

MedDRA Literature Commentary

Subject of commentary:

Journot, V, Tabuteau, S, Collin, F, Molina, J-M, Chene, G, and Rancinan, C; the ALIZE Study Group. About the necessity to manage events coded with MedDRA prior to statistical analysis: Proposal of a strategy with application to a randomized clinical trial, ANRS 099 ALIZE. Contemporary Clinical Trials 2007 Jun 7; [Epub ahead of print]

Commentary:

This article describes a five-step strategy to select “trial primary SOCs” for MedDRA coded data to aid in trial specific analysis objectives. The trial described is the ANRS 099 ALIZE trial for protease inhibitor-containing antiretroviral regimens in HIV-infected subjects. Although acknowledging some of the challenges that the design of MedDRA poses for statistical analysis of data, we wish to caution users about altering MedDRA’s structure on an *ad hoc* basis. We also want to point out the steps that the MSSO and the MedDRA user community are taking to address data analysis challenges that the authors describe.

The authors referenced MedDRA Version 3.0, a version which did not include Standardised MedDRA Queries (SMQs). The five-step process described in the paper ultimately served to reclassify many MedDRA PTs from their default primary SOC allocation (i.e., the primary SOC as defined by the released version) to SOCs which the authors felt were more appropriate for their needs. In all, they reassigned the primary SOC for 23% of their PTs, mainly from SOC *Investigations* and SOC *Ear and labyrinth disorders*.

As an example, they pointed out that in MedDRA Version 3.0, terms for “vertigo” and its variants are linked to three different SOCs, and that this caused confusion in interpretation of results. They also noted that certain investigation result terms (e.g., PT *Transaminase NOS increased*) are in SOC *Investigations* while the corresponding term for the medical condition is in another SOC. This is a well-documented design aspect of MedDRA that has been the subject of debate and discussion among the MedDRA user community for years. In November 2006, a MedDRA Blue Ribbon Panel (BRP) rejected a proposal to make SOC *Investigations* multi-axial. For more information about the BRP discussion and recommendations concerning this issue, please see the information at <http://www.meddramssso.com/MSSOWeb/activities/blueribbonpanels.htm>.

MedDRA was developed by an ICH Expert Working Group to address many of the limitations of older adverse event terminologies (e.g., COSTART). 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.

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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.

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 SOC is pre-determined within the terminology and should not be altered by users.**”*

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 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 companies if one freely assigned the PTs to SOC of their choosing and the other used the standard primary SOC allocations.

We also acknowledge that MedDRA may contain errors of which we are not aware, including incorrect primary SOC assignments. Any MedDRA core 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.

It is well-known that the design of MedDRA and its primary SOC allocation rules can pose a challenge for data analysis. To address this, the ICH MedDRA experts drafted the “*Data Retrieval and Presentation: Points to Consider*” document that describes strategies (e.g., secondary SOC analyses) for dealing with this. Like the “*Term Selection*” document, the goal of this “*Points to Consider*” is to provide a framework to foster consistent use of MedDRA in retrieval and presentation, allowing medically meaningful review and analysis of clinical data.

We appreciate the authors’ efforts to bring the challenges of analysis of MedDRA-coded data to light, but we believe a better approach than *ad hoc* structural changes is to work within the MedDRA community and with the MSSO to continue to improve MedDRA – through change requests, development of new

tools such as SMQs, and development of additional guidances – such as the *Data Retrieval and Presentation: Points to Consider*” document – as needed.

Summary:

This article describes a five-step strategy to select “trial primary SOCs” for MedDRA coded data to aid in trial specific analysis objectives in an HIV therapy trial. In all, the authors reassigned the primary SOC for 23% of their PTs, mainly from SOC *Investigations* and SOC *Ear and labyrinth disorders*.

Although acknowledging some of the challenges that the design of MedDRA poses for statistical analysis of data, we wish to caution users about altering MedDRA’s structure on an *ad hoc* basis. The type and level of customization described in this article is not possible to do in every trial considering the resources involved. We wish to stress that the MSSO and the MedDRA user community are addressing the data analysis challenges through improvements to MedDRA’s structure and by supporting the ICH-endorsed “*Points to Consider*” documents.

The MSSO supports MedDRA as an ICH standard, and we believe a better approach than *ad hoc* structural changes is to work within the MedDRA community and with the MSSO to continue to improve MedDRA – through change requests and through the development of new tools and guidances.