ACADEMY FOR RESEARCH PROFESSIONALS
2019 WINTER WORKSHOP

SAFETY of the SUBJECT
Safety of the Subject

- Key definitions
- Identifying, documenting and reporting
- Investigator reporting responsibilities
- How are research participants protected?
  - Safety related roles in clinical research
Safety of the Subject

BACKGROUND

45 CFR 46 & ICH E6 GCP Provides Guidance and Standards

- Rights, safety, and well-being of subjects
- Roles and Responsibilities of Investigators and Research Staff
- Study conduct and protocol management
- Safety reporting
- Documentation and Record Keeping
Safety Reporting
Regulatory Guidelines

➢ Adverse Events (AEs) monitoring is critical to the patient’s safety (i.e. human subjects protection) and data integrity

➢ Enhance patient safety in clinical trials by improving the quality of safety reports submitted to the FDA under the DHHS

➢ Final Rule lays of clear definitions/standards critical safety information will:
  • Accurately reported to the agency
  • Minimize uninformative reports
  • Enhance reporting – meaningful, interpretable information on humans
Safety Reporting

Adverse Events (AEs)

Multiple clinical terms used for AEs:

- Toxicity
- Side effect
- Acute or late effect
- Complication

All directed to a change *possibly* caused by a treatment /or intervention

*All terms above imply that an intervention caused the event which is NOT the definition of an AE*
Safety Reporting

Universe of Adverse Events

Relationship between:

- Adverse Events (AEs)
- Suspected Adverse Reactions (SARs)
- Adverse Reactions
Safety Reporting

Definitions

1. Adverse Event (AE)
2. Suspected Adverse Reaction (SAR)
3. Adverse Reaction (AR)
4. Adverse Event of Special Interest (AESI)
5. Unexpected
6. Serious
7. Life-Threatening
1. **Adverse Event (AE) means:**

   “any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related” (FDA 21 CFR 312.32(a))

**Adverse Experience is an Adverse Event**

- any unfavorable and unintended sign in a human subject (e.g. an abnormal laboratory finding), symptoms, or disease temporally associated with the use of the drug or with a subject’s participation in the research and
- Does not imply any judgment about causality.
- Can arise with any use of a drug (e.g. off-label use, use in combination with another approved drug), with any route of administration, formulation, or dose, including an overdose.
Safety Reporting

Definitions

FDA 21 CFR 312.32 and 312.64(b)

2. Suspected Adverse Event (SAR) means:
   “any adverse event for which there is a *reasonable possibility* that the drug caused the event” (FDA 21 CFR 312.32(a))

Suspected Adverse Reaction

- Implies a lesser degree of certainty about Causality than Adverse Reaction
- Adverse Event caused by a drug
- Subset of Adverse Events where is a *reasonable possibility that the drug caused the event*
- Requirement to Report a SAR: sponsor needs to evaluate the available evidence and make the judgement about the likelihood that the drug actually caused the adverse event

**NOTE:** The FDA ‘*reasonable possibility*’ causality standard is consistent with (ICH) E2A guidance with respect to who is responsible for making the judgment.

- ICH E2A guidance recommends judgment is based on either the investigator’s or the sponsor’s opinion.
3. Adverse Event of Special Interest (AESI) means:

“serious or non-serious adverse that is one of scientific and medical concern specific to the sponsor’s product for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate.”

**Adverse Event of Special Interest is an Adverse Event**

- Events or symptoms thought to [potentially] be associated with the investigational compound or disease under study
- Does not imply any judgment about Causality.
- Can arise with any use of a drug (e.g. off-label use, use in combination with another approved drug), with any route of administration, formulation, or dose, including an overdose.
4. **Adverse Reaction (AR) means:**

   “any adverse event caused by a drug” (FDA 21 CFR 312.32(a))

**Adverse Reactions**

- Subset of all adverse events
- There is a reason to conclude that the **drug caused the event**
5. **Unexpected means:**

“adverse event (AE) or suspected adverse reaction (SAR)

is considered

UNEXPECTED”

**Examples:**

- Not listed in the Investigator Brochure (IB)
- Not listed at the Specificity or Severity previously seen
- If an IB is not required or available
- Is *not consistent* with the Risk Information described in the general investigational plan, protocol or elsewhere in the current application
6. **Serious** means:

“any adverse event (AE) or suspected adverse reaction (SAR) is ‘**Serious**’ if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death, or
- A life-threatening adverse event, or
- Inpatient hospitalization or prolongation of existing hospitalization, or
- Substantial disruption of the ability to conduct normal life functions, or
- Persistent or significant incapacity, or
- Congenital anomaly or birth defect

Important medical events 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 subjects and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

(FDA 21 CFR 312.32(a))
Safety Reporting

Definitions

7. Life-Threatening means:

“any adverse event (AE) or suspected adverse reaction (SAR) is ‘Life-Threatening’ if, in the view of either the investigator or sponsor, its occurrence places the patient or subjects at immediate risk of death.”

