MedDRA® BEST PRACTICES

Maintenance and Support Services Organization's (MSSO) Recommendations for Implementation and Use of MedDRA

2018

ACKNOWLEDGEMENTS

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1. INTRODUCTION

The purpose of this MedDRA Best Practices document is to provide the recommendations of the MedDRA Maintenance and Support Services Organization (MSSO) for the implementation and use of MedDRA. Its objective is to promote the accurate and consistent use of MedDRA by users worldwide.

The document provides best practice considerations on several topics pertaining to the use of MedDRA. It does not specify regulatory requirements, nor does it address database issues. Organizations are encouraged to document their own best practices in organization-specific guidelines which should be consistent with this MedDRA Best Practices document.

This MedDRA Best Practices document has five sections:

- Primary System Organ Class (SOC) Allocation in MedDRA
- Single Case Reporting Using Semi-annual Version Control
- MedDRA Implementation and Versioning for Clinical Trials
- Versioning Methodology
- Recommendations for the Implementation of MedDRA Supplemental Terms

Users are invited to contact the MSSO Help Desk with any questions or comments about the MedDRA Best Practices document.

2.   PRIMARY SYSTEM ORGAN CLASS (SOC) ALLOCATION IN MedDRA

2.1   PURPOSE

This section explains the concept of the primary System Organ Class (SOC) allocation in MedDRA and why the primary SOC should not be individually selected by MedDRA users. To do so undermines one of the main goals in using MedDRA as a regulatory standard.

2.2   MedDRA AS AN ICH STANDARD

MedDRA was developed by an ICH Expert Working Group to address many of the limitations of older adverse event terminologies. In the past, organizations that used these terminologies freely "edited" them (e.g., added custom terms) to suit specific needs and to overcome their limitations. The result was a lack of any real standard terminology in the adverse event reporting regulatory environment at that time. The intent of ICH, in developing MedDRA, was to have a standard, medically rigorous, and well-maintained terminology to facilitate communication.

Specifically, some of the applications for MedDRA are:

- To aggregate reported terms in medically meaningful groupings for review, analysis and/or summary of safety data
- To facilitate identification of common data sets for evaluation of clinical and safety information
- To facilitate consistent retrieval of specific cases or medical conditions from a database
- To improve consistency in comparing and understanding safety signals and aggregated clinical data
- To facilitate electronic data interchange of clinical safety information.

The ICH also authorized a group of drug safety experts (from regulatory authorities and industry) to draft the "*MedDRA Term Selection: Points to Consider*" document as guideline for MedDRA usage in coding adverse events, medical and social history, and indications. This ICH-endorsed document states (**bold** added for emphasis):

"MedDRA is a standardized terminology. It is considered essential that ad hoc structural changes in MedDRA not occur. ***The assignment of terms across SOCs is pre-determined within the terminology and should not be altered by users.***"

2.3   THE REASON FOR A PRIMARY SOC

MedDRA is a multi-axial terminology meaning that a Preferred Term (PT) may be linked to more than one SOC. For example, PT *Dyspnoea* has a link to both SOC *Respiratory, thoracic and mediastinal disorders* (its organ system of manifestation) and to SOC *Cardiac disorders* (because of its connection to heart disease). Each PT is assigned a

primary SOC to avoid "double counting" while retrieving information from all SOCs (i.e., a cumulative SOC-by-SOC data output). The other SOCs to which a multi-axial PT is linked are called "secondary" SOCs.

In most instances, PTs relating to diseases or signs and symptoms are assigned to the prime manifestation site SOC. So, for PT *Dyspnoea*, the primary SOC is SOC *Respiratory, thoracic and mediastinal disorders*. However, there are exceptions for three types of terms:

- Terms for congenital and hereditary anomalies are assigned to SOC *Congenital, familial and genetic disorders* as the primary SOC.

- Terms for benign and malignant neoplasms are assigned to SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)* as primary SOC. This does not apply to cyst and polyp terms. These terms have as their primary SOC assignment their site of manifestation SOC

- Terms for infections are assigned to SOC *Infections and infestations* as the primary SOC.

