Common Terminology Criteria for Adverse Events (CTCAE):

Redesign and Life Cycle Management

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Introduction to CTCAE

Institutional background

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 Therapy Evaluation Program (CTEP), within NCI, 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 cancer Biomedical Informatics Grid (caBIG®) program guides NCI's efforts to transform cancer research through an integrated biomedical informatics framework, and the caBIG® Vocabularies and Common Data Element (VCDE) Workspace oversees caBIG® terminology standards and resources.

Purpose and scope of CTCAE

The purpose of the CTCAE (Common Terminology Criteria for Adverse Events) is to provide standards for the description and exchange of safety information in oncology research. It is used to define protocol parameters (such as maximum tolerated dose and dose-limiting toxicity) and provide eligibility assessment and guidelines for dose modification. The CTCAE facilitates the evaluation of new cancer therapies and treatment modalities, and the comparison of safety profiles between interventions.

The precursor to CTCAE was developed by CTEP as CTC (Common Toxicity Criteria) in 1983 to aid in the documentation and analysis of adverse effects of chemotherapy. Subsequently, CTEP maintained and updated the CTC through its third version as CTCAE v3.0, published in 2003. It comprised a list of Adverse Event (AE) terms commonly encountered in oncology therapeutic trials, accompanied by a severity grading scale for each AE.

The adoption of MedDRA® (Medical Dictionary for Regulatory Activities) terminology by the ICH (International Conference on Harmonization), NCI, industry, and regulatory bodies provided the impetus for NCI to undertake a redesign of CTCAE in 2008 to be harmonized with MedDRA. CTEP and CBIIT (Center for Biomedical Informatics and Information Technology) collaborated to make the CTCAE v4.0 structured so that it could be incorporated in the caBIG® (cancer Biomedical Informatics Grid) architecture.

The new CTCAE v4.0 standards include:

- AE terms that correspond to 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 commonly used 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:
  - Provides a scale to measure severity of clinical findings and the impact on the study participant.
  - Promotes consistency within a given grade across all AEs.
  - Provides guidance in the evaluation and documentation of severity of the AE.
  - Facilitates a common understanding of AE data shared among academic, commercial, and regulatory entities.
  - Provide framework to compare AEs across different studies.

Statement of intended use

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

- Clinical investigators and physicians
- Nurses and Clinical Research Associates (CRAs)
- Data managers and Study coordinators
- Statisticians
- Medical and technical writers
- Information technology personnel
- Regulatory personnel
- Pharmaceutical companies
- 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 redesign and inception of CTCAE v3.0 redesign 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. In resulting discussions, CTEP and FDA (Food and Drug Administration) agreed on a CTCAE redesign to be harmonized with MedDRA at the AE term level.

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 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.
- Lack of 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 redesign CTCAE v3.0.

The goals of the CTCAE redesign project were to:

- Harmonization of CTCAE with MedDRA at the AE term level.
- 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 redesign

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

- Harmonization with MedDRA:

  CTEP mandates CTCAE for AE reporting in trials it sponsors, 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.

- Establishment of a stable governance structure:
  - Establish on-going maintenance and extension policies and procedures.
  - Establish an editorial process with documentation, explicit rules for content versioning, community participation, and decision making.
  - Establish policies and processes for archival storage of versions and version management.
  - Provide training and conduct outreach activities.
- Inclusion of text definitions for both AE terms and updating descriptions of severity grades.
- 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 recommendations provided by Jim Cimino's review.

Stakeholders and participants

CTCAE redesign 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 redesign 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 redesign activities was developed and implemented. The governance structure included 12 Work Groups (WG), a Steering Committee (SC), and a Governance Group (GG) with support provided from additional groups. Participants were recruited from various government agencies (FDA, NCI) private industry (PhRMA), academia, and the MedDRA MSSO (Maintenance and Support Services Organization). Participating members are listed in Appendix A: Participating Members. The final draft version of CTCAE v4.0 was posted for public comment.

The project team leveraged Web 2.0 technology (Semantic Media Wiki) to engage subject matter experts in a collaborative work environment. 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 redesign in practical reality, incorporating the latest in oncological care, and ensured that information gained from the redesign effort benefited all participants as well as the extended 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 consisted of revision core members, CTEP physicians, Cooperative Group investigators, RNs, pharmaceutical representatives, and VCDE members. Weekly teleconference calls were held, and BiomedGT Wiki was used for ongoing editing and documentation.

The responsibility of the WGs was to revise the CTCAE content to meet the goals of the redesign project. Each WG was represented by a WG lead that 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 content and provided feedback to the WGs. The SC was comprised of members from NCI, 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 objectives and direction for the project. 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.

Technical 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 (Rochester, MN) Clinic Division of Biomedical Informatics with contributions from Apelon, Inc., Northrop 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 redesign process, establishing initial governance process, and ensuring coordination across all CTCAE entities. The program contractor also organized two face-to-face meetings with the GG to discuss the strategic vision and the long-term governance of CTCAE. The program contractor organized and facilitated all WG, SC, and GG meetings.