It does NOT include adverse events or suspected adverse event reaction that has occurred in more severe form, might have caused death” (FDA 21 CFR 312.32(a)

As with the definition of Serious, the determination of whether an Adverse Event is Life-Threatening can be based on the opinion of either the investigator or sponsor. Thus if either believes that it meets the definition of Life-Threatening, for reporting purposes, it is considered Life-Threatening.
Safety Reporting

Protocol Adherence

- Document investigators’ agreement to follow the protocol
- Adhere to the IRB-approved protocol/protocol amendments
- Only deviate from the protocol to avoid immediate hazards to subjects
- Document and report all protocol deviations to the IRB

Review ALL study documents to understand the project’s definitions for Adverse Event reporting, time to report to agencies
- Manual of Procedures (MOP)
- Standard Operating Procedures (SOP)
- Protocol
- Investigator Brochure (IB)
- IRB, sponsor, and FDA
Adverse Events Assessment

- **Identify** the *Adverse Event*
- **Report** to the Principal Investigator (PI) following protocol adherence

- **Assessment** is done by the PI or designated research team member
to determine:
  - *Severity* of event
  - *Attribution* or *Cause* of the event

- The **Assessment + Expectedness** of the event helps determine the timeliness for reporting to the IRB, sponsor or other regulatory oversight groups.
Adverse Events Assessment

Severity Assessment Tools

Tools are intended to be an agreed-upon terminology for designation, reporting, and grading of AEs that occur.

**Examples:**

- **Common Terminology Criteria for Adverse Events (CTCAE) v5.0** is used by oncology groups to determine severity of an AE.
  
  **Grading system with MedDRA codes, grade definition, symptom term**

  - Hemoglobin (Hgb) <10.0 g/dL; <10.0 g/L; 6.2 mmol/L; <
  
  - Hgb <10.0 – 8.0 g/dL; <8.0 g/L; 6.2 – 4.3 mmol/L; <
  
  - Hgb <8.0 g/dL; <4.3 mmol/L; <<80 g/L; transfusion indicates

  - Life-threatening consequences; urgent intervention indicated

  - Death


- **Cancer Therapy Evaluation Program (CTEP)** of NCI developed the original Common Toxicity Criteria (CTC) in 1980’s aiding in recognition and severity grading.

- **Medical Dictionary for Regulatory Activities (MedDRA)**

- **System Organ Class (SOC)** is a table format listing SOCs alphabetically.
Adverse Events Assessment
Assess Attribution or Relatedness

Step 1: Establish the **Severity** of the event
Step 2: Find the **CAUSE** or **ATTRIBUTION** of the event

*Is the event related to the study drugs, devices, disease or an underlying preexisting condition?*

- It is important to identify what the AE is **related to** - not merely what it is **not related** to.
- Information assists regulatory oversight groups to assess safety and protect human subjects.
Adverse Events Assessment

Questions to Determine Cause or Attribution

The Investigator determines the **Cause/Attribution** with the input from the research team & using the following questions:

- What do we know about the drug/therapy/device or classification?
- What is the temporal relationship of the AE to the study therapy?
- Does the AE improve or disappear when drug/therapy is stopped?
- If the drug/therapy is restarted, does the AE reappear? At the same severity? At the same time point?
- Is the AE a result of an existing disease signs and symptoms?
- Is the AE a worsening of baseline symptoms?
- Is the AE a result of an underlying concurrent medical condition(s) or concurrent medication(s)?
Adverse Events Assessment

Approaches to Determining Attribution (Cause)

Cause: Approach #1

Two Options:
- **Related**: Reasonable Causal relationship between the AE and ______________
- **Not Related**: No Reasonable Casual relationship between the AE and ______________

Cause: Approach #2

Five Options:
- **Definite**: clearly related to __________
- **Probable**: likely related to __________
- **Possible**: may be related to _________
- **Unlikely**: doubtfully related to ______
- **Unrelated**: clearly not related to ____
Adverse Events Documentation

- Know your protocol for **Adverse Event Reporting** requirements

- Collect information before begin study drug/or procedures
  1. Collect at start of baseline, screen or lead-in period
  2. Establish a baseline status
  3. Good record of medical history, concomitant meds, allergies
  4. Evaluate all Inclusion/Exclusion Criteria

