy/AdvEvtntGuid.pdf>
- ◎ All other events should be reported at 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.

# DOES THE EVENT QUALIFY AS A UPIRHSO?

Unexpected

- Is the event described in the protocol, IB or the informed consent?

Related

- Is the event related to participation in the research study?

Changes Risk

- Does the event place the subject or others at a different or greater risk of harm?

Action

- Does the event need to be reported promptly or at the time of continuing review?

# 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;
- ⊙ 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;
- ⊙ 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

# CONSIDERATIONS FOR MULTI-CENTER STUDIES

- ⊙ UPIRHSOs that take place at an external site (non-USF/USF Affiliate), including safety reports and adverse events, that do not require an amendment or change the risk/benefit ratio to the protocol, DO NOT need to be reported to the USF IRB. **A summary of these types of events should be included at the time of continuing review.**
- ⊙ If the UPIRHSO does require an amendment to the protocol, IB or informed consent, or changes the risk/benefit ratio, it should be reported promptly.
- ⊙ Events from protocols that are not approved by the USF IRB but involve the same drugs do not need to be reported to the IRB.

# UPIRHSOs AND PROTOCOL AMENDMENTS

- ◎ It is expected that an incident, experience, or outcome that meets the three criteria for a UPIRHSO will generally warrant 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 or others.
- ◎ The USF IRB anticipates that UPIRHSOs will frequently be accompanied by an amendment to the study.

# TO REITERATE

- ③ Events that do not meet the UPIRHSO criteria as defined in this presentation do not require submission to the USF IRB and should be included at the time of continuing review.
- ③ 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.

QUESTIONS?



# CONTACT Us

- ◎ Steven Kim, IRB Manager  
813-974-5741  
[skim@research.usf.edu](mailto:skim@research.usf.edu)
- ◎ Olivia Hart, Assistant IRB Manager  
813-974-7454  
[ohart@research.usf.edu](mailto:ohart@research.usf.edu)

*\*Portions of this presentation were borrowed from  
All Children's Hospital, St. Petersburg, FL*