The program contractor successfully coordinated over 170 participants from government, academia, and PhRMA to participate in the CTCAE redesign project. The program contractor facilitated 12 WGs, the SC, and the GG 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: Roles and responsibilities in CTCAE redesign

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 redesign 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 data systems, FDA policies Provided guidance on future governance of CTCAE	CBIIT, CTEP, DCP, FDA, MedDRA MSSO, PhRMA

Area of responsibility	Responsible group	Responsibilities	Participants
Interface between strategic vision and the redesign process	Steering Committee	Provided domain expertise and leadership Interfaced between WGs and GG Addressed cross-WG issues and ensured uniformity across WGs Reviewed user community feedback and its implementation Reviewed each draft during the redesign process	Chairs – staff of CBIIT and CTEP CBIIT, CTEP, VCDE, MedDRA MSSO, WG Leads
Redesign	Work groups	Evaluated content quality Added new toxicities Edited the terminology and grading, using the BiomedGT Wiki tool Provided expert comments and discussion on the terminology and grading Was responsible for timely completion of the assigned work	CTEP staff, CBIIT staff, Cooperative Group investigators, academic investigators, pharmaceutical representatives, VCDE members, CRAs, coding experts
Technical support for development versions	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 (Rochester, MN)
Technical compatibility with caBIG®	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 management	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 Reported progress to CBIIT and CTEP staff	Booz Allen Hamilton

Process and standard operating procedures (SOPs)

See Figure 1 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.

2. An invitation letter was sent to potential participants.

3. 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.

4. Those committed to the project were divided among the 12 WGs based on their interest and field of expertise.

5. BiomedGT Wiki site was revised to display CTCAE v3.0 terms and grades in a tabular format.

6. Simultaneously the SC and GG were constituted based on NCI recommendations.

7. The WGs conducted redesign 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.

8. Preparatory to the redesign 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.

9. 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.

10. 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, it was submitted to the MSSO for inclusion into MedDRA or a similar MedDRA term was used in CTCAE.

11. The QC process involved identification and removal of duplicates and correction of spelling and grammatical errors. (See Appendix D: Editorial Guidelines.)

12. After validation the report was sent to the SC for review and approval.

13. 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.

14. The WGs reconvened to review and update the terminology.

15. Final draft of CTCAE was compiled.

16. Textual definitions of AE terms were developed and revised by the NCI's EVS group.

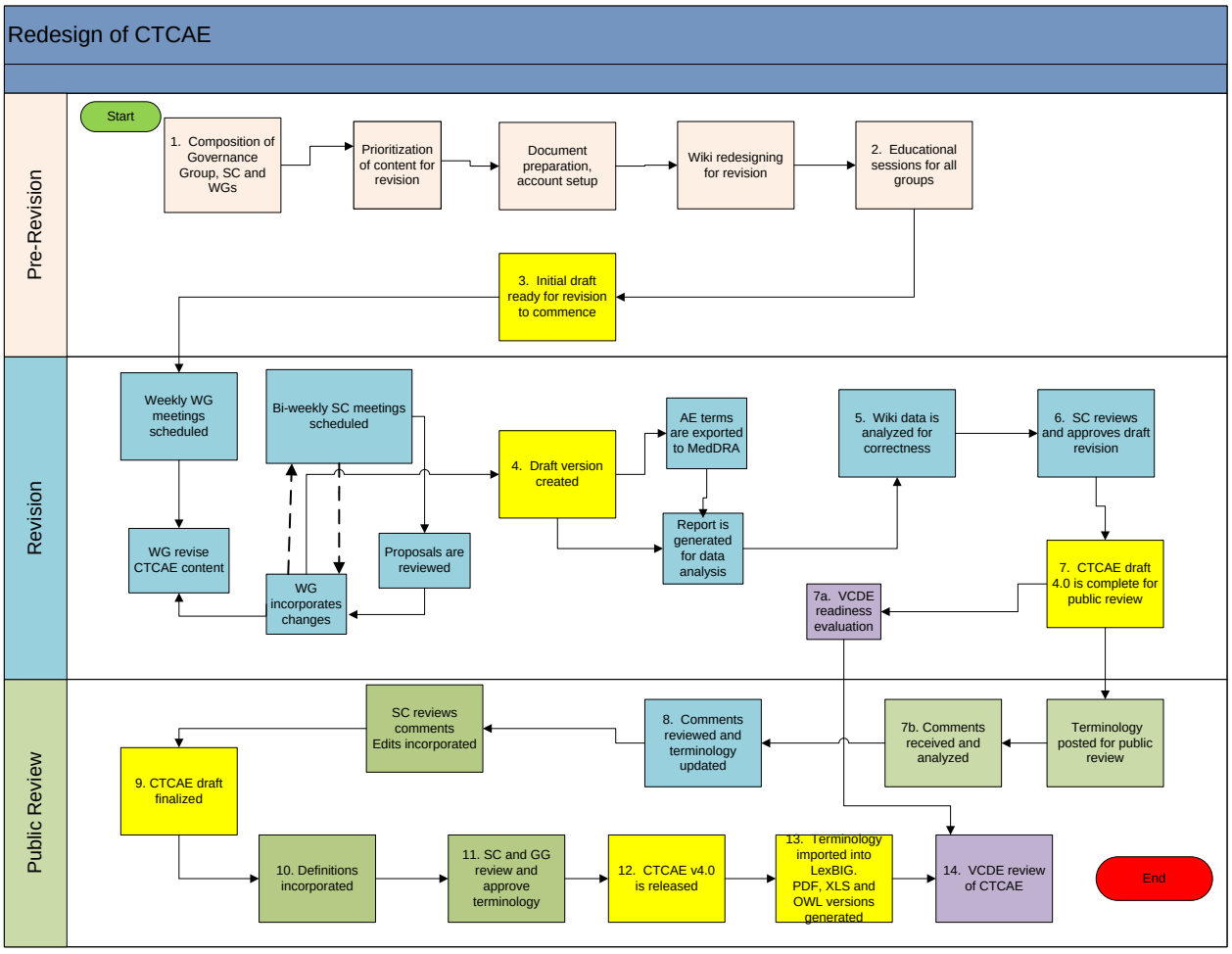
17. CTCAE draft was reviewed and approved by the SC and GG.

