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Practice of SMQs for Adverse Events in Analysis of Safety Data and Pharmacovigilance

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Abstract

MedDRA can not group adverse events that indicate the presence of a medical condition through PTs properly due to its high granularity. SMQs were developed specifically to address this issue and to maximize the likelihood that all terms related to a specific medical condition of interest can be identified. This paper describes the practical implementation of SMQs and how SMQs can be applied to search adverse events for statistical analysis and create tables, listings and graphics. SAS and PROC SQL are used to read in the SMQ dictionary files and then convert into appropriate data structure in searching for adverse events of concern. The practical techniques we present offer a good overview of SMQs and its applications in analysis of safety data and pharmacovigilance. This paper will educate all level SAS users who are interested in safety data analysis and pharmacovigilance with SAS programming.

INTRODUCTION

MedDRA (Medical Dictionary for Regulatory Activities), designed for sharing regulatory information for human medical products, is used to report adverse reaction/adverse events in clinical study reports necessary for support of drug development, pharmacovigilance and risk management. Safety data analysis and presentation with MedDRA for medically meaningful review include, capture related AE data, compute frequencies of similar AEs, and display AE data in reports such as tables, listings, and graphics.

While a highly granular terminology, MedDRA cannot have the desired harmonizing effect in the exchange of coded data. Related events that may have been represented by a single term in another terminology may be represented by more than one MedDRA PTs. Clinically related PTs might be overlooked or not recognized as belonging together because they might be in different groupings within a single SOC or they may be located in more than one SOC. Its structure doesn't perfectly support for aggregation of those reported terms in medically meaningful groupings to facilitate analysis of safety data

SMQs (Standardised MedDRA Queries) were created to standardize identification and retrieval of safety data. SMQs are a joint effort of the Council for International Organizations of Medical Sciences (CIOMS) and ICH representing both industry and regulatory authorities. An SMQ is a grouping of terms from one or more SOCs that relate to a defined medical condition or area of interest. The terms included relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data, etc. that are associated with the medical condition or area of interest. A focus of the early phase of SMQ development was to identify which areas of interest were candidates for development. Close to 100 possible topics were initially identified. The CIOMS Working Group continually reviews this list and prioritizes topics for development. Subteams work on each candidate SMQ prior to review and approval by the entire CIOMS Working Group.

The definitions of SMQs are unambiguous, and the advantages of SMQ include:

- Application across multiple therapeutic areas
- Validated reusable search logic
- Standardized communication of safety information
- Consistent data retrieval

SMQ VERSION

As with all MedDRA-based queries, users of SMQs should be aware of several factors that may influence data retrieval including dataset characteristics, data conversion processes, coding conventions, and MedDRA versioning.

MedDRA is updated twice yearly (xx.0 and xx.1). The current 15.0 version was released in May, 2012. Each SMQ relates to a specific MedDRA version. SMQs are part of each new MedDRA release, and correspond to the terms present in that version of MedDRA.

Updates to SMQs that can occur with each MedDRA version include (but are not limited to) the following:

- Creation of a new SMQ
- Rename an SMQ
- Merge an SMQ
- Restructuring of an SMQ (e.g., change in the hierarchical position of an SMQ)
- Change status of an SMQ –active or inactive
- Update SMQ description –in the distributed ASCII text file
- Update SMQ note
- Addition of PTs to an SMQ
- Change a MedDRA term status in an SMQ (Inactivation of a PT from an SMQ)
- Change of term scope (e.g., broad to narrow, or narrow to broad)
- Update MedDRA term category

The SMQ version should always correspond to the MedDRA version of the data being searched, because mismatches could produce unexpected results. If an SMQ from an older version of MedDRA is applied to data coded in a more recent version, data coded to terms that are not present in the older SMQ would not be retrieved.

For example, PT Prerenal failure was added to SMQ Acute renal failure in MedDRA

Version 15.0. Using Version 14.1 of this SMQ – which does not contain this PT – would fail to identify cases coded to this term in a database using MedDRA Version 15.0.

In Integrated Safety Summary (ISS), some datasets may contain AE data of multiple studies coded in different versions of MedDRA. This may impact aggregation of those data when a search is built with terms of an earlier MedDRA version.

