Adverse Event Assessment & Reporting

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Senior Quality Assurance Nurse Auditor
Network Operations Center
What is your current role?

A. Data Management
B. Clinical Research Nurse
C. Regulatory Affairs
D. Quality Assurance
E. Administration
F. Other
What is the definition of an Adverse Event?

A. A known toxicity of the study agent.

B. Any untoward sign or symptom that occurs during the course of a clinical trial.

C. Any event which the PI decides to report during the course of a clinical trial.

D. A side effect caused by the study agent.
## 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>
SWOG Definition

Any unfavorable and unintended change in a patient’s condition from the day protocol treatment began, REGARDLESS OF EXPECTEDNESS OR RELATIONSHIP TO RESEARCH.

## Unexpected Event

<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</strong> consistent 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>
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</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>
Data Standards for AE Terms

Medical Dictionary for Regulatory Activities (MedDRA)

Common Terminology Criteria for Adverse Events (CTCAE)
Medical Dictionary for Regulatory Activities (MedDRA)

• Dictionary of clinically validated international medical terminology
• Developed by the International Council on Harmonisation (ICH)
• Used to facilitate sharing of regulatory information internationally for human medical products
• Available in 19 languages
• http://www.meddramsso.com/
MedDRA v. 25.0 ‘Fatigue’ hierarchy displayed (MedDRA ID 10016256)

SOC: System Organ Class
HLGT: High Level Group Term
HLT: High Level Term
PT: Preferred Term
LLT: Lowest Level Term

KEY:

- SOC: System Organ Class
- HLGT: High Level Group Term
- HLT: High Level Term
- PT: Preferred Term
- LLT: Lowest Level Term
Common Terminology Criteria for Adverse Events (CTCAE)

- Developed by NCI Cancer Therapy Evaluation Program (CTEP) as the Common Toxicity Criteria (CTC) in 1983
- Fundamentally agreed upon terminology for AEs that occur in oncology research
- Current version: 5
- Early 2024: version 6
- Organized by MedDRA
  - SOC (minus Product Issue SOC)
  - LLT
## CTCAE v 5

### Immune system disorders

<table>
<thead>
<tr>
<th>CTCAE Term</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reaction</td>
<td>Systemic intervention not indicated</td>
<td>Oral intervention indicated</td>
<td>Bronchospasm; hospitalization indicated for clinical sequence; intravenous intervention indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
</tbody>
</table>

**Definition:** A disorder characterized by an adverse local or general response from exposure to an allergen.

**Navigational Note:** If related to infusion, use Injury, poisoning and procedural complications: Infusion related reaction. Do not report both.

| Anaphylaxis         | -                                            | -                                   | Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension | Life-threatening consequences; urgent intervention indicated | Death                         |

**Definition:** A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.

**Navigational Note:** -

| Autoimmune disorder | Asymptomatic; serologic or other evidence of autoimmune reaction, with normal organ function; intervention not indicated | Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism) | Autoimmune reactions involving major organ (e.g., colitis, anemia, myocarditis, kidney) | Life-threatening consequences; urgent intervention indicated | Death                         |

**Definition:** A disorder characterized by loss of function or tissue destruction of an organ or multiple organs, arising from humoral or cellular immune responses of the individual to his own tissue constituents.

**Navigational Note:** Prior to using this term consider specific autoimmune AEs

Reporting Adverse Events: CTCAE Terms

• CTCAE terms might not always be listed the way that you expect. Below are some examples of common AEs and their appropriate CTCAE v5.0 term:

  Pneumonia  ➔  Lung infection
  Thrombocytopenia  ➔  Platelet count decreased
  Shortness of breath  ➔  Dyspnea

• Each system category includes an “Other, specify” option in the rare case there is no term is available for an adverse event. Please use “other” sparingly!
Severity Rating or Grading

Measures the severity of clinical findings and impact on the participant.

Promotes consistency for severity assessment.

