

Adverse event reporting: A brief overview of MedDRA

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Abstract

Since its inception 20 years ago, the Medical Dictionary for Regulatory Activities (MedDRA) has become the lingua franca of safety reporting in a regulatory context. The standardised reporting across different regulatory regions and languages is a major strength of MedDRA. The detail offered by the large number of terms may, in principle, be considered an advantage too, but increased granularity is not without its problems. Awareness of the potential issues with MedDRA should help medical writers provide clear, transparent safety reporting.

Keywords: MedDRA, Safety reporting, SMQs

While efficacy endpoints used in clinical trials can vary greatly according to therapeutic field, stage of development, and study design, safety endpoints are usually much more uniform. Safety reporting is generally based on analysis of adverse events and safety laboratory variables. Nowadays, adverse events in most trials and indeed adverse events analysed as part of post-marketing pharmacovigilance activities are reported using the Medical Dictionary for Regulatory Activities (MedDRA). This ubiquitous dictionary is essentially a terminology database that is used for converting the event reported by the investigator (known as the 'verbatim term' or 'literal term') into a standard term in a process known as coding. Once adverse events have been properly coded, frequencies and incidences of adverse events can be analysed in the search for safety signals.

History of MedDRA

In the days before the International Conference on Harmonisation (ICH), many different coding dictionaries were used. The Food and Drug Administration, for example, preferred the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) coding system. Other commonly used systems included the International Classification of Diseases and the World Health

Organisation's Adverse Reaction Terminology. Some companies even developed their own in-house terminologies. Such a variety of coding systems hindered the comparison and pooling of safety data and represented a large burden on companies who might be forced to re-code data for submissions to different regulatory regions.

The incipient form of MedDRA (known as MEDDRA) was drawn up by a working group consisting of regulatory authorities from the UK, Spain, and France, along with industry representatives.¹ A meeting of the Council for the International Organisation of Medical Sciences (CIOMS) in 1994 suggested that this dictionary could be adopted as the global standard for adverse event coding.² The decision was enshrined by the ICH in their M1 multidisciplinary initiative (see <http://www.ich.org/products/meddra.html>). MedDRA rapidly gained ground as the preferred coding system, and today, the adverse events in most regulatory submissions are coded using MedDRA.

Operational overview

MedDRA files are only available to subscribers. The annual subscriptions are free to regulatory authorities, patient care providers, and non-profit organisations such as academic institutions and medical libraries.² Pharmaceutical companies pay a subscription on a sliding scale according to revenue. In line with its aims to be a global standard, MedDRA is available in a variety of languages (including the major European languages and Japanese) with an exact mapping between languages of terms down to the preferred term level (though lowest level terms (LLTs) may be language specific).

MedDRA is subject to revisions; new versions are issued every 6 months. The company responsible for maintenance is the MedDRA Maintenance and Support Services Organization (MSSO), contracted to the International Federation of Pharmaceutical Manufacturers and Associations. The MSSO reports to the steering committee of the ICH

through its management board. As might be expected, the changes made in early versions, when MedDRA was still finding its feet, were larger than those in later versions. MedDRA is, however, still evolving and it is therefore important to document which version of MedDRA was used for an analysis (given that, for example, preferred terms may be in different primary system organ classes (SOCs) in different versions). Certain complications may arise with long studies that have different interim analyses performed at different times with different versions of MedDRA. The recommendation is that each analysis should be performed using the most recent version of MedDRA available.

Organisation of MedDRA

MedDRA is a hierarchical system comprising five levels (see Figure 1). At the top of the hierarchy are the 26 SOCs (note these correspond to ‘body systems’ in COSTART, and some still use this term erroneously in relation to MedDRA). Most of the statistical outputs used by a regulatory writer for safety reporting will be based on preferred terms (considered to be a single medical concept), grouped into SOCs in many cases. Below the preferred terms come LLTs, which often provide synonyms for preferred terms. The availability of several LLTs for a preferred term assists in coding because there is likely to be a close match with the verbatim terms recorded by the investigator. As an aside, MedDRA uses British spelling for preferred terms and all terms above preferred terms in the hierarchy. American spelling is included for LLTs (primarily to assist in coding). When reporting MedDRA terms in free text, most would consider it acceptable to change the term to American spelling if the rest of the document uses American spelling. Likewise, it

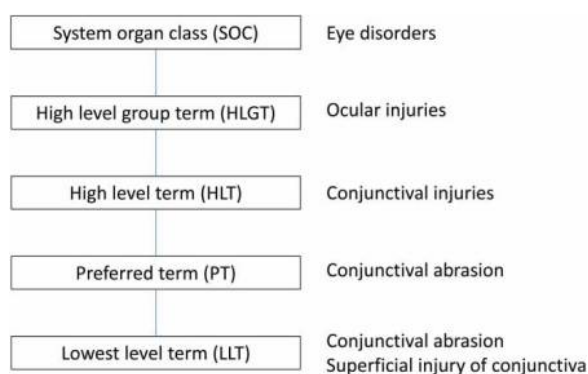


Figure 1: The MedDRA hierarchy with terms corresponding to the preferred term ‘Conjunctival abrasion’. Note that the LLT and the preferred term can be identical (examples taken from Mozzicato²).

would also be considered acceptable to change a MedDRA term from, for example, ‘acid base balance abnormal’ to ‘abnormal acid base balance’ to enhance readability.