As with all searches of MedDRA-based data, it is important to document the MedDRA and SMQ versions used.

Queries stored in an organization's system should be updated to the appropriate version of MedDRA before using them on new data.

SMQ DICTIONARY

There are two SMQ files in ASCII format with dollar sign '$' delimited, supplied with each MedDRA version.

- SMQ_LIST: List of Standard MedDRA Queries (SMQs)
- SMQ_CONTENT:Map the SMQs to a standard MedDRA hierarchy

smq_list: SMQ List contains one observation per SMQ (203 rows in Version 15.0). See the attributes associated with the columns described below.

smq_code	Unique SMQ identifier; used to join with smq_content
smq_name	Text provided in Risk Tracking Document
smq_level	Reference to value within the hierarchy of SMQs
smq_description	Description of the SMQ
smq_source	Medical references for the SMQ
smq_note	Additional information to help users understand
MedDRA_version	Identifies the associated MedDRA version
Status	A = Active. I = Inactive
smq_algorithm	if SMQ was developed for use with an algorithm, contains the Boolean expression.

A few data from smq_list as the eaxample:

smq_code	smq_name	smq_level	smq_description	smq_source	smq_note	MedDRA_version	status	smq_algorithm
20000001	Torsade de pointes/QT prolongation (SMQ)	1	Torsade de pointe	Zipes DP. Spec	1. Includes	15.0	A	N
20000002	Rhabdomyolysis/myopathy (SMQ)	1	Myopathy is a disc	Basic requireme	1. Renal im	15.0	A	N
20000003	Acute renal failure (SMQ)	1	Acute renal failure	The Merck Manual, 17th Edi		15.0	A	N
20000004	Cardiac failure (SMQ)	1	A condition in whic	Council for Inter	The CIOMS	15.0	A	N
20000005	Hepatic disorders (SMQ)	1	Disorders of the li	Harrison's Principles of Inte		15.0	A	N
20000006	Drug related hepatic disorders - comprehensive search (SMQ)	2	This SMQ is a sub-SMQ of Hepatic disorder (SI			15.0	A	N
20000007	Drug related hepatic disorders - severe events only (SMQ)	3	This SMQ is a sub-SMQ of Drug related hepatic			15.0	A	N
20000008	Liver related investigations, signs and symptoms (SMQ)	3	This SMQ is a sub-SMQ of Drug related hepatic			15.0	A	N
20000009	Cholestasis and jaundice of hepatic origin (SMQ)	3	This SMQ is a sub-SMQ of Drug related hepatic			15.0	A	N
20000010	Hepatitis, non-infectious (SMQ)	4	This SMQ is a sub-SMQ of Drug related hepatic			15.0	A	N
20000011	Liver neoplasms, malignant and unspecified (SMQ)	4	This SMQ is a sub-search of SMQ Drug related			15.0	A	N
20000012	Liver neoplasms, benign (incl cysts and polyps) (SMQ)	4	This SMQ is a sub-SMQ of Drug related hepatic			15.0	A	N
20000013	Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)	4	This SMQ is a sub-SMQ of Drug related hepatic			15.0	A	N
20000014	Congenital, familial, neonatal and genetic disorders of the liver (SMQ)	2	This SMQ is a sub-SMQ of Hepatic disorder (SI			15.0	A	N

smq_content: SMQ Content contains multiple observations per SMQ, containing PT codes, LLT codes and information on child = subordinate SMQ's (59032 rows in Version 15.0). The column names and their attributes are displayed as below.

smq_code	Unique SMQ identifier; used to join with smq_list
term_code	Can contain a MedDRA PT, LLT, or child SMQ
term_level	4 = PT, 5 = LLT, 0 = child SMQ. **Note:** a child SMQ points to other SMQs. If a child SMQ is in the list, all of the Preferred terms and Lowest Level terms from the child SMQ must be included.
term_scope	Broad (scope=1 or scope=2), narrow scope = 2, child SMQ = 0
term_category	Use with Algorithms. If child SMQ - S. If no algorithm - A.
term_weight	Used with some algorithms. 0 = default.
term_status	A = Active. I = Inactive.
term_addition_version	The version of MedDRA where the term was added to the SMQ
term_last_modified_version	The version of MedDRA where the term was last modified in this SMQ.

