Demystifying Serious Adverse Event Reporting

Elizabeth Ness, MS, BSN, RN, CRN-BC™
Director, Office of Education and Compliance
Center for Cancer Research
Disclosure for Participants

- **Criteria for Successful Completion:**
  - Attendance at 80% of the session and submission of an evaluation form.
  - There is no conflict of interest for anyone with the ability to control content for this activity.
  - National Cancer Institute is approved as a provider of nursing continuing professional development by the Ohio Nurses Association, an accredited approver by the American Nurses Credentialing Center’s Commission on Accreditation. (OBN-001-091). The approved provider unit activity number is 2021014
Agenda

1. Definition Review
2. Reporting Requirements
3. SAE Form/Database
4. Sponsor Review
5. SAE reconciliation
# Adverse Event (AE)

<table>
<thead>
<tr>
<th>U.S. Office for Human Research Protections (OHRP)</th>
<th>U.S. Food and Drug Administration (FDA)</th>
<th>International Council on Harmonization (ICH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.</td>
<td>Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be 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.</td>
</tr>
</tbody>
</table>
## Serious Adverse Event (SAE)

<table>
<thead>
<tr>
<th><strong>U.S. OHRP</strong></th>
<th><strong>U.S. FDA</strong></th>
<th><strong>ICH</strong></th>
</tr>
</thead>
</table>
| Any adverse event temporally associated with the subject’s participation in research that meets any of the following criteria:  
- results in death;  
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);  
- requires inpatient hospitalization or prolongation of existing hospitalization;  
- results in a persistent or significant disability/incapacity;  
- results in a congenital anomaly/birth defect; or  
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject’s health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition. | An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:  
- Death  
- Life-threatening adverse event  
- Inpatient hospitalization or prolongation of existing hospitalization  
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or  
- Congenital anomaly/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 subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. | Any untoward medical occurrence that at any dose:  
- results in death,  
- is life-threatening,  
- requires inpatient hospitalization or prolongation of existing hospitalization,  
- results in persistent or significant disability/incapacity, or  
- is a congenital anomaly/birth defect. |
### Unexpected

<table>
<thead>
<tr>
<th>U.S. OHRP</th>
<th>U.S. FDA</th>
<th>ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is <strong>not consistent</strong> with either:</td>
<td>An adverse event or suspected adverse reaction is considered &quot;unexpected&quot; if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.²</td>
<td>An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product)</td>
</tr>
<tr>
<td>• the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; <strong>OR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Section/Appendix in the IB that will have a listing of SAEs experienced by subjects that the sponsor considers expected for the purpose of expedited reporting - Serious Adverse Reactions That Are Considered Expected for [IND Drug] Safety Reporting Purposes**
Suspected Adverse Reaction (SAR)

• Suspected
  • Any AE for which there is a *reasonable possibility* that the drug caused the event
  • Evidence to suggest a causal relationship between the drug and AE
  • It doesn’t mean that a causal relationship cannot be ruled out
• Examples:
  • Single occurrence of an event that is uncommon and known to be *strongly associated* with drug exposure
  • One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug
  • An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group
Adverse Events of Special Interest (AESI)

• An adverse event (serious or nonserious) that is of scientific and medical concern specific to the sponsor’s product or program that requires closer ongoing monitoring and rapid communication to the sponsor

Council for International Organizations of Medical Sciences (CIOMS)
Investigator Reporting to Sponsor

• Any Serious Adverse Event (SAE)
• Any study endpoint that is an SAE when there is evidence suggesting a causal relationship between the drug and the event
• Timeframe: Immediately

21 Part 312.64 (b)
Exceptions to Expedited Reporting

• Determined by the sponsor
• Listed in the protocol
Sponsor Reporting to FDA & Investigators: IND Safety Reports

