CTCAE & Source Documentation

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Agenda

1. *Definition of AE*
2. *AE standards*
3. *AE documentation*
4. *AE and data quality*

Summary Definition

Any unwanted sign, symptom, or disease that was not seen before individual's research participation, or worsening of baseline symptom, **REGARDLESS OF EXPECTEDNESS OR RELATIONSHIP TO RESEARCH.**

Purposes of Adverse Event (AE) Monitoring

- Identify events that may have immediate effect on the safety of the participant
- Inform regulators, investigators, and others of new and important information about events
- Provide a summary of adverse experiences in order to develop the drug or regimen toxicity profile

Adverse Events

- Multiple clinical terms have been used to convey an AE including:
  - toxicity
  - side effect
  - acute or late effect
  - complication
- These terms imply intervention had a causal relationship to the event which is NOT the definition of an AE

AE Assessment

- Done by the PI with input from the research team and documented in the source (i.e., patient medical record)
- Determine event:
  - Term
  - Severity
  - Attribution
  - *Reportability of event*

Adverse Event Standard Terminology & Severity Rating Scale

MedDRA

CTCAE

Medical Dictionary for Regulatory Activities (MedDRA)

- Medical terminology used to classify AE information
- Facilitates sharing of regulatory information internationally for medical products
- Developed by the International Council on Harmonisation (ICH)
- English version updates available on March 1st and September 1st

MedDRA Structure

(version 21.1)

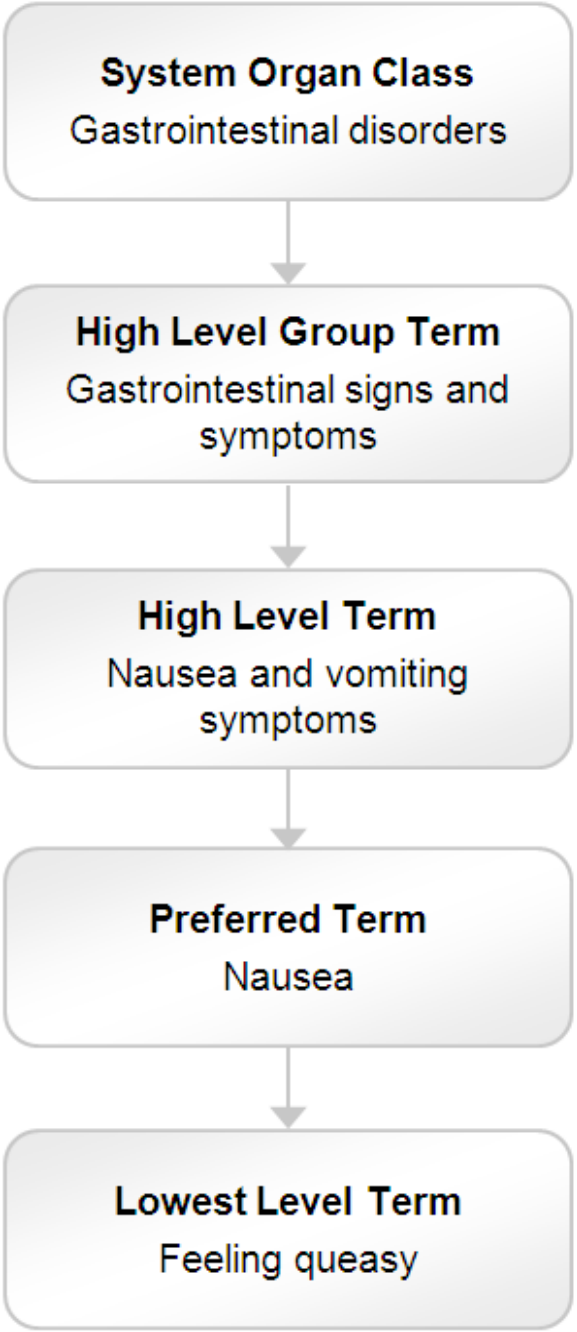
System, Organ, Class	SOC	Represents anatomical or physiological system, etiology, or purpose	26
High Level Group Term	HLGT	Links for HLTs	>330
High Level Term	HLT	Groups based upon anatomy, pathology, physiology, etiology or function	>1,730
Preferred Term	PT	Single medical concept for a symptom, sign, disease diagnosis, therapeutic indication, investigation, surgical or medical procedure and medical social or family history characteristics	>21, 900
Lowest Level Term	LLT	How information is communicated; how observation might be reported in practice	>75,800

Medical Record Note

Patient complained of feeling queasy last night.

Other LLTs:

- Nausea
- Nauseous
- Queasy
- Churning of stomach



Severity Rating Scales

- Measure severity of clinical findings and the impact on the research participant
- Promotes consistency for assessing severity
- Provides guidance in the evaluation and documentation of severity of the AE
- Facilitates a common understanding of AE data shared among research, commercial, and regulatory entities
- Provide framework to compare AEs across different studies

Common Terminology Criteria for Adverse Events (CTCAE)

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

Evolution to CTCAE

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

	May 28, 2010 Version 4.0
SOC	26
AE Terms (LLT)	790 (764 + 26 “Other”)

How to Read CTCAE

- Table format
- SOCs are alphabetical
- AE terms have a definition
- AE terms listed alphabetically in each SOC
- Each SOC has an “Other” AE term which needs to be specified
- Each AE terms has a severity rating of 1-5
- Semi-colon is read as an “or” statement
- Single dash indicates that a grade is not applicable

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 an 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.					

