

Standardised MedDRA Queries (SMQs): Beyond the Basics; Weighing Your Options

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ABSTRACT

Ordinarily, Standardised MedDRA Queries (SMQs) aim is to group specific MedDRA terms for a defined medical condition or area of interest at the Preferred Term (PT) level, which most would consider to be the basic use of SMQs. However, what if your study looks to implement the use of SMQs that goes beyond the basic use? Whether grouping through the use of algorithmic searching, using weighted terms or not, or through the use of hierarchical relationships, this paper looks to cover advanced searches that will take you beyond the basics of working with SMQs. Gaining insight to this process will help you become more familiar in working with all types of SMQs and will put you in a position to become the "go-to" person for helping others within your company.

INTRODUCTION

In working with clinical trial data, you will likely find that the area where you will handle the largest amounts of data, consisting of multiple differing types, will be with the collected safety data. However, the primary safety analysis will likely be focused on the trial's Adverse Events data.

One aspect in the analysis of Adverse Events (AEs), which will be the focus of this paper, is working with Standard MedDRA Queries or SMQs. Used to group MedDRA coded terms, they can be used to define a specific medical condition, or a particular area of interest, SMQs are lists typically consisting of like Preferred Terms (PT) and developed to aid in efficient identification of safety data key to analysis especially in terms of focusing on AEs of Special Interest. Currently there exist over 100 SMQs with more to come in future development. (International Conference on Harmonization, 2022)

SPECIAL FEATURES OF SMQ

SMQs can consist of a set of very specific terms and others are made up of less specific terms that are fixed with a description of a clinical syndrome associated with a particular adverse event or drug exposure. Some SMQs consist of a straightforward collection of terms while others have been designated to allow combinations of terms from more than one group. To address these different aspects of SMQs, each may utilize one of the following unique features:

SMQ SCOPE

Depending on the analysis need, this feature in using SMQs allows the data user to identify records of events that are highly likely to represent a condition of interest, hence a "narrow" scope. Other instances in where a data user looks to flag records that would be included in all possible cases, which includes events that may be of little or no interest upon closer consideration, hence this provides the "broad" scope of a SMQ. Generally stated, using SMQ scope will result in a "narrow" search yielding specific terms for certain events of interest while the "broad" search yields a search of terms based around sensitivity of an event. One item to note in using the SMQ scope search is that using a "broad" search of terms will include both the "narrow" terms as well as the additional "broad" terms. (International Conference on Harmonization, 2022)

SMQ CATEGORY

Categories of SMQs are used for those SMQs that are algorithmic where the broad search terms are put into divided categories so that a defined combination of terms may be applied as needed for the analysis. For categorical purposes when using the algorithmic SMQs, MedDRA has placed the narrow search

terms under Category A, and the broad search terms are always Categories B, C, D, etc. based on the values. An example from the MedDRA Introductory Guide for SMQs, Acute pancreatitis (SMQ) has the broad search terms grouped into two categories: Category B is a list of laboratory values and Category C is a list of signs and symptoms. The algorithmic use for any case of interest is discussed in more detail within a later section. (International Conference on Harmonization, 2022)

SMQ HIERARCHY

Using SMQ hierarchy allows for flexibility for the end user through their use of a series of SMQs related to one another. Similar to the traditional structure of MedDRA, a hierarchical structure, some SMQs can consist of one or more lower-level or subordinate SMQs that can potentially be combined to create a more broad-based or inclusive SMQ. For example, a user may wish to apply the entire scope of the SMQ topic to flag all cases related to a specific disorder in a database or user may even also elect to apply a single sub-SMQ, or combinations of more than one sub-SMQ, in their defined hierarchy which should be based on the user’s analysis need. One note is that with the hierarchy, some SMQs will not have a separate narrow or broad scope within the sub-SMQs. (International Conference on Harmonization, 2022)

SMQ ALGORITHMS

In addition, to the previously mentioned features, there is a not so common feature, algorithms. Not all SMQs have algorithms. The purpose of algorithms is to help to narrow down a search. Most algorithms use a combination of AEs from the various categories associated within the SMQ. One SMQ uses weights, which are discussed later, in the algorithm. Table 1 contains a list the SMQs that have an algorithm.