These primary SOC assignment rules were instituted as MedDRA was being developed in order to aggregate certain critical issues (congenital anomalies, neoplasms, and infections) into specific places in MedDRA to facilitate safety signal detection. Note that the primary SOC allocations are "hard-wired" into the MedDRA ASCII files.

2.4 CAN A PRIMARY SOC ALLOCATION BE CHANGED?

Yes, any MedDRA Commercial, Non-profit/Non-commercial, or Regulatory subscriber may submit a proposal to change the primary SOC assignment for any given term through the usual Change Request process. In considering a subscriber's request, the MSSO will carefully review the justification provided along with the already established allocation rules.

The MSSO is aware that coders and dictionary managers are sometimes asked to re-assign the default primary SOC allocation for specific PTs to one of the organization's choosing. As noted above, the MSSO strongly discourages this practice as we believe it undermines the intent of MedDRA as a standard terminology. For example, a reviewer at regulatory authority would find it difficult to compare the safety data of similar products from two different organizations if one freely assigned the PTs to SOCs of their choosing and the other used the standard primary SOC allocations.

3. SINGLE CASE REPORTING USING SEMI-ANNUAL VERSION CONTROL

3.1 PURPOSE

The purpose of this section is to provide the MSSO's recommendations regarding the issue of MedDRA versions and their implementation for spontaneous single case reports and pre-market single case reports.

3.2 OVERVIEW

The updated versions of MedDRA are both the strength of the terminology and one of its greatest challenges. Earlier terminologies were not properly maintained nor were there timely releases of these terminologies to address errors or medical advances. The MedDRA MSSO was created to address both of these issues. MedDRA is currently provided to subscribers on a semi-annual basis utilizing a rigorous medical and technical review for each change request. MedDRA versioning is an issue that affects the reporting of spontaneous single case reports and pre-market single case reports. Based on comments the MSSO has received on this issue from users of the terminology, the MSSO is making the following recommendations. These recommendations should not be viewed as official guidelines approved by regulatory authorities, however the MSSO hopes that these recommendations are taken into consideration when regulatory agencies draft guidelines regarding this issue in the future.

3.3 RECOMMENDATION

The MedDRA MSSO makes the following recommendations to the users of MedDRA in the reporting of spontaneous single case reports and pre-market single case reports:

1) MedDRA should be used for spontaneous postmarketing single case reports and premarket single case reports for serious adverse event reports.

2) All reporting should be done using the most recently released version of MedDRA. The version number of the MedDRA release used to code the report data should be included in all reports.

3) The decision to re-code historical data is left to the discretion of each individual organization.

4) A new release version of MedDRA should become the reporting version on the first Monday of the second month after it is released. To synchronize this event over the three ICH regions, the MSSO recommends midnight GMT, Sunday to Monday, for the switchover. For example :

- 1 March – MedDRA X.0 released
- First Monday of May – MedDRA X.0 becomes the reporting version

- 1 September – MedDRA X.1 released

First Monday of November – MedDRA X.1 becomes the reporting version

The stated change over date and time are used to allow all users enough time to prepare their systems to switch to the new MedDRA version.

For single case reporting, the sender and receiver of the data need to be in synchrony regarding MedDRA versions. Users who are able to quickly update and validate their systems with each release of MedDRA need be aware that if they submit a report using the updated MedDRA release prior to the receiving party switching to the updated version, the submission may be rejected or at least kicked out of automated processing and into a manual process and potential recoding, which will slow the processing of the submission.

4. MedDRA IMPLEMENTATION AND VERSIONING FOR CLINICAL TRIALS

4.1 PURPOSE

The purpose of this section is to provide the MSSO's recommendation regarding the issue of MedDRA versions and their implementation in clinical trials.

4.2 OVERVIEW

The updated versions of MedDRA are both a strength of the terminology and one of its greatest challenges. Earlier terminologies were not properly maintained nor were there timely releases of these terminologies to address errors or medical advances. The MedDRA MSSO was designed to address both of these issues. MedDRA is currently provided to subscribers on a semi-annual basis utilizing a rigorous medical and technical review for each change request. MedDRA versioning is an issue since most clinical trials run for extended periods of time (i.e., greater than 6 months) and regulatory reports also cover extended periods of time (e.g., Integrated Safety Summary).

