Redesign and Life Cycle Management

of the Common Terminology Criteria for Adverse Events (CTCAE)

Document Revision History

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1.0	Sep 1, 2008	Rajni Samavedam	Baseline version
1.1	Nov 24, 2008	Ranjana Srivastava	
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Version	Date	Changed by	Description
8.1	Jul 8, 2009	Ranjana Srivastava	Incorporated changes from Ann, Larry and Frank Hartel
8.1+Larry	July 9, 2009	Larry Wright	Provided missing sections and other edits
8.2	Jul 24, 2009	Ranjana Srivastava	Editing and formatting
9.0	Jul 29 – Aug 6, 2009	Marylyn King	Reorganized sequence and levels of headings; reformatted from scratch with a clean template; edited content for grammar and punctuation, clarity, and consistency; corrected hyperlinks to web sites; inserted auto cross-references within the document; added to the list of acronyms; formatted sources to match Modern Language Association (MLA) bibliographic style; regenerated TOC, LOT, LOF.
9.1	Aug 17, 2009	Marylyn King	Corrected the degrees and affiliations for participating members Dr. Lee Soo-Chin and Dr. Robert Lim. Also corrected alphabetizing of participating members.
9.2	Aug 19, 2009	Marylyn King	Incorporated corrections from MSSO review.

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Introduction to CTCAE

The National Cancer Institute (NCI), within the National Institutes of Health (NIH), is the principal federal agency for conducting and sponsoring research on cancer, training cancer researchers, and disseminating cancer information to the research community and to the public. The cancer Biomedical Informatics Grid (caBIG®) program serves as the foundation of NCI's biomedical informatics efforts to transform cancer research into a more collaborative, efficient, and effective endeavor. caBIG® is collaboratively created and deployed by a nationwide consortium of cancer research centers, in partnership with the NCI. caBIG® provides the overarching infrastructure to support interoperability among existing databases, knowledge stores, and software tools in terms of rules, processes, and vocabularies, to support interoperability. caBIG® draws on participation from multiple cooperating centers to ensure that the user community's needs are appropriately addressed, and that stakeholders across the enterprise will embrace the emerging vocabulary harmonization and data exchange standards. NCI has defined domain workspaces representative of the scientific focus of the different participating cancer centers. Additionally, two cross cutting workspaces, the Architecture Workspace and Vocabularies and Common Data Element (VCDE) Workspace, provide unifying frameworks, methodologies, representations, and terminologies. The VCDE Workspace is responsible for evaluating and integrating systems for vocabulary and ontology content development, as well as software systems for content delivery. It is also responsible for developing standards for the representation of ontologies and vocabularies, as well as assessments of existing systems proposed for use within caBIG®. In addition, VCDE has the responsibility for vocabulary and ontology content development, when specific and required content does not exist in a form usable by caBIG®.

The Cancer Therapy Evaluation Program (CTEP) sponsors clinical trials to evaluate new anti-cancer agents, and forges broad collaborations within the research community, including pharmaceutical and biotechnology industries, to develop new cancer treatments. The Investigational Drug Branch (IDB) implements and oversees the investigational experimental therapeutics program. IDB collaborates with academia and industry through NCI-funded grants and contracts to carry out the clinical evaluation of the novel drugs. IDB develops drug developmental plans; monitors clinical trials for safety, efficacy, and clinical pharmacology; and investigates and prepares reports concerning adverse events for all Investigational New Drugs (IND).

Purpose and Scope of CTCAE

The Common Terminology Criteria for Adverse Events (CTCAE) was first published under that name as v3.0 in 2003 by CTEP. It comprised a list of Adverse Event (AE) terms commonly encountered in oncology accompanied by a severity grading scale for each AE. The purpose of the CTCAE is to provide standards for the description and exchange of safety information in oncology research to, in turn, facilitate the evaluation of new cancer therapies, treatment modalities, and supportive measures for defining protocol parameters (such as maximum tolerated dose and dose modification) and comparing safety profiles between interventions. Since the adoption of MedDRA® (Medical Dictionary for Regulatory Activities) terminology by the ICH (International Conference on Harmonization), NCI, industry, and regulatory bodies

identified a need for CTCAE revision and harmonization with MedDRA. The revised CTCAE v4.0 standards include:

- A set of AE terms that are MedDRA Lowest Level Terms (LLTs), are organized in MedDRA System Organ Class (SOC) groupings, and that:
  - Promote consistency in AE term reporting across groups and modalities.
  - Are referenced in oncology studies to define parameters such as eligibility criteria, dose modification, dose limiting toxicity, and maximum tolerated dose.
  - Are signs, symptoms, laboratory values, and diagnoses of AEs commonly monitored in oncology research studies.
- A severity grading scale that:
  - Includes specific clinical findings and/or measurements of impact on the study participant.
  - Promotes consistency within a given grade across a System Organ Class.
  - Provides guidance in the evaluation and documentation of severity of the AE.
  - Facilitates a common understanding of data shared among academic, commercial, and regulatory entities.

Statement of intended use

CTCAE is intended for use by a wide range of health care, scientific, and administrative personnel:

- Clinicians, investigators, nurses, clinical research associates (CRAs)
- Data managers
- Study coordinators
- Statisticians
- Medical and technical writers
- Regulatory personnel
- Pharmaceutical companies
- Information technology personnel
  - Other oncology research-associated personnel

Users will be better able to systematically monitor AEs linked to oncology research and to evaluate safety outcome data of clinical trials.

Impetus for revision and inception of CTCAE v3.0 revision project

MedDRA MSSO (Maintenance and Support Services Organization) Blue Ribbon Panel in April 2006 determined that a mechanism to ‘translate’ or ‘convert’ CTCAE terms to MedDRA terms must be established in order to facilitate data exchange within internal databases and between investigators and regulatory authorities for the purpose of Serious Adverse Event (SAE) reporting. CTEP and FDA (Food and Drug Administration) agreed upon CTCAE revision to be MedDRA compliant at the AE term level.

In order to increase the accuracy of AE reporting and the usability of the terminology, the caBIG® VCDE Workspace performed a review of CTCAE v3.0 terminology. Jim Cimino of the VCDE Workspace conducted the review and presented the results to the caBIG® Workspace in 2007. Based on the VCDE vocabulary criteria, Cimino concluded that:

- CTCAE v3.0 does not meet most VCDE vocabulary criteria and is not a true controlled terminology.
- Harmonization with MedDRA is an issue.
- Codes should be used as pointers.
- Lack of standard governance and content maintenance is an issue.
    - Lack of formal evaluations of content is an issue.

NCI Center for Biomedical Informatics and Information Technology (CBIIT), via the caBIG® initiative, and CTEP collaborated to revise CTCAE v3.0.

The goals of the CTCAE revision project were to:

- Harmonize CTCAE with MedDRA,
- Revise and update adverse events and severity indicators in the CTCAE terminology,
- Make the terminology machine interpretable conforming to caBIG® vocabulary criteria,
    - Establish a formal life-cycle governance for future maintenance of CTCAE,

Criteria to be addressed in the CTCAE 3.0 revision

The VCDE group identified several areas for improvement. These included:

1. Harmonization with MedDRA:

   CTEP mandates CTCAE for AE reporting, while industry adheres to MedDRA, the ICH standard for regulatory reporting. Industry, regulators, and the NCI are best served by harmonizing CTCAE with MedDRA in the spirit of international collaboration and standardized data exchange.

2. Establishment of a stable governance structure:

   a) Establish on-going maintenance and extension policies and procedures.

   b) Establish an editorial process with documentation, explicit rules for content versioning, community participation, and decision making.

   c) Establish policies and process for archival storage of versions and version management.

   d) Provide training and conduct outreach activities.

3. Inclusion of text definitions for both AE terms and severity grades.

4. Development of formats that are machine-readable (OWL and RDF), file serialized (XLS and XML), and human-readable (PDF).

The redesign phase

During the period June 2008 to May 2009, CTCAE v3.0 was redesigned to address the shortcomings described in Jim Cimino's review.

Stakeholders and participants

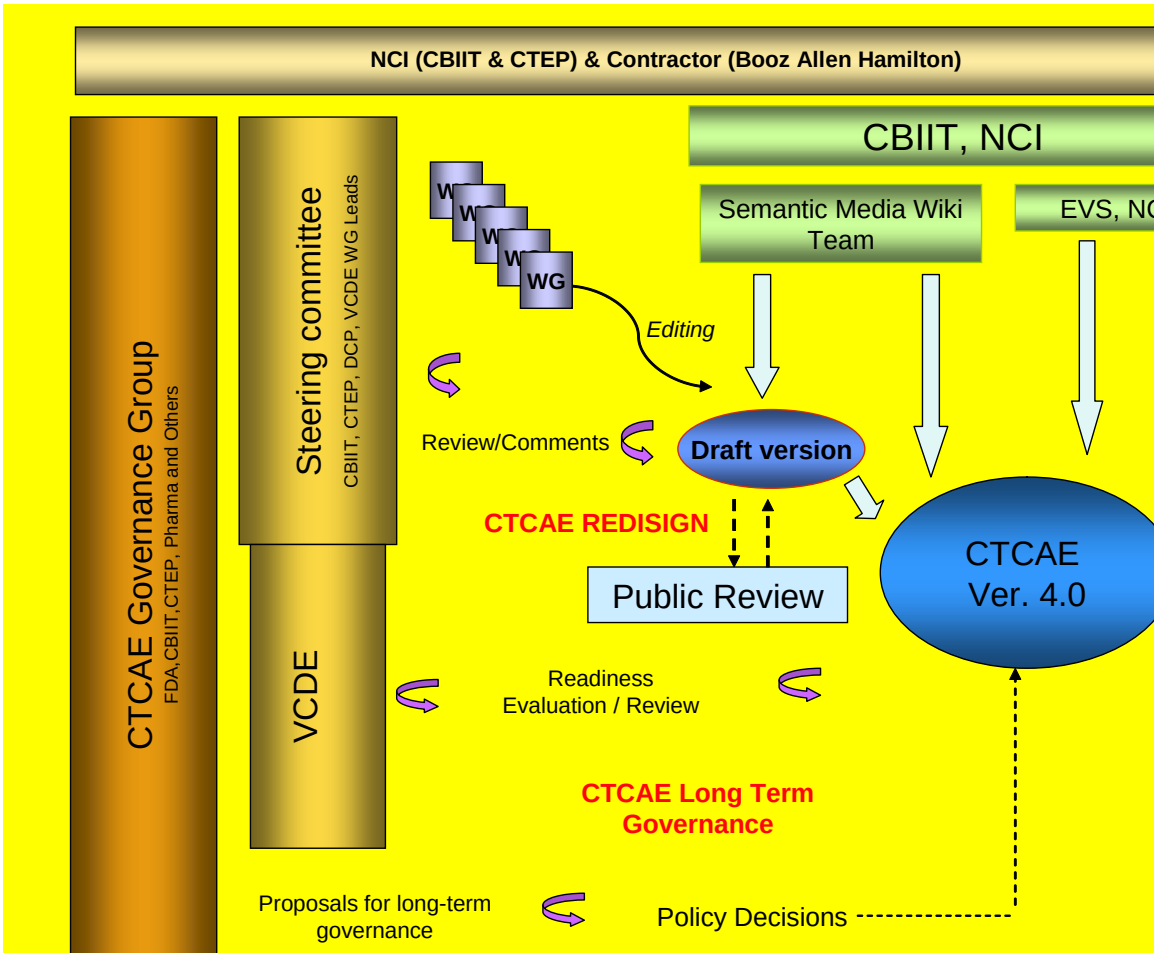
CTCAE revision was carried out with very broad participation from the oncology community, directly involving about 170 members from various organizations (see Table 1).