18. CTCAE v4.0 was released.

19. The terminology was imported into LexBIG and the PDF, XLS, and OWL versions were generated.

20. Final evaluation of CTCAE v4.0 was done to verify compliance with caBIG® review criteria.

Figure 1: CTCAE redesign process



Life cycle governance

The redesign process 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 GG was charged with addressing these issues, drawing on its broad stakeholder base and range of experience. The first

GG meeting convened September 2008 and identified five areas as important for long-term maintenance of CTCAE:

- Maintenance and extension, including identification of major and editorial 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 GG. Each subgroup provided policy recommendations that were discussed and incorporated into the final plan.

At the second GG 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 (Rochester, MN), and NCI Enterprise Vocabulary Services (EVS). The GG agreed with this framework, and also on the major aspects of the 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 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 NIH, FDA, physicians, nurses, the PhRMA, clinical researchers, MedDRA MSSO, Cancer Centers, Cooperative Groups, and others, will be established to serve as stakeholder consultants to work with the NCI 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, responses, and requests for future updates Determine if change requests are major or editorial Initiate major revisions or 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 changes Review relevant documentation and training material	NIH, FDA, physicians, nurses, 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 the technical approach to content, maintenance process, release cycles, versioning, training and education, documentation, and quality assurance 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,), 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	Acceptable or Unacceptable 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. The management of this rash as an adverse event to treatment has been limited. It is important to grade this adverse event to assist in investigating the relationship between the rash and response, in properly managing the rash, and managing dose modification.	*Acceptable 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	*Unacceptable change:* The current guidelines for grades incorporate critical thresholds in severity scales where low-grade events (Grades 1 or 2) are considered tolerable and manageable, clearly distinguished from severe or high-grade events (Grades 3 or 4).

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

Major changes are those changes that may affect the medical or clinical intent of a CTCAE term or grade (severity) scale. These changes may impact protocol parameters such as eligibility, dose limiting toxicity, maximum tolerated dose, etc.

Major changes may consist of (including but not limited to):

- Addition of new AE terms (MedDRA LLTs)
- Extraction of a critical concept from a Grade description to list it as an AE term
- Revision of existing grading scales
- Inclusion of major changes within MedDRA (e.g., addition of new SOC, etc.) when applicable to oncology

Editorial changes are those changes that do not affect the medical or clinical intent of a CTCAE term or grade (severity) scale. Editorial changes may consist of (including but not limited to):

- Spelling or punctuation errors
- Typographical errors
- Formatting irregularities

