

Standardised MedDRA Queries

Their Role in Signal Detection

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Abstract

Standardised MedDRA (Medical Dictionary for Regulatory Activities) queries (SMQs) are a newly developed tool to assist in the retrieval of cases of interest from a MedDRA-coded database. SMQs contain terms related to signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiological test data etc, that are associated with the medical condition of interest. They are being developed jointly by CIOMS and the MedDRA Maintenance and Support Services Organization (MSSO) and are provided as an integral part of a MedDRA subscription. During their development, SMQs undergo testing to assure that they are able to retrieve cases of interest within the defined scope of the SMQ.

This paper describes the features of SMQs that allow for flexibility in their application, such as 'narrow' and 'broad' sub-searches, hierarchical grouping of sub-searches and search algorithms. In addition, as with MedDRA, users can request changes to SMQs. SMQs are maintained in synchrony with MedDRA versions by internal maintenance processes in the MSSO.

The list of safety topics to be developed into SMQs is long and comprehensive. The CIOMS Working Group retains a list of topics to be developed and periodically reviews the list for priority and relevance. As of mid-2007, 37 SMQs are in production use and several more are under development.

The potential uses of SMQs in safety analysis will be discussed including their role in signal detection and evaluation.

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The terminology resulted from an International Conference on Harmonisation (ICH) initiative to overcome some perceived deficiencies of earlier terminologies, namely the lack of specificity or limited data-retrieval capabilities, and additionally to standardise and support electronic data submission. MedDRA is maintained by the Maintenance and Support Services Organization (MSSO) utilising change requests from MedDRA subscribers.

MedDRA is organised in a five-level hierarchical structure with 26 system organ classes (SOCs) as the broadest classification level. The Preferred Term (PT) is where the unique medical concept lies, and the Lowest Level Terms (LLTs) are synonyms to facilitate data entry.

Terms other than those strictly related to adverse event concepts, namely diseases, diagnoses, signs and symptoms, therapeutic indications and investigations, are also included in MedDRA, allowing to both classify what is reported as an adverse event and to capture diseases, signs and syndromes.

1. The Origin of Standardised MedDRA Queries (SMQs)

With close to 17 000 PTs in MedDRA, there is a concern that this large number of terms may impact data retrieval and signal detection. Data that were once concentrated in a single term, are now spread over many MedDRA PTs. The challenge is to make sure the terms are properly grouped for the purpose of signal detection.

Special Search Categories (SSC) were an initial attempt at providing a data-retrieval tool within MedDRA. Collections of PTs were aggregated into 13 clinical concepts. Some SSCs included 'Arrest (cardiac)'; 'Hemorrhage'; 'Thrombosis'; and 'Immediate hypersensitivity and anaphylactic reactions'.

Over time, several limitations of SSCs were identified by the user community, particularly the lack of vigorous maintenance, lack of specificity, incompleteness and unfeasibility for data retrieval and analysis. In March 2007, coincident with the release of MedDRA version 10.0, SSCs were 'retired'.

In 2002, combining efforts of the CIOMS and ICH, the Standardised MedDRA Queries (SMQs) Working Group was established, gathering together scientists from several drug regulatory authorities and other organisations along with scientists from many pharmaceutical companies and two physicians from the MSSO.

SMQs are intended to aid in case identification and their development begins with a definition of the medical concept. Following the case definition of the SMQ, MedDRA terms are then incorporated. These may be related to signs, symptoms, diagnoses, syndromes, clinical findings, laboratory and other test data, etc, that are associated with the medical condition of interest.

During development, SMQs undergo testing to ensure that they are able to retrieve cases of interest within their scope. Phase I testing aims to assess if the SMQ is in fact returning relevant cases from several testing databases. During phase II, users were asked to test the SMQs in the same way they were tested in phase I and report the results to the Working Group. Subsequently, they were released

into production and undergo regular maintenance in synchrony with MedDRA versions. In July 2006, the process was changed to merge phase II evaluation with production release of SMQs).

Other aspects of SMQs help in refining the searches. The 'narrow' and 'broad' concept terms accommodate instances when one is looking for very specific cases (narrow) or when throwing a wider net (broad) to increase the sensitivity of a search.

Another option is to use SMQs that are arranged in a hierarchy of searches with top-levels and additional sub-searches. For example, the concept 'haematopoietic cytopenias' can be approached at the top level if one is looking for all types of haematopoietic cytopenias, however, if looking solely at 'thrombocytopenias', one would apply a specific sub-search SMQ.

Finally, some SMQs are defined as algorithms, where having a logical combination of terms in the same report produces a stronger case, reducing the number of irrelevant records and improving case identification.

2. MedDRA and SMQs in Signal Detection

A feature of MedDRA that impacts on data retrieval and signal detection is its multiaxiality. A multiaxial terminology, in the simplest sense, implies the representation of a concept in more than one SOC. Giving the PT 'Influenza' as an example, it is represented primarily in the SOC 'Infections and infestations' but also has a secondary link to the SOC 'Respiratory, thoracic and mediastinal disorders'.

The possibility to look at MedDRA from different viewpoints is an advantage, but the whole of MedDRA is not multiaxial; in fact, a minority of PTs have secondary links, and in three of the 26 SOC, this feature is absent (SOC 'Investigations', SOC 'Surgical and medical procedures' and SOC 'Social circumstances').

Primary SOC allocation rules are another characteristic to bear in mind, as three MedDRA SOC, no matter where the event manifests in the body, will

always act as the primary allocation. These are: SOC 'Congenital, familial and genetic disorders', SOC 'Neoplasms benign, malignant and unspecified (incl cysts and polyps)' and SOC 'Infections and infestations'.

Preliminary signal detection tests with MedDRA and SMQs are underway at the European Medicines Agency. Disproportionality studies using proportional reporting ratios revealed that the performance of the method varies across different levels of the terminology. In certain instances, the PT level is the best option for indexing a signal, but not always. Aggregating MedDRA terms according to syndromes or diagnoses seem to find signals earlier. The novelty of SMQs requires further research to explore their ability to act in this capacity.

Of note, the Volume 9A of the Rules Governing Medicinal Products in the EU was published in final form in March 2007. The Guideline states: "Standardised MedDRA Queries (SMQs) may be used for signal detection and the use of SMQs is recommen-

ded in order to retrieve and review cases of interest..."

The size, specificity and multiability are characteristics of MedDRA that impact both the classification and the analysis of data. These characteristics, although potentially helpful, are not always enough. Additional tools such as SMQs are likely to assist in data retrieval and signal detection.

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