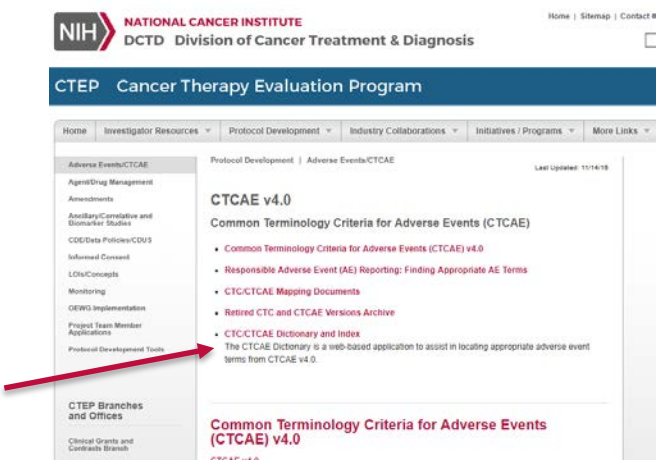
Patient has a hemoglobin level of 8.1 but based on clinical symptoms the physician decides to transfuse the patient. What is the grade of the anemia?

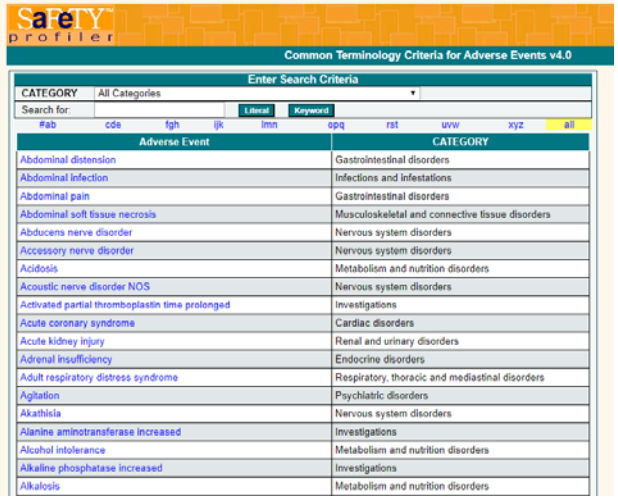
CTCAE “Other” AE Term

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

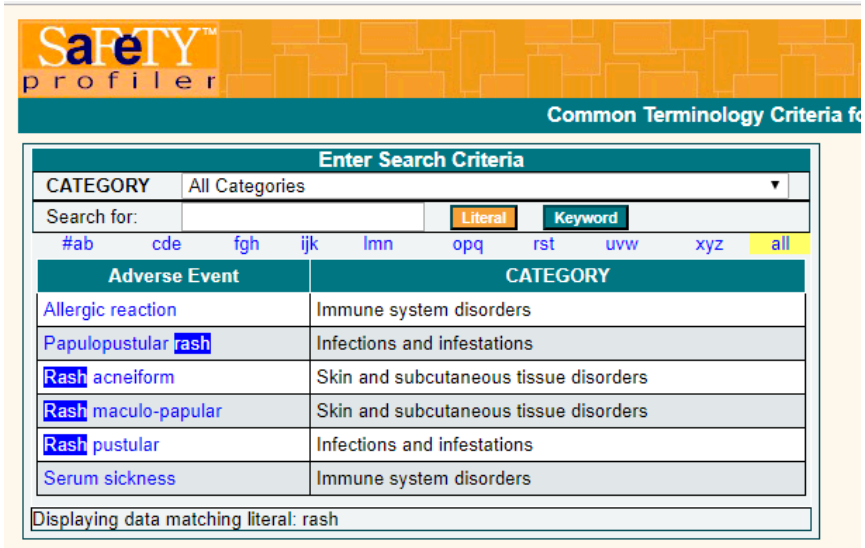
- Smartphone & tablet apps available
  - Use CTCAE 4 mobile for iPhone not CHOP version
  - Easy search feature
- NCI website
  - Search pdf version
  - NCI safety profiler
    https://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx





Search for “Rash”

- SOC: Immune system disorders
  - Allergic reaction
  - Cytokine release syndrome
  - Serum sickness
- SOC: Infection and infestations
  - Papulopustular rash
  - Rash pustular
- Skin and subcutaneous tissue disorders
  - Rash acneiform
  - Rash maculo-papular



Adverse Event Attribution

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
- IND sponsor is looking for relatedness to the IND
- Teasing out the attribution will assist in assessing the need to report the AE to regulatory groups

AE Collection and Documentation

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
- Severity rating:
  - Do you grade?
  - How so you grade?