Facilitates common understanding of shared AE data sets. Provides framework to compare AEs across different studies.
**Reporting Adverse Events: CTCAE Grade**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th>Grade</th>
<th>Grade</th>
<th>Grade</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Hemoglobin (Hgb) &lt;LLN - 10.0 g/dL; &lt;LLN - 6.2 mmol/L; &lt; LLN - 100 g/L</td>
<td>Hgb &lt;10.0 - 8.0 g/dL; &lt;6.2 - 4.9 mmol/L; &lt;100 - 80 g/L</td>
<td>Hgb &lt;8.0 - 6.5 g/dL; &lt;4.9 - 4.0 mmol/L; &lt;80 - 65 g/L; transfusion indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>

**Definition:** A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.

How to Access CTCAE

• Smartphone & tablet apps available
  • Use CTCAE+
  • Easy search feature

• NCI website
  • Search **pdf version**
The attribution code describes, in the opinion of the investigator, how likely it is that the adverse event is due to protocol treatment:

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Attribution</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated to Investigational Agent/Intervention</td>
<td>1- Unrelated</td>
<td>The AE is clearly not related to the intervention</td>
</tr>
<tr>
<td></td>
<td>2- Unlikely</td>
<td>The AE is doubtfully related to the intervention</td>
</tr>
<tr>
<td>Related to Investigational Agent/Intervention</td>
<td>3- Possible</td>
<td>The AE may be related to the intervention</td>
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<td></td>
<td>4- Probable</td>
<td>The AE is likely to be related to the intervention</td>
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<tr>
<td></td>
<td>5- Definite</td>
<td>The AE is clearly related to the intervention</td>
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</table>
Determining Attribution...

What is already known about:
- Drug or classification of the drug
- Therapy or intervention
- Expectedness

Is there a temporal relationship of the AE to the study intervention?

Does the AE improve or disappear when the intervention is discontinued?

If re-challenged with the intervention, does the AE reappear?
- At the same severity?
- At the same time point?
... Determining Attribution

1. Is the AE a result of existing disease signs and symptoms?
2. Is the AE a result of existing baseline signs and symptoms?
3. Is the AE a result of an underlying concurrent medical condition(s)?
4. Is the AE a result of an underlying concurrent medication(s)?
AE Assessment

• Obtained by nurse or investigator with input from the other members of the research team.

• Starts with a quality baseline assessment.

• Includes:
  • Physical exam
  • Review of medical record
  • Review of Laboratory Tests
  • Review of Radiology results
  • Review of Signs & Symptoms

• Solicited events vs spontaneously reported by a participant
Documentation

- Medical Record documentation should include:
  - Date the event began; include time with infusion reaction.
  - Detailed description
  - Attribution
  - Immune relationship if applicable
  - Any treatment for the event
  - Impact on the clinical trial intervention
  - Date of resolution/improvement
  - Seriousness
Example of documentation

<table>
<thead>
<tr>
<th>AE</th>
<th>Grade</th>
<th>Attribution</th>
<th>Start</th>
<th>Stop</th>
<th>Ongoing</th>
<th>Immune Related</th>
<th>Is this considered a serious AE needing expedited reporting</th>
<th>Action taken</th>
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<td>No</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Attribution: 1 definitely related; 2 unlikely related; 3 possibly related; 4 probably related; 5 unrelated

Investigators Signature: ______________________ Date: ____________________

Page: _____ of _____
Which statement represents the most complete description for adverse event reporting?

A. Ms. Smith states she had some diarrhea after her last treatment, that stopped with Imodium.

B. She stated she had 6 stools a day after her last treatment. The diarrhea stopped 4 days ago.

C. Patient states she had 6 stools a day, which is 5 above baseline.

D. She states she had 6 stools a day, which is 5 above baseline. This started 5 days after her treatment. She took Imodium, and it slowed to 2 stools a day yesterday.
Online Data Submission

Adverse Events
Online Data Submission: Adverse Events

Answer “Yes” to generate the AE Report form

Should always be at the end of the reporting period
### Online Data Submission: Adverse Events

**Instructions:** Please complete this form after each cycle.

**Reporting period start date:** 9 Dec 2020

**Reporting period end date:** 31 Dec 2020

**Were adverse events assessed during this time period?**
- Yes

**If yes, did the patient experience any adverse events during this reporting period?**
- Yes

**Date of most recent adverse event assessment:** 31 Dec 2020

**Comments**

1. If you’re not done completing this form, but want to save your work for later, check the box below and click the Save button. Note that edit checks will still fire.