The following is the sample data from smq_content.

smq_code	term_code	term_level	term_scope	term_category	term_weight	term_status	term_addition_version	term_last_modified_version
20000001	10003109	5	1	A	0	A	7.1	7.1
20000001	10003131	5	1	A	0	A	7.1	7.1
20000001	10003132	5	1	A	0	A	7.1	7.1
20000001	10003586	5	1	A	0	A	7.1	7.1
20000001	10003587	5	1	A	0	A	7.1	7.1
20000001	10003589	5	1	A	0	A	7.1	7.1
20000001	10004978	5	1	A	0	A	7.1	7.1
20000001	10004979	5	1	A	0	A	7.1	7.1
20000001	10004980	5	1	A	0	A	7.1	7.1
20000001	10004982	5	1	A	0	A	7.1	7.1
20000001	10004983	5	1	A	0	A	7.1	7.1
20000001	10007515	4	1	A	0	A	7.1	7.1
20000001	10007517	5	1	A	0	A	7.1	7.1
20000001	10007565	5	1	A	0	A	7.1	7.1

SMQ STRUCTURE

SMQs are distributed in two files. SMQ_LIST provides general information about each SMQ. Each SMQ has a status of A/I (Active/Inactive) flagged in status column, It is similar in concept to MedDRA currency.

While SMQ_CONTENT has MedDRA PT/LLT codes as well as subordinate SMQs. Terms assigned to an SMQ also have a status flag. Once a term is added to an SMQ, it will always be included in the SMQ but the status may be inactive.

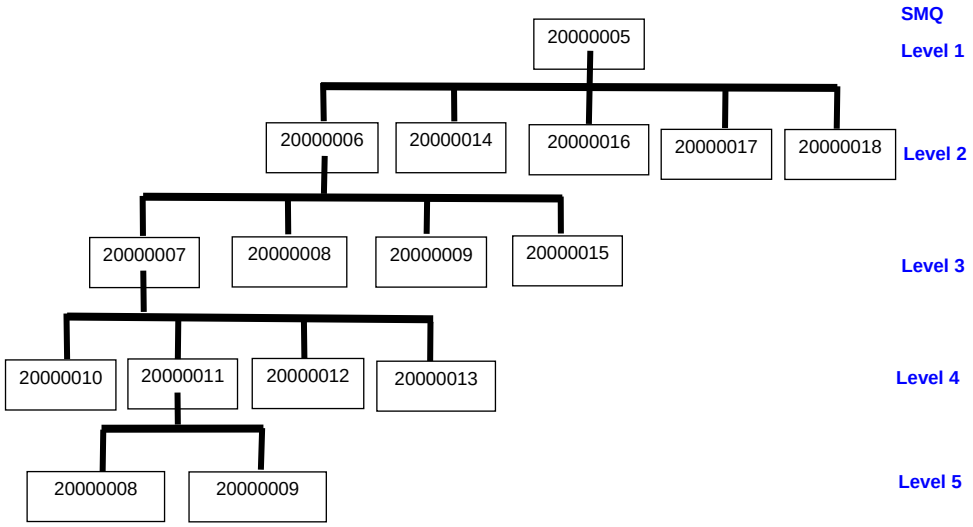
SMQ data are constructed when bring together List and Content via the identifier SMQ code. Do not include inactive SMQ terms (take status='A' and term_status = 'A' only).

SMQ names have "(SMQ)" appended to the end to ensure there is no name conflict with existing MedDRA terms, for example, "Agranulocytosis (SMQ)".The MedDRA terms are not included in the SMQ files. SMQs are constructed at MedDRA PT level. LLTs that are subordinate to an included PT are also included. The SMQ_content file includes PT and LLT codes or a child SMQ code in the term_code column. SMQs begin with 2 while PT/LLTs begin with 1. The column of term_level is used to indicate PTs, LLTs and child SMQs.