Table 1: Stakeholder Distribution

Stakeholder Organization	Number of participants
NIH	42
FDA	3
PhRMA (Pharmaceutical Research and Manufacturers of America)	23
Cooperative Groups; Academic Institutions	40
Cancer Centers	29
International	12
Other	5

Oversight and coordination of the CTCAE revision effort was provided by NCI (CBIIT and CTEP) in collaboration with the project contractor (Booz Allen Hamilton). The program staff refined the overall Project Management Plan, detailed schedules, resource allocation, and risk mitigation strategies. A governance structure to coordinate the revision activities was developed and implemented. The governance structure included 12 Work Groups (WG), a Steering Committee (SC) and a Governance Group with support provided from additional groups, as depicted in Figure 1 (see below). Participants were recruited from various government agencies (FDA, NCI-CBIIT, NCI-CTEP, DCCPS, DCP), private industry (PhRMA), and academia. For a list of participating members, see Appendix A: Participating Members.

Figure 1: Organizational Structure for CTCAE 3.0 Redesign



The project team leveraged Web 2.0 technology (Semantic Media Wiki) to engage subject matter expertise. Consequently a diverse group of people with different backgrounds and needs contributed to the project. Involving a diverse group of stakeholders helped ground the CTCAE revision in practical reality and ensured information gained from the evaluation benefits all participants as well as the overall community.

CTCAE Work Groups

Twelve Work Groups (WGs) were organized by MedDRA SOCs based on member expertise (*see* Appendix B: Work Group Organization), and each WG was assigned CTCAE v3.0 AE terms and candidate v4.0 terms. WG members attended weekly teleconference calls and edited the terminology using a collaborative editing tool, the BiomedGT Wiki.

The responsibility of the WGs was to revise the CTCAE content to meet the goals of the revision project. Each WG was represented by a WG lead who was responsible for coordinating and finalizing work in conjunction with NCI, other project members, and also served as the WG representative to the Steering Committee.

CTCAE Steering Committee

The Steering Committee (SC) served as a strategic and guiding body to provide project oversight and coordination across the CTCAE WGs. The goal of the SC was to maintain an overall balance of perspective in the CTCAE, provide oversight of day-to-day activities of the WGs, and to address cross-WG issues. In addition, the SC reviewed proposed revision content and provided feedback to the WGs. The SC was comprised of members from NCI (CBIIT and CTEP), VCDE, MedDRA MSSO, WG leads, and members from the research community. NCI staff from CBIIT and CTEP acted as Chairs of the SC and participated in bimonthly virtual meetings to provide recommendations and guidance. The voting structure for the SC was by majority. The committee chairs made the deciding vote when a majority was not reached. Work Group leads abstained from voting on issues pertaining to their own WG.

CTCAE Governance Group

The Governance Group (GG) developed the strategic vision for CTCAE and contributed toward the development of CTCAE by providing guidance and oversight. It provided recommendations for the long-term governance of CTCAE including maintenance, extension, training, education, outreach, advertisement, and quality control. The GG was comprised of members from NCI (CBIIT and CTEP), the FDA, Cooperative Groups, MedDRA MSSO, and pharmaceutical companies. All members remained on the GG until the release of CTCAE v4.0 with the option to participate in long-term governance of CTCAE.

Support groups

Semantic Media Wiki Team

The Semantic Media Wiki Team provided a collaborative terminology development tool (BiomedGT) for editing the CTCAE. This Wiki was developed by the NCI Center for Bioinformatics and the Mayo Clinic Division of Biomedical Informatics with contributions from Apelon, Inc., Northrup Grumman, and Dionne-Associates Inc. Terminology content was converted into LexGrid format as a stand-alone source in order to make it available to the caBIG® community and other interested users. The Wiki team was also responsible for periodic updates and version releases, and for report generation

NCI Enterprise Vocabulary Services (EVS)

Initial definitions for the CTCAE terms were provided by the NCI EVS based on NCI Thesaurus (NCIt) definitions already existing or written for this effort. EVS reviewed definition comments and draft revisions, and made additional changes in conjunction with CTCAE staff to create a final set of CTCAE definitions. Matching NCIt concepts were identified or created for all CTCAE AE terms, with mapping of codes between the two terminologies so that all CTCAE AE terms would have direct mappings to NCI's core reference terminology, and so that NCIt synonyms, description logic ontology modeling, and other resources can be leveraged by CTCAE users without having to be recreated in CTCAE itself.

caBIG® VCDE Group

The caBIG® VCDE Group provided expertise to ensure CTCAE compatibility with caBIG® standards, and developed the initial plan for content representation and for CTCAE maintenance and extension. The VCDE Group also carried out a readiness evaluation prior to the release of CTCAE v4.0.

Program contractor

Booz Allen Hamilton was the program contractor and was responsible for managing the operations of the CTCAE revision process, establishing initial governance process, and ensuring coordination across all CTCAE entities. The program contractor also organized two face-to-face meetings with the Governance Group to discuss the strategic vision and the long-term governance of CTCAE. All WG, SC, and Governance Group meetings were organized and facilitated by the program contractor.

The program contractor successfully recruited over 170 participants from government, academia, and PhRMA to participate in the CTCAE revision project. The program contractor facilitated 12 WGs, the SC, and the Governance Group to revise the adverse event terms, the grades. and the structure of CTCAE. The program contractor also provided project management to ensure the CTCAE groups, the Semantic Media Wiki Team, the caBIG® Vocabulary Knowledge Center, and the caBIG® VCDE Group were coordinated. Finally, the program contractor provided detailed analysis of the updated CTCAE to ensure consistency across the AE terms and grades.

Table 2 summarizes roles and responsibilities of each group, which the program contractor coordinated, during the CTCAE redesign phase.

Table 2: Summary of roles and responsibilities of participants in CTCAE redesign phase

Area of responsibility	Responsible group	Responsibilities	Participants
Oversight	CBIIT & CTEP	• Set priorities and direction • Defined the structure and processes to be used during the CTCAE revision • Prioritized and scheduled content submitted to the WGs • Ensured coordination with other NCI initiatives and activities	CBIIT & CTEP staff
Strategic Vision & Future Governance	Governance Group	• Set the strategic vision for CTCAE • Reviewed each draft of CTCAE v4.0 • Assessed impact on cancer centers, cooperative systems, FDA policies, and CTEP system • Provided guidance on future governance of CTCAE	CBIIT, CTEP, DCP, FDA, MedDRA MSSO, PhRMA

Area of responsibility	Responsible group	Responsibilities	Participants
Interface between redesign and normal revision	Steering Committee	• Provided domain expertise and leadership • Interfaced between WGs and Governance Group • Addressed cross-WG issues and ensured uniformity across WGs • Reviewed user community feedback and its implementation. • Reviewed the drafts of the each revision.	Chairs – staff of CBIIT and CTEP CBIIT, CTEP, VCDE, MedDRA MSSO, WG Leads
Redesign	Working groups	• Evaluated content quality. • Edited the terminology using the BiomedGT Wiki tool. • Provided expert comments and discussion on the terminology • Was responsible for timely completion of the assigned work	Subject matter experts
	Semantic Media Wiki Team	• Provided the collaborative terminology development tool (BiomedGT) for editing the terminology • Performed periodic updates to the terminology and generated reports of the updated terminology when necessary • Provided periodic version releases • Made the terminology available in various formats	CBIIT, Division of Biomedical Statistics and Informatics, Mayo clinic.
	VCDE Review Group	• Ensured the terminology is caBIG® compatible using several compatibility and review criteria • Performed a readiness evaluation of the terminology	caBIG®

Area of responsibility	Responsible group	Responsibilities	Participants
Project oversight	Program contractor	• Ensured coordination across the CTCAE entities • Developed standard operating procedures for review and updates of CTCAE terminology post version 4.0 • Established and communicated initial governance and priorities • Was responsible for oversight of initiative activities • Conducted WG sessions for revision. • Reported progress to CBIIT and CTEP staff	Booz Allen Hamilton

Process and standard operating procedures (SOPs)

See Figure 2 for an illustration of this process.

1. Potential WG participants were recruited based on suggestions from CBIIT, CTEP, and an open call to the general cancer research community.
   a) An invitation letter was sent to potential participants.
   b) Those expressing interest in the project were sent orientation packages with information regarding the project. Feedback regarding why individuals did not participate was solicited to more efficiently recruit participants in future.
   c) Those committed to the project were divided among the 12 WGs based on their interest and field of expertise.
   d) BiomedGT Wiki site was redesigned to display CTCAE 3.0 terms and grades in a tabular format.
   e) Simultaneously the SC and Governance Group were constituted based on NCI recommendations.
   f) The WGs conducted revision via BiomedGT Wiki with oversight and guidance from the SC Chairs and the program contractor, Booz Allen Hamilton. Unresolved WG issues were addressed and resolved by the SC during bimonthly meetings.
2. Preparatory to the revision work, participants attended educational sessions to obtain understanding of the background and goals of the project and as well as an introduction to the tools (e.g., GForge, BiomedGT Wiki, Centra, etc.)
   a) User accounts were established for each participant.
3. Revision process was commenced to create the initial draft of CTCAE v4.0.