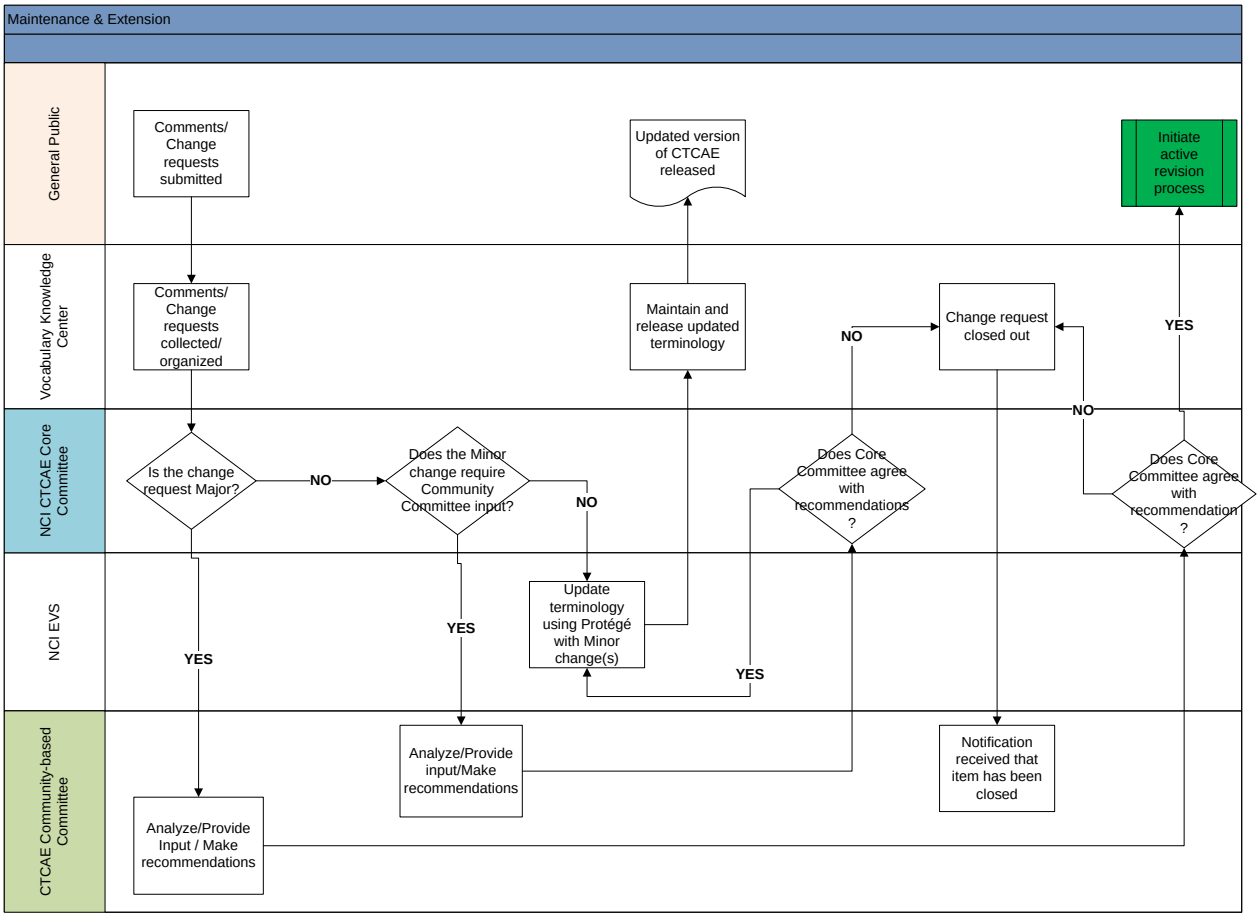
Major revisions to CTCAE will be considered every two years with a release in March to coincide with an annual complex release of MedDRA. (MedDRA is updated semiannually, with a complex release each March and a simple release each September.) Major revisions of CTCAE will gather proposals and comprehensive review comments from SMEs in the WGs.

Both major and editorial revisions will be managed by NCI EVS.

Final decisions on revision dates 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 likely that CTCAE will follow the MedDRA maintenance model in making some new terms available for use (i.e., MedDRA supplemental terms) in advance of their release in a new version of the terminology.

See Figure 2 for an illustration of the CTCAE maintenance and extension process.

Figure 2: CTCAE maintenance and extension process



The process includes the following steps.

1. Determination of the nature of the change request:

   Comments and queries from the public will be collected and aggregated by:

   - The CTCAE Help Desk managed by the CBIIT CTCAE administrator. This administrator, at times in consultation with others on the NCI Core Committee, will respond to each Help Desk Ticket. The Help Desk administrator will subsequently paste the correspondences on wiki.
   - The wiki administered by VKC. Periodically the VKC will generate a report of wiki comments and forward them to the NCI Core Committee.
   - At regularly scheduled meetings, the NCI Core Committee will review the wiki report and categorize issues, for discussion purposes, as editorial, major, or other.

- Editorial issues, when agreed upon by the NCI Core Committee, will be submitted to the EVS and all CTCAE electronic files will be updated.
- Major issues will be logged on the agenda for discussion at the next scheduled Community-based Committee meeting.

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 provide recommendations to 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.

CTCAE harmonization with MedDRA

CTCAE v4.0 (release date May 2009) is harmonized with MedDRA v12.0. Going forward, CTCAE will be harmonized annually with the latest complex release of MedDRA at the AE term and SOC levels. With each MedDRA complex release, although unlikely, there may be very limited modifications to a CTCAE (MedDRA LLT) term or code which will not impact the medical/clinical content or interpretation of CTCAE.

Major CTCAE version updates are anticipated to occur no more often than every two years. Each time a major version of CTCAE is released, it will be harmonized with the latest release of MedDRA.

Versioning

The initial planned approach to CTCAE v4.0 versioning was to assign point increments (e.g., 4.1) to deal with minor changes and subpoint increments (e.g., 4.0.1) to deal with editorial updates. However, after impact analysis regarding potential clinical processes and data systems maintenance issues, future versioning will be handled as follows:

- Major CTCAE versions will be reflected in whole-number increments (e.g., 4.0, 5.0)

- Editorial or minor updates will be associated with point increments (e.g., 5.1).
- All versions will be clearly associated with a release date in data files, electronic interfaces, and hardcopy publication formats. Change proposals and errata will be published as they become available.