- When term_level = 4, the term_code represents the PT code. All of the PTs related to the defined SMQ are included.
- When term_level = 5, the term_code contains the LLT code. The only LLTs associated with PTs used in the SMQ are lincluded.
- When term_level = 0, the term_code includes child SMQ codes. See the figure below. SMQs can have multiple levels. SMQ_Code = 20000005 for an example, this includes 5 separate SMQs (20000006, 20000014, 20000016, 20000017 and 20000018).

smq_code	term_code	term_level
20000005	20000006	0
20000005	20000014	0
20000005	20000016	0
20000005	20000017	0
20000005	20000018	0
20000006	20000007	0
20000006	20000008	0
20000006	20000009	0
20000006	20000015	0
20000007	20000010	0
20000007	20000011	0
20000007	20000012	0
20000007	20000013	0
20000011	20000208	0
20000011	20000209	0

SMQs with child SMQs may not be able to directly point to PT/LLTcode due to file structure. It is similar to the MDhierarchy-file for SOCs



Since the dictionary hierarchy impacts operation, the parent and child SMQs must be referenced and directly linked to their corresponding PT/LLT codes in the applications. This can be done by extending its structure to linear model.

SMQ1 -> SMQ2 -> SMQ3 -> SMQ4 -> SMQ5 -> PT/LLT Codes.

For example, Hepatic disorders (SMQ) in SAS data structure may looks like

smq1code	smq2code	smq3code	smq4code	smq5code	term_code	pt_code	pt_name
20000005	20000006	20000008	.	.	10000028	10000028	5'nucleotidase increased
20000005	20000018	.	.	.	10000746	10000746	Acute fatty liver of pregnancy
20000005	20000006	20000007	20000013	.	10000804	10000804	Acute hepatic failure
20000005	20000017	.	.	.	10001627	10001627	Alcoholic liver disease
20000005	20000006	20000007	20000010	.	10003827	10003827	Autoimmune hepatitis
20000005	20000006	20000007	20000012	.	10004269	10004269	Benign hepatic neoplasm
20000005	20000006	20000015	.	.	10005518	10005518	Blood fibrinogen abnormal
20000005	20000006	20000009	.	.	10008635	10008635	Cholestasis
20000005	20000014	.	.	.	10010317	10010317	Congenital absence of bile ducts
20000005	20000016	.	.	.	10010496	10010496	Congenital hepatitis B infection
20000005	20000006	20000007	20000011	20000209	10019695	10019695	Hepatic neoplasm
20000005	20000006	20000007	20000011	20000208	10019697	10019697	Hepatic neoplasm malignant

Load of SMQ

The loading of SMQ may have the following steps

1. Import SMQ_List and SMQ_Content
2. Join List and Content via SMQCODE.
3. Extend and clarify hierarchical data structure. All information in one row allows the better use for searching, displaying and reporting.
4. Join MedDRA dictionary to get PT and LLT terms (optional). Remember to include only current terms from the dictionary file (where llt_currency = 'Y' from llt.asc file).

The SMQ is used to determine if any of the PT codes or LLT codes exist in the clinical study database. These may come from a child SMQ. Remember to check only those with an active status. The codes in SMQ don't have to be joined to the MedDRA dictionary, but it will be great helpful for review with PT and LLT terms available.

Once SMQ dictionary loaded and saved in a permanent place, it is unnecessary to reload existing SMQ dictionary every time.

SMQ Merge with Study Datasets

Bring the SMQ dictionary files together with clinical trial adverse event data via PT/LLT codes and term_code to get all SMQ information on a subject level.

If MedDRA version in AE dataset differs from SMQ version, use LLT codes for merge of SMQ dictionary (default in SMQ merge macro and not PT codes).

LLT‘s, unlike PT‘s, will not disappear over time and matching LLT‘s are always available (one reason for storage of LLT codes in datasets). Note that all PTs are duplicated at the LLT level in MedDRA. In SMQ, PTs (level 4) are not duplicated at the LLT level (level 5), i.e., LLT code identical to PT code is not repeated in SMQ term code. Only PT codes are used when data merges with SMQ at PT level, and all term code should be used when data merges at LLT level.

Users can conduct a search with only PTs if the data are stored at the PT level, and conduct a search with both PTs and LLts if the data are stored at the LLT level.

FDA recommends submitting data in a single terminology and integrated safety summary(ISS) in the same version of that terminology.

