Adverse Events Part 1
Definitions

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Outline

- Define adverse event (AE)
- Define serious adverse event (SAE)
- Define life-threatening event
- Define unexpected adverse event
- Define suspected adverse reaction (SAR)
- Define unexpected adverse device effect (UADE)

Summary Definition

Any unwanted sign, symptom, or disease that was not seen before individual's research participation, or worsening of baseline symptom, **REGARDLESS OF EXPECTEDNESS OR RELATIONSHIP TO RESEARCH.**

Alias Clinical Terms

- Toxicity
- Side effect
- Acute or late effect
- Complication
- Adverse drug reaction
- Adverse drug event

Purposes of AE Monitoring

- Identify events that may have immediate effect on the safety of the participant
- Inform regulators, investigators, and others of new and important information about events
- Provide a summary of adverse experiences in order to develop the drug or regimen toxicity profile

AE Definition: OHRP

- "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."

Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, 2007

AE Definition: FDA

- “Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.”

21 CFR 312.32 (a), June 2023

AE Definition: ICH GCP

- "Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product."
  - ICH GCP Guidelines E6 (R2), November 2016
- "Any unfavourable medical occurrence in a trial participant. The adverse event does not necessarily have a causal relationship with the treatment."
  - ICH GCP **DRAFT** Guidelines E6 (R3), May 2023

Additional Definitions

- Serious
- Life-threatening
- Unexpected
- Suspected Adverse Reaction (SAR)
- Unanticipated Adverse Device Effect (UADE)

Serious Adverse Event (SAE) ….

21 CFR 312.32, ICH GCP, OHRP Guidance

Any AE occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions*
- Congenital anomaly/birth defect

OR….

...Serious Adverse Event (SAE)

21 CFR 312.32, ICH GCP, OHRP Guidance

- Important medical events (IME) that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Life-Threatening

21 CFR 312.32, ICH GCP

- "An adverse event or suspected adverse reaction is considered 'life-threatening' if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death."

Unexpected Definition: FDA

21 CFR 312.32 (a)

- Not listed in the investigator brochure (IB)
- Not listed at the specificity or severity that has been observed
- If no IB, not consistent with the risk information described in the general investigational plan or elsewhere in the current IND application
- If mentioned in the IB as occurring with the drug class or anticipated based on the pharmacological properties of the drug, but are not specifically mentioned in the IB

Unexpected Definition: OHRP & ICH GCP

OHRP Guidance:

Adverse event that is not described in terms of nature, severity, or frequency given:

- the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and
- the characteristics of the subject population being studied

ICH GCP:

Adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Suspected Adverse Reaction (SAR)

- Any AE for which there is a reasonable possibility that the drug caused the AE
- Reasonable possibility means there is **evidence** to suggest a causal relationship between the drug and AE

21 CFR 312.32 (a), June 2023

Unanticipated Adverse Device Effect (UADE)

- "Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."

21 CFR 812.3(s), June 2023

Summary

- Adverse event surveillance ensures the safety of research participants
- It's critical to understand the definition of adverse event and associated terms:
  - Serious
  - Life-threatening
  - Unexpected
  - Suspected Adverse Reaction
  - Unanticipated Adverse Device Effect

Test Your Knowledge

What is the definition of an Adverse Event?

A. A known toxicity of the study agent
B. Any untoward sign or symptom that occurs during the course of a clinical trial
C. Any event which the PI decides to report during the course of a clinical trial
D. A side effect caused by the study agent

Test Your Knowledge

What type of adverse event is the following scenario?

A research participant slips on an icy sidewalk and suffers a leg fracture requiring inpatient surgery. The investigator says this is not related to the investigational product.

A. It's not an adverse event at all
B. Adverse Event only
C. Adverse Reaction
D. Serious Adverse Event