Training and education

NCI Core Committee will oversee education and the development of training materials required for CTCAE. Educational materials and the training will be targeted for the end user in various formats:

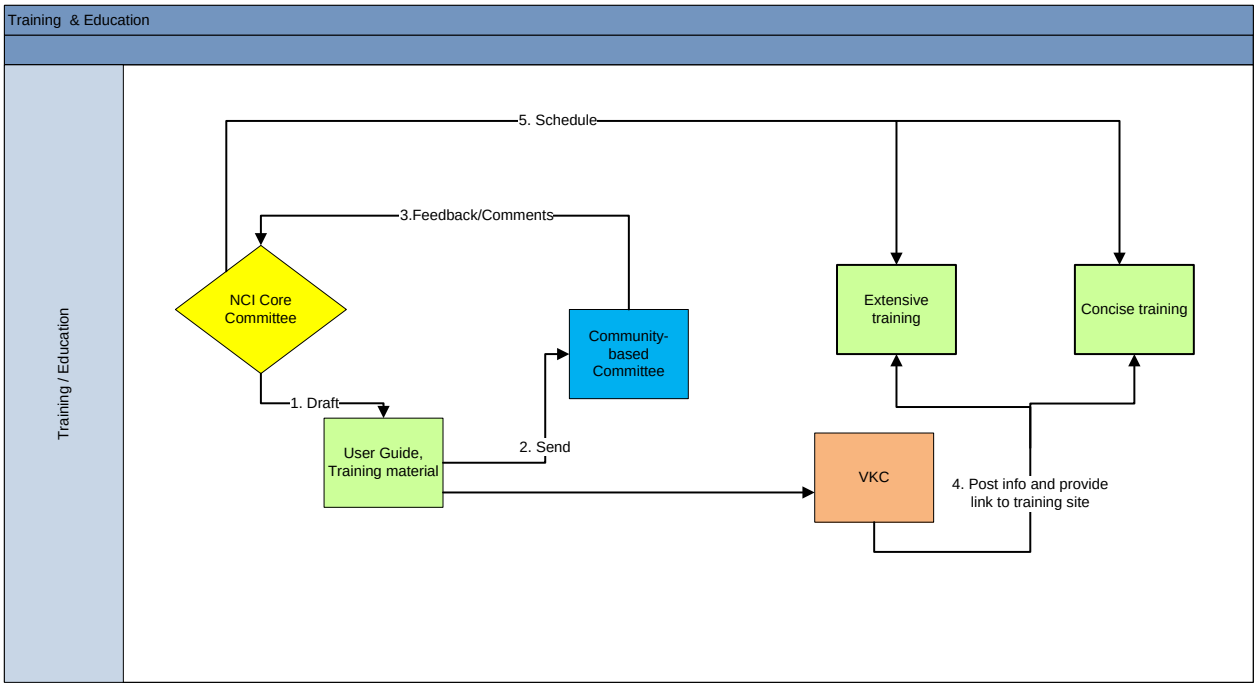
- Online training that consists of PowerPoint presentations, with or without voiceover
- Frequently asked questions (FAQ) posted on the VKC site
- Web-based interaction:
  - e-mail help for individual user queries sent to the help desk (ncictcaehelp@mail.nih.gov)
  - contributor comments and discussion gathered from the VKC discussion forum (https://cabig-kc.nci.nih.gov/Vocab/KC/index.php/Talk:CTCAE)
  - contributor comments and discussion currently gathered on the BiomedGT Wiki[1] (http://biomedgt.nci.nih.gov/wiki/index.php/CTCAE4)

Figure 3 illustrates the proposed process for training and education. The process involves the following steps.

1. NCI Core Committee, in collaboration with CBIIT Training Center, creates draft training materials and schedules training.
2. The Community-based Committee reviews the materials and provides feedback.
3. NCI Core Committee finalizes the training materials and schedules, and sends them to the VKC.
4. The VKC posts the relevant information on the wiki and provides links to the caBIG® Learning Resources Center.

[1] The BiomedGT Wiki may be replaced with another tool in the future.

Figure 3: CTCAE training and education process



Documentation and advertisement

NCI Core Committee will draft documentation for CTCAE.

Proposed documentation material will include:

- Frequently asked questions (FAQ)
- Changes from one version to another
- Mapping from one version to another
- CTCAE governance document
- Instructions and guidelines (proposed)

The process involves the following steps.

1. NCI Core Committee drafts vocabulary standards documentation, with recommendations and review comments from VCDE Group.

2. NCI Core Committee drafts CTCAE content documentation for CTCAE.

3. Community-based Committee reviews content documentation and provides feedback to NCI Core Committee.

4. NCI Core Committee sends final standards documentation and content documentation to VKC.

5. VKC announces the release of the CTCAE version and posts the documentation.

Quality assurance and quality control

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

The GG 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 Configuration Management (CM) control.

MSSO is designated as the organization to perform the QC step prior to the release of a CTCAE version 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 **Major Revision Process**:

1. NCI Core Committee collects and gives final approval for content changes.

2. WGs with the relevant domain expertise are formed and comprehensively review their content areas, including reviewing and suggesting changes.

3. An open, community-based ontology development environment (currently the BiomedGT Wiki) enables ongoing quality assurance by both WG members and project reporting and QA processes. All comments and changes are stored and available for review.

