Adverse Event Module
Part 3:
IND and IDE Reporting

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Agenda

• AE reporting type
  • Routine
  • Expedited
• Investigator’s reporting responsibilities:
  • Drugs, biologics, device: Sponsor
• Sponsor’s reporting responsibilities:
  • FDA
  • IRB (for IDE only)

Applicable Regulations

• 21 CFR Part 312.32
• 21 CFR Part 312.64
• 21 CFR Part 812.50

Applicable Guidance

• Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs — Improving Human Subject Protection (2009)
Routine AE Reporting:

**Investigator**

- To Sponsor;
  - Report all non-SAEs via case report forms
  - Timing is sponsor-dependent
  - Protocol needs to specify how to record and report non-SAEs

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Routine AE Reporting:

**Sponsor**

- Narrative or tabular summary:
  - Most frequent and most serious adverse experiences by body system
  - A summary of all safety reports submitted during the past year
  - Part of the IND or IDE annual progress report
  - No reporting responsibilities to the IRB

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**Expedited Reporting Requirements**

- Events to be reported in an expedited manner to various regulatory groups
  - Must be defined in the protocol
  - Include timeline for reporting
  - Use appropriate form
Investigator Expedited Reporting to Sponsor

- IND:
  - Any Serious Adverse Event (SAE)
  - Any study endpoint that is a suspected SAE
  - Usually within 24-48 hours
- IDE:
  - Any unanticipated adverse device effect (UADE) no later than 10 working days
- Submission format:
  - Sponsor-specific
  - FDA Mandatory MedWatch Form 3500a

Sponsor Expedited Reporting: IND

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

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
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

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

Increased Occurrence of Serious SARs
• Sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure
Unexpected Fatal or Life-Threatening SAR Reports

- 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.

Sponsor Expedited Reporting: IDE

- Any unanticipated adverse device effect (UADE) no later than 10 working days.
- Also report to IRB and Participating Investigators.
- UADE that presents an unreasonable risk.
  - Sponsor to terminate all investigations or parts of investigations presenting that risk as soon as possible.
  - Termination occurs no later than 5 working days of decision to terminate AND no later than 15 working days after the sponsor first received notice.

Research Team Handling of an ISR or UADE

1. PI reviews report and assess need to amend protocol and consent.
2. PI sends report to research team.
3. Report submitted to IRB per policy.
4. Inform participants immediately and DOCUMENT conversation and their willingness to continue.
5. Re-consent as per IRB or sponsor.
6. All reports placed in regulatory file.
7. PI amends protocol or consent.
8. All reports placed in regulatory file.
**Formats of Submission: ISR**

- 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.

**Human Gene Transfer AE Reporting**

- Institutional Biosafety committee (IBC)
- Office of Biotechnology Activities (OBA)
- Routine Content similar to FDA
  - Narrative or tabular summary
  - Due date is the same as the IND annual report
- Expedited
  - Submission format:
    - NIH OBA form
    - FDA Mandatory MedWatch Form 3500a
    - Genetic Modification Clinical Research Information System (GeMCRIS)
Key Information

- Reporter information
- Subject demographics
- Study agent (date(s) given, dose, route of administration)
- 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 If Only 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

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

**Summary**

- Routine and expedited AE reporting
- Responsibilities of the investigator and sponsor
- INDs including human gene transfer (HGT) products and IDEs