LEADING ARTICLE

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Methods and Pitfalls in Searching Drug Safety Databases Utilising the Medical Dictionary for Regulatory Activities (MedDRA)[1]

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Abstract

The Medical Dictionary for Regulatory Activities (MedDRA) is a unified standard terminology for recording and reporting adverse drug event data. Its introduction is widely seen as a significant improvement on the previous situation, where a multitude of terminologies of widely varying scope and quality were in use. However, there are some complexities that may cause difficulties, and these will form the focus for this paper.

Two methods of searching MedDRA-coded databases are described: searching based on term selection from all of MedDRA and searching based on terms in the safety database. There are several potential traps for the unwary in safety searches. There may be multiple locations of relevant terms within a system organ class (SOC) and lack of recognition of appropriate group terms; the user may think that group terms are more inclusive than is the case. MedDRA may distribute terms relevant to one medical condition across several primary SOCs. If the database supports the MedDRA model, it is possible to perform multiaxial searching: while this may help find terms that might have been missed, it is still necessary to consider the entire contents of the SOCs to find all relevant terms and there are many instances of incomplete secondary linkages. It is important to adjust for multiaxiality if data are presented using primary and secondary locations. Other sources for errors in searching are non-intuitive placement and the selection of terms as preferred terms (PTs) that may not be widely recognised. Some MedDRA rules could also result in errors in data retrieval if the individual is unaware of these: in particular, the lack of multiaxial linkages for the Investigations SOC, Social circumstances SOC and Surgical and medical procedures SOC and the requirement that a PT may only be present under one High Level Term (HLT) and one High Level Group Term (HLGT) within any single SOC. Special Search Categories (collections of PTs assembled from various SOCs by searching all of MedDRA) are limited by the small number available and by lack of clarity about criteria applied in their construction.

Difficulties in database searching may be addressed by suitable user training and experience, and by central reporting of detected deficiencies in MedDRA.

1 MedDRA is a registered trade mark belonging to the International Federation of Pharmaceutical Manufacturers Associations.

Other remedies may include regulatory guidance on implementation and use of MedDRA. Further systematic review of MedDRA is needed and generation of standardised searches that may be used 'off the shelf' will help, particularly where the same search is performed repeatedly on multiple data sets. Until these enhancements are widely available, MedDRA users should take great care when searching a safety database to ensure that cases are not inadvertently missed.

The use of the Medical Dictionary for Regulatory Activities (MedDRA) for recording and reporting adverse event data on marketed medicines becomes mandatory in the European Union[1] in 2003, and is likely to be a regulatory requirement for the US and Japan also, under the terms of the International Conference on Harmonisation[2] (ICH). MedDRA is available free of charge to regulatory authorities and to certain nonprofit-making organisations and on payment of an annual subscription to other users. The sole distributors are the MedDRA Maintenance and Support Services Organisation (MSSO) and the MedDRA Japanese Maintenance Organisation (JMO). The arrival of MedDRA as a unified standard terminology is widely seen as representing a significant improvement on the previous situation, where a multitude of terminologies of widely varying scope and quality were in use. The broad scope of MedDRA (including terms for medical and social conditions, not just adverse reaction terms) and its high specificity, with a large number of available terms, is seen as bringing particular benefits in the capability to accurately represent the clinical condition of the patient. Its hierarchical structure is also generally seen as being advantageous in facilitating data retrieval. However, there are some complexities that may cause difficulties, and these will form the focus for this paper.

Several versions of MedDRA have been issued since its release as version 2.1 in March 1999. The different versions have involved expansion of the terminology, but also changes to structure and in the location of terms. These changes have resulted from requests from users of MedDRA in the course of migrating legacy data into the new terminology, or during its routine use. In addition, the MedDRA MSSO and the JMO have undertaken exercises in standardisation of the terminology, with removal of inconsistencies and errors.

While much has been done in making the terminology consistent, and a great deal of work has been performed in developing guidelines on term selection for coding data,[3] it appears that rather less has been achieved in investigating the utility of MedDRA for one of its key functions, namely the retrieval of data or searching of safety databases. At the time of writing, only a small number of publications have considered this aspect of the use of MedDRA[4-6] and no guidelines have been issued. Database searches are pivotal to the performance of effective pharmacovigilance and in this context involve the identification of medical terms representing similar or associated medical conditions. Such searches enable the counting of particular adverse event for example, or the retrieval and presentation of collections of individual cases. Purposes to which these searches are commonly put in pharmacovigilance are shown in table I.

This paper describes the available methods for performing database searches using MedDRA and examines the contents and structure of the terminology. It focuses on aspects that may require particular care on the part of individuals performing searches, if errors in reviewing and quantifying safety are to be avoided.

The findings were garnered from personal observations during the performance of database searches carried out with various versions of MedDRA while carrying out pharmacovigilance on a number of medicines over the last 3 years.

Table I. Some Medical Dictionary for Regulatory Activities (MedDRA) rules on term location built into the terminology

Qualitative investigation results
Primary location is Investigations SOC, e.g. Blood sodium increased – Investigations SOC
Clinical correlate of the investigation: primary location is body system SOC, e.g. Hypernatraemia – Metabolism and nutrition SOC
Infection and anatomical site
Primary location is Infections and infestations SOC
Secondary location is body system SOC, e.g. Staphylococcal pneumonia – Respiratory SOC is secondary location
Neoplasms and anatomical site
Primary location is Neoplasms SOC
Secondary location is body system SOC, e.g. Colon cancer – Gastrointestinal SOC is secondary location
Congenital disorders and anatomical site
Primary location is Congenital SOC
Secondary location is body system SOC, e.g. Congenital heart disease – Cardiac SOC is secondary location

SOC = System Organ Class.