Quality Control during **Editorial Revision Process**:

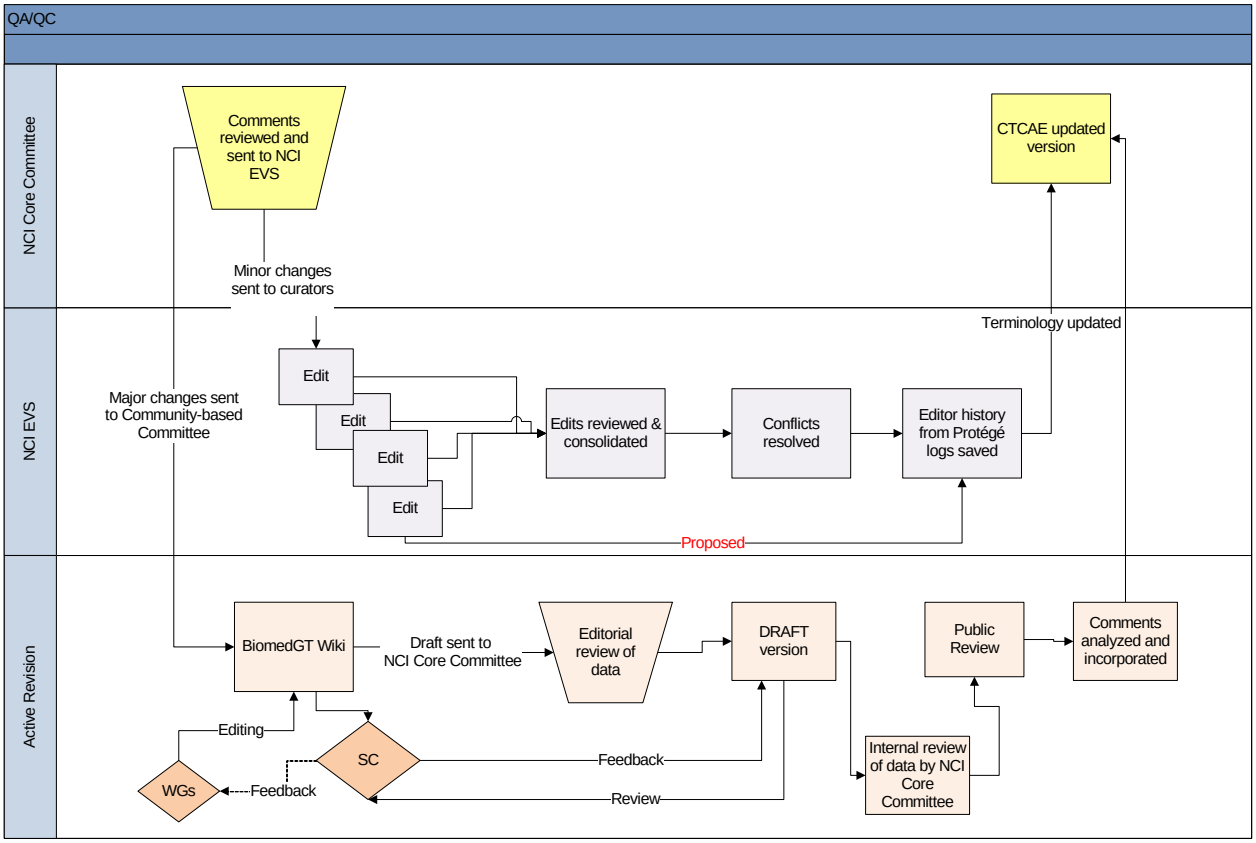
1. NCI Core Committee provides content changes.

2. NCI EVS, a team of terminology and biomedical domain experts, implements agreed changes using EVS editorial and QA processes to produce the final data files and server content.

3. A database maintains an edit history which tracks 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 4 illustrates the proposed QA/QC process for CTCAE.

Figure 4: CTCAE quality assurance and quality control process



Structure and content of CTCAE

CTCAE v4.0 constitutes a major redesign since v3.0, resulting in a new structure and content from this point forward. The new structure of CTCAE 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 v3.0 and MedDRA approaches where possible.

Summary characteristics of CTCAE v4.0

1. AE terms are grouped by 26 SOCs corresponding to the 26 MedDRA SOCs; the SOCs replace the historical CTCAE CATEGORY.

2. CTCAE AE terms are all MedDRA LLTs, with the exception of the 26 "Other, specify" a place-holder intended to elicit either other MedDRA terms or verbatim terms.

3. There are 790 AE terms, including 764 corresponding to MedDRA LLTs and 26 MedDRA SOC terms as a placeholder for verbatim terms via "Other, specify."

4. Some AE terms that were multiple concepts in CTCAE v3.0 are listed separately (single concept MedDRA LLTs) in CTCAE v4.0.

5. Legacy CTCAE v3.0 Supra-ordinate and Select terms are no longer used.

6. Some CTCAE v3.0 critical concepts within grades descriptions are now listed as unique AE terms.

7. Although the grading system remains associated with numeric indicators of 1 through 5, not all terms are associated with all grades.

