National Cancer Institute

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

The National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE) v4.0 is a list of terms used in the designation, reporting, and grading of adverse events (AEs) that occur in oncology research. CTCAE defines each AE term and associates it with a rating scale of severity, which is used to define protocol parameters, and to indicate which AEs are reasonable to document, report, and analyze for patient safety.

The NCI CTCAE v4.0 is harmonized with the Medical Dictionary for Regulatory Activities (MedDRA), a clinically validated international medical terminology that is used by regulatory authorities and the biopharmaceutical industry throughout drug development and regulatory processes. MedDRA is the AE classification dictionary endorsed by the International Conference on Harmonization (ICH).

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.					
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25-<50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characterized by the inability of the bone marrow to produce hematopoietic elements.					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors.					

History of CTCAE v4.0

The NCI Cancer Therapy Evaluation Program (CTEP) developed the original Common Toxicity Criteria (CTC) in 1982 for reporting AEs that occurred during chemotherapy trials. In 1998, the list of terms was expanded from 49 to nearly 300, and in 2003, the list was revised again to include 1,059 AE terms. The expanded list was renamed as CTCAE v3.0. CTCAE v4.0 has been developed to account for the volumes of new clinical information that have become available since 2003.

The Need for CTCAE v4.0

Data standardization is required for information to be shared over IT systems—such as caBIG®—that support clinical and basic research. In oncology research especially, it is critical to systematically monitor AEs so that new drugs and treatment regimens may be investigated and made available to patients. CTCAE v4.0 provides the vocabulary to enable such standardization and data sharing.

Categories of Use

- ☐ Biospecimens
- ■ **Clinical Trials Management**
- ☐ Data Analysis & Statistical Tools
- ☐ Data Sharing
- ☐ Genome Annotation
- ☐ Infrastructure
- ☐ Imaging
- ☐ Microarrays
- ☐ Pathways
- ☐ Proteomics
- ☐ Translational Research
- ■ **Vocabularies**

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

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caBIG® cancer Biomedical Informatics Grid®

CTCAE v4.0 Capabilities

- Aid in AE recognition and severity grading, and monitor safety data for regulatory reporting
- Define oncology research protocol parameters such as eligibility criteria, dose-limiting toxicity, maximum tolerated dose, and dose modification
- Facilitate the evaluation of new cancer therapies, treatment modalities, and supportive measures
- Standardize AE reporting across groups and modalities within the NCI oncology research community

Using CTCAE v4.0

Organization

CTCAE terms are a subset of MedDRA Lowest Level Terms (LLTs) and are listed within their MedDRA primary System Organ Class (SOC). Within the 26 SOCs, AE terms are associated with a 5-point grading scale, although not all grades are appropriate for all AE terms.

AE Term Definitions

CTCAE v4.0 includes text definitions for each AE term to promote consistent description and understanding of AEs. Definitions in the current version were drawn from the NCI Thesaurus, focusing on the terms which are most important in correctly describing adverse events, and subsequently reviewed and modified to meet the needs of CTCAE users.

CTCAE v4.0 and Related Resources

The NCI CTCAE v4.0 data files and related documents, including frequently asked questions and a Wiki, are available online at http://evs.nci.nih.gov/ftp1/CTCAE/About.html. Users are encouraged to leave comments on the Wiki since user feedback will help guide future development of AE text definitions.

Resources

Overview	https://cabig.nci.nih.gov/workspaces/VCDE/workspaces/VCDE/CTCAE
Primary Workspace	Vocabulary and Common Data Elements (VCDE) https://cabig.nci.nih.gov/workspaces/VCDE
Vocabulary Knowledge Center	https://cabig-kc.nci.nih.gov/Vocab/KC/index.php
CTCAE Wiki	http://biomedgt.nci.nih.gov/wiki/index.php/CTCAE4
caBIG® Support Service Providers	https://cabig.nci.nih.gov/esn/service_providers
CTCAE Support	ncictcaehelp@mail.nih.gov

Clinical Trials Compatibility Framework Components

Cancer Central Clinical Database (C3D); Cancer Adverse Event Reporting System (caAERS); Patient Study Calendar (PSC)

Key Contributors:

- NCI Cancer Centers Program and Cooperative Groups
- Medical Dictionary for Regulatory Activities Maintenance and Support Services Organization (MedDRA MSSO)
- Pharmaceutical Research and Manufacturers of America (PhRMA)
- U.S. Food and Drug Administration (FDA)
- Cancer Therapy Evaluation Program (CTEP)
- NCI Center for Biomedical Informatics and Information Technology (NCI CBIIT)

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