SHORT COMMUNICATION

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Effects of Coding Dictionary on Signal Generation

A Consideration of Use of MedDRA Compared with WHO-ART

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Abstract

To support signal generation a terminology should facilitate recognition of medical conditions by using terms which represent unique concepts, providing appropriate, homogeneous grouping of related terms. It should allow intuitive or mathematical identification of adverse events reaching a threshold frequency or with disproportionate incidence, permit identification of important events which are commonly drug-related, and support recognition of new syndromes.

It is probable that the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) or high level terms (HLTs) will be used to represent adverse events for the purposes of signal generation. A comparison with 315 WHO Adverse Reaction Terminology (WHO-ART) PTs showed that for about 72% of WHO-ART PTs, there were one or two corresponding MedDRA PTs. However, there were instances where there were many MedDRA PTs corresponding to single WHO-ART PTs. In many cases, MedDRA HLTs grouped large numbers of PTs and sometimes there could be problems when a single HLT comprises PTs which represent very different medical concepts, or conditions which differ greatly in their clinical importance.

Further studies are needed to compare the way in which identical data sets coded with MedDRA and with other terminologies actually function in generating and exploring signals using the same methods of detection and evaluation.

In this paper, we will look at what features are desirable in a medical terminology to facilitate the identification of signals of new safety concerns for a medicine and what functional requirements there are for safety database systems in supporting the process. We will examine how the new international standard terminology – the Medical Dictionary for Regulatory Activities (MedDRA)[1] is likely to function in this context. In particular, we will consider the possible effects of the high specificity and large size of MedDRA, when compared with the much smaller WHO Adverse Reaction Terminology (WHO-ART).

1. Requirements for Signal Generation and Exploration

The requirements of a terminology for signal generation are summarised in table I. In order to

1 MedDRA is a registered trademark of the International Federation of Pharmaceutical Manufacturers Associations.

Table I. Functional requirements of terminologies for signal detection

Facilitate recognition of medical conditions
Terms represent unique concepts
Appropriate grouping of medically-related terms
Homogeneity of groupings
Allow intuitive or mathematical identification
Adverse events which are often drug-related (e.g. Stevens-Johnson syndrome, anaphylaxis, aplastic anaemia)
Adverse events reaching a threshold frequency
Adverse events with disproportionate incidence
Support recognition of new syndromes
Accurate recording of signs/symptoms by case

distinguish between different medical conditions, it is necessary that terms at some level in the terminology represent unique or distinct medical concepts. However, because signal generation commonly demands that similar conditions are recognised together, there needs to be appropriate grouping of terms which are medically related in some way.

For example, if we find that there are two reports of hepatitis with a particular medicine, we should also wish to see in proximity to this fact any information about reports of hepatic failure, jaundice and liver enzyme abnormalities, so that all these conditions could usefully be present under a group heading. As an alternative to counting the number of reports of the individual condition, we may wish to count the numbers of reports of similar, associated conditions, falling within the grouping. It is therefore important that the groupings should be homogeneous in nature, i.e. containing terms referring to related or similar medical conditions.

There is a need for the dictionary to support some form of presentation and counting of cases, to allow either intuitive or statistical recognition of possible signals. This presentation might take the form of a visual display with counting of numbers of similar event terms, noting if these reach an arbitrary threshold. Alternatively, statistical methodologies dependent upon identifying disproportion, such as proportional reporting ratios (PRRs) might be applied. Again, these methods are dependent upon distinction between different conditions based upon the terminology employed. In addition, there is a need to be able to note the occurrence of individual or small numbers of reports of important adverse events which are commonly drug-related when they occur, such as Stevens-Johnson syndrome, anaphylaxis or aplastic anaemia. It is also important that reports comprising only signs, symptoms and/or investigation findings which could represent new syndromes should be recognisable in the database.

