The National Cancer Institute's Cancer Therapy Evaluation Program

CTCAE Implementation

JULY 30, 2006

PRODUCED BY CAPITAL TECHNOLOGY INFORMATION SERVICES, INC.

CTIS
BUILDING THE FUTURE™ TOGETHER

The CTCAE Implementation was prepared for:

Michael Montello – Project Officer
Cancer Therapy Evaluation Program
National Cancer Institute
Executive Plaza North
6130 Executive Boulevard
Rockville, MD 20852

By:

Capital Technology Information Services, Inc.
One Research Court, Suite 200
Rockville, Maryland 20850-3236
Tel: 301-948-3033
Fax: 301-948-2242
Home Page: http://www.ctisinc.com
Under Contract N02-CM-27021

Table of Contents

Record of Changes

Update Date	Brief Description
09/08/03	Initial Document Creation
06/30/06	Section 2.1.2.1 was modified to address the migration to future MedDRA versions.

1 Introduction

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v3.0, which will take effect October 1, 2003, will impact several of the CTEP Enterprise applications on various levels. In some cases (e.g., AdEERS, CDUS, etc.), the impact will be quite extensive, while other applications may require minor modifications. The information provided in this document outlines the anticipated modifications expected to most applications on a general level.

2 Overview

The NCI CTCAE v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. The following describes the organizational structure of the CTCAE and their components. A grading (severity) scale is provided for each AE term.

2.1 Organization and Components

2.1.1 Category

A Category is a broad classification of AEs based on anatomy and/or pathophysiology. Within each Category, AEs are listed accompanied by their descriptions of severity (Grade).

Note: All CTCAE-related documentation distributed refers to categories using all capital letters (i.e., CATEGORY). Because references are made to technical terms such as tables, this document uses standard grammar to refer to category.

2.1.1.1 Navigation Note

A 'Navigation Note' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same category unless the 'Navigation Note' states differently.

2.1.1.2 Other (Specify)

Each category of the CTCAE provides an Other (Specify) option for AEs that are not listed in the available AE criteria (e.g., GASTROINTESTINAL: Other (Specify); BLOOD/BONE MARROW: Other (Specify); etc.). For example, Hyperkeratosis is not a CTCAE term but is a very specific dermatologic manifestation associated with the use of a specific class of new agents. In this case, 'DERMATOLOGY/SKIN, Other (Specify)' is selected and Hyperkeratosis is entered as the actual AE term. All categories of the CTCAE allow for such specificity when the appropriate term is not included in the CTCAE.

2.1.2 Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific

event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

2.1.2.1 Harmonization with the Medical Dictionary for Regulatory Activities (MedDRA)

The International Conference on Harmonization (ICH) develops requirements for drug regulatory reporting globally and has chosen MedDRA (Medical Dictionary for Regulatory Activities) terminology to be the standard. To facilitate data transfer to the FDA and other regulatory agencies, NCI maps all CTCAE v3.0 terms to the MedDRA version currently used by CTEP. See the CTEP List of Codes and Values Web page for the MedDRA version currently being used by CTEP and see http://ctep.cancer.gov for CTEP's use of MedDRA in the Adverse Event Expedited Reporting System (AdEERS), the Clinical Data Update System (CDUS), etc.

2.1.2.2 Supra-Ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word 'Select' and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

2.1.2.3 *Select* AEs

Select AEs are AE terms, are all related to a single supra-ordinate term, are all graded using a single grading scale, and each is mapped to a MedDRA term and code. Many Select AEs are loco-regional AEs that provide over 600 new AE terms.

2.1.2.4 Short AE Name

The 'Short Name' column is new and it is used to simplify documentation of AE names on Case Report Forms.

2.1.2.5 Also Consider

An 'Also Consider' indicates additional AEs that are to be graded if they are clinically significant.

2.1.3 Grades and Grade Definitions

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild AE

Grade 2 Moderate AE

Grade 3 Severe AE

Grade 4 Life-threatening or disabling AE

Grade 5 Death related to AE

2.1.3.1 Dash

An 'Em dash' (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

2.1.3.2 Alternate Grading Criteria

Several AEs include alternate descriptions of grades depending on:

1. Patient population
2. Methodology
3. Anatomic area

2.2 Grade 5 and the Death Category

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

The Death Category is new. Only one Supra-ordinate term is listed in this category: 'Death not associated with CTCAE term – Select' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.

Important: Grade 5 is the only appropriate Grade.

This AE is to be used in the situation where a death:

- cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
- cannot be reported within a CTCAE category as 'Other (Specify)'

3 Implementation Guidelines

The purpose of this document is to provide users with a 'first-cut' of the envisioned modifications required and to solicit input. The document provides guidelines for the implementation of the CTCAE v3.0. However, these guidelines are not meant to provide solutions for all situations. Project leads and application stakeholders should review the adjustments and provide input if revisions are needed or omissions are detected.

