Adverse Events Part 3: IND and IDE Reporting

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Outline

- Expedited AE reporting
- Investigator's reporting responsibilities
- Sponsor's reporting responsibilities

Expedited Reporting Requirements

- Events to be reported in an expedited manner to various regulatory groups
  - Should be defined in the protocol
  - Include timeline for reporting
  - Use appropriate form or database

Applicable Regulations

- 21 CFR Part 312.32
- 21 CFR Part 312.64
- 21 CFR Part 812.150

Applicable Guidance

- *Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs — Improving Human Subject Protection (2009)*

Investigator Reporting to IND Sponsor

- Any Serious Adverse Event (SAE)
  - Refer to protocol for exceptions
- Timeframe:
  - Immediately
  - Most sponsors allow for 24 hours
- Submission format:
  - Sponsor-specific
  - FDA Mandatory MedWatch Form 3500a

21 CFR 312.64 (b), June 2023

Adverse Events of Special Interest (AESI)

- Adverse event that is of scientific and medical concern specific to the sponsor's investigational product for which ongoing monitoring and more rapid communication about the AE to the sponsor is merited
- May be serious or non-serious
- Usually, will follow the SAE report requirements

Council for International Organizations of Medical Sciences (CIOMS), 2021; ICH E2F

Key Information in an SAE Report

- Reporter information
- Participant demographics
- Study agent information
- Event description
- Attribution
- Narrative summary

The Narrative Summary

Description of the event:

- Information that helps to describe the event(s)
- Information that puts the event in perspective (Relevant subject history)
  - Underlying medical conditions
  - Prior surgeries or procedures
  - Family history
  - Recent events that may be a contributing factor
  - Concomitant medications – sponsor specific e.g., subject medical history, other medical conditions etc.

Supporting Documentation

- Related source documentation may accompany the report
  - When needed to explain the experience
  - When needed to support the differential diagnosis
  - Sponsor specific – not always necessary

What To Do When Limited Information Is Available

- Contact primary physician/institution
  - Document all conversations in medical record
- Submit what you have:
  - Most recent clinical evaluation, baseline history and physical
  - Provide plan for obtaining information
  - Provide a summary of the event and treatment to date
- When additional information becomes available – amend the report

Follow-up Reporting

- Change in the severity, attribution, or actual event (i.e., AE term)
- When new information on a death becomes available
- Requested by the regulatory/oversight group

IND Sponsor Reporting to FDA

- IND Safety report for 15-day reports
- 7-day IND safety report
- Follow-up IND safety report

15-day IND Safety Report

- Sponsor notifies FDA as soon as possible, but no later than **15 calendar** days for:
  - All serious and unexpected suspected adverse reaction (SUSAR)
  - Findings from other studies
  - Findings from animal or in vitro testing
  - Increased rate of occurrence of serous suspected adverse reactions

21 CFR 312.32 (c)(1), June 2023

Serious and Unexpected SAR

- Report only if there is evidence to suggest a causal relationship between the drug and the AE, such as:
  - Single occurrence
  - One or more occurrences of an event
  - Aggregate analysis of specific events
- FDA considers these as *unanticipated problems* and reportable by the Investigator to the IRB

21 CFR 312.32 (c)(1)(i), June 2023

Findings From Other Studies

- Findings from clinical, epidemiological, or pooled analysis of multiple studies
- Reports are required for studies from any source, regardless of whether they are conducted under the IND or by the sponsor

21 CFR 312.32 (c)(1)(ii), June 2023

Findings From Animal or In Vitro Testing

- Findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug
  - Mutagenicity
  - Teratogenicity
  - Carcinogenicity
  - Significant organ toxicity at or near the expected human exposure

21 CFR 312.32 (c)(1)(iii), June 2023

Increased Occurrence of Serious SARs

- Any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure

21 CFR 312.32 (c)(1)(iv), June 2023

7-day IND Safety Report

- Sponsor must notify FDA of any unexpected fatal or life-threatening SAR as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information

21 CFR 312.32 (c)(2), June 2023

IND Follow-up Safety Reporting

- Any relevant additional information obtained by the sponsor that pertains to a previously submitted IND safety report
- Submitted no later than 15 calendar days

21 CFR 312.32 (d), June 2023

Safety Reporting Formats

- Mandatory MedWatch - FDA Form 3500a
- Narrative
- Council for International Organizations of Medical Sciences (CIOMS) I Form
- Report content to include:
  - All prior ISRs about similar adverse reaction
  - Analysis of the significance of the adverse reaction given previous similar report and any other relevant information.

21 CFR 312.32 (c)(1)(v), June 2023

Research Team Handling of a Safety Report

PI reviews report and assess need to amend protocol and consent and amends if applicable

PI sends to research team and discusses if an amendment/modification is needed

Report to IRB policy

Inform participants and DOCUMENT conversation and their willingness to continue and/or reconsent

Reminders…

- Expedited events are a subset of adverse events
- All information captured on an expedited event form MUST be present in the source documents & be found on the adverse event CRF
- The protocol trumps all other reporting requirements.

…Reminders

- All expedited report forms and any response information is to be placed in the regulatory binder.
- Investigator-Sponsored studies **MUST** follow **BOTH** the Investigator and the Sponsor reporting requirements

Investigator Reporting to IDE Sponsor & IRB

- Any unanticipated adverse device effect (UADE)
- Timeframe: no later than 10 working days
- Submission format:
  - Sponsor specific
  - IRB specific

21 CFR 812.150 (a1), June 2023

IDE Sponsor Reporting to FDA & IRB

- Any unanticipated adverse device effect (UADE) no later than 10 working days
- Also report to IRB and Participating Investigators
- Submission format:
  - Cover letter
  - FDA Mandatory MedWatch Form 3500a

21 CFR 812.46 (b), June 2023

Summary

- Routine and expedited AE reporting
- Responsibilities of the investigator and sponsor
- Know your sponsor's expedited AE reporting requirements, including timeliness.
- The narrative summary is extremely important for the individual revieing the expedited AE report

Test Your Knowledge

Per FDA regulations, an Investigator is to report an SAE to the sponsor _____?

A. Immediately
B. 24 hours
C. 7 days
D. at the next monitoring visit