Abstract

One of the principal tasks of clinical trials reporting is the summarization of adverse medical events reported during the course of each trial. To do this, we rely upon standardized dictionaries of adverse events, such as COSTART and MedDRA, which facilitate the classification of events into medically relevant groupings. Our paper first will briefly describe the structure of the MedDRA dictionary and contrast it with COSTART. Then we will describe a method of using SAS and Oracle functions to code MedDRA classification of adverse event terms for clinical trial reporting purpose. We will give several detailed examples of the use of Oracle functions to do classification lookups via SAS SQL pass-through extraction of OC views. Finally, we will briefly discuss the implication on adverse event reporting in the MedDRA world.

Skill Level: Intermediate SAS, Macros, SAS ACCESS, SAS/SQL, Basic PL/SQL

Introduction

Adverse Event Reporting is heavily anchored to the standard medical coding dictionaries. Traditionally, COSTART has been used at the Ann Arbor Laboratory of Pfizer Global Research and Development. In the future the MedDRA dictionary will be used and the corporation will have a single implementation of MedDRA in terms of coding and reporting. In the meantime, before the corporate wide implementation is in place, we created a SAS shortcut to get some quick and preliminary reports, as a interim solution between now and the future. This SAS shortcut also uses OC look-up functions, which yield very good performance. The OC Look-up function, in our personal opinion, is a viable option for MedDRA reporting implementation. The sections below will discuss the details of how to use a SAS programming shortcut to map to the MedDRA dictionary in the OC data extraction process, for use in Adverse Event Reporting.

Background

FDA has been advocating the use of the MedDRA dictionary for Adverse Event coding for a number of years, although it has not mandated it yet. There has been a global initiative at Pfizer to roll-out the MedDRA implementation. However, it takes time for the global implementation to complete. At the same time, major regulatory agencies in Japan and Europe are requiring MedDRA reporting. In the absence of a corporate standard, these reports are done in an ad-hoc fashion. Further, internal teams also have the need to preview what Adverse Event Reports look like in the MedDRA world.

Comparison: COSTART versus MedDRA

Compared to COSTART, MedDRA has more hierarchy levels and more categories in each level. Figure 1 shows a comparison between the two dictionaries. When using COSTART dictionary for reporting, we have been using only two levels: the Preferred Term and Body System. There are only 13 body systems in COSTART, and AE summarization is relatively straightforward.

On the other hand, in the MedDRA dictionary, there are five levels of hierarchy, the Lower Level Term or LLT, the Preferred Term or PT, the Higher Level Term or HLT, the Higher Level Group Term or HLGT, and the Special Organ Class or SOC. Further, MedDRA supports multiaxiality, which means that a single medical concept may be represented by multiple SOCs.

There are more top level categories, 26 MedDRA SOCs verses 14 COSTART Body Systems. MedDRA has 12 times more preferred terms. In part, this is because it contains more than signs and symptoms; it includes social conditions as well.

Implications to Reporting

This has serious implications on AE reporting. We see two major challenges here. The first challenge concerns at which level to summarize, given that there are five levels in MedDRA. SOC is clearly useful, but how about the lower levels? LLT or PT?
The second challenge derives from the multiaxiality of MedDRA. Multiaxiality means one lower level term can branch up to different higher level terms. Granted there is a primary SOC for each lower level term, what if the client wants to report to a secondary SOC? This adds to the complexity for reporting in the MedDRA world.

We are raising awareness here and not attempting to provide all the answers. It seems to us that, in the implementation of MedDRA, a lot of efforts were devoted to the coding, which is warranted. Yet, not enough attention was paid to how to report in the MedDRA world. Further, we would argue that the lack of debate on how to summarize AEs in the MedDRA world is due to the fact that the internal community does not have an easy way to preview what the reports would look like. This is a major reason for us to develop some tools to map AE terms to the MedDRA dictionary for reporting purposes, giving a preview to the clinicians and medical writers of the AE reports in a MedDRA world.

The first implication to reporting is that since MedDRA is larger and more granular than COSTART, AE listings will be longer but will more accurately represent the investigator’s original term. Second, the investigator’s term will need to be quite specific in order to map as intended in MedDRA, i.e. “Hyperglycemia” maps to the Endocrine disorders SOC, while “Increased blood glucose” maps to the Investigations SOC. Next, there are more ways to summarize the data in MedDRA, so more ways to look for significant trends. Further, MedDRA is ‘multiaxial’ - there are ‘primary SOCs’ and ‘secondary SOCs’, so depending on the clinical context of a term, alternative appropriate mappings could be chosen, i.e., ‘Haemorrhagic stroke’ can map to the Nervous system disorder SOC, or to the Vascular disorders SOC. Finally, special search categories can be set up to search for reporting trends which would not be obviously related through the dictionary hierarchy.

