

Applying SMQs to Adverse Event Data

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ABSTRACT

MedDRA® is a coding system with over 18000 Preferred Terms (PTs). Therefore it can be difficult to group events that indicate the presence of a condition that typically presents itself through different PTs. Standardised MedDRA Queries (SMQs) are designed specifically for solving this problem.

SMQs feature searches with different degrees of certainty: a narrow search for PTs that indicate the condition with great certainty, a broad search for PTs that also indicate the side effects, possibly with a different origin, and an algorithmic search whereby criteria on PTs need to be satisfied to optimize the specificity of the search.

This paper describes how SMQs are defined, and how they can be applied to create tables and listings to support the statistical and clinical interpretation of safety data.

INTRODUCTION

The concept of SMQs has been part of MedDRA for over 3 years now. The SMQs were introduced by the CIOMS Working Group on SMQs. The development of SMQs is a collaboration of industry, authorities and the MedDRA maintenance organization (MSSO).

MedDRA currently (v11.0) has 58 SMQs. Examples of conditions with an SMQ available are 'Torsade de pointes/QT prolongation', 'Hepatic disorders' and 'Suicide/self-injury'. As an integral part of MedDRA the SMQs are 'versioned' in the sense that they are kept up to date with for example PTs that are introduced to MedDRA. The SMQ definitions are unambiguous, so that both industry and authorities can apply them in the same way. However, SMQs are not yet widely known and applied. This paper will help you to understand and apply SMQs.

First the SMQ definition files within MedDRA are described. Next the process of extracting the SMQ applicable Lowest Level Terms (LLTs) and PTs is explained, followed by an explanation of the various SMQ searches. Finally, a few examples are given of tables and listings on query results.

Note that SMQs can only be used on clinical data that are coded with PTs (alternatively: LLTs) from a single MedDRA version, whereby the PT's numeric identifier, for example, 10000456, must be available in the data.

SMQ DICTIONARY FILES

Within MedDRA two data files are used for the definition of the SMQs.

THE FILE SMQ-LIST

This file lists all available SMQs with their name, their unique identifying code and other descriptives.

A few rows from this file:

SMQ code	SMQ name	SMQ level	SMQ description	SMQ source	SMQ note	Dict. ver.	SMQ status	SMQ algorithm
20000001	Torsade de pointes/QT prolongation (SMQ)	1	Torsade de pointes (TdP) is a form of rapid	Zipes DP. Specific arrhythmias: diagnosis	1. Includes sudden and cardiac death terms as this	11.0	A	N
20000004	Cardiac failure (SMQ)	1	A condition in which the heart is unable to pump an	Council for International Organisation of Medical	The CIOMS Working Group discussed in	11.0	A	N
20000005	Hepatic disorders (SMQ)	1	Disorders of the liver, including signs, symptoms			11.0	A	N
20000006	Possible drug related hepatic disorders - comprehensive search (SMQ)	2	This SMQ is a sub-SMQ of Hepatic disorder			11.0	A	N

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20000007	Possible drug related hepatic disorders - severe events only (SMQ)	3	This SMQ is a sub-SMQ of Possible drug related hepatic disorders			11.0	A	N
20000044	Neuroleptic malignant syndrome (SMQ)	1	Neuroleptic malignant syndrome (NMS) is a rare	1) Levenson JL. Neuroleptic malignant syndrome	Algorithm : Category A: specific reports of	11.0	A	A or (B and C and D)
20000045	Systemic lupus erythematosus (SMQ)	1	- Chronic inflammatory autoimmune disorder	1. Guidelines for referral and	Use of weighted algorithm in this SMQ	11.0	A	A or Sum(Category Term Weight)>6
...								