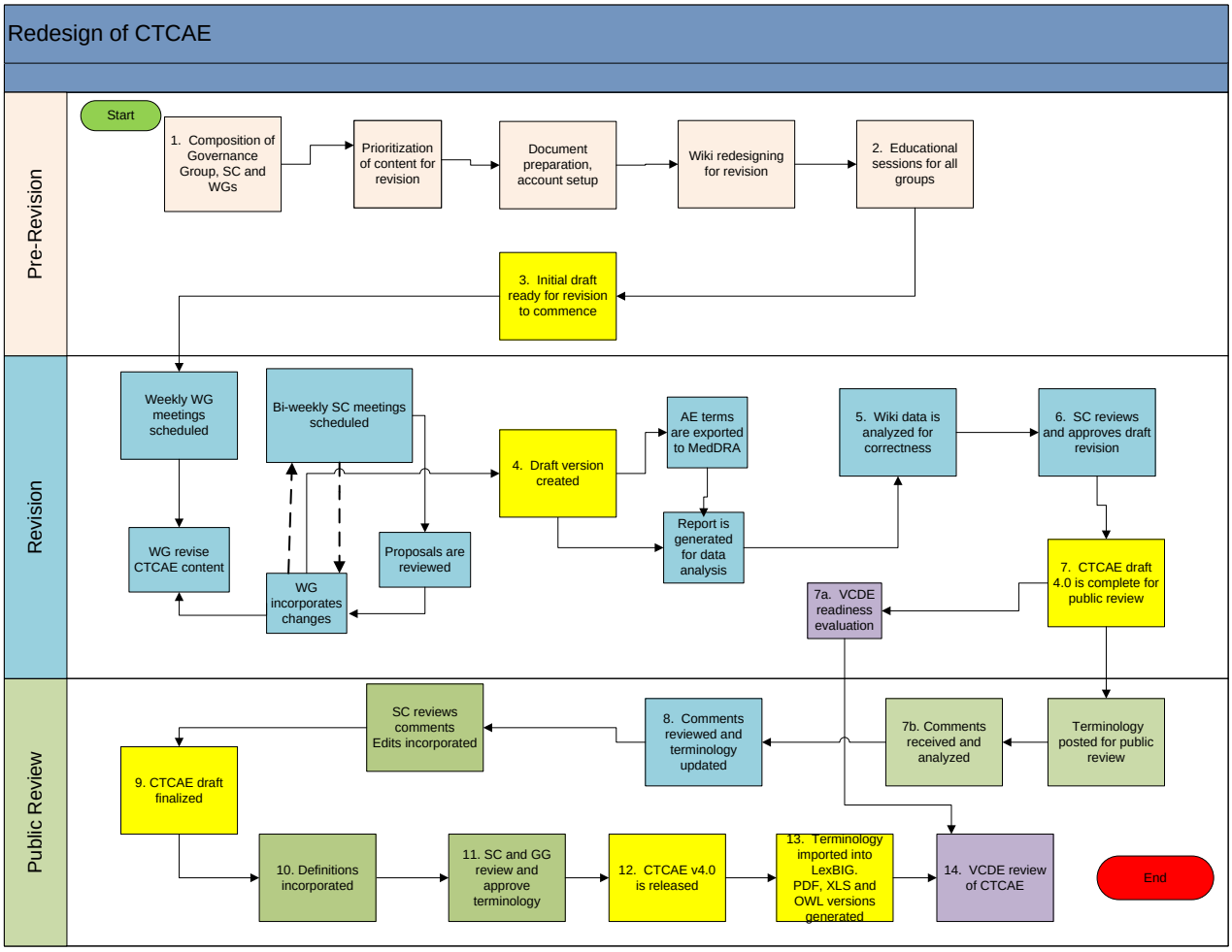
a) Weekly WG meetings were scheduled based on member availability.

b) The SC met on a biweekly basis to discuss any cross-WG issues and voted on issues raised for approval.

c) Feedback from SC was sent to the WG to incorporate changes into the draft terminology.

4. Draft version of the terminology was created.
   a) The BiomedGT Wiki tool was locked.
   b) The proposed AE terms were exported to MedDRA to check for accuracy. If a term did not exist in MedDRA, either MedDRA was requested to include the term or a similar MedDRA term was included in CTCAE.
5. The QC process involved identification and removal of duplicates and correction of spelling and grammatical errors. (*See* Appendix D: Editorial Guidelines.)
6. After validation the report was sent to the SC for review and approval.
7. CTCAE draft was posted for public review.
   a) The VCDE group evaluated the terminology and documentation to ensure readiness for the VCDE review.
   b) Comments from public review were collected, analyzed, and sorted by WGs.
8. The WGs reconvened to review and update the terminology.
9. Final draft of CTCAE was compiled.
10. Textual definitions of AE terms were developed and revised by the NCI's EVS group.
11. CTCAE draft was reviewed and approved by the SC and Governance Group.
12. CTCAE v4.0 was released.
13. The terminology was imported into LexBIG and the PDF, XLS, and OWL versions were generated.
14. Final evaluation of CTCAE v4.0 was done to verify compliance with caBIG® review criteria.

Figure 2: CTCAE Redesign Process



Life cycle governance

The redesign process (section 2.1, above) was defined and implemented to update CTCAE v3.0 to v4.0, but also to provide an ongoing governance framework to maintain CTCAE through future revision cycles. The Governance Group was charged with addressing these issues, drawing on its broad stakeholder base and range of experience. The first Governance Group meeting convened September 2008 and identified five areas as important for long-term maintenance of CTCAE:

- Maintenance and extension, including identification of major and minor changes
- Training and education
- Documentation and advertisement
- Tools and Reporting
- QA/QC

Based on these areas, five subgroups were created with volunteer membership from the Governance Group. Each subgroup provided policy recommendations that were discussed and incorporated into the final plan.

At the second Governance Group meeting, in February 2009, it was agreed that NCI should continue having primary responsibility for CTCAE, rather than transferring it to some joint or outside entity. NCI proposed a management framework for CTCAE that included an NCI Core Committee, an extended Community-based Committee, the caBIG® Vocabulary Knowledge Center (VKC) at the Mayo Clinic, and NCI Enterprise Vocabulary Services (EVS). The Governance Group agreed with this framework, and also on the major aspects of maintenance process, versioning, release cycles, training and education, documentation, quality assurance, and technical approach.

Stakeholders and participants

The plan for maintenance and curation of CTCAE will be ongoing and funded by NCI.

NCI Core Committee

A Core Committee of NCI (CTEP, DCP, others) domain experts will work with and support CBIIT administrators in supporting the ongoing maintenance of CTCAE. The NCI Core Committee will have the executive role in the governance of CTCAE.

Community-based Committee

A Community-based Committee, consisting of members from FDA, the PhRMA, clinical researchers, MedDRA MSSO, Cancer Centers, Cooperative Groups, and others, will be established to serve as stakeholder consultants to work with the Core Committee. Procedures regarding CTCAE will be addressed by this collective group.

caBIG® Vocabulary Knowledge Center (VKC)

The VKC serves as the steward of tools and documentation within the vocabulary domain. VKC provides access and support to individuals and institutions interested in utilizing or extending the vocabulary tools.

NCI Enterprise Vocabulary System (EVS)

NCI EVS staff is responsible for curation of ongoing changes to the CTCAE.

Table 3 shows a summary of the roles and responsibilities of participants in CTCAE future governance.

Table 3: Roles and responsibilities in CTCAE future governance

Responsible group	Responsibilities	Participants
NCI Core Committee	• Analyze queries and responses and requests for future updates • Determine if change requests are major or minor • Initiate major redesigns as appropriate • Maintain the change request record • Create documentation and training material • Interact with Community-based Committee and VKC	NCI(CBIIT, CTEP and DCP)
Community-based Committee	• Provide subject matter expertise input into terminology • Provide recommendations to NCI Core Committee regarding major/ minor changes • Review relevant documentation and training material	NCI, FDA, Physicians, Academicians, MedDRA MSSO, PhRMA, Statisticians, CRAs, Cancer Centers, Cooperative Groups
Vocabulary Knowledge Center	• Store queries and responses, and requests for future updates • Maintain evolving FAQ • Distribute documentation about CTCAE • Provide instructions on how to download, and help on resolving problems and bugs • Post advertisement and announcements • Compile incoming and outgoing information and communicate the same to Core Committee • Provide the resource (email, Web page,, etc.) that the public will use to make requests and ask questions	Mayo Clinic, Rochester, MN
NCI EVS	• Receive approved changes from NCI Core Committee for implementation • Provide ongoing editing and production support • Create and maintain the change history record	NCI EVS

Process and SOPs

Major aspects of maintenance process, versioning, release cycles, training and education, documentation, quality assurance, and technical approach were agreed on, and these points are presented below. Given the broad range of stakeholders and the evolving technical and standards environment, some aspects (e.g., some details of versioning cycles) were left open to further discussion and decision within the agreed management framework.

Maintenance and extension

A clear framework for change suggestions, decisions, and versioning is central to the new CTCAE lifecycle process. Decisions regarding change requests will be based on explicit criteria regarding possible types of changes (e.g., to AE term, Grade, etc.), the expected impact of changes, the decision-making process appropriate to each type of change, and the way such changes will be rolled up and labeled in successive versions of the terminology. Two illustrative examples of such requests and evaluation criteria are given in Table 4 below.

Table 4: Criteria for inclusion of change request: Two examples

Criterion	Example	'Good' or 'Bad' Change
Medical and/or scientific justification supported by current oncology practice	Some new targeted therapy interventions may result in previously unseen cutaneous eruptions described in the literature as papulopustular rash. Although little is known about their etiology and pathogenesis, there is evidence that the appearance of these eruptions is associated with improved clinical response and/or prolonged survival.	'Good' change: The need existed to consistently characterize this skin reaction. Neither CTCAE nor MedDRA listed papulopustular rash so the term was added to both.
Adherence to general guidelines for severity grades	Request to modify a lab value grading scale with increased tolerance in severity for a single study	'Bad' change: The current guidelines for grades incorporate critical thresholds in severity scales where low-grade events (1 or 2) are considered tolerable and manageable, clearly distinguished from severe or high-grade events (3 or 4).