• 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

21 Part 312.32 (c)(1)
FDA Reporting: 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

21 Part 312.32 (c)(2)
Is Event Reportable to FDA via Expedited Process?

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Investigator Responsibility</th>
<th>Sponsor Responsibility</th>
<th>Final Determination Responsibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious or life threatening</td>
<td>AEs that result in death, life-threatening situations, inpatient hospitalization or prolongation of hospitalization, persistent or significant incapacity, and so on</td>
<td>Yes (Investigator must report all serious AEs to the sponsor immediately)</td>
<td>Yes</td>
<td>An event is considered serious or life threatening, on the basis of either the investigator’s or the sponsor’s opinion.</td>
</tr>
<tr>
<td>Unexpected</td>
<td>AEs that are not listed in the investigator brochure or those not listed at the observed specificity or severity</td>
<td>No (No requirement to assess expectedness)</td>
<td>Yes</td>
<td>The sponsor is responsible for determining whether event meets the definition of unexpected.</td>
</tr>
<tr>
<td>Suspected adverse reaction</td>
<td>There is a reasonable possibility that the drug caused the event.</td>
<td>Yes (Investigator must provide sponsor with an assessment of causality)</td>
<td>Yes (Sponsor’s assessment determines reportability, regardless of investigator’s assessment)</td>
<td>The sponsor is responsible for determining whether there is a reasonable possibility that the drug caused the AE, taking into consideration the investigator’s assessment. The sponsor reports serious and unexpected suspected adverse reaction to the FDA and all participating investigators.</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; FDA, US Food and Drug Administration. Adapted from US Food and Drug Administration.²

Levit et al, 2018
Though SAE forms/databases may vary, they all have similar key components.
Key Information

- Reporter information
- Subject demographics
- Study agent (date[s] given, dose, route of administration)
- Event
- PI Attribution/Causality
- Narrative summary
The Narrative Summary

• Most important part
• Very likely that the recipient of the form does not know anything about the subject and their history
• Provides the background information necessary to assess the event and support the Investigator’s attribution
• Spell out acronyms when using for the first time
What to Include in the 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 should accompany the report
  • When needed to explain the experience
  • When needed to support the differential diagnosis
• Sponsor specific – not always necessary
• Remove PII
What To Do If Only Limited Information Is Available

• Contact treating physician/institution and document all conversations in medical record
• Submit what you have:
  • most recent clinical evaluation, baseline history and physical
  • Provide a summary of the event and treatment to date
  • Provide plan for obtaining information
• When additional information becomes available – amend the report
Expedited AE Follow-up Reporting

• As a general rule, follow-up is required when:
  • Change in the severity, attribution, or actual event (i.e., AE term)
  • New information on a death becomes available
  • Requested by the regulatory/oversight group
• As a general rule, follow-up report is *not* required when:
  • AE resolves *(resolved date will be noted on the adverse event case report form)*
Industry Sponsors

- Follow sponsor requirements for reporting
- Pharmacovigilance staff will follow up if questions
- Medical monitor makes final determination if SAE is to be filed expeditiously with the FDA
- If so, IND safety report also sent to Investigators
CCR SAE Reporting Policy OSRO #301

• Promptly notify OSRO of any events that occur that have affected adversely the safety of subjects or impact the conduct of the trial.
  • At a minimum, timely reporting of Serious Adverse Events (SAE) and other reportable safety events according to the individual protocol.
• SAE reporting FAQs
• OSROSafety@mail.nih.gov
SAE Reporting: General Information

- Point of contact is Joni Love
- Instructions for the SAE form
- SAE report form, includes PI electronic signature (form is secure after signed)
- Provide baseline H&P/labs, concomitant meds, diagnostic testing report(s) with SAE report form
- REMINDER: Remove PII
- Follow-up:
  - New SAE information
  - SAE resolution
OSRO Assessment (SOP #301-S01)

- Sponsor assessment will be done by the Medical Monitors (MMs)
- If reportable to the FDA, MM will report using a MedWatch Form 3500A
- If not reportable to the FDA, CIOMS Form sent to PI/study team/companies for non-SUSARs
- MMs contact PI to request information – send as follow up SAE report with PI signature to document new information
CTEP

• NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs
Expedited Reporting Guidelines
Phase 1 & Early Phase 2

**FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

**ALL SERIOUS** adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>Grade 1 and Grade 2 Timeframes</th>
<th>Grade 3-5 Timeframes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resulting in Hospitalization ≥ 24 hrs</td>
<td>10 Calendar Days</td>
<td>24-Hour 5 Calendar Days</td>
</tr>
<tr>
<td>Not resulting in Hospitalization ≥ 24 hrs</td>
<td>Not required</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

**Expedited AE reporting timelines are defined as:**

- “24-Hour; 5 Calendar Days” - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- “10 Calendar Days” - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

1Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

**Expedited 24-hour notification followed by complete report within 5 calendar days for:**

- All Grade 3, 4, and Grade 5 AEs

**Expedited 10 calendar day reports for:**

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

2For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.