2. Medical Dictionary for Regulatory Activities (MedDRA) and Signal Generation

MedDRA is a large terminology covering medical signs, symptoms, syndromes and diagnoses as well as social conditions, surgical and medical procedures and laboratory and clinical investigations.[1] It comprises 26 vertical axes, the system organ classes (SOCs), for example, Cardiac disorders SOC; Infections and infestations SOC; and Investigations SOC. Within each SOC there are a further four levels, comprising in descending order in the hierarchy, but in increasing number, high level group terms (HLGTs), high level terms (HLTs), preferred terms (PTs) and lowest level terms (LLTs). The structure of MedDRA is multiaxial, so that terms may be present in more than one SOC location at the same level in the terminology. This is particularly important for preferred terms, each of which is allocated a primary location within a particular SOC, but with the possibility of being present also at the same level in one or more secondary locations, in different SOCs. The structure of MedDRA is shown schematically in figure 1.

There is currently little hard evidence available as to how MedDRA will function in generating and exploring signals. At the time of writing, few organisations have experience of using MedDRA for signal generation. The US Food and Drug Admin-

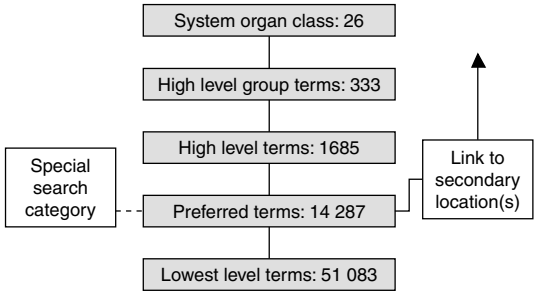

Fig. 1. The Medical Dictionary for Regulatory Activities (MedDRA) hierarchy (version 4.0 term numbers).

istration (FDA) has incorporated MedDRA into its Adverse Event Reporting System (AERS) database and is developing methodologies involving neural networks and disproportionality analyses. However, no clear data are available showing the results of using MedDRA in this regard. The UK Medicines Control Agency (MCA) has successfully used the Adverse Drug Reaction On-line Information Tracking (ADROIT) terminology for signal generation for many years, both for visual displays of data which are then reviewed by experts in signal identification, and also employing PRRs for this purpose. The ADROIT terminology was a precursor to MedDRA and shares many of its conceptual and structural features. However, the dictionaries have diverged with the passage of time, so analogies may not be valid.

3. The MedDRA Hierarchy and Implications for Finding Signals

What follows is based on current and recent versions of MedDRA, namely versions 3.2 and 3.3. A new and extensively revised version has recently become available, so that these observations will need to be checked against that updated terminology. Nevertheless, preliminary examination of the new version suggests that the principles described below will not be materially affected by the change in version.

In view of the large number of LLTs in MedDRA and their highly specific nature, it is unlikely that they will be particularly useful in generating signals. For example, there are some 87 MedDRA LLTs for various types of paraesthesia in a variety of anatomical sites. LLTs may, however, be helpful when exploring putative signals, by permitting examination of coded terms which are close to the reported conditions without the need to review the actual case narratives. This may help to focus on the most appropriate reports if large numbers of cases are involved.

At the other end of the hierarchy, as there are only about 300 HLGTs, they will probably be insufficient in number to represent adverse events in any detail and may be too broad for purposes of signal generation. However, HLGTs are likely to be of value in presenting groups of terms for searching data-sets for reports of adverse events in the process of exploration of putative signals.[2] They may also be useful for presenting graphical summary information in the form of a profile across SOCS.

It is probable that either MedDRA PTs or HLTs will be used to represent adverse events in a database for purposes of presentation or counting for signal generation. However, with some 14 000 or more PTs, it is possible that MedDRA may provide more terms than is desirable for detecting patterns of events and for reaching thresholds for signal generation, or for supporting disproportion methods.