Critical to the ongoing governance of CTCAE is classification of change requests as major or minor.

Minor changes may consist of:

- Error correction (e.g., within a Grade description the use of "and" appears between clinical descriptors when a semi-colon is correct [read as "'or"])

- Editorial correction (e.g., typographical, punctuation)
- SOC reallocation for an AE term due to MedDRA version changes

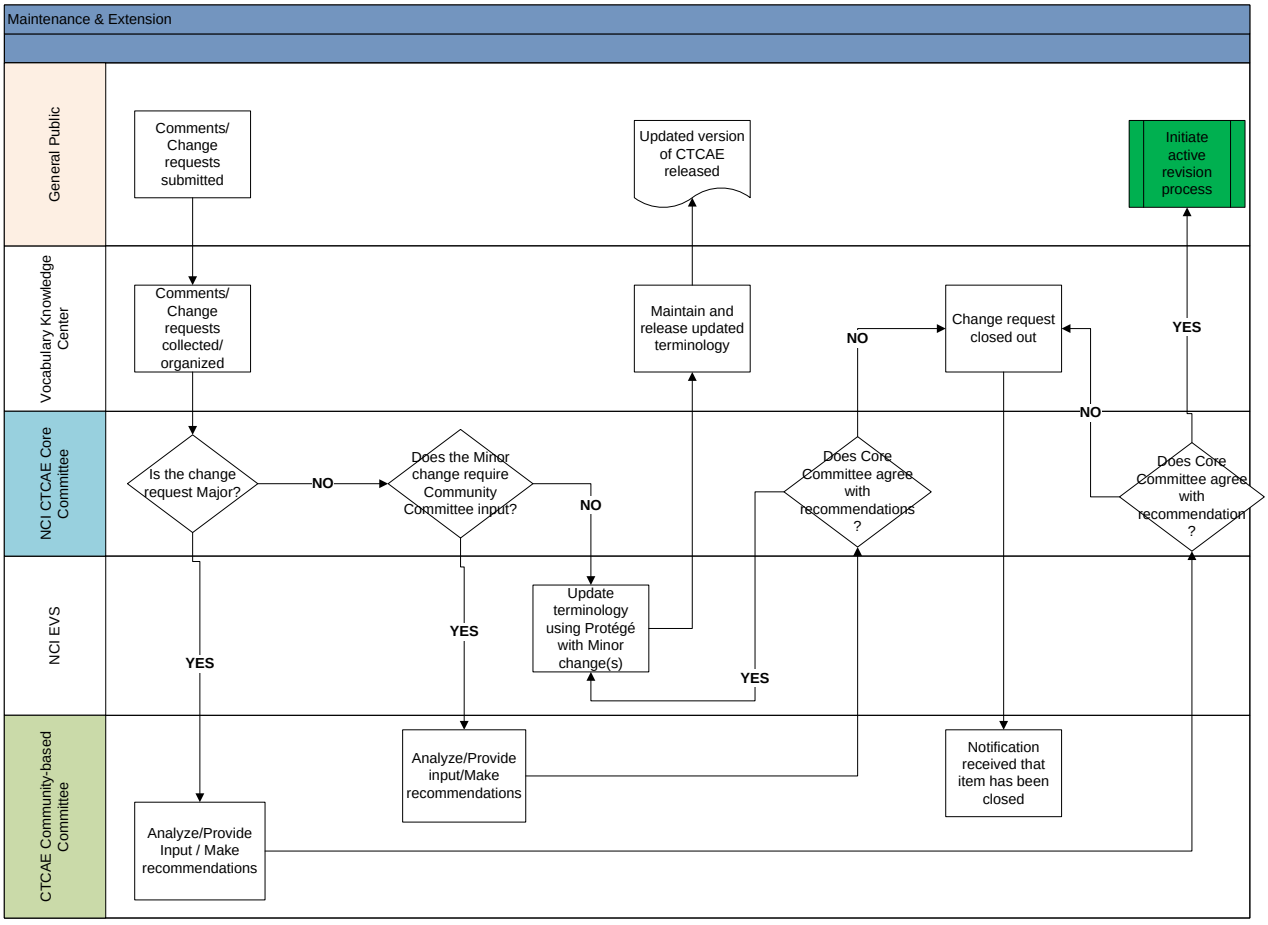
Major changes may consist of:

- Addition of new AE terms (MedDRA LLTs)
- Extraction of a critical concept within the description of a Grade to list as an AE term
- Existing grading scales revisions
- Addition of new SOC if mandated by MedDRA

Although the CTCAE governance structure is new, it is estimated that a new version of CTCAE will occur every two years in March to coincide with alternating major releases of MedDRA. (MedDRA is updated semiannually, with a major release each March and a minor release each September.) For major revisions to CTCAE, the BiomedGT Wiki will be used to gather proposals from SMEs in the WGs. Minor revisions to CTCAE will be managed in Protégé by NCI EVS.

See Figure 3 for an illustration of the CTCAE maintenance and extension process.

Figure 3: CTCAE maintenance and extension process



The process includes the following steps:

1. Determination of the nature of the change request.

   The VKC will serve to collect and aggregate comments received from the public. These will be sent to the NCI Core Committee to determine if the change requests are major or minor.

   a) If a request is identified as major, it will be sent to the Community-based Committee for discussion.

   b) If the request is identified as minor, it will be addressed by the NCI Core Committee.

      The NCI Core Committee will draft exact content to be changed and forward it to NCI EVS, which will update the terminology. After edits have been made, the VKC will release an updated version of CTCAE. In case of any conflicts, the NCI Core Committee will make a decision for its resolution.

2. Engagement of the Community-based Committee.

   The Community-based Committee will be engaged for any major change requests. This committee will determine if the justification of the request merits possible inclusion during the next revision and provide recommendations to the NCI Core Committee. The Community-based Committee may also be consulted for recommendations on minor change requests. The Community-based Committee will also work with the NCI Core Committee to provide strategic direction and vision of CTCAE going forward.

3. NCI Core Committee's evaluation of Community-based Committee recommendations.

   The Community-based Committee will send recommendations to the NCI Core Committee for a decision on whether to implement the change request. If the NCI Core Committee disagrees with the Community-based Committee, the NCI Core Committee will make a decision for resolution of the change request. The final decision of the NCI Core Committee will be communicated to the Community-based Committee and the VKC to document, close out the request, and notify the person/group submitting the change request.

Training and education

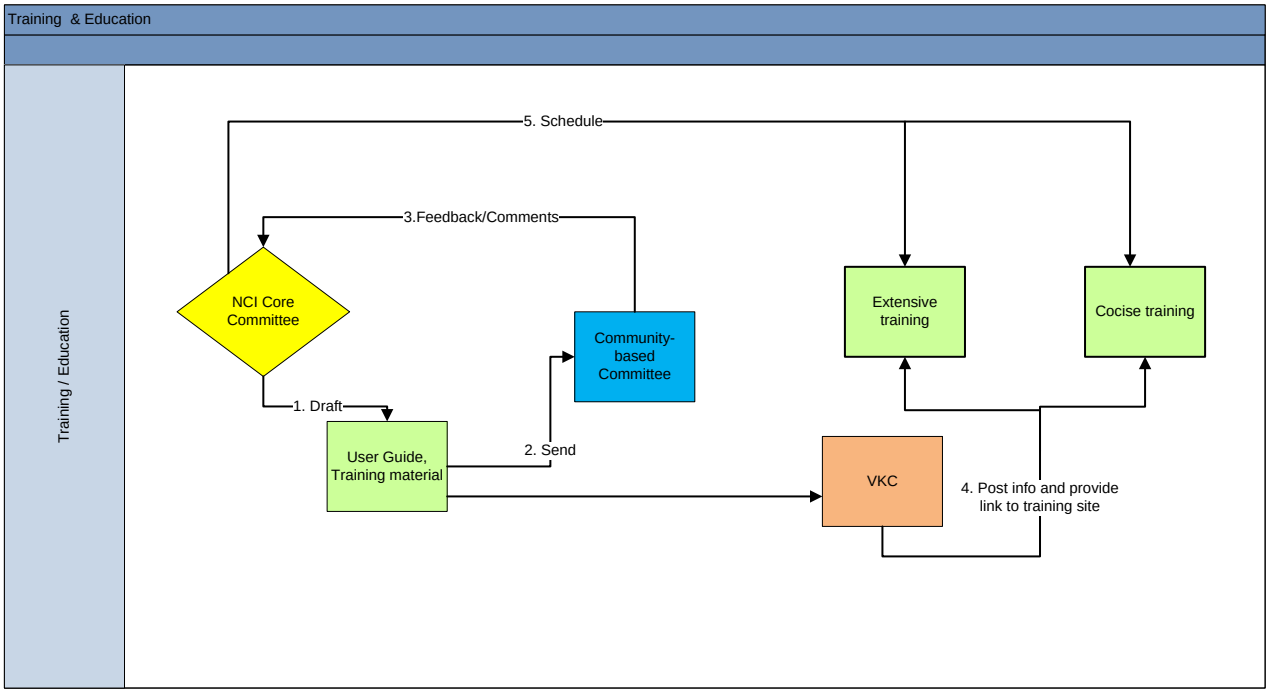
NCI Core Committee will oversee education and training materials required for CTCAE. Materials will be drafted and circulated to the Community-based Committee for feedback. Finalized materials will be sent to VKC, who will post relevant information and provide links to caBIG® Learning Resources Center.

NCI Core Committee will collaborate with CBIIT Training Center to create, schedule, and provide training of two types: concise and extensive. Educational material and the training will be targeted for the end user in various formats:

- Online training that consists of PowerPoint presentations with voiceover
- Frequently asked Questions (FAQ) posted on the VKC site
- Web-based interaction: e-mail help for individual user queries, CTCAE Help on the VKC website for user comments and requests for information, and the BiomedGT Wiki for contributor comments and discussion
- "Boot camps" for face-to-face training and education

Figure 4 shows an outline of the proposed process for training and education.

