

MedDRA “Blue Ribbon Panel”: CTCAE to MedDRA Mapping

Proposed date and location: 06 April 2006, Northern Virginia, USA

Executive Summary

This Blue Ribbon Panel (BRP) meeting is intended to address the following questions:

- Does the updated mapping of CTCAE **base terms** with the proposed six month maintenance schedule meet the needs of MedDRA users?
- Is there a need for a standardized mapping of CTCAE (Common Terminology Criteria for Adverse Events) **grades** to MedDRA?
- If yes, what are the options for mapping?
- If no, what guidance should be provided for users?

Format of the Meeting

The MedDRA Maintenance and Support Services Organization (MSSO) has scheduled a BRP meeting on the topic of mapping CTCAE base term and grade to MedDRA. The BRP is an *ad hoc* one-day meeting of industry and regulatory experts from the ICH regions to provide insight and guidance to the MSSO on a specific topic. For the purpose of this meeting on CTCAE base term and grade mapping, experts from the Cancer Therapy Evaluation Program (CTEP) and from an oncology research cooperative group will be invited to participate as panelists and observers.

The MSSO will act as facilitator and note taker for the BRP. Following the meeting, the MSSO will draft the notes and conclusions of the BRP and circulate the document to the BRP members for edit. Upon approval by the BRP members, the document will be provided to the MedDRA Management Board as a series of recommendations for next steps regarding the mapping of CTCAE grades.

MedDRA subscribers and subject experts will be invited to attend the BRP as observers. Time permitting, observers will be encouraged to question the panel and bring other relevant views to the discussion.

Background

The National Cancer Institute’s (NCI) Common Terminology Criteria for Adverse Events (CTCAE) is a descriptive terminology which is utilized for AE reporting in oncology and HIV clinical trials.

MedDRA is a clinically-validated international terminology. Within the ICH regions, it is used by the biopharmaceutical industry and regulatory agencies throughout the regulatory process, from pre-marketing to post-marketing phases. MedDRA supports the encoding, retrieval and analysis of several types of clinical information. Besides AEs (including diseases, diagnoses, signs and symptoms), MedDRA is also used to encode medical and social history, indications,

investigations, and physical examination findings. The use of MedDRA is now mandated for reporting serious adverse events (SAEs) to certain regulatory authorities.

In order to facilitate data exchange within organizations own internal databases using MedDRA and with regulatory authorities for the purpose of SAE reporting, it is necessary to establish a mechanism to 'translate' or 'convert' CTCAE terms received from the investigators to MedDRA terms. This mechanism is known as mapping from the CTCAE to the MedDRA terminology.

Current Status of the CTCAE – MedDRA Mapping

In 2003, CTEP (Cancer Therapy Evaluation Program) constructed a partial mapping of approximately half of the CTCAE v3.0 base terms to MedDRA Version 6.0 Preferred Terms (PTs). This mapping is posted on the CTEP web site. The mapping is one-directional i.e., it maps CTCAE terms to MedDRA terms; but there is no mapping in the reverse direction.

In collaboration with CTEP, the MSSO has recently updated the existing mapping to the newest version of MedDRA (9.0), using Lowest Level Terms (LLTs) instead of PTs in order to obtain a more accurate representation of CTCAE term concepts and to be consistent with recommendations in the ICH "*MedDRA Term Selection: Points to Consider*" document. Additionally, the MSSO has also mapped all the previously unmapped terms to MedDRA Version 9.0 LLTs. This updated complete mapping provides a one-to-one mapping of each CTCAE base term to one MedDRA Version 9.0 LLT (see examples below); however, it does not incorporate any mechanism for mapping the different grades of CTCAE terms.

Category	AE supra-ordinate term	Select AE	MedDRA Code (v9.0)	MedDRA LLT (v9.0)
CARDIAC ARRHYTHMIA	Conduction abnormality/atrioventricular heart block	Asystole	10003586	Asystole
CARDIAC ARRHYTHMIA	Conduction abnormality/atrioventricular heart block	AV Block-First degree	10003674	Atrioventricular block first degree
CARDIAC ARRHYTHMIA	Conduction abnormality/atrioventricular heart block	AV Block-Second degree Mobitz Type I (Wenckebach)	10027787	Mobitz type I
CARDIAC ARRHYTHMIA	Conduction abnormality/atrioventricular heart block	AV Block-Second degree Mobitz Type II	10027786	Mobitz (type) II atrioventricular block

Future Maintenance of CTCAE to MedDRA Mapping

It is proposed that the MSSO and CTEP assume joint responsibility for updating the mapping with each new version of MedDRA. The mapping will continue to be posted for download on the CTEP web site and the MSSO web site will include a link to the mapping on the CTEP web site.

Question 1 for BRP to address: Does the updated mapping of CTCAE base terms with the proposed six-month maintenance schedule meet the needs of users?

CTCAE Grades

In CTCAE v3.0, a grading (severity) scale is provided for each AE term. The terminology 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

- Not all grades are applicable to all AEs: Some AEs are listed with fewer than 5 options for grade selection; for example, CTCAE 'Palpitations' has only two grade options, i.e., Grade 1 for '*Present*' and Grade 2 for '*Present with associated symptoms (e.g., lightheadedness, shortness of breath)*'.
- The clinical descriptions represent general guidelines and not all listed criteria are required to be met for a particular grade to be assigned. For example, a patient can be diagnosed with 'Allergic reaction/hypersensitivity Grade 3' if the patient has symptomatic bronchospasm, or urticaria, or allergy-related edema/angioedema, or hypotension, or a combination of these events.