For example, if we consider a possible signal of neuropathy, depending on how the individual cases have been reported, these could be represented by MedDRA PTs in many different ways. Single reports of each might fail to reach the threshold required to be recognised as a signal. Thus, there are more than 25 different MedDRA PTs containing the word ‘neuropathy’, including Autonomic neuropathy, Mononeuropathy, Diabetic neuropathy, Entrapment neuropathy, Polyneuropathy, Optic neuropathy, Uraemic neuropathy and Mononeuropathy multiplex. Other cases

which might be relevant could be represented by many other PTs such as Guillain Barré syndrome, Miller Fisher syndrome, Meralgia paraesthetica, Piriformis syndrome, Tarsal tunnel syndrome, etc. Yet more cases could be represented among the 14 PTs for paresthesia or dysesthesia, 7 PTs for other sensory abnormalities, numerous PTs for muscle weakness, paralysis, abnormal nerve conduction tests, and so forth. Thus, it appears that at the PT level, the concept of neuropathy in which we are interested might be split up into many different terms. Whilst it is appropriate from a medical standpoint that this is so, it may not help in identifying signals, unless these PTs are grouped appropriately under HLTs which might be the key to recognition.

There are of the order of 1600 HLTs in MedDRA. This compares with about 1800 PTs in the WHO-ART terminology. The majority of WHO-ART PTs were incorporated into MedDRA during its development, although they did not necessarily retain their relationships to SOC / body system, nor were they specifically kept as PTs, many being demoted to LLTs.

WHO-ART has been widely used for many years to generate signals within pharmaceutical companies and regulatory authorities and the WHO-ART PT remains the mainstay of the signal detection system utilised by the WHO's Uppsala Monitoring Centre. It was therefore decided to carry out a study to evaluate the relationship between MedDRA PTs and HLTs and WHO-ART PTs and to explore the hypothesis that MedDRA PTs split medical concepts in a way that might complicate signal identification.

4. A Study of the Relationship Between MedDRA and WHO Adverse Reactions Terminology (WHO-ART)

4.1 Objectives

The objective of the study was to explore the numerical and conceptual relationships between the PT in WHO-ART and the PT and HLT in MedDRA, in the context of their respective utility for purposes of signal generation.

4.2 Methods

A sample of approximately one sixth of all WHO-ART PTs (as of January 2001) was taken and MedDRA version 3.3 was searched using a software browser (Medicoder, courtesy of Software Technics Ltd.) for LLTs representing the same medical concept as each WHO-ART PT. For each MedDRA LLT, the respective MedDRA PT was identified and in turn, its HLT was noted, in the primary MedDRA SOC. For every MedDRA HLT identified in this way, its subordinate PTs were found, again limiting this to the primary MedDRA SOC.

4.3 Results

There were 1892 PTs in WHO-ART, of which 315 were examined. These were mapped to 943 MedDRA PTs, via the respective LLTs. Commonly, a single WHO-ART PT represented a medical concept which was presented as several MedDRA PTs. Exceptionally, the converse applied. The results of the study are summarised in table II and table III. In order to illustrate the nature of the data, an example of the relationships between a WHO-ART PT, Cholelithiasis and the respective MedDRA PTs and HLTs is shown in table IV.

From table II, it may be seen that for about 72% of WHO-ART PTs, there were one or two corresponding MedDRA PTs and this increased to 86% of WHO-ART PTs when considering MedDRA HLTs. On the other hand, there were instances where there were many MedDRA PTs corresponding to single WHO-ART PTs, with rather less MedDRA HLTs corresponding to single WHO-ART PTs. From table III, it may be seen that in about 40% of instances, a MedDRA HLT grouped together ten or less MedDRA PTs. However, in many cases, the MedDRA HLTs grouped large numbers of PTs. In about 7% of the HLTs examined, there were more than 100 PTs included.