When multiple SMQs are selected, the possibility exists of having the same PT be a member of more than one SMQ. For example, PT with term_code=10052464 is Electrocardiogram repolarisation abnormality. SMQs 20000001 (Torsade de pointes/QT prolongation (SMQ)), 20000051 (Arrhythmia related investigations, signs and symptoms (SMQ)) , and 20000056 (Conduction defects (SMQ)) all contain this PT. This can result in a many-to-many merge issue when joining the SMQ PTs with the AE data set. One way to resolve this is to use an SQL Cartesian join, but this will alter the number of records in the resulting data set.

The following codes are for SMQ merge with study dataset by pt_code level.

```
data smq_query;
  set smq;
  if smq1name='Drug abuse, dependence and withdrawal (SMQ)' or
     smq1name='Depression and suicide/self-injury (SMQ)' or
     smq1name='Psychosis and psychotic disorders (SMQ)' or
     smq1name='Hostility/aggression (SMQ)' ;
  if term_code=4;
run;
proc sql noprint;
  create table smq_ae as
    select a.*, b.*
       from iss_ae.ae a left join smq_query b
         on a.ptcode=b.term_code;
quit;
```

SMQ SEARCH

Data search and retrieval are performed for summary and analysis of clinical trial data, pharmacovigilance, medical information questions and for a number of other purposes.

Prior to data retrieval, there may be known or potential safety issues that need detailed investigation. Information from pre-clinical studies, clinical trials post-marketing surveillance, class effects of similar products, and regulatory queries may identify areas of possible focus; these may affect the strategy for aggregating search terms, the methodology, and the way data are displayed.

Load SMQ and run against coded MedDRA terms in safety or clinical study datasets for ‘Hits’ at Pt or LLT level by the perspective of SMQs.

SMQs may have a mixture of very specific terms and less specific terms that are consistent with a description of the overall clinical syndrome associated with a particular adverse event and drug exposure. Some SMQs are a

straightforward collection of terms; others have been designed to accommodate combinations of terms from more than one group. To address these varied aspects, SMQs have certain specific design features. The search strategies, methods and tools used to retrieve data might differ based on the intended use of the output.

1). Narrow Search

The most common option is use of narrow and broad search terms.

- Broad search includes terms where term_scope = 1 or 2.
- Narrow search includes terms where term_scope = 2.

The narrow PTs have a greater likelihood of identifying only events of interest (high specificity) while the broad terms are intended to identify additional possible events (high sensitivity). Some events retrieved by the broad search terms may, upon further review, not relate to the condition of interest. The user can select the scope of the search (narrow or broad) that is most applicable to the question being asked.

Figure below is an example of narrow and broad searches.

smq_code	smq_name	smq_level	smq_algorithm	term_code	term_level	term_scope	term_category	term_weight
20000001	Torsade de pointes/QT prolongation (SMQ)	1	N	10024885	5	1	A	0
20000001	Torsade de pointes/QT prolongation (SMQ)	1	N	10026707	5	1	A	0
20000001	Torsade de pointes/QT prolongation (SMQ)	1	N	10028158	5	2	A	0
20000001	Torsade de pointes/QT prolongation (SMQ)	1	N	10028159	5	2	A	0
20000001	Torsade de pointes/QT prolongation (SMQ)	1	N	10034048	5	1	A	0
20000001	Torsade de pointes/QT prolongation (SMQ)	1	N	10034049	5	2	A	0
20000001	Torsade de pointes/QT prolongation (SMQ)	1	N	10034050	5	2	A	0
20000001	Torsade de pointes/QT prolongation (SMQ)	1	N	10034100	5	1	A	0
20000001	Torsade de pointes/QT prolongation (SMQ)	1	N	10036095	5	2	A	0
20000001	Torsade de pointes/QT prolongation (SMQ)	1	N	10036887	5	2	A	0

2). Broad Search

Narrow search terms may be applied to identify events where the specific diagnosis has been reported; however, events of reported signs and symptoms would not be retrieved. If there is additional need to find cases where no specific diagnosis (but mainly signs and symptoms) have been reported, then a broad search should be applied. By definition, a broad search includes both narrow and broad terms.

