The Fundamentals of International Clinical Research Workshop

Understanding Adverse Events

Deborah Hilgenberg
Family Health International
Goals of the Presentation

UNDERSTANDING:

- Definition of Adverse Event (AE)
- Definitions of pre-existing conditions
- Intensity of Adverse Events
- Definition of **SERIOUS** Adverse Events
- Severity vs. Seriousness of Adverse Events
- Assessment of Relatedness to Study Product
- Reporting of Adverse Events
What is an Adverse Event (AE)?

Any untoward medical occurrence in a study participant who has received study product / intervention that may or may not have a causal relationship with this treatment / intervention.

(ICH-E2A)
What is an Adverse Event (AE)?

An AE can therefore be

Any **unfavorable and unintended** sign
(including an abnormal lab finding),
symptom or disease, temporally
associated with use of a medicinal
(investigational) product / intervention,
whether or not related to the medicinal
(investigational) product / intervention

(ICH-E2A)
Definition of intervention

Excerpt from 45CFR46.102

“Intervention includes physical procedures by which data are gathered (for example, venipuncture) and manipulation of the participant or the participant’s environment that are performed for research purposes.”
What is an Adverse Event (AE)?

Not limited to DRUG Side effects. Unfavorable deviation from BASELINE health, which includes:

- Worsening of conditions present at onset of the study
- Patient deterioration due to primary disease
- Intercurrent illness or event, i.e., flu, accident
- Events related or possibly related to concomitant medications
What is an Adverse Event (AE)?

Unwanted Effects

- Symptoms (headache, nausea)
- Syndromes of disease
- Physical findings (elevated BP, lump)
- Abnormal lab values
- Overdoses
- Toxicities
What is Baseline?

Protocol designated time point from which changes in status are measured.

Depends on the study design, but should be the same for all participants in the study.

Be sure to clearly indicate in protocol.
Pre-existing Conditions

- Any chronic, recurring condition identified prior to enrollment, whether present at enrollment or not.

- Example: diabetes, herpes, hypertension

- Do thorough screening to assess and document pre-existing conditions

- Document any concomitant meds at baseline
Pre-existing Conditions

- Pre-existing condition is not an AE EXCEPT when it increases in severity or frequency

Example: A patient at baseline with mild asthma, continues to have mild asthma throughout study period: **not** an AE.

Example: Same patient is hospitalized with severe asthma: **is** a serious adverse event
How Would You Describe an AE?

- Wherever possible, adverse events should be described in terms of a change in the status or diagnosis NOT the action taken or outcome.

- Example: “decrease in Hb from 10.1 to 7.3”

- Example: “influenza” rather than stomach cramps, fever, chills.
Expected vs Unexpected AE

An *expected* AE is any adverse reaction whose nature and intensity are consistent with that documented in the Investigators Brochure or the general investigational plan.
An *unexpected* AE, the specificity and intensity of which is not consistent with the current IB or other risk observation: whether or not it has been anticipated because of the pharmacologic properties of the study agent.
Intensity of the Adverse Event

All adverse events will be assessed by the investigator using the protocol defined grading system.

If the protocol has no defined grading system, then guidelines such as the following will be used to assess intensity:
Intensity of the Adverse Event

- **Mild**: Transient or mild discomfort (<48 hours); no medical intervention/therapy required and do not interfere with the patient’s daily activities

- **Moderate**: Some limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
Severity of the Adverse Event

- **Severe**: Marked limitation in activity, interrupts participant’s usual daily activity and may require medical intervention/therapy, hospitalization possible

- **Life threatening**: Extreme limitation in activity; significant assistance required; significant medical intervention/therapy required; hospitalization or hospice care probable
What Is a Serious Adverse Event?

SERIOUS Adverse Events (SAEs) are defined as follows:

- **Death** during the period of protocol defined surveillance
- **Life threatening** (defined as a subject at immediate risk of death at the time of the event)
What is a **Serious** Adverse Event?