Table II. The relationship between WHO Adverse Reactions Terminology (WHO-ART) preferred terms (PTs) and Medical Dictionary for Regulatory Activities (MedDRA) PTs and high level terms (HLTs)

MedDRA : WHO-ART ratio	MedDRA PT : WHO-ART PT frequency (%)	MedDRA HLT : WHO-ART PT frequency (%)
1	185 (58.7)	220 (69.8)
2	41 (13)	52 (16.5)
3	23 (7.3)	16 (5.1)
4	20 (6.3)	11 (3.5)
5	10 (3.2)	4 (1.3)
6	5 (1.6)	4 (1.3)
7	7 (2.2)	2 (0.6)
8	4 (1.3)	2 (0.6)
9	2 (0.6)	0
10	2 (0.6)	0
11-20	12 (3.8)	4 (1.3)
21-30	3 (1.0)	0
>30	1 (0.3)	0

In summary, the findings of the study demonstrated that in many instances, a single WHO-ART PT would be represented by many (or very many) MedDRA PTs. On the other hand, a single WHO-ART PT would be represented by rather less MedDRA HLTs. However, each MedDRA HLT in turn may group together many or very many MedDRA PTs. The study identified some nonhomogeneous groupings of PTs under HLTs in MedDRA, and simple examination of the names and content of some MedDRA HLTs exemplifies the nature of the problem, as shown in table V. These terms and groupings have remained in version 4.0 of MedDRA.

4.4 Discussion

If we accept that WHO-ART PTs represent single medical conditions, using MedDRA at the PT level might theoretically lead to failure to recognise signals, because the concepts are split up into many MedDRA PTs, which might be distributed in different parts of the terminology. Whilst each MedDRA HLT may group together large numbers of MedDRA PTs, this is probably not important for signal generation and recognition, provided that the PTs so grouped are similar in nature, comprising similar medical concepts. We might then refer to such HLTs as being homogeneous in the medical concepts they include.

It is more problematic when a single HLT comprises PTs which represent very different medical concepts, or conditions which differ greatly in their clinical importance. These might be undesirable to group together and consider as single terms for signal generation purposes.

Basing signal identification on nonhomogeneous groupings of PTs may lead to false-positive results, by lumping together different conditions

Table III. Number of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) per corresponding MedDRA high level term (HLT) [primary SOC location only]

Number of MedDRA PTs per HLT	Frequency (%)
0-10	39.7
11-20	21.9
21-30	11.4
31-40	6
41-50	6.7
51-60	2.5
61-70	2.2
71-80	1.3
81-90	0.6
91-100	0.6
100-199	6
>200	0.9

SOC = system organ class.

inappropriately. Conversely, if we are trying to identify signals by using HLTs with a method involving disproportion, we might dilute out a signal of an important condition which was represented by one PT collected together under an HLT with large numbers of less important and less specific PTs. For example, we might fail to recognise a signal of neuroleptic malignant syndrome (NMS) if we were to subsume that PT under the HLT febrile disorders. Finding a number of reports presented merely as febrile disorders might not make us suspect that NMS could be occurring. On the other hand, our interest in a putative signal of ventricular arrhythmia might be unwarranted if all the reports merely comprise extrasystoles. If using methods involving display of tables of adverse events, such as the 'Alert Print' employed by the MCA, it would be appropriate to show and count PTs under the

Table IV. Medical Dictionary for Regulatory Activities (MedDRA) terms corresponding to the single WHO Adverse Reaction Terminology (WHO-ART) preferred term (PT) Cholelithiasis