When a compound is in early phase development or has only recently been marketed, it may be advisable to use the broad search.

3). Hierarchy Search

Several SMQs have a hierarchical structure (containing child SMQs). It provides SMQs with multiple levels of analysis. One or more levels of sub-searches can increase the specificity. The user can select the search that is most applicable to the question being asked or a combination of sub-search SMQs as needed.

An example of a hierarchical SMQ is illustrated below (SMQ Haematopoietic cytopenias). The medical condition of interest is thrombocytopenia. SMQ Haematopoietic cytopenias may be too inclusive because sub-searches for decreases of other hematopoietic cell lines (e.g., SMQ Haematopoietic leukopenia) are included. A user may wish to select only the sub-search SMQ Haematopoietic thrombocytopenia in this instance.

4). Algorithm SMQs

An algorithm search may be used to refine a particular search. It provides a certain combination in between that of the narrow and the broad search, by including all narrow search PTs, and adding some broad search PTs defined in the algorithm.

The broad terms of algorithmic SMQs are subdivided into categories that could be groupings of organ-specific signs or symptoms, laboratory terms, etc. For example, in Acute pancreatitis (SMQ), the narrow search category is labled A, while the broad search terms are grouped into two categories: Category B is a list of laboratory values and Category C is a list of signs and symptoms. The algorithm for Acute pancreatitis (SMQ) defines a case of interest as a record coded with one of the Category A (narrow scope) terms OR a record coded with one of the Category B AND one of the Category C terms.

smq_code	smq_name	smq_level	smq_algorithm	term_code	term_level	term_scope	term_category	term_weight
20000022	Acute pancreatitis (SMQ)	1	A or (B and C)	10000097	4	1	C	0
20000022	Acute pancreatitis (SMQ)	1	A or (B and C)	10000119	5	1	C	0
20000022	Acute pancreatitis (SMQ)	1	A or (B and C)	10000335	5	1	C	0
20000022	Acute pancreatitis (SMQ)	1	A or (B and C)	10000429	5	1	C	0
20000022	Acute pancreatitis (SMQ)	1	A or (B and C)	10000647	4	1	C	0
20000022	Acute pancreatitis (SMQ)	1	A or (B and C)	10000971	5	2	A	0
20000022	Acute pancreatitis (SMQ)	1	A or (B and C)	10001426	5	1	C	0
20000022	Acute pancreatitis (SMQ)	1	A or (B and C)	10001482	5	1	B	0
20000022	Acute pancreatitis (SMQ)	1	A or (B and C)	10002015	5	1	B	0
20000022	Acute pancreatitis (SMQ)	1	A or (B and C)	10002016	4	1	B	0
20000022	Acute pancreatitis (SMQ)	1	A or (B and C)	10002018	5	1	B	0

In some cases, SMQ term weight may be used with an algorithm. Weightings are assigned to particular terms for signs, symptoms and laboratory results to help identify cases. The weight system for broad terms was developed empirically and relates to the frequency of the terms and the probability that these relate to the well-known occurrence in patients receiving these drugs.

A term weight indicates the relevancy of each category within the algorithm. For example, terms in Systemic lupus erythematosus (SMQ) are grouped into 9 categories with Category A being the narrow scope terms and Categories B through I being the broad scope terms. Each broad scope Category is assigned a weight from 1 to 3. The PTs in the case report are grouped according to the pre-determined categories. Occurrence of multiple PTs within a category is counted only once for each subject. Based on the algorithm for Systemic lupus erythematosus (SMQ), a case of interest is a record coded with one of the Category A (narrow scope) terms OR a record with various broad search categories terms with a sum of the category weights greater than 6.