Figure 4: CTCAE training and education process



Documentation and advertisement

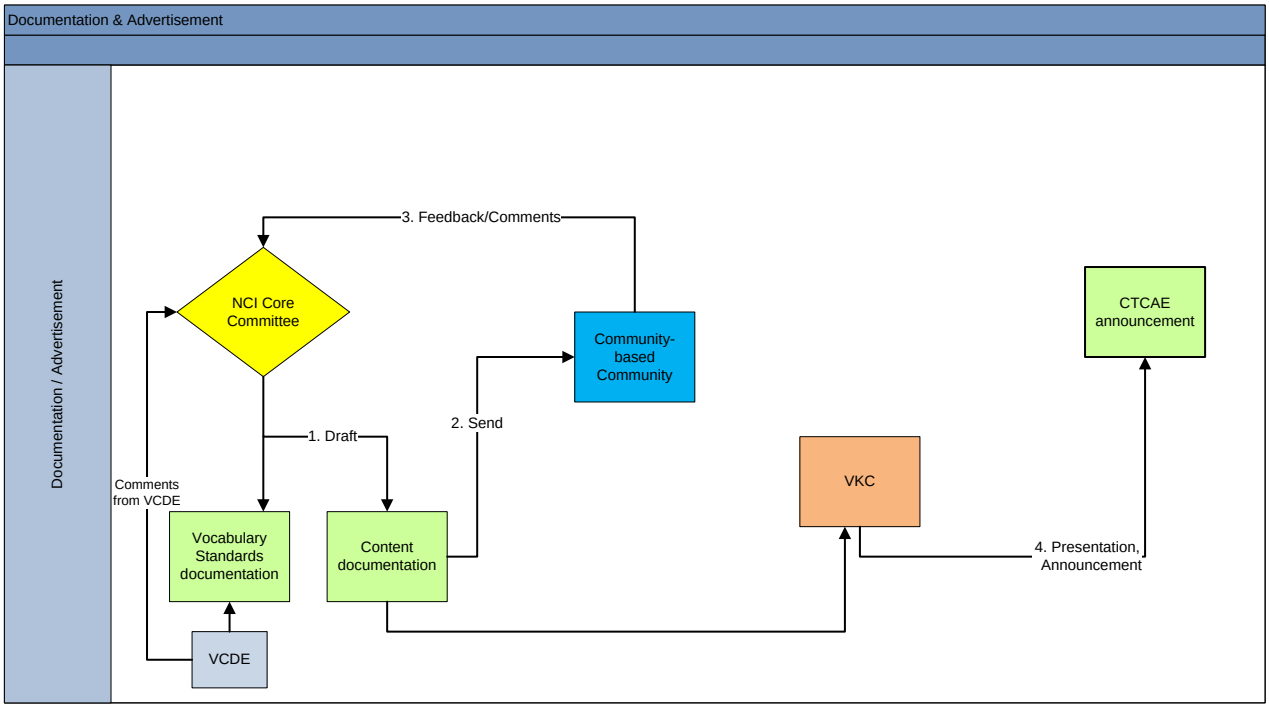
NCI Core Committee will draft content documentation for CTCAE. The documentation material will be circulated to the Community-based Committee for feedback. NCI Core Committee will also oversee vocabulary standards documentation. VCDE Workspace will provide recommendations for the vocabulary standards documentation. Finalized materials will be sent to VKC, who will post relevant announcements.

Proposed documentation material will include:

- Frequently Asked Questions (FAQ)
- Changes from v3.0 to v4.0
- Mapping from v3.0 to 4.0
- CTCAE Governance document
- Instructions and guidelines (proposed)

Figure 5 illustrates the proposed process for documentation and advertisement for CTCAE.

Figure 5: CTCAE documentation and advertisement process



Quality assurance and quality control

The CTCAE Core Committee will work towards implementing a defined QA/QC process for CTCAE.

The Governance Group recommended that the QA/QC process for CTCAE be based on the process followed by MSSO, which includes developing terminology rules and conventions; queries to validate the rules and conventions prior to the release of a new version; SOPs to handle changes to CTCAE; metrics to measure the performance of the maintenance organization; and other QC procedures, such as a review process and CM control.

MSSO is designated as the organization to perform the QC step prior to a CTCAE release to verify that all MedDRA LLTs used in CTCAE have the correct term name, term code, and primary SOC assignment. This step was proved essential at the release of CTCAE v4.0, and therefore will continue to be part of the QA/QC procedures.

Quality Control during **Minor Editing Process**:

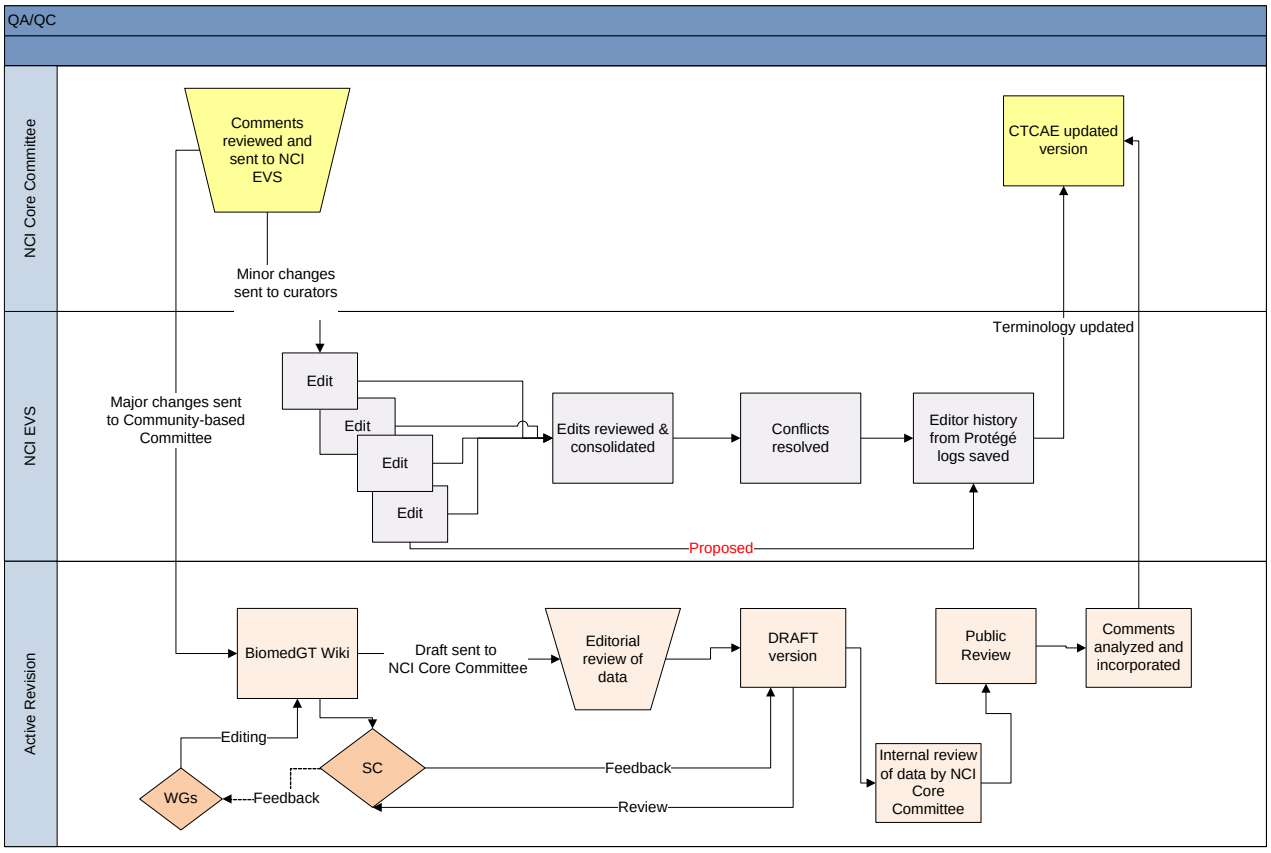
1. NCI Core Committee provides content changes with clinical input.
2. NCI EVS, a team of domain experts in basic and clinical subject areas that has knowledge of terminology best practices, edits the terminology in Protégé environment.
3. BiomedGT Wiki generates an edit history which is maintained in the database to track all changes to the baselines over the editing period.

Quality Control during **Major Editing Process**:

1. NCI Core Committee provides content changes.
2. WGs with the relevant domain expertise review the changes.
3. The BiomedGT Wiki, which is an open, community-based ontology development environment, enables ongoing quality assurance as all WG members access it to edit content.
4. The BiomedGT Wiki team generates a weekly report run against the established editing guidelines set up earlier. (This can be done either by the NCI Core Committee or BiomedGT Wiki team.) The report can be redesigned to capture editorial errors and make automatic corrections, e.g. extra spaces, periods, semicolons, etc.
5. BiomedGT Wiki generates an edit history which is maintained in the database to track all changes to the baselines over the editing period.

A list of editorial checks performed on CTCAE prior to publication is given in Appendix D: Editorial Guidelines. Figure 6 shows an outline of the proposed QA/QC process for CTCAE.

Figure 6: CTCAE quality assurance and quality control process



Structure and content of CTCAE 4.0

The structure of CTCAE v4.0 is constrained by the need to support existing reporting and analysis practices and systems in use at NCI and elsewhere, and to conform to existing CTCAE 3.0 and MedDRA approaches where possible.

Two-level hierarchical structure

CTCAE v4.0 AE terms are organized in a two level hierarchy, with SOCs drawn from MedDRA at the top level and the AE terms at the second level. CTCAE v4.0 contains 790 AE terms, 764 of which correspond to single MedDRA AE terms selected as best suited to reporting of cancer-related adverse events, and 26 of which are "Other, specify." These AE terms are organized according to their primary assignment in MedDRA to one of the 26 SOCs shown below.