4.3 OPTIONS CONSIDERED

For coding with MedDRA in clinical trials, it is understood that many organizations may not want to re-code data as frequently as MedDRA updates are available. As such, it is assumed that a project or a trial will "freeze" (i.e., utilize the same version of MedDRA for the entirety of the project or trial) on a version of MedDRA and then optionally re-code at a later milestone in the project/trial.

For purposes of this sectiondocument, a project is defined as a series of related individual clinical trials. Therefore, when the term project is used in this section it is referencing all of the subordinate clinical trials as a group.

There are several options available for versioning with relative merits and issues. A brief discussion of the options follows:

Option 1 – "Freeze" at the initiation and for the life of a project and report with same version of MedDRA.
- All trials within the project would be coded with the same version of MedDRA.
- All reports would be generated with the same version of MedDRA.
- Supports consistency of coding and analysis within related trials.
- Reports and analyses performed are done within the context of the same version of terminology in which the data were coded.
- Causes issues, especially for longer running projects, for the development of the label that will utilize a more recent version of MedDRA as well as not taking advantage of MedDRA improvements with subsequent releases.
- Requires the storage of multiple versions of MedDRA and the maintenance of an organization's MedDRA coding conventions with each version of MedDRA.

Option 2 – "Freeze" at the initiation of a project and report with most recent version of MedDRA.
- All trials within the project would be coded with the same version of MedDRA.
- All reports would be generated with the same version of MedDRA.
- Supports consistency of coding and analysis within related trials.
- The most recent version of MedDRA would be used for reporting utilizing the structure of the most recent version. For example, if a PT moved from one HLT to another in the version used for reporting, it would be output to a different HLT than it was originally coded.
- Depending upon the length of the trials or project, the differences in versions used to code and report could become more significant.

Option 3 – "Freeze" at the initiation of each trial within a project, and report with the most recent version of MedDRA.
- Coded trial data is coded in the most recent version of MedDRA.
- Less of a difference in time between the significant volume of trial data (Phase III) and label development.
- Takes advantage of MedDRA improvements in subsequent versions.
- Depending upon the length of the trials or project, the differences in versions used to code and report could become more significant.

Option 4 – Hold all coding to the completion of each trial and utilize the most recent version of MedDRA for coding and reporting.
- Coding for the trial would likely be more consistent.
- Loads a significant workload stress at the end of each trial.
- Does not allow for any analysis of coded data to be performed prior to the completion of the trial.

Option 5 – "Freeze" at the beginning of each trial within a project and optionally re-code data with the latest version at the conclusion of the trial based on criteria defined within project plan. Always output the data utilizing the most recent version of MedDRA.
- The organization would review the collection of changes against thresholds developed and documented in the project plan. If there is a medical benefit to re-coding the data, the data would be re-coded to the most recent version of MedDRA. Otherwise, the reports are generated with the most recent version of MedDRA.
- Long running trials would be updated and better analyzed with the latest version of MedDRA.
- Less of a difference in time between the most significant volume of trial data (Phase III) and label development.
- Project level reports would utilize the current version of MedDRA.

Option 6 – Re-code the trial data for all trials in a project on an ongoing basis with the most recent version of MedDRA.

- All trial data would be updated with each version and would provide consistency for reporting.
- Removes reconciliation issues with post-market data since post-market data will report with the current version of MedDRA.
- Requires re-coding of all trials to be updated to the current version of MedDRA.

4.4   RECOMMENDATION

For clinical trial data, the MSSO recommends Option 5 or 6 (described above). These options are the feasible from an implementation standpoint and allow organizations to choose which option is best for their process.

5. VERSIONING METHODOLOGY

5.1 PURPOSE

The purpose of this section is to describe the various versioning methods that may be applied to data when an organization implements a new version of MedDRA.

5.2 OVERVIEW

Each organization should have a versioning strategy that should be documented. The versioning strategy may differ between safety databases and clinical trial databases. For example, there may be no need to update clinical trial data from older trials if the data are not presently used or will not be used in the future. On the other hand, postmarketing safety data may be required to be reported in the current (or near-current) version of MedDRA, and version update recommendations then apply.