The columns of this file:

1. **SMQ code:** an 8-digit number starting with digit 2, uniquely linked to the SMQ name. This number refers to the file SMQ-content. (Note that all MedDRA terms have a corresponding unique 8-digit number, where those of LLTs and PTs and alike start with digit 1.)
2. **SMQ name:** the name of the SMQ.
3. **SMQ level:** the hierarchical level of the SMQ (explained later). MedDRA version 11.0 has 58 SMQs with level 1, and 84 subordinate SMQs with level 2, 3 or 4.
4. **SMQ description,** with inclusion/exclusion criteria. This text can have more than 2000 characters.
5. **SMQ source,** for example medical references. This text can have more than 2000 characters.
6. **SMQ note** on scope and development process. This text can have more than 2000 characters.
7. **Dictionary version:** the MedDRA version to which the SMQs apply. This must match with the MedDRA version of the coding in the clinical data that will be queried.
8. **SMQ status:** can be either 'A' for active or 'I' for inactive. Only active SMQs may be used in queries.
9. **SMQ algorithm:** not applicable for most SMQs, as indicated by value 'N'. Currently only 5 SMQs have a formula specified for use within SMQ's algorithmic search (explained later).

THE FILE SMQ-CONTENT

This file essentially lists all LLTs and PTs that are part of the SMQs. There are also 18 SMQs that have a hierarchical definition, i.e. they are defined as consisting of other, so-called, subordinate SMQs.

A few rows from this file:

SMQ code	Term level	Term code	Term scope	Term category	Term weight	Term status	Term added	Term modified
20000004	5	10068000	1	A	0	A	11.0	11.0
20000005	0	20000006	0	S	0	A	8.0	8.0
20000005	0	20000014	0	S	0	A	8.0	8.0
20000005	0	20000016	0	S	0	A	8.0	8.0
20000006	0	20000007	0	S	0	A	8.0	8.0
20000006	0	20000008	0	S	0	A	8.0	8.0
20000019	4	10015251	2	A	0	A	10.0	10.0
20000019	4	10015871	2	A	0	A	8.0	8.0
20000019	5	10065228	2	A	0	A	9.0	9.0
20000019	4	10066183	2	A	0	I	9.1	10.0
20000019	5	10066178	2	A	0	A	9.1	9.1
20000019	5	10066179	2	A	0	A	9.1	9.1
20000019	5	10066180	2	A	0	I	9.1	10.0
20000019	4	10059919	1	A	0	A	9.0	9.0
20000019	4	10059920	1	A	0	A	8.0	8.0
20000045	5	10013071	2	A	0	A	9.0	9.0
20000045	5	10013446	2	A	0	A	9.0	9.0
20000045	4	10018910	1	H	3	A	9.0	9.0
20000045	5	10012485	1	B	1	A	9.0	9.0
20000045	4	10025130	2	A	0	A	9.0	9.0
20000045	4	10034759	1	G	2	A	9.0	9.0
20000045	4	10034972	1	B	1	A	9.0	9.0
20000045	4	10035618	1	E	3	A	9.0	9.0
20000045	4	10042893	1	I	3	A	9.0	9.0
...								

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The columns of this file:

1. **SMQ code:** an 8-digit number starting with digit 2, uniquely refers to an SMQ as named in file SMQ-list.
2. **Term level:** indicator for the type of MedDRA term that the value in Term code refers to. Either 4 for PT, 5 for LLT, or 0 for subordinate SMQ (explained later).
3. **Term code:** an 8-digit number with the numeric identifier value of a MedDRA term. If the first digit is 1 then the term refers to an LLT / PT, if it is a 2 then it refers to a subordinate SMQ.
4. **Term scope:** indicates to which scope a term belongs (not applicable for rows on subordinate SMQs); 1 for broad scope, and 2 for narrow scope. Note that broad search -explained later- consists of both broad and narrow scope terms.
5. **Term category:** A, B, C, D, ...; S for rows on subordinate SMQ
6. **Term weight:** the term category weight, applicable only for algorithmic search that uses weighing.
7. **Term status:** can be either 'A' for active or 'I' for inactive. Only active terms are used in queries.
8. **Term added:** version of MedDRA in which the SMQ was first made available.
9. **Term modified:** version of MedDRA in which the SMQ was last modified.

Columns 5 and 6 are used only for SMQs that have algorithmic search (explained later). The last two columns are for administrative use only.