- Blood and lymphatic system disorders
- Cardiac disorders
- Congenital, familial and genetic disorders
- Ear and labyrinth disorders
- Endocrine disorders
- Eye disorders
- Gastrointestinal disorders
- General disorders and administration site conditions
- Hepatobiliary disorders
- Immune system disorders
- Infections and infestations
- Injury, poisoning and procedural complications
- Investigations
- Metabolism and nutrition disorders
- Musculoskeletal and connective tissue disorders
- Neoplasms benign, malignant and unspecified (incl cysts and polyps)
- Nervous system disorders
- Pregnancy, puerperium and perinatal conditions
- Psychiatric disorders
- Renal and urinary disorders
- Reproductive system and breast disorders
- Respiratory, thoracic and mediastinal disorders
- Skin and subcutaneous tissue disorders
- Social circumstances
- Surgical and medical procedures
- Vascular disorders

AE terms as concepts

Each AE term is represented in CTCAE as a separate concept, with its own unique code, definition, and other related terms. Below is sample information for one concept:

Preferred Name:	Cushingoid	
Concept Code:	E123456	
MedDRA Code:	10011655	
NCIt Code:	C37938	[PLANNED]
Definition:	Resembling the signs and symptoms of Cushing's disease or syndrome: buffalo hump obesity, striations, adiposity, hypertension, diabetes, and osteoporosis, usually due to exogenous corticosteroids.	
Related terms:	Cushingoid	[MedDRA PT 10011655]
	Cushing-like build	[MedDRA LLT 10011654]
	Cushingoid facies	[MedDRA LLT 10011656]
	Moon face	[MedDRA LLT 10027953]
Also consider:	Hyperglycemia	[PLANNED]
	Hypokalemia	
Notes:	[none currently included]	

The structure of each concept, also used for other CTCAE contents, is described below:

- **Preferred Name** is the term used for this concept in CTCAE. For AEs, it is normally a MedDRA Preferred Term (PT), although a few AE concepts correspond to MedDRA LLTs that are not PTs; the 26 'Other, specify' concepts appearing for each SOC are an entry point for other specified values and have no direct MedDRA equivalent; and severity grade concepts are not in MedDRA.
- **Concept Code** is a unique, stable identifier assigned to each concept in CTCAE, providing consistent codes for both MedDRA and non-MedDRA content.
- **MedDRA Code** is present for all SOC and AE concepts taken from MedDRA, and is the code for the MedDRA term used as the CTCAE Preferred Name.
- **NCIt Code** exists for all AE terms except the 26 'Other, consider' terms, and will be added soon to support cross-terminology lookup, browsing, and ontologic reasoning not directly part of CTCAE itself.
- **Related Terms** gives details of all related MedDRA terms with their MedDRA term types and codes. Where CTCAE uses more than one MedDRA term from a single MedDRA PT group, CTCAE editors have selected which terms are appropriately placed in each concept. Non-MedDRA synonyms and other terms are of interest for some purposes, but problematic given regulatory requirements; links to matching NCIt concepts provide an interim solution pending future policy review.
- **Also consider** relationships point to related AE concepts that might also apply in cases in which the current AE applies.
- **Definitions** were initially drawn from NCI Thesaurus, but have gone through extensive review and revision to become part of CTCAE.
- **Notes** sometimes appear with additional information about a concept.

Other, Specify: For each SOC, there is also one 'Other, specify' concept that is meant to elicit other MedDRA LLTs or verbatim terms rather than to directly describe an adverse event.

Severity grading of adverse events is a fundamental and unique feature of CTCAE. It defines comprehensive criteria for the severity grading of all adverse events, as well as specific criteria to be applied to each individual AE term included in CTCAE. A generic set of severity grade concepts is defined, providing guidelines for the grading of individual AE concepts and also any non-standard AEs (either MedDRA or verbatim) that may be recorded. The generic grades with their definitions are shown in Table 5 below:

Table 5: Adverse event grading and definitions

Preferred Term	Synonym	Definition
Grade 0 Adverse Event	No Adverse Event	Sign/symptom within normal limits

Preferred Term	Synonym	Definition
Grade 1 Adverse Event	Mild Adverse Event	An adverse event that is asymptomatic; or involves mild or minor symptoms; or is of marginal clinical relevance; or consists of clinical or diagnostic observations alone; or for which intervention is not indicated; or for which only non-prescription intervention is indicated.
Grade 2 Adverse Event	Moderate Adverse Event	An adverse event for which only minimal, local, or noninvasive intervention (e.g. packing, cautery) is indicated; or that limits instrumental activities of daily living (ADLs, e.g., shopping, laundry, transportation, or ability to conduct finances).
Grade 3 Adverse Event	Severe Adverse Event	An adverse event that is medically significant but not life-threatening; or for which inpatient care or prolongation of hospitalization are indicated; or that is an important medical event that does not result in hospitalization, but may jeopardize the patient or may require intervention either to prevent hospitalization, to prevent the AE from becoming life-threatening or causing death; or that is disabling; or that results in persistent or significant disability, incapacity, or limitation of self care activities of daily living (ADLs, getting in and out of bed, dressing, eating, getting around inside, bathing, or using the toilet).
Grade 4 Adverse Event	Life-threatening Adverse Event	An adverse event that has life-threatening consequences; for which urgent intervention is indicated; that puts the patient is at risk of death at the time of the event if immediate intervention is not undertaken; or that causes blindness or deafness (need to decide if unilateral or bilateral).
Grade 5 Adverse Event	Fatal Adverse Event	Death.

AE term grading provides grade-specific child concepts covering all possible grades for each AE. In the example of Cushingoid, only three grade concepts are defined as appropriate:

Preferred Name: Grade 1 Cushingoid

Concept Code: E123457

Is Grade: Grade 1 Adverse Event

Definition: Mild symptoms; intervention not indicated.

Preferred Name:	Grade 2 Cushingoid
Concept Code:	E123458
Is Grade:	Grade 2 Adverse Event
Definition:	Moderate symptoms; medical intervention indicated.

Preferred Name:	Grade 3 Cushingoid
Concept Code:	E123459
Is Grade:	Grade 3 Adverse Event
Definition:	Severe symptoms; medical intervention or hospitalization indicated.

Unique precoordinated Preferred Names are created in a consistent way from the parent AE (MedDRA) term and assigned to each AE grade concept. Each of these has an "Is_Grade" logical relationship linking it to the appropriate generic grade concept.

CTCAE's logical hierarchy starts with the top CTCAE node, with increasingly specific child concepts placed under a single parent at each level. This single-parent is-a hierarchy follows MedDRA principles, and is designed to facilitate analysis and reporting of AE data. An example is illustrated below.

CTCAE

Adverse Event Severity Grade

Grade 0 Adverse Event

....

Grade 5 Adverse Event

Adverse Event by System Organ Class

Blood and lymphatic system disorders

Bone marrow hypocellular

Grade 1 bone marrow hypocellular

…

…

…

Vascular disorders

Semantic relationships other than parent-child "is-a" relationship include the following:

- Grading relationships, linking graded AE concepts to the corresponding generic grade concept
- "Also Consider" relationships to other CTCAE concepts that may apply when a particular AE is encountered
- Coded external references to corresponding MedDRA terms and NCIt concepts
- Related-term associations to other MedDRA LLTs

No attempt is made to provide formal logic-based definitions for concepts, although the link to NCIt will provide some support for users wanting such ontological features. There is also no attempt to provide formal encoding of the AE severity grading criteria, an important but extremely challenging task well beyond the current scope of CTCAE.

CTCAE concepts represent every node in this hierarchy as a stable, clearly defined meaning. Each concept is assigned a permanent, unique identifier not encumbered with any potentially problematic semantic or structural characteristics. Significant changes in meaning will be implemented by retiring old concepts and creating new concepts, with new codes, representing the new meaning. Concept history will allow users to track such changes, and mapping documents between versions provide guidance on how to interpret and implement such transitions.

Stable semantics and quality control are integral to the editorial process. Trivial changes in terms or other properties without creating a new concept are allowed only where the underlying meaning is unchanged. All changes are reviewed by both the Core Committee and EVS editors, and all major changes are also reviewed by the Community-based Committee. CTCAE is tightly coupled with both MedDRA and NCIt, requiring that changes at the AE term level are cross-checked with both sources and that any new terms be vetted and approved MedDRA terms. NCIt expert editors maintain the contents in Protégé following standard NCIt QA policies, ensuring additional careful and ongoing oversight of potential issues of ambiguity, redundancy, or obsolescence.

CTCAE versioning will reflect all changes with updates to numbering and associated dating. As described earlier, major revisions will be reflected in whole-number increments (5.0 will be next), minor revisions in point increments (e.g., 4.1). It is planned that major revisions will happen no more often than every two years, with minor revisions every six months, but final decisions on revision dates and levels will be made by the NCI Core Committee in close consultation with the Community-based Committee, carefully evaluating the number and types of changes and the balance between requirements for stability and responsiveness. It is planned that more limited editorial corrections and additions will be useful between point releases, but the criteria and numbering policies for this are currently under discussion. It is likely that CTCAE will follow the MedDRA maintenance model in making some new terms available for use in advance of their release in a new version of the terminology. All versions will be clearly associated with a release date in data files, electronic interfaces, and hardcopy publication formats

Formats

The reference version is maintained as a Web Ontology Language (OWL) data file. It will normally be edited in Protégé, and published electronically via LexBIG. LexBIG will make

CTCAE available via the LexEVS API and caGrid. Additionally, the OWL file will be available for download, browsing and search on the NCI BioPortal site. A publication program uses LexBIG to produce redistributable file versions in PDF, delimited ASCII, Excel and rich text formats. CTCAE will also be added to NCI Metathesaurus, making it available in a wide variety of ways with rich mappings and other associations to other biomedical terminologies. Support for computer interface and system implementers will be provided via LexEVS support and BioPortal support. The BiomedGT Wiki, VKC and the CTEP site will provide information on downloading the various versions of the terminology. CTCAE v 4.0 will also be available in the form of a printed booklet.

User Interface

CTCAE content can be browsed through multiple user interfaces like BiomedGT Wiki and NCI BioPortal. BiomedGT Wiki has published a tabular version of the terminology. CTCAE Quick Reference is a downloadable PDF version of the main CTCAE data and guidelines, and largely mimics the v3.0 paper format (~5" x 7"), although it is also available in a larger 8½" x 11" format.

Implementation of CTCAE v.4.0

A single version of CTCAE (v 4.0) will be used. Use of a single version will reduce the complexity and expense of maintenance and will decrease the level of effort to implement and maintain a robust AE reporting. CTEP requires the following protocols to convert to the new version, CTCAE v4.0:

- All CTEP-sponsored protocols
- All protocols that utilize CTEP data systems that do not have a CTEP status of "Complete" or "Administratively Complete"; e.g. Clinical Data Update System (CDUS) Reporting and Adverse Event Expedited Reporting System (AdEERS),

As of June 11, 2009, CTEP is in the midst of ongoing discussions regarding which protocols to change, and when and how to change them. Some protocols are still using CTC v2.0, and others are using CTCAE v3.0. Although CTEP has proposed a tentative implementation date of October 2009 for CTCAE v4.0, there is no definitive directive as yet. More details regarding timelines and implementation strategies will be released in the near future. Therefore:

- If the protocol is a CTEP study, continue as is until CTEP announces a timeline and process for updating to CTCAE v4.0.
- If the protocol is a non-CTEP study, check with the sponsor and/or investigator.

