Everything You Need To Know About Standardised MedDRA Queries

Rajkumar Sharma, Genentech Inc.,
A member of Roche Group, South San Francisco, CA

ABSTRACT

MedDRA (Medical Dictionary for Regulatory Activities) is very commonly used in Pharmaceutical and Biotech industry to classify adverse events information associated with the use of biopharmaceuticals and other products. In order to retrieve cases related to drug safety problem, often users combine MedDRA Preferred Terms from different System Organ Class (SOCs). The challenge with this approach is that different users may select different set of Preferred Terms to identify cases for the same drug safety problem. Also MedDRA has over ~ 18000 of Preferred Terms (PTs), which makes it difficult to group events that indicate the presence of condition that typically presents itself through different PTs. Standardised MedDRA Queries(SMQs) were developed to solve this problem. SMQs are grouping of MedDRA terms, ordinarily at the Preferred Term levels that relate to defined medical condition or area of interest. SMQs are intended to aid in the identification and retrieval of potentially relevant individual case safety reports. Since SMQs are driven by medical concept and not by any specific company or product it also eliminates any product specific bias. This paper provides in-depth knowledge on Standardized MedDRA Queries (SMQs) and how to use them for identifying and retrieving safety data.

INTRODUCTION

SMQs arose out of recognized need of the MedDRA user community for standard tools to assist in the identification and retrieval of safety data. CIOMS (Council of International Organization for Medical Sciences) working group and MSSO (MedDRA Maintenance and Support Services Organization) carried out joint efforts to develop Standardized MedDRA Queries. Before SMQ, MedDRA special search categories were developed to address similar need but after many years of use, the biopharmaceutical community concluded that SSC did not adequately address the need. In early 2002, MSSO began to develop MedDRA Analytical Groupings (MAGs). MAGs were defined as collection of terms from any level of MedDRA hierarchy (except Lower Lever Terms) and from any, several or all MedDRA SOCs (System Organ Class).

While MAGs were being developed at MSSO, an independent initiative by the CIOMS was started to address the need for special queries/groupings using MedDRA coded data; their groupings were called Standardised Search Queries (SSQs). It was apparent that MAGs and SSQs were quite similar and were both intended to fulfill the perceived need for a safety data retrieval tool. Thus, CIOMS and MedDRA, in interest of user community, decided to carry out joint efforts to develop safety data retrieval tool. In November 2003, the ICH MedDRA Management Board endorsed the cooperative effort, and the ICH process was adopted for the development of SMQs.

SMQ DICTIONARY FILES

MSSO provides two SMQ files in flat ASCII format - 1) SMQ list and 2) SMQ Contents. A paid subscription of MedDRA is required to access SMQs.

SMQ-LIST

This file contains one observation per SMQ. It contains list of all available SMQs with their name, their unique identifying code and other details. Below is the more detail about the structure of this file.

Field Name	Description
SMQ_code	Eight-digit numeric code assigned to the SMQ, which starts with "2"
SMQ_name	Name for the SMQ, each SMQ carries "(SMQ)" at the end of the name

SMQ_level	Value between 1 and 5 identifying the level of the SMQ within the hierarchy of SMQs; 1 is the most general, 5 is the most narrow
SMQ_description	Description of the SMQ including inclusion and exclusion
SMQ_source	Source for the development of the SMQ (e.g., medical references)
SMQ_note	Note for users to better understand the scope and development process for the SMQ. The description of the algorithm used is included (if applicable), as well as the definition of categories
MedDRA_version	MedDRA version to use in conjunction with this SMQ
Status	Status of the SMQ. "A" = An active SMQ; "I" = An inactive SMQ
SMQ_Algorithm	If the SMQ was developed for use with an algorithm, the Boolean expression of the algorithm is included. "N" if the SMQ does not utilize an algorithm

SMQ-CONTENT:

This file contains multiple observations per SMQ. It contains list of all LLTs(Lower Level Terms) and PTs (Preferred Terms) and sub-ordinate SMQs that are parts of the SMQs.

SMQ_code	Eight-digit code assigned to the SMQ
Term_code	Subordinate term code; it could be a code for MedDRA PT, LLT, or child SMQ
Term_level	MedDRA hierarchy level of the term (4=PT, 5=LLT) or 0 (zero) for a child SMQ
Term_scope	Defines the MedDRA term as a member of the broad scope (1), narrow scope (2) of the SMQ search, or a child SMQ (0) (zero)
Term_category	The category is assigned a single alphabetical letter depending upon the algorithm applied. If the SMQ does not use algorithms, then all Term_category values are assigned "A." For a child SMQ, this field is assigned "S."
Term_weight	Term weight is used for some SMQ algorithms. "0" is used as default
Term_status	Identifies a term as active within this SMQ or inactive within this SMQ. When a term is added to an SMQ, the value is set to "A" for Active. The term can be flagged as "I" for inactive if the term is no longer used in the SMQ.
Term_addition_version	Identifies the version of MedDRA in which this term was added to the SMQ
Term_last_modified_version	Identifies the version of MedDRA in which this term was last modified in this SMQ

SMQ DESIGN CONCEPT

SMQs may include very specific as well as less specific terms that are consistent with description of the overall clinical syndrome. While some SMQs are a straightforward collection of terms; others have been designed to accommodate combination of terms from more than one group. SMQs have certain specific design futures which user can take advantage of as per need.