MedDRA is denominated a multiaxial system. This means that a given preferred term can belong to different high-level terms, high-level group terms, and therefore SOCs. There is always however, a primary SOC with which a given preferred term is associated. For example, urinary tract infection is usually placed in the ‘gastrointestinal disorders’ SOC. But this event is clearly also an infection and so can also belong to the ‘infections and infestations’ SOC, which would be considered the secondary SOC. According to MedDRA, this flexibility is an advantage of MedDRA. In practice, I have never seen an analysis of secondary SOCs (in pre-submission documents, though the approach may conceivably be used more often for pharmacovigilance purposes). So if you are interested in infections because the investigational medicinal product suppresses the immune system, it is not particularly helpful if isolated infections are spread over a range of SOCs diluting the safety signal. An alternative to analysis of secondary SOCs is to use a standardised MedDRA query (SMQ).

Standardised MedDRA queries

As mentioned above, similar types of event (such as infections) can be assigned to different SOCs. In addition, there are some preferred terms that map to a single SOC. For example, the preferred term ‘platelet count decreased’ maps to the SOC ‘Investigations’ while the closely related preferred term ‘thrombocytopenia’ maps to the SOC ‘Blood and lymphatic system disorders’. Even an analysis of secondary SOCs would be unable to combine these terms in the search for a safety signal. To overcome this problem, MedDRA allows what are known as SMQs, which replaced the now obsolete special search categories.³

An SMQ is essentially a list of preferred terms that relate to a specific medical condition,⁴ such as anaphylactic reaction (which could be manifest in a number of different events, each belonging to different SOCs). SMQs are in constant development through collaboration between the CIOMS and ICH. Updates are issued along with the 6-monthly updates to MedDRA itself. New SMQs may be developed, sometimes on the request of MedDRA users, for example, if there is concern about a particularly novel adverse effect for a new drug. It should be stressed that the SMQs cannot be tailored

by the users and are not designed according to the specifications of the drug companies; the CIOMS and ICH committees have the ultimate say. When a database is analysed using an SMQ, all events that match terms in the SMQ list will be retrieved. Clinical judgement must then be applied to determine whether the results represent a significant safety signal.

Is MedDRA a panacea?

The developers of MedDRA would have us believe that MedDRA coding is objective given the high granularity of the LLTs and that it is clinically validated because it is developed and maintained by medical experts.² This may very well be true but, according to a systematic review of coding of adverse events in clinical trials, there is little evidence to support this affirmation (and the authors also noted how surprising it was that the system that forms the basis for all regulatory safety reporting has been subject to so little publicly available research on the topic).⁵ The only study which assessed the correlation between coding of verbatim terms by two blinded coders found that 12% were coded differently.⁶ The authors did, however, note that training for investigators in recording verbatim terms could improve the quality of coding. If coding is subjective, there is in theory potential for influence to be exerted (either intentionally or inadvertently) to enable a favourable outcome. However, adverse events are generally coded independently prior to analysis of the data (only on very rare occasions might the coding of an adverse event be queried and such a query would be documented). The potential for such influence would therefore seem limited.

MedDRA has also been criticised for being too granular. With the COSTART system, there were ~1200 terms. MedDRA however, has ~18 000 preferred terms and 66 000 LLTs.² The problems associated with granularity have been alluded to above, and more advanced search strategies such as analysis of secondary SOCs and SMQs, if performed, can go some way to alleviating the problem. But typically, the summary of product characteristics or package insert will summarise adverse events by frequency. In a summary table that presents adverse events reported with an incidence of 5% or more, a more general concept that is broken down into several more granular concepts may disappear from the table.

In some cases though, the criticism runs deeper and MedDRA (which do not forget is essentially an industry initiative in collusion with ICH and

regulatory authorities) has been accused of providing drug companies with enough wriggle room to hide safety signals. Perhaps, the most notorious case was the trial of the antidepressant paroxetine in adolescents, in which suicidal tendencies were coded as aggression or exacerbation of depression.⁷ This is an example often used by critics of the pharmaceutical industry as an example of a broken system (see, e.g. Ben Goldacre's book, *Bad Pharma*⁸). Although this example was tragic and shocking, we should remember that drugs are regularly pulled from development because of safety issues though this is rarely a newsworthy event (an obvious selection and reporting bias is in operation here).

With the increased transparency and more rigorous requirements for disclosure of trial data, in time it will presumably become possible to track drugs whose development is discontinued for safety reasons and compare these drugs with those that are withdrawn from the market after approval. In addition, detailed pre-approval data will be available for analysis in cases when drugs are withdrawn after approval. This should give a more accurate and objective picture of how well MedDRA fares in detecting safety signals and could give some indications as to how and why some drugs slip through the safety net. In the meantime though, medical writers should be aware of the need to document how adverse events are coded, including providing a glossary for mapping the verbatim terms reported by the investigators and the preferred terms to which these events have been coded.

Conclusions

MedDRA has both strengths and weaknesses. The standardisation across regulatory regions and languages is certainly welcome. The large number of preferred terms and LLTs may be considered a strength in some senses in that it may allow more objective coding but a weakness in that it may mask certain safety signals. Unfortunately, little information is available on the sensitivity (how many 'bad' drugs are detected before approval) and specificity (how many 'good drugs' are discontinued from further development). Likewise, the constant evolution MedDRA could be considered a strength in that it can adapt to new situations but a weakness in that it may create problems when comparing similar sets of data coded with different versions of MedDRA. Awareness of these issues can help regulatory writers ensure that safety reporting is as clear and transparent as possible.

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Author information

A chemist by training, but starved of career opportunities in Spain, Greg Morley made the switch first to translation and editing, and then medical writing. He now has more

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