DETERMINE THE COLLECTION OF LLT/PT TERMS THAT ARE PART OF THE SMQ

To explain the determination of LLTs/PTs that are part of an SMQ we will use an example.

First we select an SMQ of interest by reviewing the SMQ names in the SMQ-list file (only SMQs with SMQ status Active may be used). This results in a corresponding SMQ code. Assume we are interested in Haemolytic disorders, which has SMQ code 20000019.

Now we continue with the file SMQ-content. Its last two columns are omitted. We restrict the rows to those that have the SMQ code that we selected before, and that have active Term status. This results in:

SMQ code	Term level	Term code	Term scope	Term category	Term weight	Term status
20000019	4	10015251	2	A	0	A
20000019	4	10015871	2	A	0	A
20000019	5	10065228	2	A	0	A
20000019	5	10066178	2	A	0	A
20000019	5	10066179	2	A	0	A
20000019	4	10059919	1	A	0	A
20000019	4	10059920	1	A	0	A
...						

LLTs AND PTs

Because clinical data may have been coded with LLTs or with PTs (or both), the SMQ definition has been designed to accommodate either of these cases:

- For clinical data that have the PT codes available the SMQ-content rows on PTs (Term level 4) are sufficient, and the rows on LLTs can be ignored.
- For clinical data that have the LLT codes available (PTs absent) not only the SMQ-content rows on LLTs are needed, but also those on PTs. Note that within MedDRA each PT has a collection of underlying LLTs which always also includes the PT itself as an LLT, and the LLT identical to the PT uses the same numeric identifier as the PT. E.g., the PT Headache has LLTs like Pounding in head, Head pain and Headache, whereby Headache uses the numeric identifier 10019211, both for the LLT and the PT. Using this knowledge, it was decided not to include LLTs that are also a PT separately within the SMQ definition. Instead, each SMQ-PT row can simply be regarded as an SMQ-LLT row too.

In the remainder, we assume that our clinical data have the PT codes available, so that we now omit the rows for LLTs. We also omit the columns for SMQ code and Term status. This results in:

Term level	Term code	Term scope	Term category	Term weight
4	10015251	2	A	0
4	10015871	2	A	0
4	10059919	1	A	0
4	10059920	1	A	0
...				

The column Term level is now not needed anymore.

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If there are rows that have Term level 0 then the SMQ uses a hierarchical definition. This means that the SMQ is based on the definition of, so-called, subordinate SMQs, and the following additional step is needed:

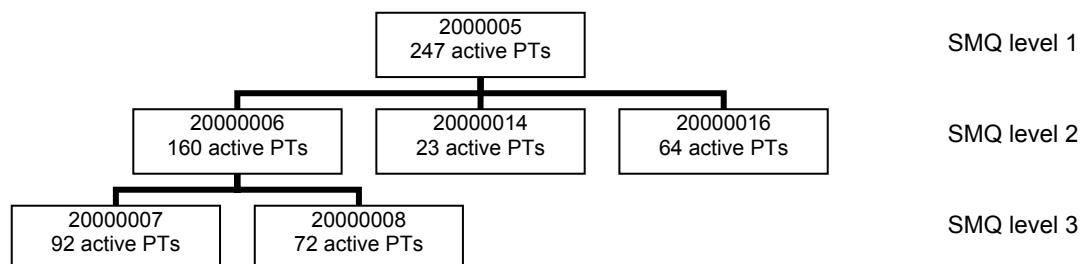
HIERARCHY

Each row that has Term level 0 has to be replaced with the rows of the subordinate SMQ whose code is given in Term code. A subordinate SMQ can in turn have its own subordinate SMQs.