Bridge to the Future: SAS + OC look up functions
If we forego the multiaxiality and begin more simply with using just the primary pathway through the MedDRA hierarchy, we can get started as follows.

As shown in figure 2, first, we have a MedDRA table set up that contains all investigator terms and their corresponding LLTs and assigned higher level terms (HLTs, HLGTs, SOCs). This assumes a prior, separate coding effort to assign MedDRA LLTs to investigator-reported adverse event terms, an activity that can be either manual or software assisted. This MedDRA table is stored in a schema that is accessible by the Oracle Clinical database. Second, we write some simple look-up functions in OC, using PL-SQL. We chose to write one function for each level in the MedDRA hierarchy, since this was the simplest and most flexible. Then we compiled and placed the look-up functions in the OC schema where we want to try out your MedDRA mappings of Adverse Events. If the table of mapped investigator terms is large, then we should add an index on investigator term. Next, we modified the standard data extract views for Adverse Events, incorporating one or more of these lookup functions within the SAS SQL PASSTHROUGH part of the view, creating the extra fields necessary to hold as many levels of the classification hierarchy as desired for summary reporting. We tried to use field names that will make sense to previously coded summary reporting programs, so we would not need to write new summary programs. The result is an AE data extract view that dynamically maps all previously coded Adverse Events to any level of the MedDRA hierarchy. The real significance of this is not the mapping itself, which has to be done external to this short-cut, but rather the fact that this process is identical to how we were handling COSTART terms, so many of our standard AE summary reports can now be generated for comparison purposes.

Figure 2 shows an example of the PL/SQL lookup function. It takes the investigator term v_inventext and returns only the mapped Lowest Level Term, in this particular example, v_llt. It also provided an informative error message for un-mapped terms.

Figure 4 is an example that calls the above lookup function in the SAS extraction code. Note that the lookup function is stored inside the OC database and called in the SAS SQL Passthrough portion of the code, which is executed inside the Oracle database and therefore quite fast. The field names passed back should correspond to what the summary reporting programs expect. SOCs and other higher level terms can be looked up similarly and can be added if needed.
CREATE OR REPLACE FUNCTION get_ae_medr_llt(v_invtext IN VARCHAR2) RETURN VARCHAR2 IS
   v_llt VARCHAR2(100);
   CURSOR c1 IS
      SELECT PREF.llt_text
      FROM dsd$meddra_ref meddra
      WHERE meddra.text = v_invtext;
   BEGIN
      OPEN c1;
      FETCH c1 INTO v_llt;
      IF (c1%NOTFOUND) THEN
         v_llt := 'MEDDRA LLT NOT FOUND';
      END IF;
      CLOSE c1;
      RETURN v_llt;
   EXCEPTION
      WHEN OTHERS THEN
         v_llt := 'UNEXPECTED ERROR';
      RETURN v_llt;
   END get_ae_medr_llt;
/

Output
What does one discover from this exercise? Figure 5 shows some of the differences between the reports coded with COSTART and with MedDRA. Here are some examples of the major differences in categorization between MedDRA and COSTART. First, in COSTART there are a large number of AEs in the unspecific category of ‘Body as a whole’. These AEs have moved to more specific System Organ Classes (SOC) in MedDRA. Second, in MedDRA, cardiovascular is split into two SOCs, ‘Cardiac disorders’ and ‘Vascular disorders’. Next, in MedDRA, there are both ‘Nervous System disorders’ and ‘Psychiatric disorders’. Further, ‘Special senses’ is more specific in MedDRA – there are ‘Ear and labyrinth disorders’ and ‘Eye disorders’.

Implications
What are many implications for the pharmaceutical business when we switch to MedDRA reporting? Here is a sample of them.

- IBs
- IND Annual Reports
- NDA Submissions
- Informed Consent
- Product Labels
- Cut-off at Lower Percentage?
- Collapse Several Categories?

The impact on product labeling is perhaps the most important one: For example, current labels show all reported AE’s above a certain percentage, say 1 or 2%, but if the categories are doubled for the same universe of AE’s, then the percentages need to be
revised downward and the list becomes much longer.

**Summary**
To summarize, we created an easy way to code without jumping through too many organizational hoops. It is straightforward and provides a way to quickly prototype different AE reports using the MedDRA dictionary. In short, it meets the needs between now and the future, when a global implementation of can take over this task.

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