MedDRA PT	HLT for this PT	PTs under this HLT
Bile duct obstruction due to calculus	Obstructive bile duct disorders (excluding neoplasm)	
Bile duct stone		Bile duct obstruction due to calculus
		Bile duct stone
		Bile duct obstruction (excluding calculus)
		Bile duct obstruction NOS
		Biliary tract internal pressure increased
		Oddi's sphincter constriction
Cholelithiasis	Cholecystitis and cholelithiasis	
Cholelithiasis obstructive		Cholelithiasis
		Cholelithiasis obstructive
		Cholecystitis acute NOS
		Cholecystitis chronic NOS
		Cholecystitis NOS
Ileus paralytica[a]	Non-mechanical ileus	
		Ileus paralytic
		Ileus spastic
		Mechanical ileus
		Megacolon acquired
		Megacolon NOS
		Subileus
Pancreatitis due to gallstones	Acute and chronic pancreatitis	
		Pancreatitis due to gallstones
		Oedematous pancreatitis
		Pancreatic pseudocyst
		Pancreatitis acute
		Pancreatitis acute on chronic
		Pancreatitis aggravated
		Pancreatitis chronic
		Pancreatitis haemorrhagic
		Pancreatitis necrotising
		Pancreatitis NOS
		Pancreatitis relapsing

a Lowest level terms 'Gallstone ileus' and 'Obstruction of intestine due to gallstone' map to this PT. In addition, PTs 'Gallstone in bile duct removal' and 'Cholelithotomy' map to the HLT 'Biliary tract and gall bladder therapeutic procedures'.

HLT = high level term; **NOS** = not otherwise stated.

Table V. Examples of nonhomogeneous high level terms

High level term	Examples of subordinate preferred terms
Coagulopathies and bleeding diatheses	Hyperfibrinogenaemia, Hypofibrinogenaemia
Ventricular arrhythmias and cardiac arrest	Ventricular extrasystoles, Cardiac arrest
Gastrointestinal atonic and hypomotility disorders	Constipation, Oesophageal reflux, Ileus paralytic
Febrile disorders	Pyrexia, Neuroleptic malignant syndrome

respective HLTs and HLGTs which in turn would provide summary counts.

There remain, however, some potential difficulties. Thus, some related medical concepts are separated in MedDRA under different SOCs. In particular, a distinction is made between investigational findings and clinical conditions. Hence, the PT Hyponatraemia is found under the Metabolism and Nutrition SOC, whilst the corresponding laboratory test result of Serum sodium reduced is present only in the Investigations SOC. Likewise for the PT Torsades de pointes in the Cardiac SOC, whilst Electrocardiogram QT prolonged is present under the Investigations SOC. It is essential to bear this divarication in mind when reviewing data coded in MedDRA.

From a different perspective, a benefit of using MedDRA lies in its high specificity. This increases the probability that, having found a possible signal, the cases which it comprises represent what was actually experienced by the patient. There is less likelihood than with WHO-ART or Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) that the cases will appear within a signal as a result of misclassification or coding artefact. In other words, the link between the reported adverse event and the signal which has been generated should remain intact with MedDRA.

5. Conclusions

Signal generation is an evolving discipline. New constraints and uncertainties may be imposed by the introduction of a new terminology. However, they need to be set in the context of the existing wide variations in approach to signal generation between different organisations and the wide gap which exists between regulators and pharmaceutical companies on what constitutes an individual signal and what needs to be done about it. Indeed, there is no universally agreed definition for a signal (although there have been proposals)[3] nor on the strength of the evidence which should be used to identify a signal.[4]

Medical terminologies provide the database blocks upon which are built various methods for detecting signals of new adverse reactions to medicines. We are familiar with the use of existing terminologies, such as WHO-ART and COSTART and have adapted our techniques to take account of their shortcomings. Evans et al.[5] have described the routine use of PRRs at the MCA for identifying possible signals. The ADROIT dictionary used in that establishment was a precursor to MedDRA and its specificity is not dissimilar. It would be interesting to look at the effectiveness of using PRRs employing different levels of MedDRA to detect possible signals.

MedDRA is a new terminology and we do not yet know how best it will be used in pharmacovigilance. However, its use is becoming mandatory for pharmaceutical companies and many regulatory authorities.[6] Studies are needed to compare the way in which identical data sets coded with MedDRA and with other terminologies would function in generating and exploring signals using the same methods of detection and evaluation and if necessary, ways must be found to make it function effectively in the context of signal generation.

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