smq_code	smq_name	smq_level	smq_algorithm	term_code	term_level	term_scope	term_category	term_weight
20000045	Systemic lupus erythematosus (SMQ)	1	A or Sum(Category Term Weight)>6	10002030	5	2	A	0
20000045	Systemic lupus erythematosus (SMQ)	1	A or Sum(Category Term Weight)>6	10000617	5	1	B	1
20000045	Systemic lupus erythematosus (SMQ)	1	A or Sum(Category Term Weight)>6	10006527	5	1	C	2
20000045	Systemic lupus erythematosus (SMQ)	1	A or Sum(Category Term Weight)>6	10003246	4	1	D	3
20000045	Systemic lupus erythematosus (SMQ)	1	A or Sum(Category Term Weight)>6	10000809	5	1	E	3
20000045	Systemic lupus erythematosus (SMQ)	1	A or Sum(Category Term Weight)>6	10000707	5	1	F	1
20000045	Systemic lupus erythematosus (SMQ)	1	A or Sum(Category Term Weight)>6	10000268	5	1	G	2
20000045	Systemic lupus erythematosus (SMQ)	1	A or Sum(Category Term Weight)>6	10000549	5	1	H	3
20000045	Systemic lupus erythematosus (SMQ)	1	A or Sum(Category Term Weight)>6	10000155	5	1	I	3

Using an algorithm may reduce the amount of “noise”, i.e., non-relevant cases, which means that the subject can be selected for the algorithmic search if a subject has

- at least an event if term category A and/or
- a combination of events from an algorithm, such as at least one in each of Term categories B, C and D (in non-weight based algorithm) or whereby the sum of event’s term weight is more than a defined criteria,

It is more likely to identify a case of interest than isolated broad search terms. Using an algorithmic SMQ without applying the algorithm (i.e., simply applying the narrow and broad searches) will yield different results from those obtained using the algorithm. The order of applying these approaches may depend on resources, expertise, systems or other factors.

SMQ REPORTING

Search results should be evaluated against the query originally posed. A search that is too narrowly focused might exclude events of potential relevance; a search that is too broad might make it difficult to identify a trend or signal because of the dilution. In depth analysis requires medical expertise to define terms that should be aggregated.

Careful interpretation is required when grouping terms that correspond to a potential event or medical condition for analysis (whether a syndrome or not). The SMQ is to identify trends that may require further analysis, including review of individual cases. An interdisciplinary discussion might be helpful to identify the most suitable methods and tools relevant to the query.

Be aware of data characteristics, organization-specific data entry conventions, data sources, the size of the data, and the version of MedDRA used for coding all data. Search strategies should be documented. For complex queries, create a data analysis plan including a definition of the medical condition of interest.

When presenting adverse event data, it is important to display and to group related events (i.e., events that represent the same condition of interest) so that the true occurrence rate of an event is not obscured.

In general, queries should be built on PTs and grouping terms. Unless very specific concepts (e.g., bacterial species) are needed, avoid using LLTs to build queries.

Present the data in a way that allows for easy recognition of patterns of terms potentially related to the relevant medical conditions. There are various ways to do this ranging from a full listing of terms to sophisticated statistical approaches and modeling.

Tables

Table displays such as Safety Reports (annual, quarterly, and ad-hoc requests) may facilitate understanding for the reviewers or regulatory agencies by:

- Providing an overview of data distribution; helping identify areas of special interest that may need in depth analysis
- Grouping terms aggregate related PTs (one PT will be counted only once for a subject in preventing over-counting of terms); facilitating identification of medical conditions of interest

DSUR as the example, is based on the Risk Tracking Document (RTD). Many marketed drugs have a RTD. RTD includes the SMQs plus Preferred Terms as text. Clinical study data should be searched for LLT codes, PT codes and PT terms.

The adverse events can be displayed by PT with decreasing frequency. The search output alone may not suffice for data assessment (e.g., counts and percentages of PTs in a medical condition). Some statistical analysis methods such as Chi-square /Fisher's exact tests, hierarchical Bayesian mixture model may be conducted.

Graphics

Graphical displays can be useful especially with large datasets. Such displays allow quick visual representation of potential signals. Histograms, bar charts, and pie charts can be useful as can more complex, statistically-derived displays (e.g., data mining algorithms).

Listings

Historically, the standard approach has been to display data by Body System (or System Organ Class) and Preferred Term corresponding to SOCs and PTs in MedDRA. Depending on the reason for the output, it might be beneficial to use the primary SOC and PT display; both clinical and postmarketing data can be displayed by primary SOC and PT.

The SOC order can be based upon the relative importance of each SOC in AR/AE reports. Use of the Internationally Agreed Order may be applicable to certain regulatory functions, e.g., the SPC guideline and PSURs. Organizations that share data should agree on the order of SOCs when preparing data for presentation. It is also necessary to refer to individual demographics.