SMQzzCD	SMQzzNAM	ALGORITHM
20000022	Acute pancreatitis (SMQ)	A or (B and C)
20000021	Anaphylactic reaction (SMQ)	A or (B and C) or (D and (B or C))
20000048	Anticholinergic syndrome (SMQ)	A or (B and C and D)
20000225	Drug reaction with eosinophilia and systemic symptoms syndrome (SMQ)	A or (B and C and D) or (B and C and E) or (B and D and E)
20000157	Eosinophilic pneumonia (SMQ)	A or (B and C)
20000212	Generalised convulsive seizures following immunisation (SMQ)	A or (B and C)
20000211	Hypotonic-hyposensitive episode (SMQ)	A or (B and C and D)
20000044	Neuroleptic malignant syndrome (SMQ)	A or (B and C and D)
20000045	Systemic lupus erythematosus (SMQ)	A or Sum(Category Term Weight)>6
20000219	Tumour lysis syndrome (SMQ)	A or (B and C)

Table 1: SMQs and Corresponding Algorithms

Example of an Algorithmic Search

Within an SMQ, each term is associated with a category. Terms with CATEGORY = A are associated with the terms that have a narrow scope. These terms are AEs that are most likely associated with the condition so they by themselves qualify the event for that SMQ. However, terms that are broad in scope have different categories and the combination of AEs based on the category determine if the AEs combined qualify as an SMQ. For example, SMQ of Acute pancreatitis (SMQ) has three categories (A, B, C) and uses an algorithm to help reduce the number of ‘potential’ AEs. Thus, as shown in Table 1 Acute pancreatitis (SMQ) has an algorithm of {A or (B and C)}. This indicates that if a subject has one AE in category A, then the subject is said to have Acute pancreatitis. Or if a subject has an AE in category B **and** an AE in category C, then the subject is said to have Acute pancreatitis. However, if a subject only

has an AE in category B **or** only has an AE in category C, then based on the algorithm it would not be classified as Acute pancreatitis.

This may be easier to understand with an example. Using Acute pancreatitis (SMQ), Table 2 shows a partial list of AEs associated with Acute pancreatitis (SMQ) along with their corresponding category.

CATEGORY	PT
A	Pancreatitis
A	Pancreatitis acute
A	Pancreatitis relapsing
B	Hyperbilirubinaemia
B	Lipase abnormal
B	Lipase increased
B	Pancreatic enzymes abnormal
B	Pancreatic enzymes increased
C	Abdominal distension
C	Abdominal pain
C	Abdominal tenderness
C	Gastrointestinal pain
C	Jaundice
C	Nausea
C	Vomiting

Table 2: Partial List of Preferred Terms for Acute pancreatitis (SMQ) and Associated Category

In Table 3, the sample data shows all the AEs that are indicated as acute pancreatitis when looking at just the preferred term and not considering the categories and the algorithm. To refine this list, the categories need to be incorporated so that the algorithm can be implemented as shown in Table 4.

USUBJID	AEDECOD	ASTDT	SMQ03NAM	SMQ03SC	SMQ03CAT
ABC-001-001	Headache	2015-12-01			
ABC-001-001	Pancreatitis	2016-01-01	Acute pancreatitis (SMQ)	NARROW	A
ABC-001-001	Headache	2016-01-31			
ABC-001-001	Nausea	2016-03-02	Acute pancreatitis (SMQ)	BROAD	C
ABC-001-001	Hypotension	2016-03-02			
ABC-001-001	Angioedema	2016-05-20			
ABC-003-002	Abdominal distension	2016-02-02	Acute pancreatitis (SMQ)	BROAD	C
ABC-003-002	Chest discomfort	2016-02-03			
ABC-003-002	Hyperbilirubinaemia	2016-02-03	Acute pancreatitis (SMQ)	BROAD	B
ABC-003-002	Blood pressure decreased	2016-02-04			
ABC-003-002	Anaphylactic reaction	2016-03-02			
ABC-003-002	Jaundice	2016-04-15	Acute pancreatitis (SMQ)	BROAD	C
ABC-003-002	Pancreatitis acute	2016-05-03	Acute pancreatitis (SMQ)	NARROW	A

