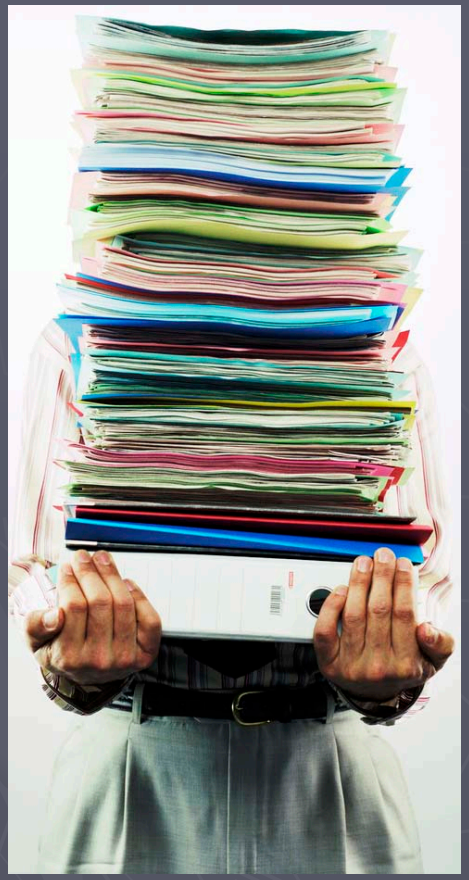


Guidance on Unanticipated Problems (UPs) and Adverse Events (AEs)

Bertha deLanda
IRB Training Specialist
Research Compliance Office
March 2010

OUTLINE

- AE (adverse event)
  - SAE (serious adverse event)
- UP (unanticipated problem)
  - Unexpected
  - Related
  - Harmful
  - How does an AE become a UP?
- Resources

Definitions – AE

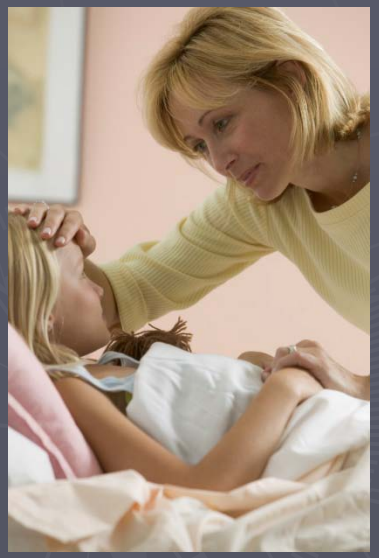
"any untoward or unfavorable medical occurrence in a human subject, temporally associated with... a research study, whether or not it is related to the study"

- Can encompass both psychological and physical harms
- Are not promptly reported to the IRB

OHRP Guidance on Reviewing and Reporting UPs Involving Risks to Subjects or Others and Adverse Events

Definition – SAE
Serious Adverse Event

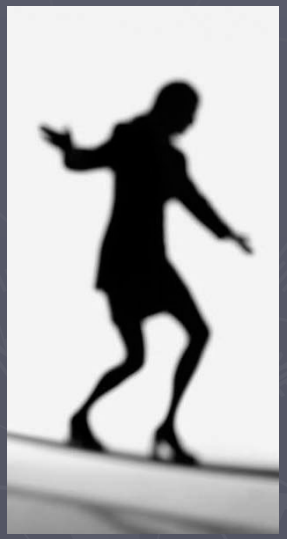
- SAE is an AE (untoward or unfavorable medical occurrence in a subject) that:



1) Results in death
2) Is life-threatening
3) Results in hospitalization (or prolongation of existing stay)
4) Results in a persistent or significant disability/incapacity
5) Results in a congenital abnormality/defect
6) May jeopardize subject health, and requires surgery/medical intervention to prevent other 5 criteria

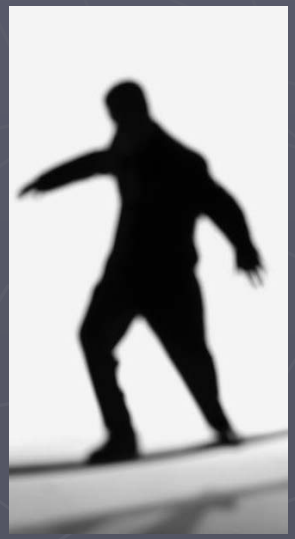
OHRP Consideration

OHRP considers some SAEs and AEs important events because they may:



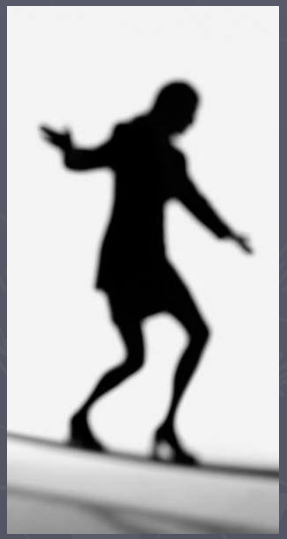
SAEs/AEs are submitted during the continuing review process

but modifications to the protocol or the ICF can be submitted at any time



OHRP Consideration

OHRP considers some SAEs and AEs important events because they may:



- suggest that the research places subjects or others at a greater risk of harm than what was previously known
- warrant changes in the protocol, ICF procedures/documents

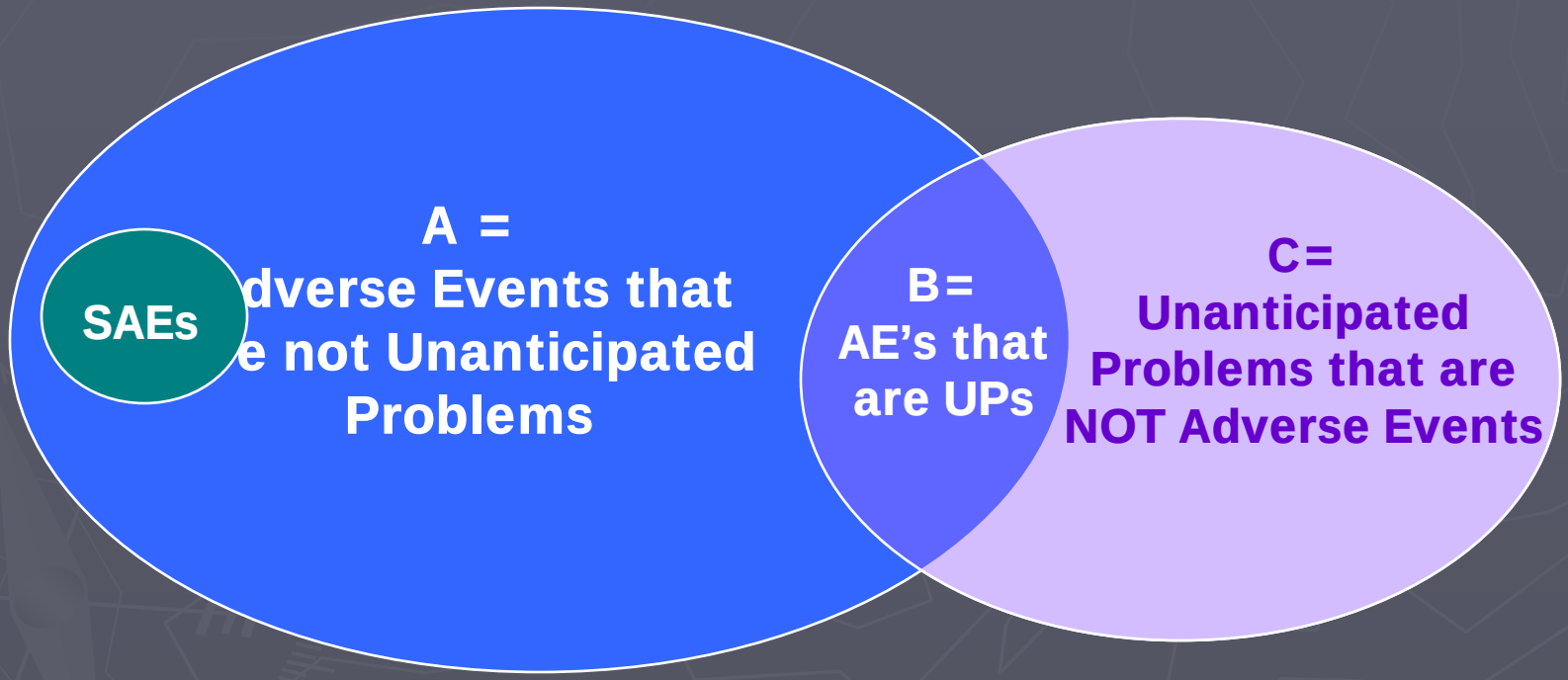
OHRP Definition – UPs

"Any incident, experience, or outcome that meets **ALL** of the following criteria:"

1) **unexpected** (in terms of nature, severity, specificity or frequency)
2) **related** or possibly related to participation in a study
3) places subject or others at a **greater risk of harm*** than was previously recognized

