



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

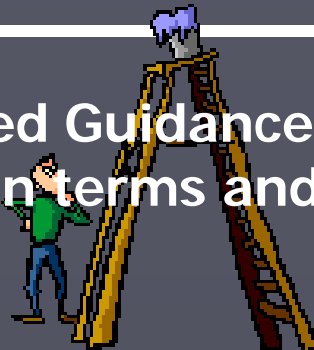
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# OUTLINE

- AE (adverse event)
  - SAE (serious adverse event)
- UP (unanticipated problem)
  - Unexpected
  - Related
  - Harmful
- Reporting



Revised Guidance GUI-P13 –  
expanding on terms and providing clarity



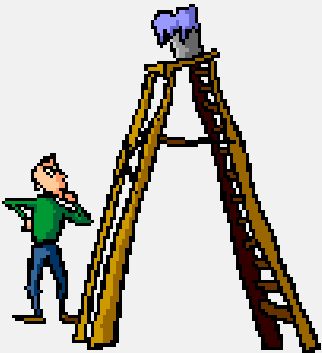
# Definition – AE Adverse Event

“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”

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

The vast majority of adverse events occurring in human subjects research **are not** unanticipated problems



# 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

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# 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

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# OHRP Definition – UPs

- a) the research procedures described in the **protocol related documents**, and
- b) the **characteristics** of the subject population being studied



- **Protocol-related documents:**

Refer to

- the IRB-approved research protocol
- informed consent documents
- investigator brochure
- protocol
- package insert or label



- **Characteristics** of the subject population:

Refer to

- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the event/side effect
- and the subject's predisposing risk factor profile for the adverse event



# Assessing whether an event is unexpected...

Examples of unexpected events:



- liver failure occurring in a subject without any underlying liver disease IF liver disease was not listed as a potential risk
- liver failure if the documents only refer to elevated hepatic (liver) enzymes or hepatitis as a potential risk



# Assessing whether an event is related or possibly related:

**Adverse events may be caused by one or more of the following:**



1. the procedures involved in the research; or
2. an underlying disease, disorder, or condition of the subject; or
3. other circumstances

In general, events that are determined to be at least partially caused by **1** would be considered **related** to participation in the research,

whereas events determined to be *solely* caused by **2** or **3** would be considered **unrelated** to participation in the research.



Related



Patient  
w/Cancer  
and  
Diabetes

Unrelated

OHRP defines *possibly related* as follows:

There is a *reasonable possibility*\* that the adverse event may have been caused by the procedures involved in the research

\* modified from the definition of *associated with use of the drug* in FDA regulations at 21 CFR 312.32[a]

# Assessing whether an event places subjects/others at a greater risk of harm

- Events need not be “serious” to qualify as “placing participants at greater risk of harm”
- “Not serious” events can still be UPs
- Harm does not have to occur!
  - \* means that it placed participants at greater risk of harm (physical or psychological) than previously thought



A research associate leaves a laptop with subject information unattended in a public place. It is found later on; doesn't seem to be tampered with.

Given: this event is unanticipated and related to the study.  
What would make this event:

- *serious?*
- *harmful?*
- *a UP?*



If the end result of the event puts the subject at any greater level of risk it is a UP

The seriousness of the event is not the only criteria in deciding whether or not an event is harmful

Whether or not harm occurred may also not be an indicator of a UP



- A behavioral researcher conducts a study in students that involves a survey about early childhood experiences.
- One student has a psychological reaction (intense sadness/depressed mood) that resolved w/o intervention.
- This is a UP that must be reported because the event was:
  - (a) unexpected
  - (b) related to participation in the research and
  - (c) suggested that the research places subjects at a greater risk of harm than was previously known or recognized



## Procedure/Process for UP/SAE/AE Reporting:

- Investigator/monitoring entity reports UP to IRB
- IRB member(s):
  - Evaluates
  - Ensures immediate action taken to protect participants
  - Appoints subcommittee/consultant (if needed)
  - Investigates/requests corrective action plan
- At convened IRB meeting, members:
  - Deliberate
  - Vote on UPs
  - Request corrective action plan
  - Report onward (if UP)
    - ❖ To institutional official; regulatory agencies and sponsors, as required



PD is  
notified of  
IRB  
decisions

# Reported UPs

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



- ❖ Are promptly reported to the IRB
  - ✘ within 5 days of the PD discovery if death/life-threatening situation occurs
  - ✘ within 10 days for all other UPs
- ❖ Initially determined to be UPs by monitoring entity, sponsor or PD
- ❖ IRB makes the final UP determination
- ❖ SAE/AEs
  - ✘ summarized at Continuing Review by the PD
  - ✘ should follow the approved monitoring plan
    - E.g., if DSMB was formed, report(s) must be attached to protocol
  - ✘ can be determined by IRB to be a UP