8. General guidelines for grade descriptions have been revised. (*See* Appendix C: General Grade Guidelines.)

9. Common grades for most "Pain" and "Other, specify" terms have been established.

10. Formal definitions for AE terms are derived mostly from definitions provided by NCI Thesaurus.

11. Formal, ongoing governance for future maintenance of CTCAE has been established.

12. CTCAE v4.0 is available in PDF as well as electronic formats (OWL, XML, Excel, ASCII).

*** For more information, visit CTCAE on the caBIG® Knowledge Center at https://cabig-kc.nci.nih.gov/Vocab/KC/index.php/CTCAE ***

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 corresponding to MedDRA LLTs 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	Metabolism and nutrition disorders
Cardiac disorders	Musculoskeletal and connective tissue disorders
Congenital, familial, and genetic disorders	Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)
Ear and labyrinth disorders	Nervous system disorders
Endocrine disorders	Pregnancy, puerperium and perinatal conditions
Eye disorders	Psychiatric disorders
Gastrointestinal disorders	Renal and urinary disorders
General disorders and administration site conditions	Reproductive system and breast disorders
Hepatobiliary disorders	Respiratory, thoracic and mediastinal disorders
Immune system disorders	Skin and subcutaneous tissue disorders
Infections and infestations	Social circumstances
Injury, poisoning and procedural complications	Surgical and medical procedures
Investigations	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. Following is sample information for one concept:

Preferred Name:	Cushingoid	
Concept Code:	E123456	
MedDRA Code:	10011655	
NCIt Code:	C37938	
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	

Structural elements per concept

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.

Definitions were initially drawn from NCI Thesaurus, but have gone through extensive review and revision to become part of CTCAE.

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.

Notes sometimes appear with additional information about a concept.

"Other, specify" concept

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 each AE

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 Appendix C: General Grade Guidelines.

Single-parent is-a hierarchy

Severity grading of AE terms 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

Other semantic relationships

Semantic relationships other than the 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

Concerns and considerations regarding concepts

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.

Data access

CTCAE is available in many forms, reflecting the diverse needs of users including clinical, research, and computational applications.

Complete CTCAE terminology data are available in the OWL data file, LexEVS server, and EVS terminology browsers. These forms are of particular interest to those engaged in building computer-based systems or processing biomedical data.

- **Web Ontology Language (OWL) data file:** This is the reference version. It will normally be edited in Protégé, and published electronically via LexBIG.
- **LexBIG** makes CTCAE available via the LexEVS API and caGrid.
- **EVS browsers** provide CTCAE, from LexEVS, in three different interfaces:
  - NCI BioPortal provides download, browse, and search options for CTCAE and other terminologies.
  - NCI Term Browser is replacing NCI BioPortal (by February 2010) as the primary interface for browsing CTCAE.
  - NCI Metathesaurus Browser provides CTCAE with over 70 other terminologies in an integrated, concept-based environment that is especially useful for finding mappings and related content from outside CTCAE.

Core end-user CTCAE terminology data are available in print and data file forms. These forms are of particular use to those seeking to apply CTCAE in clinical settings, as well as reviewers and editors considering possible changes.

- **BiomedGT wiki**, which was used to develop the CTCAE v4.0, continues to provide a browsable version of core content with comments.
- **Document files** include two PDF versions and an Excel spreadsheet described on and available from the EVS CTCAE distribution directory (see http://evs.nci.nih.gov/ftp1/CTCAE/About.html).
- **CTCAE Booklets** (NIH Publication No. 09-5410) are in high demand and supply cannot be guaranteed. However, when available, orders of up to 10 copies may be sent without charge. Information is available at http://www.cancer.gov/cancertopics/factsheet/NCI/order-publications .
- **NCI Metathesaurus** includes CTCAE, making it available in a wide variety of ways with rich mappings and other associations to other biomedical terminologies.

The BiomedGT Wiki includes a link to the FTP site where the OWL data file and the various document files are stored. 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 links for downloading the various versions of the terminology, available at http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

Implementation of CTCAE

Intellectual property

CTCAE is in the public domain and is free to be used, copied, or distributed without payment of license fees or royalties, for any commercial or non-commercial purpose. CTCAE 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.

Table 5: Comparison of MedDRA v12.0 to CTCAE v4.0

MedDRA v12.0	CTCAE v4.0
ICH standard	NCI standard
Wide range of clinical information	AE terms
Wide range of indications	Oncology
No grading scale	Grading (severity) scale
Coding, retrieval, and analysis of clinical data (pre- and post-marketing)	Clinical research tool to standardize and compare AEs
Regulatory reporting (supports electronic submissions)	Set protocol parameters
	Monitor safety data
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)	26 System Organ Classes (SOCs) 764 AE terms (MedDRA LLTs) 26 SOC placeholder for verbatim ("Other, specify") 3,057 AE grade terms
5-Level hierarchy (System Organ Class; High Level Group Terms; High Level Terms; Preferred Terms; >67,000 Lowest Level Terms	2-Level AE term hierarchy: MedDRA SOCs and small subset of MedDRA LLTs most often encountered in oncology interventions
English and multiple other languages	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-sponsored clinical research 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 pharmaceutical industry and regulatory authorities. 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 reporting within the ICH community.