USUBJID	AEDECOD	ASTDT	SMQ03NAM	SMQ03SC	SMQ03CAT
ABC-010-004	Anaphylactic reaction	2015-01-01			
ABC-010-004	Headache	2016-03-25			
ABC-010-004	Cough	2016-05-01			
ABC-010-004	Abdominal distension	2016-05-03	Acute pancreatitis (SMQ)	BROAD	C
ABC-010-004	Nausea	2016-05-03	Acute pancreatitis (SMQ)	BROAD	C
ABC-010-004	Swelling	2016-06-01			

Table 3: Example of AEs in Acute pancreatitis (SMQ) without Algorithm

SMQzzCAT is a sponsor-defined variable to capture the category associated with the preferred term within the SMQ. These categories are important when utilizing the algorithm. Using the Acute pancreatitis (SMQ), we know that if preferred term is from Category A then it is 'Acute pancreatitis (SMQ)'. Or if a subject has a preferred term from Category B **and** C then it is 'Acute pancreatitis (SMQ)'. Rules regarding timeframe of when the AEs occurred are study dependent. For this example, only AEs that fall within one day of each are being considered as a case for the SMQ.

When implementing algorithms, multiple AEs could be used to qualify a subject for having the indicated SMQ. Because of this, those AEs need to be tied together somehow. Thus, another sponsor-defined variable, SMQzzRID, is created to tie AEs together based on the algorithm. How SMQzzRID is populated would also be sponsor specific. In this example, it is just an incremental counter. As seen in Table 4, AEs in category A have a unique SMQzzRID value, but AEs that are in categories B and C within one day of each other have the same SMQzzRID to indicate that these two AEs together is what qualified for the Acute pancreatitis (SMQ).

USUBJID	AEDECOD	ASTDT	SMQ03NAM	SMQ03CAT	SMQ03RID
ABC-001-001	Headache	12/1/2015			
ABC-001-001	Pancreatitis	1/1/2016	Acute pancreatitis (SMQ)	A	1
ABC-001-001	Headache	1/31/2016			
ABC-001-001	Nausea	3/2/2016			
ABC-001-001	Hypotension	3/2/2016			
ABC-001-001	Angioedema	5/20/2016			
ABC-003-002	Abdominal distension	2/2/2016	Acute pancreatitis (SMQ)	C	1
ABC-003-002	Chest discomfort	2/3/2016			
ABC-003-002	Hyperbilirubinaemia	2/3/2016	Acute pancreatitis (SMQ)	B	1
ABC-003-002	Blood pressure decreased	2/4/2016			
ABC-003-002	Anaphylactic reaction	3/2/2016			
ABC-003-002	Jaundice	4/15/2016			
ABC-003-002	Pancreatitis acute	5/3/2016	Acute pancreatitis (SMQ)	A	2
ABC-010-004	Anaphylactic reaction	1/1/2015			
ABC-010-004	Headache	3/25/2016			
ABC-010-004	Cough	5/1/2016			
ABC-010-004	Abdominal distension	5/3/2016			
ABC-010-004	Nausea	5/3/2016			
ABC-010-004	Swelling	6/1/2016			

Table 4: Example of AEs in Acute pancreatitis (SMQ) Based on Algorithm

When comparing the SMQzzNAM in Table 3 and Table 4, implementing the algorithm the number of Acute pancreatitis (SMQ) went from three subjects having eight episodes to two subjects having four episodes. Thus, implementing the algorithm allowed for further refinement of the AEs to be investigated.

