



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

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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:

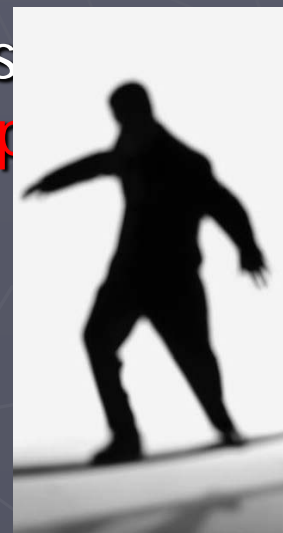
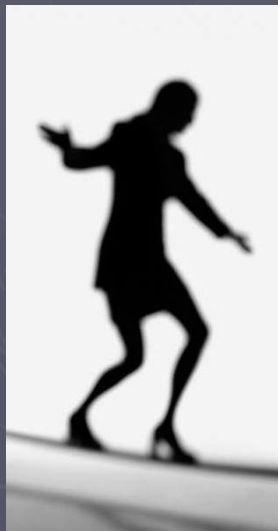


- 1) Results in death
- 2) Is life-threatening
- 3) Results in hospitalization (or prolongation of existing stay)
- 4) Results in a persistent or significant disability/incapacity
- 5) Results in a congenital abnormality/defect
- 6) May jeopardize subject health, and requires surgery/medical intervention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

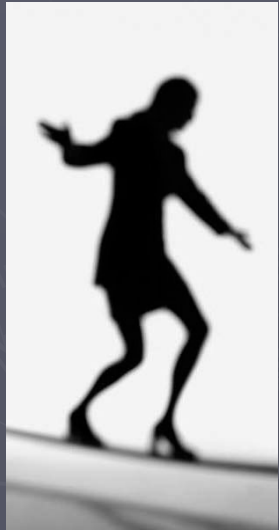
OHRP Consideration

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

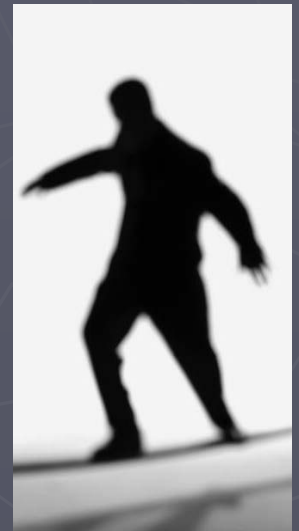
- suggest that the research places subjects at a greater risk of harm **than what was previously known**
- warrant changes in the protocol, ICF procedures/documents



OHRP Consideration



SAEs/AEs are submitted during the continuing review process but modifications to the protocol or the ICF can be submitted at any time