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 Clinic (Rochester, MN)	WG
Anscher, Mitchell	MD, FACR, FACRO	Virginia Commonwealth University	WG
Aplenc, Richard	MD, MSCE	University of Pennsylvania	WG
Bratslavsky, Gennady	MD	NCI, Urologic Oncology Branch	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

Last name, first name	Title/Degree	Affiliation	CTCAE Group
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
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DeCoronado, Sherri	MS, MBA	NCI	Wiki Support
Della Zanna, Gary	DO, MSc	NCI/DCP/ GI Division	WG
Deshmukh, Vikrant	M.SC., M.S.	University of Utah School of Medicine	WG
Dienstmann, Rodrigo		Brazilian National Cancer Institute	SC
Dorian, Stephen		RTOG	WG
Doyle, Austin	MD	IDB, CTEP, NCI	WG, SC
Dubois, Nathalie		EORTC	GG
Edgerly, Maureen	RN, MA, OCN, CCRN	NCI, Medical Oncology Branch	WG
Edwards, Beatrice	MD, FACP	Northwestern University	WG
Enayti, Linda		Eisai Medical Research Inc. NJ	WG
Ennis, Brenda	CCRP, CHIM		WG
Epstein, Joel	MD	U of Illinois	WG

Last name, first name	Title/Degree	Affiliation	CTCAE Group
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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
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Last name, first name	Title/Degree	Affiliation	CTCAE Group
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Ivy, Percy	MD	IDB, CTEP, NCI	GG, WG
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Jenckes, Ann	MPH, CCRP	Memorial Sloan-Kettering Cancer Center	WG
Kaltman, Jonathan	MD	Pediatric Cardiology	WG
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Krause, Connie	RN	Genentech	WG
Kummar, Shivaani	MD	NCI	WG, SC
Kurkjian, Carla	MD	IDB, CTEP, NCI	WG
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Lager, Joanne	MD	GSK	GG
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Last name, first name	Title/Degree	Affiliation	CTCAE Group
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Lemery, Steven	M.D	FDA	GG
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MacDonald, Jean	MPH	ECOG Coordinating Center	WG
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Millikan, Randy	PhD, MD	UT MD Anderson Cancer Center	WG
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Last name, first name	Title/Degree	Affiliation	CTCAE Group
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Monge, Eileen	RN, BSN	Genentech, Inc.	WG
Monroe, Lindsey	CCRP	Mayo Clinic Arizona	WG
Mungal, Salvatore		Duke	SC
Murgo, Anthony	MD	IDB, CTEP, NCI	WG
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Nastari, Lisa	RN	Genentech	WG
Nickas, James	PhD	Genentech	GG
Noreiga, Valeria	RPh	Schering-Plough Research Institute, Buenos Aires	WG
Nunez, Susan	MD	NIH, Endocrinology	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
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Last name, first name	Title/Degree	Affiliation	CTCAE Group
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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	BSN, MEd	CBIIT, NCI	GG, SC, WG
Seymour, Lesley	MD	NCIC	GG
Shimada, Yasuhiro	MD	National Cancer Center Hospital,JCOG, Japan	SC
Shotland, Larry		Audiology	WG
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Last name, first name	Title/Degree	Affiliation	CTCAE Group
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Snyder, Debbie		NIMH	WG
Stockler, Martin	MBBS, MSc, FRACP	Sydney Cancer Centre, Camperdown,Australia	SC
Streicher, Howard	MD	IDB, CTEP, NCI	WG
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Sward, Kathy	PhD, RN	U of Utah	WG
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Takebe, Naoko	MD	IDB, CTEP, NCI	WG, SC
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Tolk, Christine		CDISC	GG
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Trimble, Ted	MD	CIB, CTEP, NCI	GG, SC, WG
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Vass, Hilary		Astra Zeneca	WG
Voss, Simon	BSc, MBBS, FFPH, FFPM	Lilly	GG

Last name, first name	Title/Degree	Affiliation	CTCAE Group
Watkins-Bruner, Deborah	RN, PhD, FAAN	University of Pennsylvania School of Nursing	WG
Wen, Patrick	MD	Brigham and Women's Cancer Center	WG
Womack, Laurie	RRT, CRTT	IDB, CTEP, TRI	WG
Wright, Jackie		Amgen	WG
Wright, John	MD	IDB, CTEP, NCI	WG
Wright, Larry		CBIIT, NCI	GG, SC
Yancey, MaryAnn	MSN, AOCN		WG
Yang, Chih-Hsin	MD, PhD	National Taiwan University	SC
Yasko, Alan	MD	Northwestern Medical Faculty Foundation	WG
Yee, Wendy	PhD	NHLBI, NIH	WG
Yusuf, Yazici		NYU Med Center	WG
Zhao-Wong, Anna	MD, PhD	MedDRA, MSSO	GG, SC
Zimmerman, Nessa	RN	TRI Contractor for CTEP, NCI	SC
Zukin, Mauro	MD	INCa , Brazil	SC
Zwiebel, Jamie	MD	IDB, CTEP, NCI	WG

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

Work Group Number	MedDRA SOC
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; 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

Word	Rule
	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”
po	Change to "oral"
Infection (in definitions)	Do not use "infection" in the definition of any AE that is not an infection term

Word	Rule
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 No Grade 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
CIT	Center for Information Technology (NIH)
CM	Configuration Management
CRA	Clinical Research Associate
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCP	Division 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
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

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