SMQ WEIGHTS

SMQ weights can also be used in the algorithms. The weights determine the relevancy of the category. As of MedDRA 25.0 there is only one SMQ, Systemic lupus erythematosus (SMQ), that uses an algorithm based on weights. For Systemic lupus erythematosus (SMQ), there are nine categories and those are associated with three different weights (International Conference on Harmonization, 2022). Table 5 lists all the weights associated with each category. Notice that PT in category A does not have a weight associated with it because based on the algorithm any AE in category A is narrow scope and is most likely associated with the condition thus qualifies as an SMQ on its own. Only the terms with broad scope have a weight associated. (International Conference on Harmonization, 2022).

CATEGORY	DEFINITION	TERM WEIGHT
A	Narrow terms	Not applicable
B	Photosensitivity	1
C	Oral ulcers	2
D	Arthritis	3
E	Serositis	3
F	Renal disorder	1
G	Neurologic disorder	2
H	Haematologic disorder	3
I	Immunologic disorder	3

Table 5: Weights Associated with Broad Scope Classes for SLE SMQ (International Conference on Harmonization, 2022)

Example of Use of Weights in an Algorithmic Search

Algorithms based on weights are implemented the same way as algorithms based on the categories. The difference is with weights, the weights are summed to see if a combination of AEs can classify the set of AEs as an episode. In order for an AE(s) to be considered Systemic lupus erythematosus (SMQ) using the algorithm specified in the "Introductory Guide for Standardized MedDRA Queries (SMQs) Version 25.0" an AE must be in category A **or** the combination of identified potential AEs have a sum of category term weight greater than 6 (International Conference on Harmonization, 2022).

Table 6 shows a partial list of AEs associated with Systemic lupus erythematosus (SMQ) along with their corresponding category and weight.

SCOPE	CATEGORY	WEIGHT	PREFERRED TERM	PT CODE
Narrow	A		Acute cutaneous lupus erythematosus	10057928
...				
Narrow	A		Lupus-like syndrome	10050551
...				
Narrow	A		SLE arthritis	10040968
Narrow	A		Subacute cutaneous lupus erythematosus	10057903
Narrow	A		Systemic lupus erythematosus	10042945

SCOPE	CATEGORY	WEIGHT	PREFERRED TERM	PT CODE
...				
Broad	B	1	Solar dermatitis	10041303
Broad	C	2	Mouth ulceration	10028034
...				
Broad	D	3	Arthritis	10003246
Broad	D	3	Polyarthritis	10036030
...				
Broad	E	3	Shrinking lung syndrome	10067739
Broad	F	1	Autoimmune nephritis	10077087
...				
Broad	F	1	Proteinuria	10037032
...				
Broad	G	2	Partial seizures	10061334
...				
Broad	H	3	Lymphopenia	10025327
...				
Broad	I	3	LE cells present	10024062

Table 6: Partial List of Preferred Terms for Systemic Lupus Erythematosus (SLE) (SMQ) and Associated Class.

Like algorithms based on categories only, rules regarding timeframe of when the AEs occurred are study dependent. For this example, only AEs that fall within one day of each are being considered as a case for the SMQ.

If the algorithm is based on weights, then either an AE in category A qualifies for the indicated SMQ or a combination of broad scope AEs may qualify. In order for the combination of broad scope AEs to qualify, the category associated with each preferred is determined using the list of preferred terms associated with the SMQ. Once the categories are determined then the weights can be assigned. A sponsor-defined variable, SMQzzWT is used to capture the weight assigned to each category. Once the weights are determined, then AEs can be grouped based on study specific rules for grouping AEs (e.g., use AEs within one day of each other), the weights can be summed. If the sum of the weights is greater than 6 then the combination of AEs qualifies for the SMQ.

In the Table 7, rows 2 and 4 fall in category D and have a weight of 3 and row 5 falls in category G with a weight of 2. If we use the rule that the AEs have to be within one day, then only rows 4 and 5 would be sum and the sum is 5. Therefore, this group of AEs is not considered System lupus erythematosus (SMQ). However, for subject ABC-01-002 row 6 is in category A and this by itself is in the SMQ. Rows 10 – 12 are in categories E, C, and I respectively and have weights 3, 2, and 3. These AEs all occurred within one day of each other so the weights can be summed, and the total sum is 8 which greater than 6. Thus, this group of AEs is an SMQ. Similarly subject ABC-01-003 has one AE in category A and three AEs that are potential for SMQ on rows 16 – 18. These AEs are in categories D, F, and H with weights of 3, 1, and 3. The sum of the weights is greater than 6 so these AEs combined is an episode for the SMQ.