The modifications listed below are suggested as general instructions, when appropriate, for all applications across the CTEP Enterprise. Users can expect to see these modifications applied to CTEP applications beginning October 1, 2003.

3.1 General Modifications

3.1.1 Limiting by the appropriate CTCAE Version

All screens (and any additional queries) using CTCAE to report Adverse Events specific to a study, should always limit the Categories, Adverse Events and Grades to the appropriate version of the CTCAE that was assigned to the protocol (e.g., Adverse Events [CTC] section in AdEERS).

3.2 Data Entry Screens (those used to report Adverse Events)

The following changes are proposed, when appropriate, for Web screens (e.g., CDUS-Web, AdEERS, etc.) used to capture Adverse Events for a study.

3.2.1 Selecting Categories

The List of Values for selecting Categories must be limited to version appropriate for that study.

3.2.2 Selecting Adverse Events

The List of Values for selecting Adverse Events should be limited to selected Category and appropriate version. This List of Values will display AEs as well as Supra-ordinate terms. In the event a Supra-ordinate term is selected, an associated Select AE must be selected. (Refer to New Select AE Field below).

3.2.3 Displaying Supra-Ordinate Terms

All Adverse Events associated with Select AEs (i.e., Supra-ordinate terms) will be displayed in the List of Values with an asterisk (*).

Note: The asterisk above is a proposed symbol for identification purposes and may be replaced with a different symbol prior to implementation.

3.2.4 Displaying Irrelevant Supra-Ordinate Terms

Irrelevant Supra-ordinate terms will be displayed with a plus sign (+).

Note: The plus sign above is a proposed symbol for identification purposes and may be replaced with a different symbol prior to implementation.

3.2.5 Selecting Grades

List of Values for selecting Grades should be limited to selected Category, AE, and the appropriate CTCAE version.

3.2.6 New 'Select AE' Field

A new field, labeled Select AE, will be added to the screens (e.g., CDUS Web, AdEERS, etc.) for use when reporting Adverse Events for a study. This field will be placed after the Adverse Event field and will have a list of values that will display all the Select AE (site/type/organ/structure) for the selected Adverse Event (and for selected Category and appropriate version).

3.2.6.1 Validations for Select AE

a) The new 'Select AE' field (and associated validations) will be enforced ONLY if the CTCAE version associated with the study is not v2.0.

b) Database check will be added to ensure that the Select AE field is not null when the AE is associated with one or more Select AEs.

c) Database check will be added to ensure that the Select AE field is not populated when AE is not associated with any Select AEs.

3.3 Reports (Study-Specific)

Following are changes to reports displaying Adverse Events for a study.

a) AEs will now be displayed as a concatenation of the AE/Supra-ordinate term and the Select AE, whenever present.

3.4 Query Wizards and Query Screens

Following are changes to the interfaces/screens (e.g., AdEERS Query Wizard, General Adverse Event Report) used to query Adverse Event data.

a) The list of selectable values for CTCAE related fields (Category, AE, Select AE, Grade) on the query screens, will default to the latest version of the CTCAE.

b) The user will be provided flexibility to switch to any version of the CTCAE, and the List of Values in the CTCAE-related fields will change accordingly.

c) Search options will not be restricted to only the selected CTCAE values. Options will include search capability to corresponding mapped values to other CTCAE versions based on CTEP-provided mapping to the latest CTCAE version. Refer to the CTCAE Mapping Documents available from the CTEP Web site at http://ctep.cancer.gov/reporting/ctc.html:

- About CTCAE Mapping
- CTC v2.0 to CTCAE v3.0

d) Retrieved data will be presented in the following ways:

- Study specific adverse event data will be displayed using CTCAE information, appropriate for the CTCAE version associated with the protocol.
- Data across studies will be consolidated for display purposes, by grouping aggregations using the Adverse Event from the latest version.

3.5 Data Exchange

3.5.1 Import to CTEP

Following are changes to applications involving data exchange (importing to CTEP database [e.g., SmartLoader]).

a) All business rules for data validation will be checked against the CTCAE version appropriate for the study.

3.5.2 Export from CTEP

Following are changes to applications that involve data exchange (exporting from the CTEP database) (e.g., AdEERS XML):

a) The AE will be displayed as a concatenation of the AE (or Supra-ordinate Term) and Select AE (if appropriate). The AE/Supra-ordinate term and Select AE will be separated by a colon (:).

Note: The colon sign above is a proposed delimiter and may be replaced with a different symbol prior to implementation.