Sponsors, sites, and/or investigators determine whether to use CTCAE for AE reporting within protocols, which CTCAE version to use, and when a protocol changes from one CTCAE version to another.

CTCAE Harmonization with MedDRA

CTCAE v4.0 is harmonized at AE term level and higher-level SOC categories with MedDRA, thus harmonizing with other regulatory bodies and making local FDA reporting easier as well as

cross study/cross institution analysis more feasible. CTCAE provides its own severity grading, together with its own text definitions of the meaning of AE terms and grades. We expect that NCI definitions are in line with how other MedDRA users understand those terms, although the lack of definitions in MedDRA widens the margin of uncertainty.

CTCAE v4.0 data is harmonized with the latest version of MedDRA (v12.0). MedDRA updates occur on a semi-annual basis, while major CTCAE updates are anticipated to occur every two years. Therefore, each semi annual update of MedDRA will not have an impact on CTCAE and the latter does not need to be updated simultaneously. For each annual MedDRA update, the change may result in a minor update in CTCAE, in which case the update process will follow the process for minor update. Each time that CTCAE is updated, however, it will be harmonized with the latest version of MedDRA.

Intellectual property

CTCAE v4.0 is free to be used, copied, or distributed without payment of license fees or royalties, for any commercial or non-commercial purpose. CTCAE v4.0 content is not subject to copyright restrictions. Users may freely modify CTCAE terminology and documentation. However, any such modified content or documentation may not be identified or represented as being the CTCAE content or documentation, or part of the CTCAE content or documentation.

Community acceptance

There are no other community standards in this domain that have been used to grade toxicity. CTCAE has been used within the NCI oncology community since 1984 and is widely accepted across the broader oncology community. Industry adheres to the ICH standard: MedDRA for regulatory reporting since 1999. Although there is no regulatory requirement in the United States on the use of MedDRA, the FDA voluntarily complies with MedDRA in its Adverse Event Reporting System (AERS): AERS, which monitors for new adverse events and medication errors that might occur with marketed products, is in compliance with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonization, and is coded to terms in MedDRA. Also, World Health Organization Adverse Reaction Terminology (WHO-ART) is a four-level hierarchical structure that has been updated with MedDRA terms.

Table 6: Comparison of CTCAE 4.0 with MedDRA 12.0

CTCAE 4.0	MedDRA 12.0
NCI standard	ICH standard
AE terms	Wide range of clinical information
Oncology	Wide range of indications
Grading (severity) scale	No grading scale
Clinical research tool to standardize and compare AEs	Coding, retrieval, and analysis of clinical data (pre- and post-marketing)
Set protocol parameters	Regulatory reporting (supports electronic submissions)
Monitor safety data	

CTCAE 4.0	MedDRA 12.0
• 26 System Organ Classes (SOCs) • 764 AE terms (MedDRA LLTs) • 26 SOC placeholder for verbatim (Other, specify) • 3,057 AE grade terms	• 26 System Organ Classes (SOCs) • 333 High Level Group Terms (HLGT) • 1,699 High Level Terms (HLT) • 18,483 Preferred Terms (PT) • 67,159 Lowest Level Terms (LLT)
English	Available in nine languages, including English

Throughout the MedDRA hierarchy each term is assigned a unique code without redundancy. The subset of MedDRA LLTs that are listed as CTCAE terms are checked for redundancy using Excel. When a proposed CTCAE term is not a MedDRA term, NCI, as a subscriber to MedDRA, submits a request for term inclusion to the MedDRA MSSO as outlined on the MedDRA MSSO subscriber website.

Reporting requirements

Both CTCAE and MedDRA data are currently submitted to FDA.

- CTCAE is the AE severity grading scale whose use is mandated by CTEP, NCI.
- Safety data from CTEP clinical research activities are reported to FDA using CTCAE.
- MedDRA is a clinically validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry throughout the entire regulatory process, from pre-marketing to post-marketing activities, and for data entry, retrieval, evaluation, and presentation.
- MedDRA was designed for the specific use of sharing regulatory information for human medical products between PhRMA and regulators. MedDRA terminology use is mandatory within regulatory agencies in Japan and the European Union and is supported by the US FDA.
- Although the US FDA does not mandate the use of MedDRA, the FDA AERS is in compliance with the international safety reporting guidance (ICH E2B) issued by the ICH. Adverse events in AERS are MedDRA coded. All other ICH country participant members mandate the use of MedDRA and do not accept alternate terminologies.
- LOINC (Logical Observation Identifiers Names and Codes) and SNOMED (Systematized Nomenclature of Medicine) are currently not applicable standards for AE within the ICH community.

Summary characteristics of CTCAE v4.0

Highlights of CTCAE v4.0 are as follows:

1. CTCAE AE terms are all MedDRA LLTs, with the exception of the 26 “Other, Specify” intended to elicit either other MedDRA terms or verbatim terms.

2. AE terms are grouped by 26 MedDRA SOCs, replacing the historical CTCAE CATEGORY.
3. A total of 790 AE terms, including 764 MedDRA terms and 26 "Other, Specify."
4. Supra-ordinate terms are no longer used.
5. Several new AEs have been added.
6. Multiple AEs are separated.
7. Many CTCAE v3.0 critical concepts within grades are now listed as unique AE terms.
8. Though the grading system remains associated with numeric indicators of zero through 5, not all terms are associated with all grades.
9. General guidelines for grade descriptions have been revised. (*See* Appendix C: General Grade Guidelines.)
10. Common grades for all "Pain" and "Other, Specify" terms have been established.
11. Formal definitions for AE terms are derived mostly from definitions provided by NCI Thesaurus.
12. Formal, ongoing governance for future maintenance of CTCAE has been established.
13. CTCAE v4.0 will be available in pdf as well as electronic formats (OWL, XML, Excel, ASCII).

Appendices

Appendix A: Participating Members

Last name, first name	Title/Degree	Affiliation	CTCAE Group
Alberti, Dona	BSN, RN	Wisconsin	WG
Anadkat, Milan	MD	Washington University School of Medicine	WG
Andrist, Carol		Mayo	WG
Anscher, Mitchell	MD, FACR, FACRO	Virginia Commonwealth University	WG
Aplenc, Richard	MD, MSCE	University of Pennsylvania	WG
Bratslavsky, Gennady			WG
Bressler, Linda	PharmD	CALGB	GG, WG
Brooks, Beth	MSc	BC Children's Hospital	WG
Busaidy, Naifa	MD	MD Anderson Cancer Center	WG
Carroll, Madeline	RN, MSA	Duke University Medical Center	WG
Chen, Alice	MD	IDB/CTEP/DCTD/NCI	GG, SC, WG
Chen, Helen	MD	IDB, CTEP, NCI	WG
Colevas, Dimitri	MD	Stanford	WG, SC
Cotliar, Jonathan	MD	University of California, Los Angeles	WG
Cunningham, Jean	RN, BA	Novo Nordisk Inc.	WG
Dancey, Janet	MD	IDB, CTEP, NCI	WG
Dansky, Ullmann Claudio	MD	IDB, CTEP, NCI	WG
de Groot, John	MD	M D Anderson Cancer Center	WG
de la Rosa, Grace	RPh	Schering-Plough Research Institute	WG
DeCoronado, Sherri	MS, MBA	NCI	Wiki Support
Della Zanna, Gary	DO, MSc	NCI/DCP/ GI Division	WG
Deshmukh, Vikrant			WG
Dienstmann, Rodrigo		Brazilian National Cancer Institute	SC
Dorian, Stephen		RTOG	WG
Doyle, Austin	MD	IDB, CTEP, NCI	WG, SC
Dubois, Nathalie		EORTC	GG

Last name, first name	Title/Degree	Affiliation	CTCAE Group
Edgerly, Maureen	RN, MA, OCN, CCRN	NCI, Medical Oncology Branch	WG
Edwards, Beatrice	MD		WG
Enayti, Linda		Eisai Medical Research Inc.NJ	WG
Ennis, Brenda	CCRP, CHIM		WG
Epstein, Joel	MD	U of Illinois	WG
Esmaeli, Bita	MD, FACS	MDAnderson	WG
Espinoza,-Delgado Igor	MD	IDB, CTEP, NCI	WG, SC
Farooki, Azeez	MD	Memorial Sloan-Kettering Cancer Center	WG
Finkle, John	MD, FACP, FACC	Glaxo Smith Kline	WG
Finnigan, Shanda	RN	CTEP, NCI	SC
Foster, Kathleen	RN, BA	NCI	WG
Garay, Carlos		Sanofi Aventis	GG
Giatanio, Bruce	MD	University of Pennsylvania	WG
Gwede, Clement	PhD, MPH, RN	MRC-CANCONT	WG
Hahn, Lyon Olwen	MD	University of Chicago	WG, SC
Hamilton, Michael	MD	Avalon Pharmaceuticals	GG, WG
Harris, Roberta	RN, MSN, OCN	West Virginia University Hospital	SC
Harrison, Judy	MD	MedDRA, MSSO	SC
Hartel, Frank	PhD	CBIIT, NCI	GG
Hawkins, Erin	RN	Duke Comprehensive Cancer Center	WG
Heinze, Robin		CALGB Statistical Center	WG
Higgins, (Casavant) Kerry		Harvard	WG
House, Maggie	RN,BSN	Prostate and Urologic Cancer Research Group	WG
Hunt, Christine	MD, FACP	Glaxo Smith Kline	WG
Ibrahim, Amna	MD	CDER, FDA	GG
Ivy, Percy	MD	IDB, CTEP, NCI	GG, WG
James, Danelle	MD	UCSD Moores Cancer Center	WG