* including physical, social, economic or psychological harm

General Relationship Between AEs/UPs

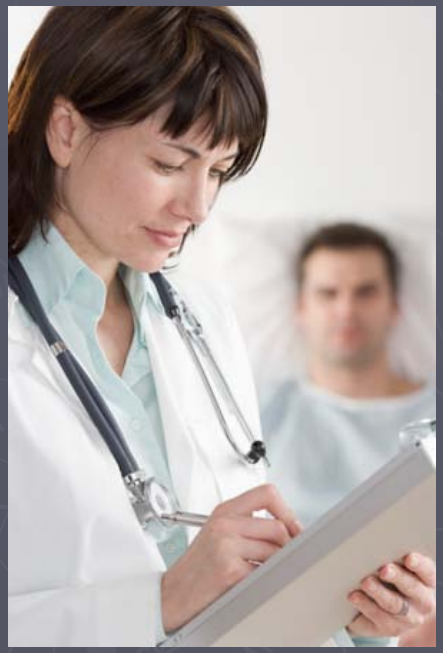


Under 45 CFR 46: Do not report A; Report B and C

UPs

45 CFR 46.103(a) and 45 CFR 46.103(b)(5)

"Unanticipated problems involving risks to subjects or to others"



- Are promptly reported to the IRB
  - within 5 days of the PD discovery if death/life-threatening situation occurs
  - within 10 for all other UPs
- Initially determined to be UPs by monitoring entity, sponsor or PD
- IRB makes the final UP determination

Unexpected

- Example:

  Informed consent (or IB) states that you will get a slight rash at the injection site.

  Leland comes down with a rash from head to toe.

  Unexpected?

  Yes; severity was not expected

Related

- Leland comes down with a rash before administration of a medication.

  Related?

  No; he did not receive the drug before the rash

Related :

"there is a reasonable possibility that the adverse event may have been caused by the procedures involved in the research"

(FDA: "associated with the drug")

Harmful

- The informed consent states that you may receive a minor rash within a few hours after administration of a drug.

  The rash was so severe, Leland was hospitalized and was unable to go to work.

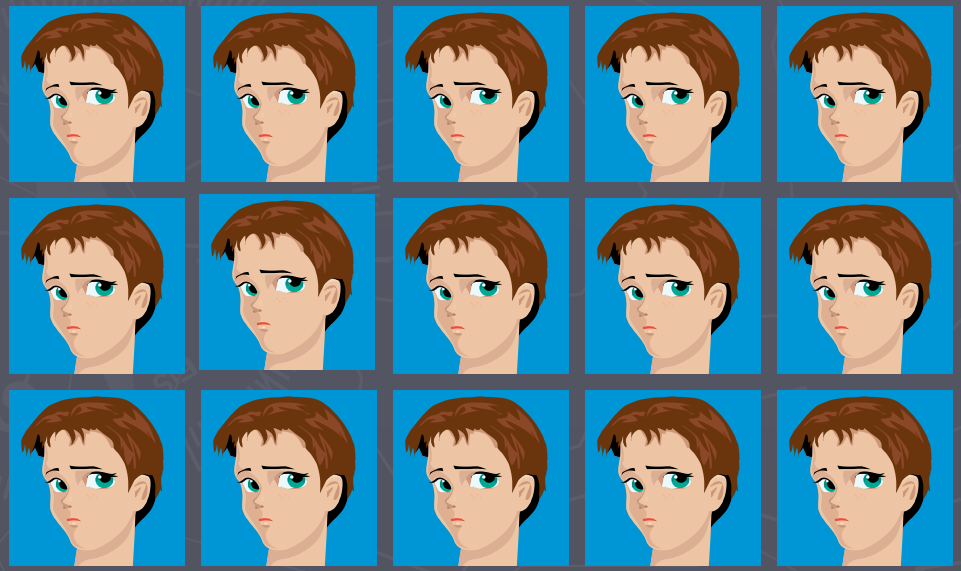
Harmful?

Yes; it placed Leland at physical and economic risk (in terms of lost wages)

How does an AE become a UP?

Leland has a bad reaction to a drug that was anticipated to last a few days, that now has lasted a few weeks.

The rash worsens over time and is now diagnosed as Stevens-Johnson Syndrome.



- ☑ Harmful
- ☑ Related
- ☑ Unexpected

Resources

- GUI-P13
- 45 CFR 46.103(b)(5)

- Guidance On Reviewing and Reporting Unanticipated Problems"

  http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm

- FDA Guidance: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127346.pdf