- **Requires inpatient hospitalization** or prolongation of existing hospitalization during the period of protocol defined surveillance
- Any event that results in **congenital anomaly or birth defect**
- Any event that results in a **persistent or significant disability/incapacity**
What is a **Serious** Adverse Event?

– Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.
Serious vs Severe

- **Serious**: “Serious AE” is a regulatory definition (21 CFR 312.32)

- **Severe**: Severe is defined as an intensity classification (mild, moderate, severe)

Severe AE ≠ Serious AE
Assessment of Relatedness

In a clinical trial the study product/intervention must always be suspect.

All SAEs must have their possible association/relationship to study product assessed by a binary system by using the following question:

- Is there a reasonable possibility that the AE may have been caused by the investigational product/intervention?

NO- not associated
YES- associated
Assessment of Relatedness

- **Associated**: The event is **temporally related** to the administration of the study product/intervention and no other etiology explains the event.

- **Not Associated**: The event is **temporally independent** of study product/intervention and/or the event appears to be explained by another etiology.

- **Related**: timing, product info, clinical judgment
Assessment of Relatedness

- Investigator’s assessment – part of documentation but not a factor in determination of what is reported in the study

- Other Contributing factors:
  - Medical history
  - Other Medication
  - Lack of Efficacy
Documentation of SAE

- SAE form
- Adverse Event Case Report Form
- Source documents
- ALL must match and be complete
- Principal Investigator (or other designated investigator) must sign SAE report.
Reporting SAEs to the Sponsor

Reporting timeframes:

- Deaths and Life-threatening events that are Associated – within 24 hours of site awareness

- Other SAEs that are both Unexpected and Associated – within 72 hours of site awareness
Where to send SAE Reports

All SAEs are reported to DMID through the pharmacovigilance contractor PPD
Reporting SAE to the Sponsor

3 ways to submit reports:

– FAX to 1-888.488.9697
– Phone 1.800.201.8725 “SAE Hotline”
– Email dmidpvg@wilm.ppdi.com
SAE FAX TRANSMITTAL
DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID)

TO: MA/PVG Department

FAX #: 1-888-468-9697

DATE: ___/___/____

(TODAY'S DATE)

FROM: ____________________________

PROTOCOL #: ______________________

INVESTIGATOR NAME: ____________________________

SAE Phone #: 1-800-201-8725

TOTAL PAGES: ______

(INCLUDING COVER PAGE)

PHONE#: ____________________________

SUBJECT #: ____________________________

(INVESTIGATOR #: ____________________________

(IF APPLICABLE)

☐ INITIAL SAE REPORT SUBMISSION ☐ FOLLOW-UP SAE REPORT SUBMISSION

Check all documents included with this Fax:

☐ SAE Report Form

☐ Discharge Summary (when the SAE involves hospitalization)

☐ Other relevant information (medical record progress notes, lab/diagnostic test results, Autopsy etc.)

Comments:

____________________________________________________________________________________

____________________________________________________________________________________

____________________________________________________________________________________

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Division of Microbiology and Infectious Diseases

SERIOUS ADVERSE EVENT REPORT FOR SINGLE STUDY PRODUCT

PPD SAE HOTLINE 1-800-201-8725  PPD SAE FAX LINE 1-888-488-9697

<table>
<thead>
<tr>
<th>Site Name/Number</th>
<th>Center Number</th>
<th>Subject Number</th>
</tr>
</thead>
</table>

Date site aware of event | Initial Report Date | Follow-up # _ Date |
Follow-up # _ Date | Follow-up # _ Date | Follow-up # _ Date |

1. Age at onset of SAE | Gender: | Male | Female | Weight: | lbs/ | kgs/ | gms/ |

2. Please indicate SAE category from the following choices (all that apply):
   - Death
   - Immediatly Life-threatening
   - Persistant/Significant Disability/Incapacity
   - Other, specify: ________________
   - Result in Congenital Anomaly
   - Serious as assessed by the Investigator
   - Hospitalization/Prolonged Hospitalization