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.					

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.

BL or Medical History or Both?

1. A-fib on screening ECG, asymptomatic, no prior history
   - No repeat required before dosing
   - Repeat BL ECG was normal

2. A-fib on screening ECG, asymptomatic, prior history
   - No repeat required before dosing
   - Repeat BL ECG was normal

BL or Medical History or Both?

1. Abnormal screening labs
   - Repeat BL labs normal
   - No repeat BL labs

- Does your protocol define when an abnormal lab becomes an AE?
  - If so, same can be applied to screening/BL labs

BL or Medical History or Both?

1. History of hypertension controlled on 1 medication, BL BP 118/76
2. History of hypertension controlled on 1 medication, BL BP 124/78
3. No history of hypertension, BL BP 126/82

NOTE: CTCAE definition of AE term "hypertension" is "A disorder characterized by a pathological increase in blood pressure; a repeatedly elevation in the blood pressure exceeding 140 over 90 mm Hg"

AE Collection

- Usually begins at the initiation of study intervention
  - May be from start of consent or confirmation of eligibility
- Followed to resolution or stabilization

Subjective 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
  - Use open ended questions
- Diaries

Objective AE Collection

- PE findings
- Radiographic findings
- Laboratory findings
- Incidental findings w/o subjective findings

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 Events Assessment and Documentation – Impact on Data Quality

Data Quality in Clinical Trials

- Highly regulated environment with strong emphasis on safety surveillance and data quality
- Increasing need for harmonization of safety reporting regulations globally

Coding of AE Data

- Most data entered on Case Report Forms are "coded" in some form
- Facilitates storage, retrieval, analysis, and presentation of data
- Some coding is performed by investigators at point of data entry
  - For example, numeric codes for severity of adverse event: 1= mild, 2= moderate, etc.
- Other coding of text data is performed by the sponsor company after data collection
- Accuracy of initial coding determines accuracy of analysis

Impact of Documentation on Coding AE Data…

- Appropriate coding requires clear initial data (i.e., documentation)
- Ambiguous information
  - Congestion (nasal, liver, sinus, pulmonary?)
  - Cramp (muscle, menstrual, abdominal?)
  - Pain (pain where?)
- Ambiguous abbreviations
  - MI (myocardial infarction or mitral incompetence?)
  - Decreased BS (breath sounds, bowel sounds or blood sugar?)

…Impact of Documentation on Coding AE Data

- Vague information
  - Patient felt “fuzzy”, “weird”, “experienced every adverse event”
- Non-specific information
  - “Left wrist edema” versus “Injection site edema left wrist”

Vignette #1…

- Vaccine clinical trials
- Patient calls 1 day after receiving first vaccine complaining of pain at injection site
- What other questions might you need to ask?
- How can CTCAE assist with this?

…Vignette #1

- Injection site reaction

1	2	3	4	5
Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection.				

- Pain

1	2	3	4	5
Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
A disorder characterized by the sensation of marked discomfort, distress or agony.				

Vignette #2…

- Patient comes in for PE after starting on a clinical trial which has known skin toxicities. The medical record note indicates that a rash was noted on patient's face and upper back.
- What other information about the rash AE will you need to know before selecting the correct AE term?

…Vignette #2…

- Papulopustular rash

1	2	3	4	5
Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death
A disorder characterized by an eruption consisting of papules (a small, raised pimple) and pustules (a small pus filled blister), typically appearing in face, scalp, and upper chest and back. Unlike acne, this rash does not present with whiteheads or blackheads, and can be symptomatic, with itchy or tender lesions.				

…Vignette #2…

- Rash acneiform

1	2	3	4	5
Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death
A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.				

…Vignette #2

- Rash maculo-papular

1	2	3	4	5
Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	-	-
A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritis.				

Vignette #3…

- Patient has a history of hypertension controlled on 1 medication. Baseline BP = 118/76.
- BP is a potential toxicity so patients are asked to maintain a BP log.
- After 2 weeks on study, BP has been slightly increasing with the last 3 readings 134/88, 134/82, and 136/84. Though asymptomatic, PI decides to increase current anti-hypertensive drug.
- What is the grade of hypertension?
- What is the impact on the grade if the PI decides to add a 2nd anti-hypertensive agent?

…Vignette #3

- Hypertension

BL: 118/76
Recent: 134/88, 134/82, and 136/84

1	2	3	4	5
Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)	Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated Pediatric: recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated	Stage 2 hypertension (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 Pediatric: Same as adult	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated Pediatric: Same as adult	Death
A disorder characterized by a pathological increase in blood pressure; a repeatedly elevation in the blood pressure exceeding 140 over 90 mm Hg.				

Benefits of Quality AE Data

- Selection of the correct AE term, grade and attribution may be complex
- Accurate and timely information about AEs is critical for research participant safety
- Quality AE data (i.e. term, severity and attribution) allows for better communication among sponsors, investigators, and regulatory agencies about drug/biologic products
  - Benefits medical professionals
  - Benefits patients

QUESTIONS

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