NARROW SEARCH

This search is geared towards identifying cases that are highly likely to represent the condition of interest. Narrow search consists of all PTs that indicate the condition with great certainty.

BROAD SEARCH

This search is geared towards identifying all possible cases, including some that may prove to be of little or no interest on closer inspection. A broad search includes both the "narrow" terms and the additional "broad" terms, often of less-specific nature (Figure 1).

A narrow search on SMQ "Acute Renal Failure" ((MedDRA ver 15.1) yields 17 PTs and a broad search yields 43 PTs. As you can see there is a substantial difference between results of narrow search vs broad. The difference is because narrow search is more specific (cases highly likely related to a specific condition) while broad search is more sensitive (all possible case).
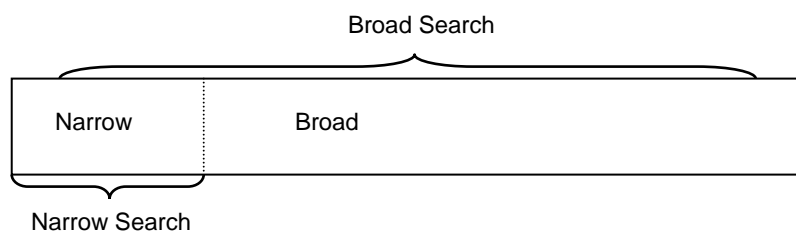

Figure 1. Narrow and Broad Search

ALGORITHM

In addition to narrow and broad searches, for some SMQs an algorithmic search approach is available. Algorithmic search is a combination of search terms from various sub categories of the broad search terms. Algorithmic searches are more likely to identify case of interest than isolated broad search. An algorithmic search may reduce amount of noise (non-relevant cases) which may be present in broad searches. However, algorithmic search is not available for all SMQs. An example of algorithmic SMQ is *Acute Pancreatitis* where the broad search terms are grouped into two categories: Category B which is a list of laboratory values and Category C which is a list of signs and symptoms. The algorithm for *Acute Pancreatitis* defines a case of interest as a record coded with a combination of at least one term of Category B and one term of Category C.

Please note that use of an algorithm is not required to retrieve cases of interest from algorithmic SMQs. Users can apply algorithm when it is expected to that a large number of cases will be retrieved by broad search. Applying algorithm may reduce total number of cases and help identify more relevant ones (increase specificity).

HIERARCHY

Some SMQs are related to each other in hierarchical relationship. These SMQs consists of one or more subordinate SMQs that could be combined to create a super ordinate, more inclusive SMQ. In some of these hierarchical SMQs, there are no "narrow" and "broad" categories within the subordinate SMQs (sub-SMQs).

 The hierarchy is to provide flexibility to users. For example a user may wish to apply entire scope of the SMQ topic (Haematopoietic cytopenia SMQ including all sub SMQs - see figure 2) to retrieve cases related to Haematopoietic cytopenia or a user can elect to apply a single sub-SMQ (e.g. Haematopoietic leucopenia) or a combination of sub-SMQ as per need.