Effective Date: May 5, 2011
Expedited Reporting Guidelines
Late Phase 2 and 3

**FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**

**NOTE:** Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

**ALL SERIOUS** adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>Grade 1 Timeframes</th>
<th>Grade 2 Timeframes</th>
<th>Grade 3 Timeframes</th>
<th>Grade 4 &amp; 5 Timeframes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resulting in Hospitalization ≥ 24 hrs</td>
<td></td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not resulting in Hospitalization ≥ 24 hrs</td>
<td></td>
<td>Not required</td>
<td>10 Calendar Days</td>
<td>24-Hour 5 Calendar Days</td>
</tr>
</tbody>
</table>

**NOTE:** Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

**Expedited AE reporting timelines are defined as:**

- **“24-Hour; 5 Calendar Days”** - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.

- **“10 Calendar Days”** - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

1Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

**Expedited 24-hour notification followed by complete report within 5 calendar days for:**

- All Grade 4, and Grade 5 AEs

**Expedited 10 calendar day reports for:**

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

2For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.

Effective Date: May 5, 2011
Comprehensive Adverse Events and Potential Risks (CAEPR)

• NCI-generated list of reported and/or potential AEs associated with an agent currently under an NCI IND/IDE
• Once sufficient patient experience is available, CAEPR provides the relative AE frequency for the Informed Consent Document (ICD) Risk List
• Tool to help clinical sites prepare their IC document
Sources for CAEPR Information

• Primary Source:
  • Investigator’s Brochure

• Secondary Sources:
  • Company Safety Reports
  • Package Insert for agents commercially available
  • Publications and Abstracts
  • SAE Reports
Specific Protocol Exceptions to Expedited Reporting (SPEER)

- Section of the CAEPR
- Protocol specific exceptions to expedited reporting
- AEs listed on the SPEER should be reported expeditiously by investigators to the NCI via AERs *ONLY IF* they exceed the grade of the event listed in parentheses after the event
- Multiple investigational agents and the same AE is listed on the multiple SPEERs, use the lower of the grades to determine if expedited reporting is required
**Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 5.0 Term)**

<table>
<thead>
<tr>
<th>Likely (&gt;20%)</th>
<th>Less Likely (&lt;=20%)</th>
<th>Rare but Serious (&lt;3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLOOD AND LYMPHATIC SYSTEM DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ENDOCRINE DISORDERS</strong></td>
<td></td>
<td>Hypothyroidism (Gr 2)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL DISORDERS</strong></td>
<td>Abdominal pain (Gr 3)</td>
<td>Constipation (Gr 2)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>Diarrhea (Gr 3)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Dry mouth (Gr 2)</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Dyspepsia (Gr 2)</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Gastrointestinal fistula²</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal hemorrhage³</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal perforation⁴</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mucositis oral (Gr 3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea (Gr 3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral pain (Gr 2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting (Gr 3)</td>
<td></td>
</tr>
</tbody>
</table>
CTEP Evaluation of Expedited AE Report

- Investigation Drug Branch (IDB) Senior Investigator reviews submitted report
- If insufficient documentation for independent evaluation, contractor will request from site
- Independent review/assessment of AE, attribution
  - Held for annual report
  - Filed with the FDA and report sent to NCI investigators within 1 day after submitting to the IND
SAE Reconciliation: Sponsor

• Typically, SAE data are stored and managed in a separate database from the rest of the trial data

• Process
  • Comparison of SAE data in the clinical database and the safety database
  • Review the discrepancies
  • Resolve the discrepancies
  • Make the necessary adjustments safety database
• **OSRO SOP 301-S02**
SAE Reconciliation: Site

All AEs submitted as SAEs need to have the same AE term, grade and attribution on both the SAE form and the routine AE CRF. If additional AEs are included in the report, those need to be on the AE CRF.

Research Nurse should send SAE reports including follow ups to Data Manager and ensure CRIS documentation supports the SAE.

Data Manager will use CRIS as the main source first and if discrepancies exist between source and SAE report, DM will follow up with the Research Nurse.
Team Process for Expedited Reporting to the Sponsor

- Who identifies SAEs/AEIs?
- Are there ever any disagreements about reporting? If so, how is consensus reached?
- Who writes the narrative summary?
  - What is the process for PI review and “approval”?
- Who is responsible for completing and submitting to the Sponsor?
- What resources do you use to assist you with reporting if you know you have a time crunch and need help?
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 case report form
Reminders

• Some events that initially appear to meet expedited reporting requirements may be excluded from 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 file.
Selected References


QUESTIONS