# Adverse Events Part 2: Assessment & Documentation

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# Outline

- AE assessment
- AE documentation
- Common AE data elements collected on case report forms (CRF)

# Baseline Signs/Symptoms (S & S)

- S & S present when the participants starts treatment (e.g., 1st day pre-dosing)
- Usually don't include s & s that occurred and resolved between the time of eligibility screening to the starting of dosing
  - Consider adding to Medical History CRF
- Severity rating

# AE Assessment

- Done by the PI with input from the research team
- Determine:
  - Event Term
  - Severity of event
  - Attribution of event
- Seriousness and unexpectedness of the event triggers expedited reporting requirements

# 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
- 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/

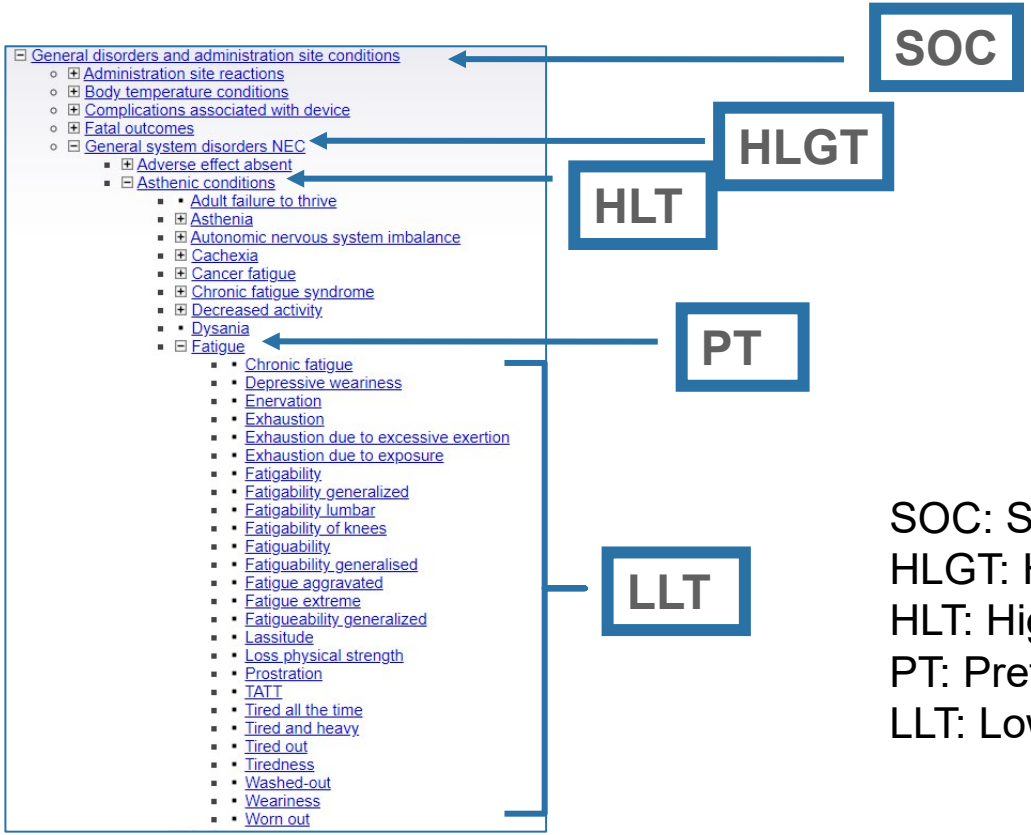
# MedDRA Structure

## *(version 26.0; March 2023)*

| | | | |
|---|---|---|---|
| System, Organ, Class | SOC | Highest level of the terminology, and distinguished by anatomical or physiological system, etiology, or purpose | 27 |
| High Level Group Term | HLGT | Subordinate to SOC, superordinate descriptor for one or more HLTs | 354 |
| High Level Term | HLT | Subordinate to HLGT, superordinate descriptor for one or more PTs | 1,855 |
| Preferred Term | PT | Represents a single medical concept | 25,916 |
| Lowest Level Term | LLT | 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) | 86,714 |

# MedDRA 'Fatigue' Hierarchy Displayed

## (*MedDRA ID 10016256)*




**KEY**

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

# Severity Rating Scales

- 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 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
- Organized by MedDRA
  - SOC (minus Product Issue SOC)
  - AE term - LLT