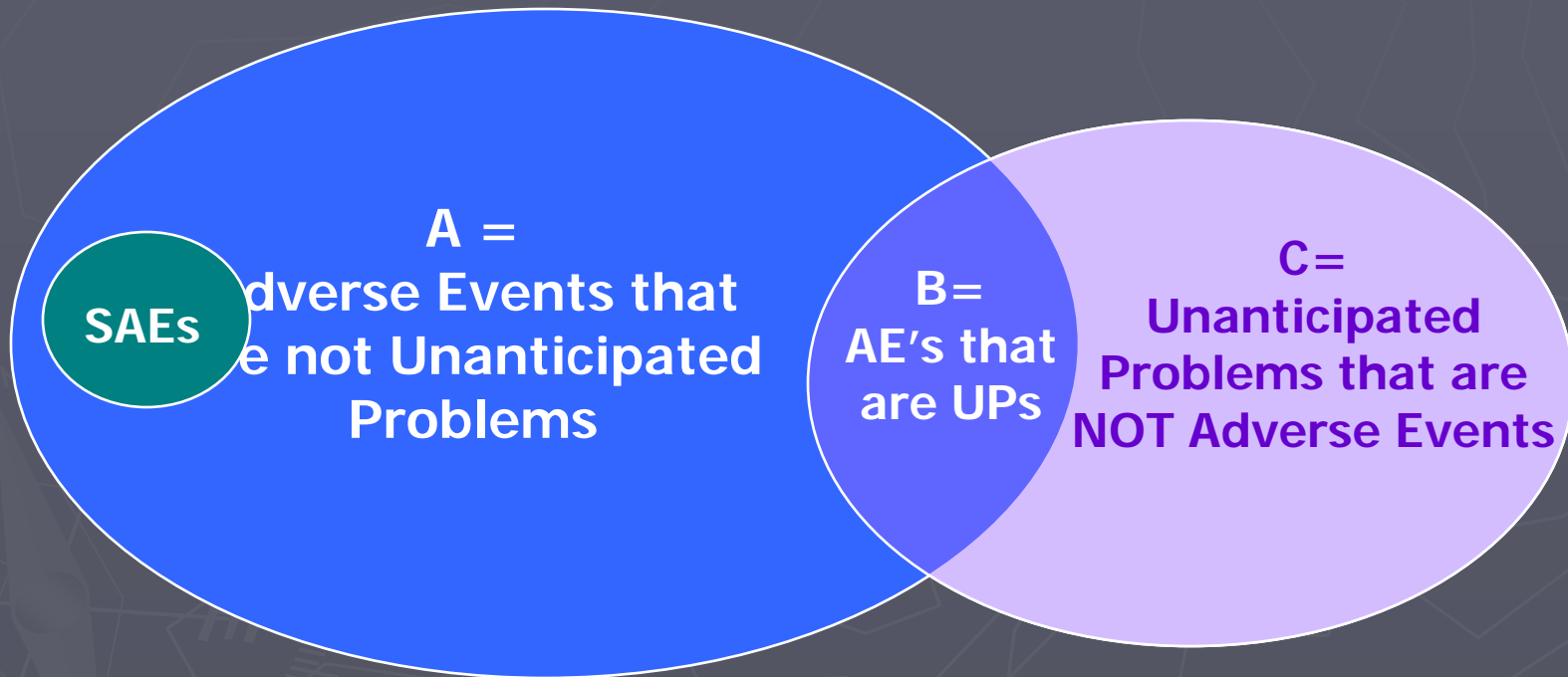
OHRP Definition – UPs

“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 states that participants will have ECG pads put on various sites on the face and neck.

Leland comes down with a rash at the pad sites.

Unexpected?

Yes; rash was not expected



Related

- ▶ Leland comes down with a rash before participating in a study but after consenting.

Related?

No; he had the rash before the study was conducted.

Related :

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



Harmful

- ▶ The informed consent states that you may receive a minor rash within a few hour of using the pads.

The rash was so severe, Leland was hospitalized and was unable to go to work because it turned out he was allergic to the gel used for the study.

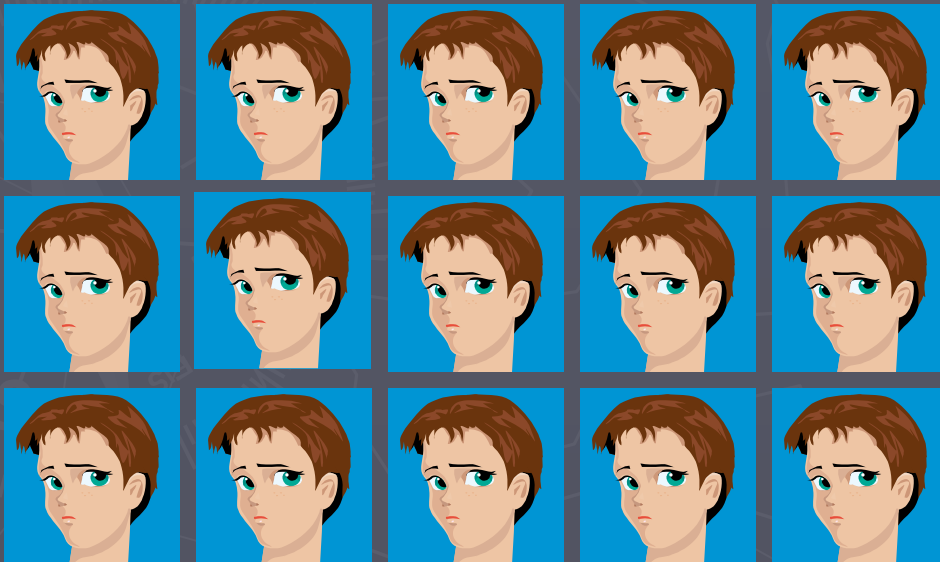


Harmful?

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

How does an AE become a UP?

Leland has a mood swing because of the questions he was subjected to, which was mentioned in the ICF as a possible reaction. But after a few weeks, his mood swing becomes a depression.



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>