SEARCH TERMS

PTs are not duplicated at the LLT level in SMQ_CONTENT file. User can conduct search with PTs if data are stored at PT level or with PTs and LLTs if data are stored at LLT level because in MedDRA all PTs are duplicated at LLT level.
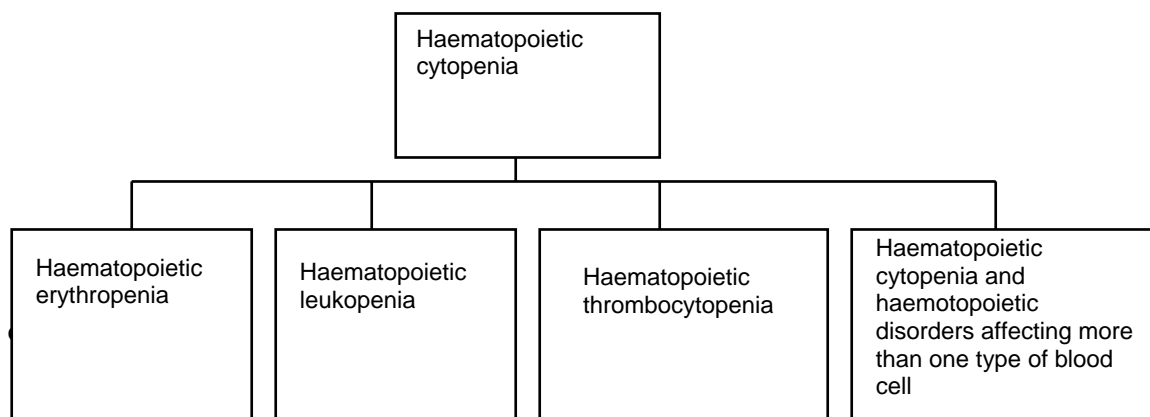
```
                        ┌──────────────────────┐
                        │ Haematopoietic       │
                        │ cytopenia            │
                        │                      │
                        └──────────────────────┘
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Figure 2. Hierarchical SMQ

Searches defined for SMQs vary from SMQs to SMQs. Not all searches are defined for all SMQs. For example one SMQ may have algorithmic search defined but it may not be defined for other SMQ. Whether a SMQ has algorithmic search defined or not is clear from "SMQ Algorithm" column in SMQ-list file explained above. However the existence of "narrow" and "broad" search is not very clear from SMQ-list file. Some SMQs do not have any narrow scope PTs and thus no narrow search. Some SMQs do not have any broad scope PTs. Also, searches (narrow, broad, etc) are intended to improve the quality of the query result by increasing the specificity and reducing the noise level. Users could use an SMQ as list of MedDRA terms without any special searches.

STATUS OF SMQs
Each SMQ has an assigned status. The status can be "active" or "inactive". User can find the status information of SMQ in the SMQ status column from the SMQ-list file. An active SMQ is the one that is currently maintained by MSSO. An inactive SMQ is no longer maintained but it is available in the SMQ ASCII file for at least one release.

SMQ VERSION
SMQs are released with each new release of MedDRA. It is recommended that users use SMQ with data coded with same version of MedDRA. It is possible Preferred Terms (PTs) within SMQs gets updated with release of new version of MedDRA. Mismatch of version between SMQ and MedDRA coded data could produce unexpected results

USING SMQs ON CLINICAL SAFETY DATA
SMQs could be merged with an adverse event dataset to identify number and percentage of patients falling under a particular SMQ. Merge can be done using PTs and a flag can be created to identify patients/events if there is a match between SMQ and adverse event dataset. User can also use different SMQs features i.e. "narrow", "broad" to identify patients under each category. The findings can be summarized in table format similar to an adverse event table as shown below.

Table 1
Number (%) of patients with at least one adverse event by treatment and selected SMQ (Narrow Scope)
All Treated Patients

SMQ	Treatment A (N = xx)	Treatment B (N = xx)
	n (%)	n(%)
Acute Renal Failure	x(x.xx)	x(x.xx)
Torsade de pointes/QT prolongation	x(x.xx)	x(x.xx)
Anaphylactic reaction	x(x.xx)	x(x.xx)

Table 2
Number (%) of patients with at least one adverse event by treatment, selected SMQ and PT (Narrow Scope)
All Treated Patients

SMQ Preferred Term	Treatment A (N = xx)	Treatment B (N = xx)
	n (%)	n(%)
Acute Renal Failure		
PT 1	x(x.xx)	x(x.xx)
PT 2	x(x.xx)	x(x.xx)
PT 3	x(x.xx)	x(x.xx)
⋮	⋮	⋮
Torsade de pointes/QT prolongation		
PT 1	x(x.xx)	x(x.xx)
PT 2	x(x.xx)	x(x.xx)
PT 3	x(x.xx)	x(x.xx)
⋮	⋮	⋮
Anaphylactic reaction		
PT 1	x(x.xx)	x(x.xx)
PT 2	x(x.xx)	x(x.xx)
PT 3	x(x.xx)	x(x.xx)
⋮	⋮	⋮

Above examples are based on narrow search. If users want to compare treatment on broad search then a clinical interpretation may be needed as broad search PTs are not very specific. It is possible that user sometime may see marked difference between treatment groups based on broad search but not on narrow search. In such cases, close inspection of underlying PTs (broad search PTs) may be needed to reduce noise (irrelevant cases). Also, data retrieved using HLTs (High Level Terms) and HLGTs (High Level Group Terms) may differ from those retrieved by related SMQs. SMQs are likely to retrieve more events than HLGTs because SMQs include more terms from other SOCs.

BENEFITS OF USING SMQs
There are many benefits of using SMQs. Below is the list of few
- Consistent data retrieval
- Application across multiple therapeutic areas
- Standardized communication of safety information
- Validated reusable search logic
- Maintenance by MSSO/JMO

LIMITATION OF SMQs
Even though SMQs are very useful there are some limitations as noted below
- Do not cover all medical concepts or safety issues
- Will evolve and undergo further refinement

CONCLUSION
Standardised MedDRA Query (SMQ) is a very useful addition to MedDRA. SMQ offers consistent and non drug specific safety data retrieval as SMQ are based on medical concept. SMQ has many features which provide users lot of flexibility to retrieve safety data based on need. SMQ is a powerful tool which could be used to better understand safety profile of a drug pre and post marketing.

REFERENCES

Introductory Guide for Standardised MedDRA Queries (SMQs) Version 15.1, MSSO, September 2012

CONTACT INFORMATION

Rajkumar Sharma
Genentech, Inc., A member of Roche Group
1 DNA Way, South San Francisco, CA 94080
sharmar.rajkumar@gene.com

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