

NCI Common Terminology Criteria for Adverse Events (CTCAE) v3.0 and v4.0

Comparison and Summary of Changes

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Purpose, Scope and Advantages of the Revision

- Harmonize CTCAE with MedDRA
- Revise and update adverse events and severity indicators (grading) in the terminology
- Make the terminology machine interpretable, conforming to caBIG Vocabulary criteria
- Establish a formal, ongoing governance for future maintenance of CTCAE and continue to evolve CTCAE to better meet the needs of the users in academia, regulatory agencies and industry
 - CTCAE and MedDRA will be harmonized with each major MedDRA release, major CTCAE version releases will occur “no more often than every two years”
- CTCAE only available in English so far, while MedDRA is available in 10 languages
 - CTCAE use in non-English speaking regions will be facilitated



Organization and Responsibilities

- Revision was carried out as an open collaboration with twelve working groups
 - Organized by MedDRA SOC
 - Weekly online meetings starting in July 2008 up to February 2009
- Draft was released for public review in March 2009
 - Public review period until end of April 2009
- First release of v4.0 end of May 2009
 - Based on MedDRA v12.0



Major Changes CTCAE v3.0 to v4.0

- All AE terms are **single concept MedDRA LLTs (v12.0)**
- AE terms are grouped by 26 MedDRA SOCs, replacing the CTCAE category
- There are 790 AE terms including 26 “Other, specify” placeholders for documentation of verbatim terms
- Critical concepts in grades are now unique AE terms
- Grading aiming for consistency within SOCs
- Though the grading system is still 1-5, not all terms have all the grades
- Revised general guidelines for grade descriptions and provision of formal definitions for AE terms based on NCI Thesaurus



CTCAE v4.0 Browser

Example: Fatigue



Tabular

Definition

Related Terms

Factbox

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-



Tabular

Definition

Related Terms

Factbox

A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities.



CTCAE v4.0 Browser

Example: Fatigue

Tabular

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Chronic fatigue (Source: MedDRA)
Exhaustion (Source: MedDRA)
Exhaustion due to excessive exertion (Source: MedDRA)
Exhaustion due to exposure (Source: MedDRA)
Fatigability (Source: MedDRA)
Fatigability generalized (Source: MedDRA)
Fatigability lumbar (Source: MedDRA)
Fatigability of knees (Source: MedDRA)
Fatigue (Source: MedDRA)
Fatigue aggravated (Source: MedDRA)
Fatigue extreme (Source: MedDRA)
Fatigueability (Source: MedDRA)
Fatigueability generalised (Source: MedDRA)
Lassitude (Source: MedDRA)
Prostration (Source: MedDRA)
Tired all the time (Source: MedDRA)
Tired out (Source: MedDRA)
Tiredness (Source: MedDRA)
Washed-out (Source: MedDRA)
Weariness (Source: MedDRA)
Worn out (Source: MedDRA)

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Facts about CTCAE4 General disorders and administration site conditions: Fatigue

[CTCAE4 Adverse Event Fatigue](#)

[CTCAE4 Grade1](#) Fatigue relieved by rest

[CTCAE4 Grade2](#) Fatigue not relieved by rest; limiting instrumental ADL

[CTCAE4 Grade3](#) Fatigue not relieved by rest, limiting self care ADL

[CTCAE4 Grade4](#) -

[CTCAE4 Grade5](#) -



Removed Categories

- Category names that are broad, non-specific and include AE terms associated with multiple SOCs have been removed
 - Growth and Development
 - Hemorrhage/Bleeding
 - Pain
 - Syndromes
 - Death

- However:
 - CTCAE still has 4 death terms: Death NOS, Sudden death NOS, Death neonatal, Fetal death



Removed and Changed Terms

- Terms were deleted for any of these reasons:
 - Rarely or never reported
 - Duplicates (e.g. „Pharyngeal“ listed in GI and pulmonary categories)
 - Medical concepts were identified that better represent the AE in current oncology research or practice
- About 28% of the terms were multiple concepts and where split or mapped to only one MedDRA term, as appropriate
 - v3.0 **Fatigue (malaise, lethargy, asthenia)** (G1-4), v4.0 with 3 separate MedDRA LLTs **Fatigue** (G1-3), **Malaise** (G1-2), **Lethargy** (G1-2)

New Terms

- Addition of new terms supplying concepts that were missing and identifying new concepts
- Examples:
 - Missing concepts
 - Unintended pregnancy
 - Sleep apnea
 - New concepts
 - Reversible posterior leukoencephalopathy syndrome

Grading of Events

	v3.0	v4.0
Grade 1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**
Grade 4	Life-threatening or disabling	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE	Death related to AE

- ***Instrumental ADL:** preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- ****Self-care ADL:** bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.
- Semi-colon (;) represents „or“ in the new CTCAE tables.