It is possible for a subject to have multiple episodes and to have multiple AEs within an episode. In order to distinguish between the episodes, the sponsor-defined variable, SMQzzRID, is created to tie AEs together based on the algorithm. As mentioned previously how SMQzzRID is populated would be sponsor specific. In this example, it is the 3-digit subject ID concatenated with a hyphen to an incremental counter. Thus, as illustrated in Table 7, AEs in category A have a unique SMQzzRID value,

but AEs that are within one day of each other and have a sum of weights greater than 6 have the same SMQzzRID to indicate that these three AEs together is what qualified for the Systemic lupus erythematosus (SMQ).

Row	USUBJID	AEDECOD	ASTDT	SMQ53NAM
1	ABC-01-001	Headache	2015-12-01	
2	ABC-01-001	Arthritis	2016-01-01	
3	ABC-01-001	Headache	2016-01-31	
4	ABC-01-001	Arthritis	2016-03-02	
5	ABC-01-001	Partial seizures	2016-03-02	
6	ABC-01-002	SLE arthritis	2016-02-02	Systemic lupus erythematosus (SMQ)
7	ABC-01-002	Chest discomfort	2016-02-03	
8	ABC-01-002	Blood pressure decreased	2016-02-04	
9	ABC-01-002	Anaphylactic reaction	2016-03-02	
10	ABC-01-002	Shrinking lung syndrome	2016-04-15	Systemic lupus erythematosus (SMQ)
11	ABC-01-002	Mouth ulceration	2016-04-15	Systemic lupus erythematosus (SMQ)
12	ABC-01-002	LE cells present	2016-04-16	Systemic lupus erythematosus (SMQ)
13	ABC-01-003	Lupus-like syndrome	2015-01-01	Systemic lupus erythematosus (SMQ)
14	ABC-01-003	Headache	2016-03-25	
15	ABC-01-003	Cough	2016-05-01	
16	ABC-01-003	Polyarthritis	2016-05-03	Systemic lupus erythematosus (SMQ)
17	ABC-01-003	Proteinuria	2016-05-03	Systemic lupus erythematosus (SMQ)
18	ABC-01-003	Lymphopenia	2016-05-03	Systemic lupus erythematosus (SMQ)

Row	SMQ53SC	SMQ53CAT	SMQ53WT	SMQ53RCID
1				
2				
3				
4				
5				
6	Narrow	A		002-1
7				
8				
9				
10	Broad	E	3	002-2
11	Broad	C	2	002-2
12	Broad	I	3	002-2
13	Narrow	A		003-1
14				

Row	SMQ53SC	SMQ53CAT	SMQ53WT	SMQ53RCID
15				
16	Broad	D	3	003-2
17	Broad	F	1	003-2
18	Broad	H	3	003-2

Table 7: Example of AEs in System lupus erythematosus (SMQ) Based on Weights

Therefore, when implementing the algorithm, the number of Systemic lupus erythematosus (SMQ) went from three subjects having eleven episodes to two subjects having four episodes. Giving further refinement of the AEs to be investigated.

CONCLUSION

As shown, the use of MedDRA SMQs search has much to offer. Using SMQs offers more than its common use of matching terms to their respective Preferred Term MedDRA value which may likely be related to the medical condition or area of interest. The multifaceted aspects of the use of SMQs will help you reach associated terms well beyond the normal scope. Whether using the SMQ search for terms based around specificity (narrow scope), or instead to use a search for sensitivity (narrow and broad), both routes can take your search for specific terms or groupings further than the most common approach. You could even take your search containing a mix of both broad and narrow scopes further with the use of searches that would add categories and their specific algorithms to help gain a clearer focus around your specific need and area of interest. Regardless, all these methods of using SMQs can be highly beneficial through their design to help find terms consistent with clinical syndromes associated with your adverse event and drug exposure of interest.

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