SMQ APPLICATIONS

The aims of SMQ applications are to:

- Highlight distribution of ARs/AEs
- Comparing frequencies of ARs/AEs for spontaneous reports or incidence for studies.
- Analysis of a specific safety concern
- Identify patient subpopulations (e.g., pediatric and elderly, gender-specific) at risk
- Identify areas for in depth analysis

The user should first review the list of available SMQs to determine which of them may be applicable to the question being asked. If an SMQ seems applicable, the user should check the documentation in the SMQ Introductory Guide to understand the purpose and definition of the SMQ. The user may also wish to review the term contents of the SMQ.

Following application of the selected SMQ on coded data, search results (i.e., retrieved data) should then be evaluated against the question originally posed. Generally, more cases/events will be retrieved than will eventually be subjected to analysis due to "noise". This is a more significant consideration for "broad" searches but in principle also applies to "narrow" searches.

SMQs are applied in the clinical trials and pharmacovigilance – especially for aggregate data – where the safety profile has yet to be fully established. In this instance, most (if not all) available SMQs may be used, possibly on a routine basis. Alternatively, a user can apply an SMQ (or SMQs) that relates to a previously identified area of interest (e.g., from pre-clinical data or class effect) for further evaluation.

Volume 9A speaks out on SMQs: SMQs may be used for signal detection and the use of SMQs is recommended in order to retrieve and review cases of interest where signals are identified from adverse reaction databases. A Signal

is an event with an unknown causal relationship to treatment that is recognized as worthy of further exploration and continued surveillance, for example, an adverse event occurring more commonly in a treatment group compared to a placebo group, a clustering of events common to a medical condition or syndrome occurring more commonly in a treatment group compared to a placebo group, occurrence of a rare adverse event with a near zero background incidence rate, an adverse event with a positive dechallenge & rechallenge. Signal generation initially shows signal score for each PT in narrow SMQ (if narrow and broad options available)

- Shows aggregate signal score for entire “narrow” SMQ
- Shows signal score for individual PTs within that “narrow” SMQ

Safety Profile Overview such as PSUR,ISS, etc.	SMQs may help aggregate relevant cases for ongoing review of specific safety issues in periodic safety reports. SMQs may also be used for other routine reviews of aggregate data (e.g., reports of lack of efficacy) in the context of a periodic report.
Targeted Safety Study	When developing a data analysis plan for a targeted safety study, consider using the narrow terms of an SMQ to aggregate events of interest.
Emerging Safety Signal	If suspect an emerging signal of pancreatitis for a new HIV product. SMQ Acute pancreatitis can be applied to the data.
Signal detection	The entire set of SMQs may be used on the database for signal detection. The user may wish to use the narrow terms or more specific levels of hierarchical SMQs (i.e., a sub-search SMQ) to minimize dilution of the signal.
Signal case alert	SMQs may be used to create a “watch list” (e.g., an automated notification system) to alert the user of incoming cases needing urgent review.
Single Case Alert	A medical issue of interest needs to be communicated to a regulatory authority as part of an agreed risk management plan. The SMQ narrow search or more specific levels of a hierarchical SMQ may be applied to identify potential cases of interest.
Post-marketing	A specific SMQ or a selection of SMQs may be used to retrieve relevant cases for subsequent medical review

CONCLUSIONS

Sorting related adverse events into categories can be challenging. There may be incomplete groupings of terms for a medical condition or syndrome as such terms may be distributed among different SOCs. Customized searches may be useful for further investigation of medical concepts of interest. For example, a customized search may be used to determine the number of cases or events of interest in response to a regulatory query.

In certain situations, users may wish to design a specific search in addition to the overview by SOCs.

- Further examination of clusters seen in Primary SOC output
- Previously identified safety concerns (e.g., known class effects, results from toxicology and animal studies, etc.)
- Monitoring events of special interest
- Responding to regulatory queries

To fully understand the scope of the SMQ and to properly apply search options such as algorithms and weightings, users should carefully read Introductory Guide for Standardised MedDRA Queries (SMQs) before applying SMQs.

REFERENCES

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