

Adverse Events of Special Interest and MedDRA Upgrades: A Dilemma and Proposed Solution

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ABSTRACT

Adverse Events of Special Interest are those events thought to be [potentially] associated with the investigational compound or disease under study. Reporting on Adverse Events of Special Interest is an emerging and ever more critical aspect related to characterizing the safety profile of a compound.

Standard MedDRA Queries (SMQs), or grouping of terms that relate to the defined medical condition or area of interest, exist to select all events similar in some way (e.g., Malignancies). However, SMQs may be either too general or, in some cases, too specific for a project team to use 'straight out of the box'. It's also possible that there are not enough existing MedDRA SMQs to accommodate the needs of a project team.

In addition, as Events of Special Interest lists become more numerous and detailed, the potential coding changes caused by MedDRA updates every six months necessitate the team re-review these lists twice a year (after each upgrade) in order to ensure the ESI lists remain accurate.

As a result, this paper discusses a SAS macro developed specifically to easier facilitate the identification, selection and maintenance of Adverse Events of Special Interest. Specifically, this macro was created to (1) create a single vertical structure SAS dataset from multiple ESI Excel worksheets, and (2) to identify any MedDRA coding differences in Events of Special Interest between different versions of MedDRA.

INTRODUCTION

In order to understand the processing of Events of Special Interest as it relates to this paper it's essential to know how ESI lists are currently developed and maintained. Events of Special Interest are identified and developed by the project team in conjunction with external agencies and/or experts in the therapeutic area in which the investigational compound is being developed.

As doctors and consultants are not typically as SAS-adept as Programmers, these Events of Special Interest lists are maintained in an Excel Spreadsheet with multiple worksheets - each worksheet containing a single Events of Special Interest list.

Once the list(s) has been finalized then the SAS programming really begins. The lists(s) are then converted to a SAS dataset by employing a SAS macro (Version 9+) that dynamically reads in all spreadsheets and generates a single vertical-structured SAS dataset which also dynamically numbers the list(s) - each category has a distinct code at this point.

From that point on, every time MedDRA is updated the SAS macro also produces a Medical review-ready spreadsheet which lists any (and there are always some!) differences in ESIs between the prior and current versions of MedDRA. For example, just between a minor MedDRA version change (Version 11.0 to 11.1) there were 771 new coding changes (occurring between the mapping of Preferred Term and System Organ Class. The macro is then employed to identify and report differences between the prior and current MedDRA versions and produce an Excel file which allows the medical team to easily view the differences (and then update the Excel spreadsheet with new MedDRA codes).

STEP 1: CREATING INITIAL EVENTS OF SPECIAL INTEREST (ESI) SPREADSHEETS

Although this first step does not require any SAS code per se, it is critical as the standard structure Excel spreadsheet makes possible the use of a SAS macro to process these worksheets. As mentioned above, the first step required in this process is for the medical team to provide the list(s) of Adverse Events of Special Interest. This spreadsheet will be named 'ESI' and consist of 3 columns: 'TYPE', which contains the level of MedDRA coding (SOC, HLG, HLT, PT and LLT), the second column 'NAME' contains the actual name of the MedDRA code (e.g., 'Headache'), and the third column, 'CODE' contains the actual 8 character MedDRA code (see below). Note CTYPE column can contain any or all MedDRA code types (e.g., LLT, PT, HLT, HLG and SOC). Please see Figure 1 (below) for an example of the spreadsheet structure.

Figure 1
Example of Events of Special Interest Excel File

	A	B	C
1	CTYPE	NAME	CODE
2	SOC	xyz	12345678
3	PT	xyz	12345678
4	PT	xyz	12345678
5	PT	xyz	12345678
6	PT	xyz	12345678
7	PT	xyz	12345678
8	PT	xyz	12345678
9	PT	xyz	12345678
10	PT	xyz	12345678
11	PT	xyz	12345678
12	PT	xyz	12345678
13	PT	xyz	12345678
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STEP 2: CREATING THE SINGLE SAS DATASET FROM INITIAL ESI SPREADSHEETS

STEP 2.1: Read in all worksheets in Excel file by using the 'excel' libname feature (below):

```
LIBNAME XYZ EXCEL '\\AE CODES\ESI.XLS' ;

proc sql;
  create table sheets as
  select distinct upcase(memname) as dsn2, memname as dsn
  from dictionary.columns
  where upcase(libname)='EXBK' and upcase(memtype)='DATA' and index(memname, '$');
QUIT;
```

STEP 2.2: UPDATING THE SINGLE SAS DATASET: CREATE METADATA FILE FOR SAS MACRO ARRAY PROCESSING (SEE ART CARPENTER REFERENCE)

```
data sheets2;
```

```

set sheets;
ord=input(dsn2,ord.);
run;

data _null_;
set sheets2 end=eof;
i+1;
ii=left(put(i,3.));
call symputx('esi' || ii,trim(dsn));
call symputx('esix' || ii,trim(tranwrd(dsn,'$','')));
call symputx('tesi' || ii,compress(tranwrd(dsn2,'$','')));
if eof then call symput('esicnt',ii);
RUN;