Example¹: SMQ 20000005 is a hierarchical SMQ. Looking at file SMQ-content:

SMQ code	Term level	Term code	Term scope	Term category	Term weight	Term status	Term added	Term modified
20000005	0	20000006	0	S	0	A	8.0	8.0
20000005	0	20000014	0	S	0	A	8.0	8.0
20000005	0	20000016	0	S	0	A	8.0	8.0
20000006	0	20000007	0	S	0	A	8.0	8.0
20000006	0	20000008	0	S	0	A	8.0	8.0
...								

its definition can be depicted graphically as follows:



Thus SMQ 20000005 includes all PTs part of its subordinate SMQs 20000006, 20000014 and 20000016, whereby in turn SMQ 20000006 includes all PTs part of its subordinate SMQs 20000007 and 20000008. Note that SMQs 20000007 and 20000008 are not disjunct: four PTs are included in both SMQs. Therefore, the number of PTs in SMQ 20000006 is not the sum of the number of PTs in its subordinate SMQs.

The SMQ levels presented to the right of the above graph correspond to the column SMQ level in the SMQ-list file. The highest possible value for SMQ level is 4.

If at the beginning we would have selected SMQ 20000005 then (recursively) resolving all subordinate SMQs to active PT rows would now result in

Term level	Term code	Term scope	Term category	Term weight
4	10003827	1	A	0
4	10008909	1	A	0
4	10018704	1	A	0
4	10019717	1	A	0
4	10019727	1	A	0
...				

The rows on active PTs
from SMQs 20000007,
20000008, 20000014
and 20000016

The subordinate SMQs typically have a specific medical interpretation, but all of them relate to the SMQ with SMQ level 1 that they're part of, for example

Gastrointestinal nonspecific inflammation and dysfunctional conditions
consists of three subordinate SMQs

Gastrointestinal nonspecific inflammation

Gastrointestinal nonspecific dysfunction

Gastrointestinal nonspecific symptoms and therapeutic procedures

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Continuing with our example SMQ, 20000019, the remaining SMQ details are merged onto the clinical data, whereby the SMQ's Term code is matched to the PT code in the clinical data:

Clinical data - the adverse events			SMQ details				Searches (explained below)
Patient	PT text	PT code	Term code	Term scope	Term category	Term weight	
101	Erythroblastosis foetalis	10015251	10015251	2	A	0	narrow/broad broad
101	Reticulocyte percentage abnormal	10059919	10059919	1	A	0	
101	Wrist fracture	10048049					
102	Headache	10019211					
102	Extravascular haemolysis	10015871	10015871	2	A	0	narrow/broad
102	Back pain	10003988					
102	Headache	10019211					
103	Reticulocyte percentage increased	10059920	10059920	1	A	0	broad
103	Erythroblastosis foetalis	10015251	10015251	2	A	0	narrow/broad

All the clinical events that have Term scope filled are part of the SMQ. Within an SMQ we can identify three types of searches.

SEARCHES WITHIN AN SMQ

BROAD SEARCH

All PTs² included in an SMQ are part of the so-called broad search. This includes terms that indicate the condition of the SMQ with great certainty, but also terms that might merely indicate a possible side effect, possibly with a different origin. For example, the broad search of SMQ Depression and suicide/self-injury includes clearly SMQ-indicative PTs like Depression, Poisoning deliberate and Suicidal ideation, but also the less indicative PTs like Drug abuse and Tearfulness, which may occur also to non-depressed, non-suicidal individuals.

Of course, when looking for signals that indicate an SMQ's condition we typically would like to distinguish between the more certain indicators and the mere possible side effects indicators. Therefore two additional searches have been defined, both based on the broad search terms.

NARROW SEARCH

The narrow search consists of all PTs that indicate the condition with great certainty. It is therefore a selection of the broad search terms, namely those that have narrow scope (Term scope 2).

In the above example on broad search, the PTs Depression, Poisoning deliberate and Suicidal ideation are part of the narrow search, whereas broad search PTs Drug abuse and Tearfulness are not part of the narrow search.

In the above table, with SMQ 20000019 applied to our clinical data, the searches that the events are part of are presented to the right. (Note that SMQ 20000019 does not have algorithmic search defined.)

ALGORITHMIC SEARCH

Whether the algorithmic search is defined for certain SMQ follows from the column SMQ algorithm in the SMQ-list file.

An algorithmic search provides a certainty in between that of the narrow and the broad search, by including all narrow search PTs, and adding broad search PTs based on the patient's available combination of PTs.