- Follow Up **AE** to resolution or stabilization
  1. Follow Up is required for **AE**’s that cause:
     - Interruption or discontinuation of study drug or
     - Those that are present at the End of Study Treatment
Adverse Events Documentation

- Notify subjects of follow up needed per protocol Early Termination Visit
- Request subjects sign a **Release of Information (ROI)** to provide referral and event documentation from outside hospitals/or clinics
- Pursue medical records for ongoing AEs
- Actively monitor, ensure care for, and document AEs
- Report AEs to the IRB/Safety Committee and comply with any specific guidance
- Always follow to resolution or stabilization
Adverse Events Documentation

**Progress Note**

1. All AEs should be documented in the patients’ medical record (EMR) including any workup or necessary treatment

2. A good Progress Note documenting the AE will contain both good clinical practice (GCP) and good clinical research practice documentation
   - Date the AE began
     - *Note:* Important to note time (especially with infusions or drug administration reactions)
   - Treatment for AE
     - *Note:* Example - no treatment needed; further testing to diagnose event; hospitalization; dose reduction; holding of study intervention
   - Event description in enough detail that a CTCAE term or MedDRA grade can be assigned as part of data management activities
   - Attribution of the AE
     - *Note:* Sort out if there is more than one therapy or drug given
Adverse Events Documentation

Progress Note

3. Before documenting AEs, understand how AEs should be collected

4. Prevent bias collection. *Patients should not be questioned regarding specific events that might be anticipated while on the study.*

5. AEs should be spontaneously reported from a patient with ‘*open ended questions*’ during the examination and evaluation

6. Date AE resolved

7. If ongoing AE worsens or improves in its severity or its relationship to the study drug changes, documentation should continuously be collected
Regulatory Reporting

Reports to Regulatory Oversight Groups

IRB

1. Routine

- Report to IRB at time of Annual Continuing Review
- Minimum brief statement that
  - There has been no unanticipated problems (UPs).
  - Report if AE occurred at expected frequency and level of severity, as documented in the research Protocol, the Informed Consent and Investigator’s Brochure (IB)
  - IRBs may require a summary of all AEs report that occurred on the protocol since the past annual review or since start of study
- May report in table form
- IRBs may require a summary of all AEs report that occurred on the protocol since the past annual review or since start of study

2. Expedited – Necessary for Serious AEs
Regulatory Reporting

Safety Reports to Regulatory Oversight Groups

FDA

- The Sponsor will report to the FDA in a summary fashion of all AEs in the annual report required by all IND
- Exception: if investigator-initiated IND, then investigator responsibility to report to the FDA
- Local IRB will ask if you had any regulatory agency communication. If ‘Yes’ then a copy of the report will be requested by your IRB.

Institutional Biosafety Committee (IBC) and Office of Biotechnology Activities (OBA)

- Protocols using recombinant DNA will require annual reports to IBC/OBA
- OBA will be informed in the annual report required for all recombinant DNA studies.
Regulatory Reporting

Safety Reports to Regulatory Oversight Groups

Sponsor

- Completion of the AE CRF – if electronic – will inform of a routine AE

Investigator

- Completion of the AE CRF – if electronic – will inform Sponsor of a routine AE
- Per FDA regulations and according to the protocol reporting timetable, the investigator must
  - Record any non-serious events (enter onto the CRF)
  - Report to the Sponsor
- Contact the Sponsor when knowledgeable of AE and submission is coming
- Contact the Medical Director for resources and queries
Regulatory Reporting

Expedited Adverse Events Report Forms

**Expedited Adverse Events**
- Subset of AEs required expedited reporting to regulatory agencies

- Alias Terms:
  - Serious Adverse Events
  - Serious Adverse Experience
  - Expedited Adverse Events
  - Adverse Drug Reaction
Regulatory Reporting

Expedited Adverse Events Report Forms

“Key Information”

- Reporter information
- Subject demographics
- Study agent - *date(s)/time given, dose, administration route*
- Event
- Attribution (Cause)
- Narrative Summary
- Investigator signature
- Life-threatening
- Or require hospitalization
Regulatory Reporting

Expedited Adverse Events Report Forms

“The Narrative Summary”

**Most important section of AE summary form**

- Describe the event as if the reader (recipient) of the form does not know anything about the subject or their history
- Provide background information necessary to assess the event and support the Investigator’s attribution (Cause)

Description of the Event: “Tell a Story”

- Information that describes the event(s)
- Information that puts the events in perspective - Relevant Subject History
  - Underlying medical conditions; prior surgeries/procedures; family history; recent events that may be a contributing factor
  - Concomitant Medications – sponsor specific e.g., subject medical history, other medical conditions
Regulatory Reporting