Last name, first name	Title/Degree	Affiliation	CTCAE Group
Jenckes, Ann	MPH, CCRP	Memorial Sloan-Kettering Cancer Center	WG
Kaltman, Jonathan	MD		WG
Kane, Robert	MD	FDA	GG
Kelsey, John	DDS, MBA	FDA	GG
Kennedy, Paula	RN, BNSc	Duke University Medical Center	WG
Kopp, Jeffery	MD	NIDDK, NIH	WG
Krause, Connie	RN	Genentech	WG
Kummar, Shivaani	MD	NCI	WG, SC
Kurkjian, Carla	MD	IDB, CTEP, NCI	WG
Lacouture, Mario	MD	Northwestern University	WG, SC
Lager, Joanne	MD	GSK	GG
Lassman, Andrew	MD	Memorial Sloan-Kettering Cancer Center	WG
Lee, Soo-Chin	MBBS	National University Cancer Institute, Singapore	SC
Lemery, Steven	M.D	FDA	GG
Lenihan, Daniel	MD	Department of Cardiology	WG
Lewis, Frey	PhD/Informatics	U of Utah	SC
Lim, Robert	BSc, MBChB	National University Cancer Institute, Singapore	SC
Little, Richard	MD	CTEP/DCTD/NCI	WG
Loechelt, Brett	MD	Children's National Medical Center	WG
Lois, Nesbitt	RN, MN, ET	NSABP Biostatistical Center	SC
MacDonald, Jean	MPH	ECOG Coordinating Center	WG
Mahoney, Michelle R.		Cancer Center Statistics	SC
Maris, Nina	RN	Schering-Plough Research Institute	GG
Mendonca, Eneida	MD, PhD	University of Chicago	WG
Millikan, Randy	PhD, MD	UT MD Anderson Cancer Center	WG
Minasian, Lori	MD	DCP, NCI	GG, SC, WG

Last name, first name	Title/Degree	Affiliation	CTCAE Group
Minig, Lucas		NIH	WG
Monge, Eileen	RN, BSN	Genentech, Inc.	WG
Monroe, Lindsey	CCRP	Mayo Clinic Arizon	WG
Mungal, Salvatore		Duke	SC
Murgo, Anthony	MD	IDB, CTEP, NCI	WG
Nana-Sinkam, Patrick	MD	Davis Heart and Lung Research Institute	WG
Nastari, Lisa	RN	Genentech	WG
Nickas, James	PhD	Genentech	GG
Noreiga, Valeria	RPh	Schering-Plough Research Institute, Buenos Aires	WG
Nunez, Susan			WG
Obeid, Jihad	MD	Weill Cornell Medical College	WG, SC
Okuno, Scott	MD	NCCTG	WG
O'Leary, Maura	MD	Childrens Oncology Group	WG
Olsen, Elise	MD	Duke University Medical Center	WG
Ondrey, Frank G.	MD PhD	University of Minnesota	WG
Owonikoko, Taofeek	MD, PhD	Emory University School of Medicine	WG
Perl, Shira	MD	NIDDK/NIH	WG
Ratteree, Bashi	RN, BSN, CCRP	OHSU Cancer Institute	WG
Reeves, Dianne		NCI CBIIT	SC
Remick, Scot	MD	West Virginia University	WG, SC
Riben, Mike	MD	MD Anderson	WG, SC
Ridge, John	MD	Fox Chase Cancer Center	WG
Rosenstein, Don	MD	NIMH	WG
Ross, Marlo	RPh	Genentech	WG
Rufo, Lynn		Cephalon, Inc.	SC
Sajeel, Chowdhary,	MD	University of South Florida	WG
Samuel, Gwen		Bristol-Myers Squibb	WG
Schelman, William	MD, PhD	CSC	WG
Scotti, Debra		JNJ	WG
Seibel, Nita	MD	CIB, CTEP, NCI	WG
Setser, Ann	RN	CBIIT, NCI	GG, SC, WG

Last name, first name	Title/Degree	Affiliation	CTCAE Group
Seymour, Lesley	MD	NCIC	GG
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Appendix B: Work Group Organization

Work Group Number	MedDRA SOC
1	Blood and lymphatic system disorders Immune system disorders Infections and infestations
2	Cardiac disorders Vascular disorders
3	Ear and labyrinth disorders Eye disorders
4	Psychiatric disorders Nervous system disorders
5	Gastrointestinal disorders Hepatobiliary disorders
6	Metabolism and nutrition disorders Endocrine disorders
7	General disorders and administration site conditions Neoplasms benign, malignant and unspecified (incl cysts and polyps) Social circumstances
8	Musculoskeletal and connective tissue disorders Skin and subcutaneous tissue disorders
9	Renal and urinary disorders Investigations
10	Reproductive system and breast disorders Congenital, familial and genetic disorders Pregnancy, puerperium and perinatal conditions
11	Respiratory, thoracic and mediastinal disorders
12	Injury, poisoning and procedural complications Surgical and medical procedures

Appendix C: General Grade Guidelines

Grade 0 No Adverse Event

- Sign/symptom within normal limits

Grade 1 Mild Adverse Event (any of the following)

- Minor
- Mild symptoms and intervention not indicated
- Non-prescription intervention indicated
- No specific medical intervention
- Asymptomatic laboratory finding only
- Radiographic finding only
- Marginal clinical relevance

Grade 2 Moderate Adverse Event (any of the following)

- Intervention indicated
- Minimal, local, noninvasive intervention (e.g. packing, cautery)
- Limiting instrumental ADL (e.g., shopping; laundry; transportation; ability to conduct finances)

Grade 3 Severe Adverse Event (any of the following)

- Medically significant but not life-threatening
- Inpatient or prolongation of hospitalization indicated
- Important medical event that does not result in hospitalization but may jeopardize the patient or may require intervention either
    - to prevent hospitalization or
    - to prevent the AE from becoming life-threatening or potentially resulting in death
- Disabling - results in persistent or significant disability or incapacity
- Limiting self care ADL (e.g., getting in and out of bed; dressing; eating; getting around inside; bathing; using the toilet)

Grade 4 Life-threatening Adverse Event (any of the following)

- Life-threatening consequences
- Urgent intervention indicated
- Urgent operative intervention indicated
- Patient is at risk of death **at the time of the event** if immediate intervention is not undertaken

Grade 5 Fatal Adverse Event

- Death

Appendix D: Editorial Guidelines

Word	Rule
[General punctuation]	
	No period at the end of grade description
	No extra spaces between words
	A semi-colon represents an "or"
	Use e.g., (for example) rather than i.e. (that is)
Asymptomatic	Use in Grade 1 only
Disabling	Use in Grade 3 and not in Grade 4
Indicated vs. required	Use "Indicated" instead of "required"
Intervention	Grade 1: Use "Intervention not indicated" instead of "no intervention indicated"
	Grade 2:Minimal intervention indicated Grade 2: Medical intervention indicated Grade 2: Local intervention indicated Grade 2: Noninvasive intervention indicated
	Grade 3: Endoscopic stenting indicated Grade 3: Endoscopic intervention indicated Grade 3: Operative intervention indicated Grade 3: Operative debridement Grade 3: Complete resection or reconstruction of injured organ/structure indicated Grade 3: Interventional radiology indicated Grade 3: Invasive intervention indicated Grade 3: Hospitalization / prolongation of hospitalization indicated
Therapy vs. intervention	Use "therapy" instead of "intervention"
Immediate medical intervention	Change to "Urgent medical intervention"
Limiting vs. interfering (in ADL)	Use "limiting" instead of "interfering" Use "limiting instrumental ADL" Use "limiting self care ADL"
Age appropriate ADL	Delete "age appropriate ADL" from all grade descriptions except the Other, specify
self care vs. self-care	Use "self care" and not "self-care"
Life-threatening vs. life threatening	Use "Life-threatening" instead of “life threatening”
Operative vs. surgical	Use "Operative" instead of surgical
Radiologic vs. radiological	Use "radiologic" instead of “radiological”
Major intervention **Emergent operative intervention** **Emergency intervention**	Use “Urgent Operative” instead of “major/emergent/emergency”

Word	Rule
po	Change to "oral"
Infection (in definitions)	Do not use "infection" in the definition of any AE that is not an infection term
noninvasive vs. non-invasive	Use "noninvasive" instead of "non-invasive"
mm Hg vs. mmHg	Should be "mm Hg" (with a space)
Other, Specify General Grading Scale	Grade1: Mild or minor; marginal clinical relevance Grade2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL Grade3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated. Disabling; limiting age-appropriate self care ADL Grade4: Life-threatening; at risk of death at the time of the event if immediate intervention is not undertaken Grade5: Death
Pain, General Grading Scale	Grade1: Mild pain Grade2: Moderate pain; limiting instrumental ADL Grade3: Severe pain; limiting self care ADL No Grade 4 or 5

Appendix E: Acronyms

AdEERS	Adverse Event Expedited Reporting System
ADL	Activities of Daily Living
AE	Adverse Event
AERS	Adverse Event Reporting System
caBIG®	Cancer Bioinformatics Grid
CBIIT	Center for Biomedical Informatics and Information Technology
CDUS	Clinical Data Update System
CRA	Clinical Research Associate
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Progrram
DCCPS	Division of Cancer Control and Population Sciences
DCP	Department of Cancer Prevention
EORTC	European Organization for Research and Treatment of Cancer
EVS	Enterprise Vocabulary System
FAQ	Frequently asked questions
FDA	Food and Drug Administration
GG	CTCAE Governance Group
IND	Investigational New Drug
ICH	International Conference on Harmonization
IDB	Investigational Drug Branch
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
LLT	Lowest Level Term
LOINC	Logical Observation Identifiers Names and Codes
MedDRA	Medical Dictionary for Regulatory Activities
MSSO	Maintenance and Support Services Organization
NCIt	NCI Thesaurus
NCIt	NCI Thesaurus

NIH	National Institutes of Health
OWL	Web Ontology Language
PDF	Portable Document Format
PT	Preferred Term
QA	Quality Assurance
QC	Quality Control
PhRMA	Pharmaceutical Research and Manufacturers of America
RDF	Resource Description Format (machine-readable file format)
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
SC	CTCAE Steering Committee
SME	Subject Matter Expert
SNOMED	Systematized Nomenclature of Medicine
SOC	System Organ Class
SOP	Standard Operating Procedure
VCDE	Vocabularies and Common Data Elements
VKC	caBIG® Vocabulary Knowledge Center
WG	CTCAE Work Group
WHO	World Health Organization
WHO-ART	WHO Adverse Reaction Terminology
XLS	Microsoft Excel spreadsheet file format
XML	Extensible Markup Language

Appendix F: References

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Appendix G: Acknowledgements

MedDRA is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).