For the algorithmic search each of the SMQ PTs is assigned to a Term category (column in file SMQ-content). Each such category represents one expression of an SMQ condition, for example, category B might represent laboratory values that might occur in relation with the condition, whereas category C is one type of possibly related side effects, and category D another type of possibly related side effects. Note that for SMQs with algorithmic search defined the Term category A coincides with the narrow search.

Two examples will clarify the application of an algorithmic search.

Example: non-weight based algorithm

The SMQ Neuroleptic malignant syndrome (SMQ code 20000044) has the algorithm A or (B and C and D), which means that a patient can be selected for the algorithmic search if the patient has:

- at least an event in Term category A, and/or
- a combination of events, at least one in *each* of the Term categories B, C and D.

For each algorithmic-selected patient we also will identify the events that actually led to the selection: with this algorithm all events in category A, and all events in categories B, C and D if the patient has events in all three categories B, C and D. If, for example, the patient has events in categories A and D, but not in B and C, then only the events in category A will be identified as contributing to the algorithmic selection.

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The application of this SMQ's algorithmic search on clinical data might look as follows:

Clinical data - the adverse events			SMQ details				Searches
Patient	PT text	PT code	Term code	Term scope	Term category	Term weight	
201	Neuroleptic malignant syndrome	10029282	10029282	2	A	0	narrow/algor/broad
201	Serotonin syndrome	10040108	10040108	2	A	0	
201	Depressed level of consciousness	10012373	10012373	1	D	0	broad
201	Hyperpyrexia	10020741	10020741	1	B	0	
202	Pyrexia	10037660	10037660	1	B	0	broad
202	Dystonia	10013983	10013983	1	C	0	
202	Headache	10019211					broad
202	Muscle necrosis	10028320	10028320	1	C	0	
203	Oculogyric crisis	10030071	10030071	1	C	0	algor/broad
203	Blood pressure increased	10005750	10005750	1	D	0	
203	Headache	10019211					algor/broad
203	Pyrexia	10037660	10037660	1	B	0	
203	Unresponsive to stimuli	10045555	10045555	1	D	0	algor/broad

With these data two patients are selected for the algorithmic search, namely 201 and 203.

For patient 201 only the two category A (narrow search) events actually contribute to the patient being selected for algorithmic search. Because no category C events occurred, the events in categories B and D do not contribute to the algorithmic selection.

Patient 203 was selected for the algorithmic search because he has events in all of the categories B, C and D, so that all events in these categories actually contribute to the patient being selected.

Example: weight-based algorithm

Of the 5 currently available SMQs with an algorithmic search, only the SMQ Systemic lupus erythematosus (SMQ code 20000045) has a weight-based algorithmic search, whereby the column Term weight is used too. Note that the value of Term weight is constant per Term category, and does not vary between PTs in a category. The Term category A has Term weight 0: this category contains the narrow search terms, which as such already qualify for algorithmic search. The algorithm for this SMQ is $A \text{ or } \text{Sum}(\text{Category Term Weight}) > 6$. This means that a patient can be selected for this search if the patient has:

- an event in Term category A, and/or
- a combination of events whereby the sum of event's Term weights is more than 6, whereby each Term category contributes only once in the summation.

The events that actually lead to a patient being selected for the algorithmic search are also identified: all events in category A, and all events in all other categories if the sum of Term weights is more than 6. Thus with the weight-based algorithm, per patient either only the narrow search events are selected, or all of the broad search events (which includes the narrow search events).

The application of this SMQ's algorithmic search on clinical data might look as follows:

Clinical data - the adverse events			SMQ details				Searches
Patient	PT text	PT code	Term code	Term scope	Term category	Term weight	
301	Syphilis test false positive	10042893	10042893	1	I	3	algor/broad
301	Haemolysis	10018910	10018910	1	H	3	
301	Adnexitis	10001317					algor/broad
301	Petit mal epilepsy	10034759	10034759	1	G	2	
302	Pleurisy	10035618	10035618	1	E	3	broad
302	Pericardial rub	10049759	10049759	1	E	3	
302	Photosensitivity reaction	10034972	10034972	1	B	1	broad
303	Haemolysis	10018910	10018910	1	H	3	
303	Headache	10019211					narrow/algor/broad
303	Lupus encephalitis	10025130	10025130	2	A	0	
303	Photosensitivity reaction	10034972	10034972	1	B	1	broad

With these data two patients are selected from the algorithmic search, namely 301 and 303.