```

STEP 2.3: USE MACRO ARRAY PROCESSING TO CREATE A SINGLE VERTICAL STRUCTURE ESI DATASET

```

%macro xls2ds;
%do j=1 %to &esicnt;
PROC IMPORT OUT= work.esi_&&tesi&j.
DATAFILE= "\\AE Codes\Spreadsheets\esi.xls"
DBMS=EXCEL2000 REPLACE;
SHEET="&&esi&j.";
GETNAMES=YES;
RUN;

/***** Create permanent SAS Datasets *****/
data xyz.esi_&&tesi&j. (outrep = solaris);
set esi_&&tesi&j.;
run;

proc append base=xyz.esi data=xyz.esi_&&tesi&j.;
run;

%end;
%mend xls2ds;
%xls2ds

```

STEP 3: COMPARING AND UPDATING THE SINGLE SAS DATASET DURING MEDDRA UPGRADES

STEP 3.1: COMPARING NEW MEDDRA VERSION TO PRIOR MEDDRA VERSION

With each new MedDRA upgrade there are bound to be hundreds, if not thousands, of differences in MedDRA coding hierarchies. As mentioned previously, just for PT differences between MedDRA Version 11.0 and 11.1 there were 771 new coding combinations. For example, lower level terms could be re-mapped into different higher level terms or codes at any coding level could be added or removed. Since we only want to focus on what is different among ESI codes (and not all codes), it's critical to see if any project ESIs have been impacted by the MedDRA upgrade. In order to do this the ESI dataset is merged (by the relevant coding level) with the entire MedDRA hierarchy. The steps to doing this are as follows:

1. Read in esi dataset and transpose by code, type and name (this will give a sas dataset with each distinct code and the name of each distinct esi category (so there could be a single code associated with multiple esi categories))
2. Populate variable code depending on with appropriate meddra code (hlgt, hlt, llt, pt or soc)
3. Determine if ESI MedDRA code (hlgt, hlt, llt, pt or soc) is not in new meddra version but was in old, write to a *.csv file (one for each code category)
4. Write out to an excel spreadsheet all new MedDRA codes that exist in new version but not prior version.
5. Write out an excel spreadsheet of meddra codes that exist in multiple esi categories (for medical confirmation)
6. Create a single Excel file (See Figure 2) which contains the following spreadsheets:
 - A. Step 3 - Each MedDRA Code that was in Old Version of MedDRA but not New Version
 - B. Step 4 - Each MedDRA Code that exists in new MedDRA version but was not in Previous Version
 - C. Step 5 - A list of MedDRA codes that exists in multiple ESI categories (just for medical review)

Figure 2
Example of Excel File for Team Review

	A	B	C	D	E	F
1	CODE	TYPE	NAME	ESI_CATEGORY 1	ESI_CATEGORY2	ESI_CATEGORY3
2		1 PT	Term 1	ESI 1		
3		2 PT	Term 2	ESI 1		
4		3 PT	Term 3	ESI 2	ESI 4	
5		4 PT	Term 4	ESI 3		
6		5 PT	Term 5	ESI 1		
7		6 PT	Term 6	ESI 4	ESI 8	
8		7 PT	Term 7	ESI 1		
9		8 PT	Term 8	ESI 5		
10		9 PT	Term 9	ESI 1		
11		10 PT	Term 10	ESI 6		
12		11 PT	Term 11	ESI 1		
13		12 PT	Term 12	ESI 1	ESI 4	ESI 7
14		13 PT	Term 13	ESI 3		
15		14 PT	Term 14	ESI 4		
16		15 PT	Term 15	ESI 7		
17		16 PT	Term 16	ESI 4		
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STEP 3.2: UPDATING THE SINGLE SAS DATASET

SEE STEP 2

STEP 3.3: COMPARING NEW MEDDRA ESI TO PREVIOUS MEDDRA ESI

This is to check to ensure that the steps in Step 3.2 were carried out successfully. This is done by simply using a 'proc compare' of the previous ESI dataset to the current ESI dataset. This will also list/confirm that any coding changes made between MedDRA versions were re-mapped.

CONCLUSION

As Events of Special Interest are becoming more critical to assessing the safety profile of a compound it's essential that a SAS macro or other tool be employed to automate this process, primarily to ensure quality but also to gain efficiencies, especially as the ESI lists become longer and/or more numerous. Standard MedDRA Queries were created to fulfill this need but, at present, SMQs are not comprehensive or specific enough to meet the entire needs of different Therapeutic areas. In addition, current Events of Special Interest individual lists may be in excess of one thousand codes.

The macro described in this paper automates both the generation of the initial Event of Special Interest dataset as well as helps maintain this list over multiple MedDRA versions (which are currently occurring twice a year) by reporting the differences between the prior and current MedDRA versions as it relates to the Events of Special Interest.

ACKNOWLEDGMENTS

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RECOMMENDED READING

Carpenter, Art. 2004. Carpenter's Complete Guide to the SAS Macro Language, Second Edition. Cary, NC: SAS Institute, Inc.

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