Expedited Adverse Events Report Forms

“The Narrative Summary”

Supporting Documentation:

- Related source documentation should accompany the report
- Remove ALL patient identifiers on documents
  - When needed to explain the experience
  - Necessary to support the differential diagnoses
  - Sponsor specific – not always necessary
Expedited Adverse Events Report Forms

“What To Do If Only Limited Information Available”

- Contact treating physician/institution
- Document all conversation in medical record
- Submit what you have:
  - Most recent clinical evaluation, baseline history & physical
  - Provide plan for obtaining information
  - Provide a summary of the event and treatment date
- When additional information becomes available – amend the report. Provide dated sequelae follow up information
- Discuss with protocol medical monitor
- Always have principal investigator sign and date each version.
- Use only the original version.
Regulatory Reporting

Expedited Adverse Events Report Forms

“Follow Up Reporting”

Follow-up is required when:

- There’s a change in the cause/or relatedness of the event
- New information on a death becomes available
- Requested by the regulatory /or oversight group

Follow-up report is NOT required when:

- AE resolves
- Resolved date will be noted on the Adverse Event case report form
Regulatory Reporting

Expedited AE Reporting REMINDERS

Expedited Events are a subset of Adverse Events

- All information captured on an Expedited Event form MUST be:
  - Presented in the source documents AND
  - Found on the Adverse Event case report form (CRF)

- Some events that initially appear to meet Expedited Reporting requirements may be exclude from the Expedited Reporting as per the protocol

***The protocol trumps all other reporting requirements.***

- All expedited report forms and any response information from the regulatory/oversight group is to be placed in the Regulatory Binder.
Regulatory Reporting

Unanticipated Problem (UP) **Definition**

An incident, experience, or outcome that meets all of the following criteria:

- Nature, severity, or frequency is *unexpected* for the **subject population** or **research activities** – as described in the:
  - IRB approved protocol,
  - Supporting documents, and
  - Informed Consent Document (ICD)

- Related or possibly related to participation in the research

- Suggests the research may place the **subject or others** at a *greater risk of harm* than previously recognized
  - Physical, psychological, economic, or social harm

- Protocol deviations/violations are UPs need to be reported to IRB

**Examples:**

- Malfunctioning infusion pump results in drug being given over 15 minutes vs 1 hour – even f subject doesn’t have AEs
- Ineligible subject who receives protocol intervention without any Aes subject received more drug (10-times) than per protocol
Regulatory Reporting

Unanticipated Problems (UP)

OHRP and FDA require that ‘Unanticipated Problems’ be reported to the IRB

➢ OHRP:
  • Written procedures for ensuring prompt reporting to IRB, appropriate institutional officials of any Unanticipated Problems involving risks to subjects or others - 45 CFR 46.103(b)(5)

➢ FDA:
  • Follow written procedures for ensuring prompt reporting to IRB, appropriate institution officials, and FDA of any Unanticipated Problems involving risks to human subjects or others - 21 CFR 56.108(b)
  • The Investigator shall also assure that he/she will promptly report to the IRB all unanticipated problems involving risks to human subjects or others - 21 CFR 312.66
Regulatory Reporting

*FDA Adverse Events that are Unanticipated Problems (UP)*

- **FDA Report** (7-days)
  - Unexpected Fatal OR Life-Threatening (SARs)

- **Change Protocol & ICD**
  - Unanticipated Problems (UPs)

- **IND Safety Report** (15-days)
  - Serious and Unexpected Suspected Adverse Reaction Findings from another study/animal/vitro testing
  - Increased rate SARs
Regulatory Reporting

Correction Action Plan for Unanticipated Problems

- Revised protocol:
  • Modify Inclusion/Exclusion Criteria to mitigate the newly identified risks
  • Implement additional procedures for monitoring subjects
- Suspend enrollment of new subjects
- Terminate the research
- Informed Consent:
  • Revise the IC document
  • Provide additional information about newly recognized risks to previously enrolled subjects >> Re-consent subjects
  • Inform enrolled subjects
- Increase monitoring activities
- Encrypt laptop computers, no identifiable information on laptops
- Provide training and/or re-training
- Submit OHPRS and work with appropriate institutional officials
Regulatory Reporting

**FDA/OBA** are looking for an Attribution (Cause) as it relates to an investigational drug/product.

**IRB** is looking for Attribution (Cause) as it relates to the research.

**Sponsors** may use either one or a combination.

**This means that an Event that is to be reported to a Sponsor may not necessarily be reported to the IRB or FDA.**
QUESTIONS?