3. Study Product Name
   Note: If blinded, indicate as such

4. Dose, Route, Schedule of Study Product(s) at SAE Onset

5. Date Study Product First Started (DD/MM/YYYY)

6. Date Study Product Last Taken prior to onset date of this event (DD/MM/YYYY)

7. Event (Keyword or Cause of Death)

8. Onset Date (DD/MM/YYYY)

9. Severity
   - Mild
   - Moderate
   - Severe
   - Life-Threatening
   - Death

10. Relationship to Study Product
   - Not associated
   - Associated

11. If Not Associated
   - complete below
   - Is event related to:
     - study procedure? specify ________________
     - other condition? specify ________________
     - other drug? specify ________________

12. Study Product Status
   - Due to event dose was: 
     - Increased
     - Reduced
     - Unchanged
     - Permanently Discontinued
     - Temporarily Withheld
     - Not applicable for one time dose
     - Other, specify: ________________

13. Outcome of Event
   - choose only one:
   - Ongoing
   - Resolved without sequelae Date / / (DD/MM/YYYY)
   - Resolved with sequelae Date / / (DD/MM/YYYY)
   - State sequelae: ________________
   - Death Date of Death: / / (DD/MM/YYYY)
   - Autopsy: | Not Done | Done (Provide Report) | Planned | Status Unknown

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27 February, 2004 Version 1.0
### List Relevant Lab/Diagnostic results below OR attach copies of the results.
#### 14. Relevant Laboratory Tests
- [ ] No relevant laboratory tests
- [ ] Pending specify test:

<table>
<thead>
<tr>
<th>Test</th>
<th>Collection Date (DD/MMM/YYYY)</th>
<th>Result</th>
<th>Site Normal Range</th>
<th>Collection Date of test previous to this SAE</th>
<th>Result of test previous to this SAE</th>
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#### 15. Relevant Diagnostic Tests (EX: MRI, CT Scan, Ultrasound)
- [ ] No relevant diagnostic tests
- [ ] Pending specify test:

<table>
<thead>
<tr>
<th>Test</th>
<th>Date Performed (DD/MMM/YYYY)</th>
<th>Results/Comments</th>
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#### 16. CONCOMITANT MEDICATIONS
- [ ] No relevant concomitant medications

List relevant concomitant medications the subject was taking up to 1 month prior to SAE onset.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Start Date DD/MMM/YYYY</th>
<th>Stop Date DD/MMM/YYYY</th>
<th>Total Daily Dose</th>
<th>Indication</th>
<th>Suspect</th>
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### Event Summary

(Include chronological details of event, associated signs and symptoms, alternative etiologies including concomitant medications suspected, medical management and relevant past medical history below, or attach summary. Use the example provided in the SAE Recording and Reporting Guidelines and include all information. Attach additional pages if needed.)

<table>
<thead>
<tr>
<th>Date (DDMMYYYY) Submitted or Faxed To:</th>
<th>Follow-up report:</th>
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<tbody>
<tr>
<td>Initial report:</td>
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<tr>
<td>- PPD  / / N/A</td>
<td>- PPD  / / N/A</td>
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<tr>
<td>- IRB  / / N/A</td>
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<td>- Data Center / / N/A</td>
<td>- Data Center / / N/A</td>
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<tr>
<td>- Other  / / N/A</td>
<td>- Other  / / N/A</td>
</tr>
</tbody>
</table>

Completed by (signature): ___________________  Completed by (print): ___________________  Date: __ / __ / __

Investigator(signed): ___________________  Investigator (print): ___________________  Date: __ / __ / __
Expedited Reporting by Sponsor to the FDA (IND)

- If the SAE results in death or is considered by the PI to be life-threatening
- And is unexpected (Not listed in the Package insert or Investigational Brochure)
- And is related (reasonable suspected causal relationship) between the IP and the event
- An expedited report must go to the FDA within 7 calendar days
Expedited Reporting to the FDA (IND)

- If the SAE meets any of the other serious criteria (Causes hospitalization or prolonged hospitalization, etc.)
- And is unexpected (Not listed in the Package Insert or Investigational Brochure)
- And is related (Reasonable suspected causal relationship between the IP and the event)
- An expedited report must go to the FDA within 15 calendar days
SAE Follow-up

- It is a rare occurrence when all details of a SAE are known when the initial report is submitted.

