Adverse Event Module
Part 2:
Assessment and
Documentation

Agenda
• AE assessment
• AE documentation
• Common AE data elements collected on case report forms

AE Assessment
• Done by the investigator with input from the research team
• Determine
  • Event term
  • Severity of event
  • Seriousness of event
  • Attribution of the event
Data Standards for AE Term

- 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
- Used to facilitate sharing of regulatory information internationally for human medical products
- Developed by the International Conference on Harmonisation (ICH)
- MedDRA translations in 10 languages

MedDRA Structure

<table>
<thead>
<tr>
<th>System, Organ, Class</th>
<th>SOC</th>
<th>Highest level of the terminology, and distinguished by anatomical or physiological system, etiology, or purpose</th>
<th>26</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Level Group Term</td>
<td>HLGT</td>
<td>Subordinate to SOC, superordinate descriptor for one or more HLTS</td>
<td>335</td>
</tr>
<tr>
<td>High Level Term</td>
<td>HLT</td>
<td>Subordinate to HLGT, superordinate descriptor for one or more PTs</td>
<td>1,721</td>
</tr>
<tr>
<td>Preferred Term</td>
<td>PT</td>
<td>Represents a single medical concept</td>
<td>21,612</td>
</tr>
<tr>
<td>Lowest Level Term</td>
<td>LLT</td>
<td>Lowest level of the terminology, related to a single PT as a synonym, lexical variant, or quasi-synonym (Note: All PTs have an identical LLT)</td>
<td>74,880</td>
</tr>
</tbody>
</table>
Severity Rating Scales

- Provide a scale to measure severity of clinical findings and the impact on the participant
- Promotes consistency within a given grade across all AEs
- Provides guidance in the evaluation and documentation of severity of the AE
- Facilitates a common understanding of AE data shared among academic, commercial, and regulatory entities
- Provide framework to compare AEs across different studies

Mild, Moderate, Severe Scale

- Mild
  - Awareness of sign, symptom, or event, but easily tolerated
- Moderate
  - Discomfort enough to cause interference with usual activity and may warrant investigation
- Severe
  - Incapacitating with inability to do usual activities or significantly affect clinical status, and warrants intervention
Common Terminology Criteria for Adverse Events (CTCAE)

- Developed by the Cancer Therapy Evaluation Program (CTEP) of NCI as the Common Toxicity Criteria (CTC) in 1983
- Assist in the recognition and grading severity of adverse effects of chemotherapy
- Fundamentally intended to be an agreed upon terminology for the designation, reporting and grading of AEs that occur in oncology research

Evolution to CTCAE

<table>
<thead>
<tr>
<th>Year</th>
<th>Categories</th>
<th>AE Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983</td>
<td>18</td>
<td>49</td>
</tr>
<tr>
<td>1998</td>
<td>24</td>
<td>295</td>
</tr>
<tr>
<td>2003</td>
<td>28</td>
<td>&gt;900</td>
</tr>
</tbody>
</table>

May 28, 2010
Version 4.0

SOC: Blood and lymphatic system disorders

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
</tr>
</tbody>
</table>

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

SOC: Blood and lymphatic system disorders
### SOC: Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>Increase of &lt;4 stools per day over baseline; mild increase in ostomy output compared to baseline</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Increase of &gt;=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Death related to AE</td>
</tr>
</tbody>
</table>

**Grade Definitions**

- **Grade 1**: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2**: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- **Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- **Grade 4**: Life-threatening consequences; urgent intervention indicated.
- **Grade 5**: Death related to AE

* **Instrumental ADL** refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** **Self care ADL** refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

### CTCAE “Other” AE Term

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening consequences; urgent intervention indicated.</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death related to AE</td>
</tr>
</tbody>
</table>

* **Instrumental ADL** refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** **Self care ADL** refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

### How to Access CTCAE

- Smartphone apps
- All versions of CTCAE are found on CTEP’s website: [http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)
World Health Organization

- Table with severity or grades each w/description
  - Grade 0 = No event or WNL
  - Grade 1 = Mild
  - Grade 2 = Moderate
  - Grade 3 = Severe
  - Grade 4 = Life-threatening
- Updates with MedDRA terms
- Developed in English
- Translations into French, German, Spanish, Portuguese, and Italian
- Used by drug regulatory agencies and pharmaceutical manufacturers in many countries

FDA Guidance for Prevention Vaccine Trials

- Clinical and Laboratory Abnormalities
  - Mild (Grade 1)
  - Moderate (Grade 2)
  - Severe (Grade 3)
  - Potentially Life Threatening (Grade 4)
- Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

AE Assessment

- Determine
  - Event terminology
  - Severity of event
  - Seriousness of event
  - Attribution of the event
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

- Is the AE a result of existing disease signs and symptoms?
- Is the AE a result of existing baseline signs and symptoms?
- Is the AE a result of an underlying concurrent medical condition(s)?
- Is the AE a result of an underlying concurrent medication(s)?

Attributions: Approach 1

When having two options, the choices are typically:
- Related: reasonable causal relationship between the AE and ______
- Not related: no reasonable causal relationship between the AE and ______
Attributions: Approach 2

When having five options, the choices are:
- Definite—clearly related to __________
- Probable—likely related to __________
- Possible—may be related to __________
- Unlikely—doubtfully related to __________
- Unrelated—clearly not related to __________

Fill in the Blank for Approach 1 & 2
- Trick is filling in the “blank”
- IRB is looking for relatedness to the research
- Sponsor is looking for relatedness to the product
- Teasing out the attribution will assist in assessing the need to report the AE to regulatory groups

AE Collection…
- Should be spontaneously reported or elicited from a participant
- To prevent bias, participants should not be questioned regarding specific events that might be anticipated while on the study
- Diaries
  - Paper vs. electronic
  - Pro’s and Con’s
**...AE Collection**

- Begins at the initiation of study intervention
  - Collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participant
- Followed to resolution or stabilization

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**What’s Next?**

Documentation ➔ Recording ➔ Reporting

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**AE Documentation**

- Healthy volunteers
  - Document on CRF
- Patient volunteers
  - All AEs document in medical record
- Date the AE began
  - Include time with infusion reaction
- Treatment for the AE
- Description of the event
- Attribution of the AE
- Date(s) the AE improved and/or resolved
Recording Adverse Events

- Data abstraction activity
- AE recorded on case report form (CRF)
- Which AEs to record is protocol dependent
- Common elements:
  - Date the AE began
  - Treatment for the AE
  - Description and severity/grade of the AE
  - Attribution of the AE
  - Date the AE resolved

Summary

- AE assessment
- AE documentation
- AE recording