# Evolution to CTCAE

| | 1983<br>Version 1.0 | 1998<br>Version 2.0 | 2003<br>Version 3.0 |
|---|---|---|---|
| Categories | 18 | 24 | 28 |
| AE Terms | 49 | 295 | >900 |

| | May 28, 2010<br>Version 4.0 | November 27, 2017<br>Version 5.0 |
|---|---|---|
| SOC | 26<br>*(doesn't include MedDRA SOC "Product Issues")* | 26<br>*(doesn't include MedDRA SOC "Product Issues")* |
| AE Terms | 790 | 837 |

# SOC: Blood and Lymphatic System Disorders

| | Grade | | | | |
|---|---|---|---|---|---|
| **Adverse Event** | **1** | **2** | **3** | **4** | **5** |
| Anemia | Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; < LLN - 100 g/L | Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L | Hgb <8.0 - 6.5 g/dL; <4.9 - 4.0 mmol/L; <80 - 65 g/L; transfusion indicated | Life-threatening consequences; urgent intervention indicated | Death |
| 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. | | | | | |

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

# SOC: Gastrointestinal Disorders

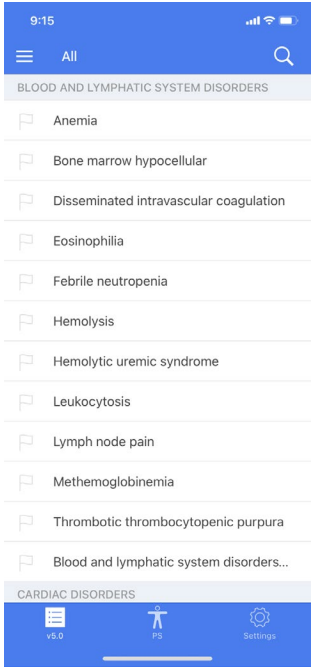
| | Grade | | | | |
|---|---|---|---|---|---|
| **Adverse Event** | **1** | **2** | **3** | **4** | **5** |
| Diarrhea | Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline | Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline | Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL | Life-threatening consequences; urgent intervention indicated | Death |
| Definition: A disorder characterized by frequent and watery bowel movements. | | | | | |

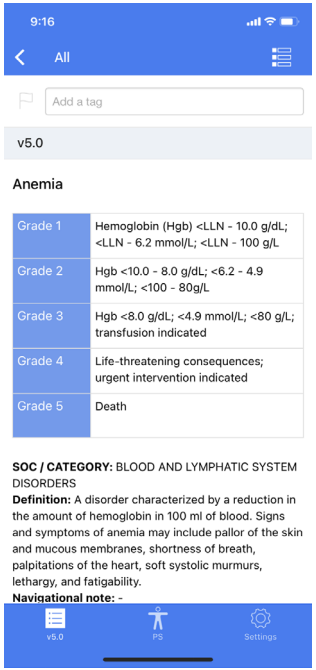
# CTCAE “Other” AE Term

| Grade | Description |
|---|---|
| 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 |

# How to Access CTCAE

- Smartphone & tablet apps available
  - Use CTCAE+
  - Easy search feature
- NCI website
  - Search pdf version



# 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*

# 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

- 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…

- Starts with a quality baseline assessment
- Includes review of:
  - Physical Exam findings
  - Laboratory values
  - Radiology results
  - Review of systems/symptoms
- Begins:
  - Time of consent or
  - Initiation of study intervention or
  - Start of a placebo lead-in period/observational period intended to establish a baseline status

# …AE Collection

- Solicited events
  - List of events in a diary
  - Consider prevention of bias
- Spontaneously reported or elicited from a participant
  - Through open-ended questions
  - During examination or other evaluation
- Followed to resolution or stabilization
  - See protocol, manual of procedures, CRF instruction manual or other guidelines for specifics

# AE Documentation

- 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

# Adverse Event Case Report Form

- 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

- Quality baseline assessment is the first step in assessing an adverse event (AE)
- AE assessment includes open ended questions plus review of any examinations and laboratory or radiological report
- AE assessment includes determine the causality of the event
- All AEs that are document, may not be abstracted on a CRF

# Test Your Knowledge

The attribution of an adverse event can be determined by the study coordinator if they are a nurse.

A. True
B. False