- Expect follow up with every SAE, especially those that contain new safety information.
Resolution

All AE/SAEs should be followed:
- Until event has stabilized
- Condition returns to baseline
- Condition is resolved
- Condition no longer meets the SAE criteria
Periodic Reporting of Adverse Events

- AEs must be entered into the CRF per protocol guidelines.
- AEs may be categorized according to intensity of the event or relationship with the study medication.
- IRBs may have guidelines for reporting adverse events (annual reports).
- Content and Structure of periodic reports depends on the study (e.g., Grade 3, related to specific organ system, or related AEs).
The most important responsibilities of investigators and sponsors of clinical research studies:

- Protection of human subjects.
- Collection of clean and reproducible data.
Safety Oversight

Review of all safety data on an ongoing basis (Laboratory, AE, SAE) by oversight committees such as Data Safety Monitoring Board (DSMB), Safety monitoring committees (SMC), independent safety monitors (ISM), Sponsor, FDA, other regulatory agencies
Protocol Development

A well written clinical protocol addresses the following issues:

- Careful identification of possible AEs
- Proper collection of pre-existing conditions and concomitant meds
- Description of procedures for monitoring the occurrence of AEs
- Appropriate medical and toxicity management for participants experiencing AEs
- Standardized AE reporting
Case Study

A thin 9 year old girl, Mary, is consented, enrolled and is having her blood drawn using a 21 gauge needle attached to a vacutainer.

The startled child screams and moves, dislodging the needle. Pressure is immediately applied, but a hematoma 12 mm in diameter results. Distal pulses are intact, there is no cyanosis, and movement of the extremities unimpaired.
Case Study

- Is this an AE?
  - Yes

- Is This an SAE?
  - No

- Intensity?
  - mild/moderate

- Relatedness?
  - Yes, it was a related AE

- Site responsibility: Complete AE CRF, follow until AE is resolved
The team evaluates the child in 7 days. The lesion is purplish and bleeding slightly, but resolving. 14 days later the lesion is completely healed.
Case Study

- Site responsibility: Update AE CRF, AE is resolved
A thin 9 year old boy, John is consented, enrolled and is having his blood drawn using a 21 gauge needle attached to a vacutainer.

The startled child screams and moves, dislodging the needle. Pressure is immediately applied, but a hematoma 12 mm in diameter results. Distal pulses are intact, there is no cyanosis, and movement of the extremities unimpaired.
Case Study

Mother brings the child back in 3 days. Lesion at puncture site is hot, swollen, red and tender. The hematoma site has abcessed and the child is hospitalized for incision and drainage and intravenous antibiotics.
Case Study

- Is this an AE?  
  - Yes
- Is this an SAE?  
  - Yes
- Intensity?  
  - Severe
- Relatedness?  
  - Yes, it was a related AE
Case Study

- Site responsibility: Complete AE CRF
- Complete DMID SAE Form
- Report to PPD regulatory within 72 hours
- Report to EC/IRB according to local regulations
- Follow until resolved
UNDERSTANDING:

- Adverse Event defined as an untoward medical event during enrollment in a clinical study.
- Chronic, recurring condition at baseline is not an AE if it recurs during study, i.e. asthma, herpes, arthritis, unless increase in severity or frequency
- PI or designated clinician must assess intensity and relatedness
- Serious Adverse Events well defined in regulations
- Ensure source documentation and CRFs and SAE form match
- When in doubt, report it
- Patient safety is paramount