For patient 301 the sum of Term weights for the events in categories G, H and I is $2+3+3 = 8$, so that all broad search events contribute to the patient being in the algorithmic search.

Patient 302 has two events in the category E, but because each category is used only once in the algorithmic summation the sum of weights is only $1+3 = 4$. Therefore the patient is not in the algorithmic search.

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Patient 303 has an event in category A, which is the only reason why patient qualifies for the algorithmic search. The events in categories B and H do not have sufficient summed weight.

THE SEARCHES THAT ACTUALLY EXIST FOR AN SMQ

Not all SMQs have all types of searches defined. Whether algorithmic search is defined immediately follows from the column SMQ algorithm in file SMQ-list. The existence of broad and narrow search is however not immediately clear from the file SMQ-list, but must be derived from the available scopes of the SMQ's PTs.

Some SMQs do not have any narrow scope PT and thus have no narrow search.

Some SMQs do not have any broad scope PTs. Presenting broad search findings for such an SMQ would mistakenly suggest that these could be other than the narrow search findings. One could therefore say that (meaningful) broad search does not exist for these SMQs.

It would be good if the information on existence of broad and narrow search were added to the file SMQ-list, for example, by adding a column named NARROW with possible values 'Defined', 'Equals Broad' or 'Not defined', so that this information does not need to be derived as described above.

PRESENTING SMQ FINDINGS

TABLES

The patients and events selected by an SMQ can be summarized in tables similar to how we would present any other adverse event data. That means presenting meaningful incidences, whereby patients are counted only once per SMQ, PT or whatever category is presented. In this way incidences never exceed 100%. And these incidences can be used to calculate the p-values for tests of treatment effect on an SMQ/search, to assist in the interpretation.

SMQ overview table

This table presents the number and percentage of patients per SMQ and defined search. With a reference to a footnote the SMQs are indicated that do not have a definition for narrow search or (meaningful) broad search.

Table 1 Number (%) of patients with at least one adverse event starting in-treatment, for selected SMQs. By SMQ/search and treatment group. All-Subjects-Treated group.

SMQ	Search	Placebo (N=210)	Active (N=198)	p-value
		n (%)	n (%)	Fisher exact, two-sided
Torsade de pointes/QT prolongation	Broad	3 (1.4)	11 (5.6)	0.03
	Narrow	2 (1.0)	1 (0.5)	1.00
Hepatic disorders *	Broad	0 (0.0)	0 (0.0)	-
Dyslipidaemia **	Narrow	1 (0.5)	1 (0.5)	1.00
Dementia *	Broad	1 (0.5)	1 (0.5)	1.00
Anaphylactic reaction	Broad	4 (1.9)	6 (3.0)	0.53
	Algorithmic	2 (1.0)	3 (1.5)	0.68
	Narrow	1 (0.5)	1 (0.5)	1.00

Based on MedDRA 11.0. A patient can have adverse events in more than one SMQ / search.

* Narrow search is not defined; ** Broad and Narrow search are identical; if defined then Algorithmic search is shown

The incidences are comparable between the two treatments except for the broad search of SMQ Torsade de pointes/QT prolongation.

SMQ Preferred Term table

This table is a logical extension on the SMQ overview table. It presents per SMQ and defined search the number and percentage of patients for the various contributing PTs.

Note that patients are counted only once per SMQ search / PT, so that the counts for individual PTs do not necessarily add up to the counts for the total of the SMQ search that they contribute to. For example, for the narrow search of SMQ Torsade de pointes/QT prolongation (TdP) the placebo group (see Table 2) has PTs Long QT syndrome and Ventricular tachycardia, with respectively 2 and 1 patient, but the total over PTs has not 3 but only 2 patients (patient 1009 is counted for both PTs but only once for narrow search total, as becomes clear in the listing that follows later).