Mapping Existing Data from v3.0 to v4.0

- Mapping of can be done at 2 levels
 - v3.0 Term to v4.0 Term
 - v3.0 Grade to v4.0 Grade
- NCI provides 2 freely available mapping documents for each one of these options
 - The Grade to Grade Mapping Document is much more granular and allows for a better representation of the actual data when converted
- The difference in granularity is due to the fact that a single v3.0 AE term can map to different MedDRA LLTs depending on grade. Example:

v3.0	v4.0
Allergic reaction (G1-5) - includes anaphylaxis (G4)	Allergic reaction (G1-5) <u>and</u> Anaphylaxis (G 3-5)
Liver dysfunction/failure (G2-5) - includes jaundice (as G2)	Hepatic failure (G3-5) - starting with mild encephalopathy. Abnormal LFTs, with appropriate grading, are in the SOC 'Investigations'.



Mapping Existing Data from v3.0 to v4.0

v3.0	v4.0
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Liver dysfunction/failure (G2-5) - includes jaundice (as G2)	Hepatic failure (G3-5) - starting with mild encephalopathy <u>and</u> Blood bilirubin increased (G1-4) is in the SOC 'Investigations' (defined as: "A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. An excess of bilirubin is associated with jaundice.")
Tinnitus (G2-4)	Tinnitus (G2-3)



Possible Implications when Switching to New Version

- Changes in safety profiles? - **unlikely**
 - Overall medical concepts remain unchanged
 - Precision in reported terms likely to improve significantly
- Shifts in numbers of cases in the different severity categories? - **possible**
 - Possible „downgrading“ of some AEs
 - Hepatic failure: previously any encephalopathy = Grade 4, new rules mild encephalopathy = Grade 3
 - Possible „upgrading“ of some AEs
 - Hypertension: cut-off moved from 150/100 down to 140/90 (reflects current accepted medical standards)
- Overall, changes appear driven by sound medical considerations



Be aware of (1)

Issues with definition of AE terms:

- Bronchial obstruction and Bronchial stricture
 - v4.0:
 - A disorder characterized by blockage of a bronchus passage, most often by bronchial secretions and exudates
 - A disorder characterized by a narrowing of the bronchial tube
 - Exactly the same grading information
- Presyncope and Dizziness
 - v4.0:
 - An episode of lightheadedness and dizziness which may precede an episode of syncope
 - A disorder characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking



Issues with naming conventions across terminology:

- Vaginal obstruction and Vaginal stricture
versus
Fallopian tube obstruction and Fallopian tube stenosis

Be aware of (3)

Grading not mutually exclusive/ overlap between concepts:

- Same description of grade 1 for Wound complication and Wound dehiscence
 - Incisional separation of $\leq 25\%$ of wound, no deeper than superficial fascia
- Overlap between concepts
 - Lethargy
 - Grade 1: Mild symptoms, reduced alertness and awareness
 - Grade 2: Moderate symptoms; limiting instrumental ADL
 - Depressed level of consciousness
 - Grade 1: Decreased level of alertness
 - Grade 2: Sedation; slow response to stimuli; limiting instrumental ADL
 - Grade 3: Difficult to arouse
 - Grade 4: Life threatening consequences
 - Grade 5: Death

Missing AE terms:

- Aphasia
 - Only Dysphasia up to grade 3 is covered
 - In contrast, Aphonia is a separate AE Term in addition to Voice alteration and Hoarseness

Be aware of (5)

Mapping issues:

v3.0 Adverse event/ Short name	v4.0 Adverse event term
Cardiac ischemia/infarction	Myocardial infarction
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS])	Hemolytic uremic syndrome
Nail changes	Nail loss
Hemorrhage/Bleeding – Other (Specify)	Vascular disorders – Other, specify



THANK YOU for your attention!

- National Cancer Institute, Common Terminology Criteria for Adverse Events v4.0. NCI, NIH, DHHS. May 29, 2009
 - <http://biomedgt.nci.nih.gov/wiki/index.php/Category:CTCAE4> (web-based CTCAE browser)
 - http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.02_2009-09-15_QuickReference_8.5x11.pdf (pdf download)
- The cancer Biomedical Informatics Grid (caBIG®) program Vocabulary Knowledge Centre
 - <https://cabig-kc.nci.nih.gov/Vocab/KC/index.php/CTCAE>
- National Cancer Institute, Centre for Bioinformatics. Redesign and Life Cycle Management of the Common Terminology Criteria for Adverse Events (CTCAE). August 19, 2009