5.3 OPTIONS CONSIDERED

Users should choose the most optimal approach based on their organization's characteristics. The optional methods described below can be used to document the extent to which an organization has applied a new version of MedDRA. These methods should not be interpreted as regulatory requirements but may be used to communicate effectively between and within organisations.

The table below summarizes the types of versioning methods:

Method	Description	Resource Intensity	Data Accuracy
1	Begin to use new version for coding new data; no recoding of existing data	Least	Least
2	Identify verbatim terms linked to non-current LLTs and recode existing data		
3	Identify verbatim terms linked to non-current LLTs and recode existing data and Recode verbatim terms to new LLTs that are direct or lexical matches	↓	↓
4	Identify verbatim terms linked to non-current LLTs and recode existing data and Recode verbatim terms to new LLTs that are direct or lexical matches and Recode verbatim terms to new LLTs that are more accurate concepts	Most	Most

Table 5-1 Types of Versioning Methods

This list may not be inclusive; other versioning methods may be used. Depending on how MedDRA data are stored in the database, additional steps may be needed to ensure consistency in data retrieval and reporting, including medical review of the data after the version method has been applied.

Note that Method 4 is the most resource intense and Method 1 is the least. There are additional points to consider: recoding to LLTs that are new direct matches or more accurate concepts (Method 4) provides the most accurate data compared to the other methods.

The MSSO and the Japanese Maintenance Organization (JMO) provide tools to assist the user in comparing the changes between MedDRA versions. The Version Report (provided by the MSSO and JMO) is a spreadsheet listing all changes between the current version of MedDRA and the one previous to it; this spreadsheet is provided with each new release of MedDRA. The MSSO also provides the MedDRA Version Analysis Tool (MVAT) that facilitates identification and understanding of the impact of changes between any two MedDRA versions, including non-consecutive ones.

6. RECOMMENDATIONS FOR THE IMPLEMENTATION OF MedDRA SUPPLEMENTAL TERMS

6.1 PURPOSE

The purpose of this section is to provide the MSSO's recommendations regarding the issue of utilization of MedDRA supplemental terms.

6.2 OVERVIEW

The maintenance of MedDRA by the MSSO was designed, and has been implemented, to provide a rapid and accurate response to subscriber Change Requests. When Change Requests are received by the MSSO, the subscriber receives an initial acknowledgement of the receipt of the request within 48 hours of receipt by the MSSO. The Change Request is then processed through an international medical team, and a final disposition is sent to the subscriber within 7-10 calendar days from initial receipt by the MSSO. Approved Change Requests are designated as supplemental changes to MedDRA and are posted on the MSSO website for review by all users. In the original plan of the MedDRA Change Request process, it was anticipated that a situation might occur where, following a final pre-release review of the terminology, a supplemental term may not be included in the next official MedDRA release; this has not happened to date. The MSSO has modified it processes so that, once a supplemental term is added, it is considered part of the MedDRA terminology and will not be deleted.

There is, however, an issue with using supplemental MedDRA terms. Supplemental releases are not considered "official" MedDRA releases. Organizations that use supplemental MedDRA terms do so at risk. The risk is not that the term will not be included in the next release of MedDRA, but that not all organizations and regulators are able to accept them as current valid terms. From a regulator standpoint, the risk for a submitting organization will be a possible slow down in processing because the submission will be viewed as an exception. Exception processing may include manual recoding or rejection of the submission. One needs to take into consideration the validation processing that is implemented as part of the acceptance of e-submissions when forming a policy on the use of supplemental MedDRA terms in a filing.

6.3 RECOMMENDATIONS

The MSSO makes the following recommendations:

1. Organizations should use supplemental terms internally based on their business needs.
2. Organizations that share data with other organizations need to have a clear understanding of the other organization's position on the use of supplemental terms.
3. Organizations submitting regulatory reports need to be aware of the receiving regulatory agency's position on the use of supplemental terms

4. If a regulatory agency does not use supplemental terms, an organization should limit use of supplemental terms for reporting.

5. If the use of supplemental terms is necessary, the organization should coordinate its reporting with the regulator.