CTCAE Grades and MedDRA

Question 2 for BRP to address: Is there a need for a standardized mapping of CTCAE grades to MedDRA?

Mapping essentially serves as a translation or conversion from one terminology to the other. The question is whether there should be a standardized conversion/mapping performed by the MSSO and CTEP as for the existing mapping of base terms or whether individual users should convert grade terms as they see appropriate (i.e., on an *ad hoc* basis).

Here are some pros and cons for both approaches:

Standardized mapping

- The mapping is done by the maintenance groups of both terminologies
- Convenience and time savings for users of both terminologies
- Ensures consistency during the translation/conversion process from CTCAE to MedDRA
- The mapping is actively maintained
- However, due to the complexity and characteristics of both CTCAE (one grade could have many listed adverse events) and MedDRA (single medical concept at PT/LLT level), any standardized mapping may not fit all users' needs

Mapping by users on an *ad hoc* basis

- The mapping is performed by an individual user during his/her work/coding process, who may or may not have in-depth knowledge of either terminology
- Inconvenient and time consuming for users of both terminologies
- The translation/conversion from CTCAE to MedDRA likely varies from user to user, creates inconsistency in coding, and opens the opportunities for errors
- There is no maintenance required by the MSSO/CTEP

Question 3 for the BRP to address: If yes to the standardized grade mapping, then what are the options?

Given the fact that these two terminologies were built upon very different philosophies, the MSSO recommends the panel consider all possible solutions for a better mapping.

The MedDRA terminology in general does not support severity indicators. CTCAE is a severity grading system whose purpose is to compare results between trials.

MedDRA PTs/LLTs are single medical concept based, whereas CTCAE terms have no such requirement. A CTCAE base AE term may represent more than one concept; for example, 'Infection with Grade 3 or 4 neutrophils'. In MedDRA, the infection concept and the low neutrophil count concept would have to be represented by separate PTs/LLTs. The grade descriptions in CTCAE may also represent multiple concepts such as that for 'Allergic reaction/hypersensitivity Grade 3', whose description is 'Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension.' As noted above, a patient is not required to have all listed conditions for a particular grade to be assigned. Adding to the complexity of obtaining an accurate mapping is the fact that the data are typically collected in a format that only states that a patient had 'Allergic reaction/hypersensitivity Grade 3' and there is no further information characterizing the particular signs and symptoms/ laboratory values associated with the event.

As a result, two possible mapping solutions are proposed:

- One to one mapping

In this mapping, the CTCAE grades would be treated as one concept and in general, mapped to the same LLT that the base CTCAE term is mapped to (see examples of 'Allergic reaction/hypersensitivity Grade 1', 'Leukocytes (total WBC) Grade 2', and 'Vasculitis Grade 3' in the table below).

However, exceptions would have to be made for those grades that are represented by MedDRA LLTs that are different from their base terms, for example, CTCAE base term 'Allergic reaction/hypersensitivity' is represented by MedDRA LLT *Hypersensitivity* under PT *Hypersensitivity*, whereas its grade term 'Allergic reaction/hypersensitivity grade 4' is represented by MedDRA LLT *Anaphylaxis* under PT *Anaphylactic reaction*.

Examples:

CTCAE v3.0 Term	MedDRA LLT	MedDRA PT
Allergic reaction/hypersensitivity Grade 1	<i>Hypersensitivity</i>	<i>Hypersensitivity</i>
Allergic reaction/hypersensitivity Grade 4	<i>Anaphylaxis</i>	<i>Anaphylactic reaction</i>
Leukocytes Grade 2	<i>White blood cell count decreased</i>	<i>White blood cell count decreased</i>
Vasculitis Grade 3	<i>Vasculitis</i>	<i>Vasculitis</i>

- Advantage:
 - A simple one to one mapping which is easy to use
 - A practical approach in dealing with verbatims having only 'CTCAE+Grade' without any specific information regarding associated signs and symptoms
 - A different LLT is assigned to the specific grades that represent a different concept from its base term in MedDRA
- Disadvantage:
 - Some detailed medical information is lost during this conversion if the investigator site reports the CTCAE grade plus specific associated signs and symptoms

- One to many mapping

In this case, one CTCAE grade would be mapped to the all possible MedDRA LLTs that match to the listed conditions of that particular grade.

This option only makes sense if the investigator provides all related adverse events when also providing the main diagnosis grade term; for example, 'Allergic reaction/hypersensitivity grade 2 with rash and dyspnea'. However, in reality, it is typically only the main CTCAE term that is provided and it is rare that further information relating to associated signs and symptoms is provided.

Question 4 for the BRP to address: If no to the standardized grade mapping, what guidance should be provided for users?

In the absence of a standardized mapping of CTCAE term grades to MedDRA, are there any other strategies that users should consider to reconcile the information coded with the two terminologies? Please keep in mind not only the practicalities of data systems management, but also patient safety and regulatory considerations.

In summary, the MSSO encourages MedDRA users to actively participate in this discussion. Please forward your comments to MSSOhelp@ngc.com. We look forward to the opportunity to work with you on this important issue. Detailed information about the meeting will be posted on the MSSO web site when available.