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Table 2 Number (%) of patients with at least one adverse event starting in-treatment, for selected SMQs. By SMQ/search, preferred term and treatment group. All-Subjects-Treated group.

SMQ = Torsade de pointes/QT prolongation

SMQ search	Preferred term	Placebo (N=210)	Active (N=198)
		n (%)	n (%)
Broad	* TOTAL *	3 (1.4)	11 (5.6)
	Long QT syndrome	2 (1.0)	0 (0.0)
	Loss of consciousness	1 (0.5)	0 (0.0)
	Syncope	1 (0.5)	11 (5.6)
	Ventricular tachycardia	1 (0.5)	1 (0.5)
Narrow	* TOTAL *	2 (1.0)	1 (0.5)
	Long QT syndrome	2 (1.0)	0 (0.0)
	Ventricular tachycardia	1 (0.5)	1 (0.5)

SMQ = Anaphylactic reaction

SMQ search	Preferred term	Placebo (N=210)	Active (N=198)
		n (%)	n (%)
Broad	* TOTAL *	4 (1.9)	6 (3.0)
	Anaphylactic reaction <i>A</i>	1 (0.5)	1 (0.5)
	Asthma <i>B</i>	0 (0.0)	1 (0.5)
	Flushing <i>C</i>	1 (0.5)	3 (1.5)
	Hypotension <i>D</i>	2 (1.0)	2 (1.0)
	Sneezing <i>B</i>	2 (1.0)	2 (1.0)
Algorithmic	* TOTAL *	2 (1.0)	3 (1.5)
	Anaphylactic reaction	1 (0.5)	1 (0.5)
	Flushing	0 (0.0)	2 (1.0)
	Hypotension	1 (0.5)	2 (1.0)
	Sneezing	1 (0.5)	1 (0.5)
Narrow	* TOTAL *	1 (0.5)	1 (0.5)
	Anaphylactic reaction	1 (0.5)	1 (0.5)

Based on MedDRA 11.0. A patient can have adverse events in more than one SMQ / search / term. Only selected SMQ / searches with at least one event are shown in this table.

A clinical interpretation is particularly needed when comparing treatments on a broad search since the broad search PTs may not be very specific. In our example the SMQ TdP (Table 1) shows a marked difference between placebo and active treatment on the broad but not on the narrow search. When inspecting the underlying contributing PTs (Table 2) it is clear that the main reason for the difference is an increased number of syncopes on active treatment. If it is known that the active treatments causes syncopes as a result of orthostatic hypotension it is also clear that it need not be the case that the active treatment causes TdP. So, while a comparison of a narrow search should be unambiguous, results of a comparison of a broad search require further clinical investigation. For this purpose it is also essential to provide adequate supporting data on an individual basis.

LISTINGS

Listings of the events selected by an SMQ (and summarized in tables) are essential for the correct clinical interpretation of the SMQs findings.

Listing 1 Adverse events in selected SMQs, starting in-treatment. By SMQ, treatment as treated and patient. All-Subjects-Treated Group.

SMQ = Torsade de pointes/QT prolongation

Treatment	Patient	Reported term/ Preferred Term	Start/ Stop	Relationship/ Intensity	SAE	Narrow search*
Placebo	1009	QT long syndrom/ PT=Long QT syndrome	Day 20/ Day 22	Unlikely/ Moderate		X
		Tachycardia/ PT=Ventricular tachycardia	Day 21/ Day 52	Possible/ Severe	SAE	X

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	1036	Fainting/ PT=Syncope	Day 67/ Day 71	Unlikely/ Mild		-
	1077	QT long syndrom/ PT=Long QT syndrome	Unknown/ Day 52	Possible/ Moderate		X
		LOC/ PT=Loss of consciousness	Day 78/ Day 78	Likely/ Mild		-
Active	1011	Fainting/ PT=Syncope	Day 102/ Day 103	Unlikely/ Mild		-
	1022	Tachycardia/ PT=Ventricular tachycardia	Day 21/ Day 52	Possible/ Severe	SAE	X
	1030	Fainting/ PT=Syncope	Day 56/ Day 57	Unlikely/ Mild		-
		Fainting/ PT=Syncope	Day 95/ Day 96	Unlikely/ Mild		-
	1056	Fainting/ PT=Syncope	Day 12/ Ongoing	Unlikely/ Mild		-
(...)						