2. Save this form, but don’t submit to SWOG yet.

---

**CRF History**

- 283430 - Adverse Events: Assessment
- 283430 - Treatment
- 283430 - On Tx Vital Status 2021-01-31
Online Data Submission: Adverse Events

Click the pencil icon to enter data on the first line.
Online Data Submission: Adverse Events

Use the arrow to select the CTCAE term from the drop-down menu

Use the arrow to select the grade from the drop-down menu
**Online Data Submission: Adverse Events**

---

### Form Instructions

- **Red asterisk** before a field denotes that it is required by the system for rules evaluation.
- **Start date of this course/cycle**
  - 9 Dec 2020
- **Start date of first course/cycle (derived)**
  - 9 Dec 2020

### Adverse Event Terms (CTCAE v6.0)

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Attribution to Study Intervention</th>
<th>Hospitalization</th>
<th>Life-threatening</th>
<th>Death</th>
<th>Disability</th>
<th>Congenital</th>
<th>Birth Defect</th>
<th>Other</th>
<th>SAE Report (derived)</th>
<th>AE Entry Date (derived)</th>
<th>Time Zone (Derived)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough (1) Mild symptoms; nonprescription intervention indicated</td>
<td>Unlikely</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11 Apr 2023 06:15:44 PM</td>
<td>Eastern Standard Time</td>
</tr>
</tbody>
</table>

**INSTRUCTIONS:** After entering new or modified data in the table above, adverse events must be submitted to CTEP-AERS for rules evaluation by saving the Expedited Reporting Evaluation CRF in Rave.

**Comments:**

_If you’re not done completing this form, but want to save your work for later, check the box below and click the Save button. Note that edit checks will still fire._

Save this form, but don’t submit to SWOG yet.

---

*(2018) CTEP Guidance for recording adverse event start & end dates*
Online Data Submission: COVID-19

If you choose “Other, specify,” specify further in the text box.

Use the Comments as needed for further explanation.
Nuances in AE Reporting
Common Reporting Errors

- Non-clinically significant lab abnormalities
- Symptoms vs Condition
- Procedure vs disease that resulted in the procedure
- Progression
- Not reporting baseline conditions that worsen or reoccur after previously resolving.
Grading based on the use of Medication

Just because someone is taking a medication, does not mean that they have the condition.

- Prophylactic use
- Medications have multiple uses
## Grading conditions present at Baseline

Not all events can be assigned a grade at baseline.

<table>
<thead>
<tr>
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<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>Abnormal glucose above baseline with no medical intervention</td>
<td>Change in daily management from baseline for a diabetic; oral antihyperglycemic agent initiated; workup for diabetes</td>
<td>Insulin therapy initiated; hospitalization indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Adult: Systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg; Pediatric: Systolic/diastolic BP &gt;90th percentile but &lt; 95th percentile; Adolescent: BP ≥120/80 even if &lt; 95th percentile</td>
<td>Adult: Systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg if previously WNL; change in baseline medical intervention indicated; recurrent or persistent (≥24 hrs); symptomatic increase by &gt;20 mm Hg (diastolic) or to &gt;140/90 mm Hg; monotherapy indicated initiated;</td>
<td>Adult: Systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated;</td>
<td>Adult and Pediatric: Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Increase of &lt;4 stools per day over baseline; mild increase in ostomy output compared to baseline</td>
<td>Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL</td>
<td>Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
</tbody>
</table>
Which Cycle does an AE get reported in?

**Screening**
- 4/8/22
- Dyspnea grade 2
- Anemia grade 2

**Registration**
- 4/24/22 / NOON
- Labs at 9:00 am
- Physical at 9:30 am

**Cycle 1**
- 4/27/22 / NOON Tx
- Labs drawn at 9:00 am
- Physical at 9:30 am

**Cycle 2**
- 5/25/22 / Noon Tx
- Labs drawn at 9:00 am
- Physical at 9:30 am

**Adverse events**
- Anemia gr 1
- Dyspnea gr 3
- Albumin gr 1

**Adverse events**
- Anemia gr 0
- Dyspnea gr 2
- Albumin gr 1
- Fatigue gr 1

**Adverse Events**
- Anemia gr 1
- Dyspnea gr 1
- Albumin gr 1
- Fatigue gr 2
Below are some events that occurred during Cycle 1. Which one(s) should be reported, based on general SWOG guidance on AE reporting:

1. Fatigue, gr 1, attributed to working long hours, was 0 at baseline.
2. Increased non-fasting glucose, previously WNL. Not clinically significant.
3. Shortness of breath gr 2, same as baseline.
4. 5% weight loss, found on Day 1 of Cycle 2, prior to treatment.

A. All listed events
B. Fatigue & Shortness of Breath
C. Fatigue, increased glucose & weight loss.
D. Fatigue, increased glucose & shortness of breath.
Adverse Event Escape Room

https://docs.google.com/presentation/d/1cm_d1q8VsnkJd5R4vPUCXZ4s3UfYzMO02lWxD17RE/preview?slide=id.p
Questions