Listing is based on MedDRA version 11.0.

* all events are within SMQ's Broad search; X = event also falls within Narrow search.
Note that this SMQ does not have Algorithmic search.

SMQ = Anaphylactic reaction

Treatment	Patient	Reported term/ Preferred Term	Start/ Stop	Relationship/ Intensity	SAE	SMQ search*	
						Narrow	Algor.
Placebo	1021	Flushing/ PT=Flushing	Day 81/ Day 112	Possible/ Severe		-	-
	1043	Anaphylactic reaction/ PT=Anaphylactic reaction	Day 2 Day 18	Possible/ Severe	SAE	X	X
		Sneezing/ PT=Sneezing	Day 5/ Day 90	Unlikely/ Moderate		-	-
	1051	Hypotension/ PT=Hypotension	Unknown/ Ongoing	Possible/ Moderate		-	-
	1067	Some sneezing/ PT=Sneezing	Day 1/ Day 2	Unlikely/ Moderate		-	X
		Hypotension/ PT=Hypotension	Day 91/ Day 92	Possible/ Severe		-	X
Active	1008	Sneezing/ PT=Sneezing	Day 1/ Ongoing	Unlikely/ Moderate		-	-
		Asthma/ PT=Asthma	Unknown/ Day 112	Possible/ Severe		-	-
	1027	Anaphylactic reaction/ PT=Anaphylactic reaction	Day 98 Day 99	Possible/ Moderate		X	X
(...)							

Listing is based on MedDRA version 11.0.

* all events are within SMQ's Broad search; X = event also falls within this search.

A few remarks on the algorithmic search findings for SMQ Anaphylactic reaction as presented in the listing:

- The fact that algorithmic search inspects the patient's combination of PTs is visible in the listing: for patient 1067 Sneezing is part of the algorithmic search, but for patient 1043 it is not.
- The timing of events plays no role in the algorithmic search. For example, patient 1067 has Sneezing and Hypotension which makes the patient qualify for algorithmic search. However, there are many days in between these events, so that a clinical interpretation most likely will conclude that the SMQ signal for this patient is irrelevant.

Ignoring timing issues might be considered a flaw of the algorithmic search. However, introducing requirements on timing and for instance chronology of events would make the derivations for algorithmic search very complex, if not impossible.

CONCLUSION

SMQs are a very useful addition to MedDRA. The unambiguously defined groupings of PTs of an SMQ ensure that all manifestations of a condition are captured. For the SMQ search a patient is counted only once, even if the patient experienced multiple SMQ-contributing PTs. The resulting counts of unique patients enable a statistically meaningful comparison and analysis of the SMQs. However, findings of specially the broad and algorithmic searches typically require a case-by-case evaluation, for a correct clinical interpretation.

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RECOMMENDED READING

Introductory Guide for Standardised MedDRA Queries (SMQs) Version 11.0, MSSO, March 2008

This document is part of the MedDRA materials, and renewed with each new version of the dictionary.

A paid subscription to MedDRA is required. - www.meddramsso.com

Council For International Organizations Of Medical Sciences (CIOMS) - www.cioms.ch

This is where the Working Group on SMQs is based.

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¹ For this example, SMQ 20000005 has been simplified. In reality the hierarchy of this SMQ is even more extensive, and the number of active PTs per SMQ differ accordingly.

² We have restricted the SMQ definition to PT rows only, and now use the term PT in the remainder of the document. However, if all (LLT) rows would have been kept instead, then in remainder of the document the term LLT should be read instead of PT.