MedDRA version 5.1 was accessed using Medicoder browser and Mediminer database search software (Software Technics Ltd) as well as the beta version of the TRW MedDRA browser (TRW Inc.), in order to confirm that the observations remained valid at the time of writing.

1. Methods of Searching Databases Coded with the Medical Dictionary for Regulatory Activities (MedDRA)

These have been reviewed by Brown.[4] However, since that publication, it has become apparent that the mode of implementation of MedDRA varies within the user community. Some database systems are capable of supporting the full MedDRA structure, permitting searching by SOC location as well as by the secondary location(s) of terms (multiaxial searching). In addition, these systems store the full MedDRA hierarchy, with all five levels, allowing searches to be performed on group terms (High Level Terms [HLTs] and High Level Group Terms [HLGTs]) as well as at subordinate levels (Preferred Terms [PTs] or Lowest Level Terms [LLTs]). Other systems are constrained by the number of secondary locations that can be stored, or can only record the primary SOC location for any term. In addition, some systems are incapable of storing all levels of MedDRA. Additional variability has been introduced by the practice of some users of choosing which of the available SOCs for a given PT or LLT should be primary and which should be secondary, and indeed adapting this according to product, clinical trial, or the circumstances of the individual case report. Thus far, there has been no regulatory guidance on this topic, although the (non-mandatory) guidelines on term selection[3] suggest that users should not change the allocation of terms to SOC and such customisation would appear to undermine the objective of having a standard unified terminology.

For purposes of the present review, we will assume that MedDRA has been implemented as intended by the ICH M1 Expert Working Group, without adaptation by the user and that the database system has incorporated the full MedDRA data model. It will also be assumed that, as each version of MedDRA has been implemented on the database, the location of terms in the database associated with cases are automatically updated in accordance with the latest version, so that all terms are located as in version 5.1, and not in a variety of locations according to previous versions.

The level of MedDRA that is best suited for identification of unique medical conditions is theoretically the PT, although for some purposes involving counting of cases, the HLT may be more appropriate.[7] While there are many examples where LLTs representing unique concepts are actually grouped under individual PTs, searches involving LLTs would generally be too extensive to be practicable. Moreover, the US FDA has fixed the PT as its required level for communication of the elements of the individual case safety report, so this will probably be the focus for US-based users, although the European regulators require transmission of LLTs. The hierarchical structure

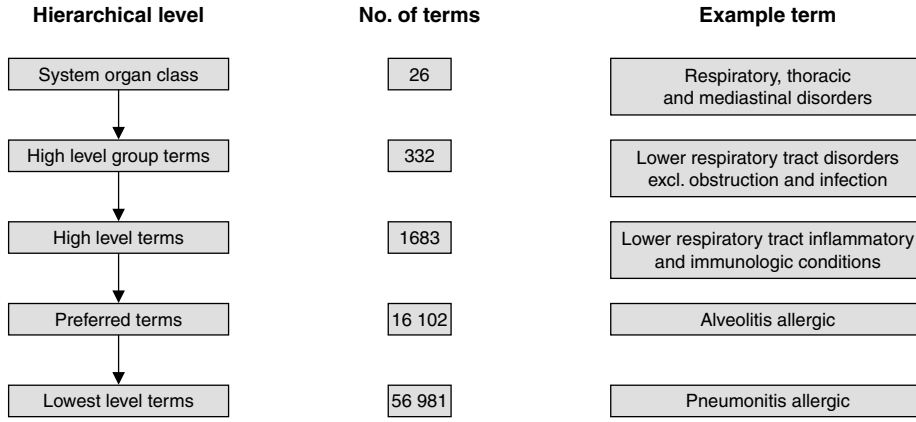

Fig. 1. Medical Dictionary for Regulatory Activities (MedDRA) hierarchy (version 5.1).

of MedDRA is shown in figure 1. MedDRA SOCs are shown in table II, and table III shows an example of the MedDRA multiaxial structure.

There are two principle methods of searching databases coded with MedDRA. The first constructs a search based on the whole of MedDRA – all SOCs are explored for the presence of relevant terms in this type of search (figure 2). For example, we might construct from the entire MedDRA dictionary a list of all PTs considered relevant to liver damage, or to renal failure. The result is a list of PTs constituting a Special Search Category (SSC) that may then be applied to any safety database at any time. However, it is necessary to review the SSC when a new version of MedDRA appears, to find out whether any new relevant PTs have been added to MedDRA and require to be incorporated in the SSC. There is a small number of SSCs built into MedDRA, as shown in table IV: their utility is described in section 7.

Table II. Examples of purposes of data retrieval in pharmacovigilance

Identifying similar cases for exploration of a possible ADR signal
Reviewing safety issues in periodic safety update reports
Presentation of cumulative data such as for IND reports
Responding to regulatory authority enquiry on specific safety concerns
Carrying out risk evaluation as part of a benefit-risk analysis
Reviewing cases in preparing Core Safety Information
Presenting safety data in support of a marketing authorisation application
Preparing supporting documentation for a safety variation application
Developing responses to medical information enquiries

ADR = adverse drug reaction; **IND** = Investigational New Drug.

In the second type of search, shown in figure 3, the safety database itself is explored initially. A list of PTs included in the database may be generated and a selection of the relevant PTs is made from this list. The list of selected relevant terms is then used to search the database for the associated cases. Variations on this approach are possible – the initial list of PTs may be shown organised under the respective MedDRA SOCs, with or without their superordinate HLTs or HLGTs. Alternatively, the database may be visualised directly and selections made at different levels. For example, in a search for cases of heart failure, it would be reasonable to include the HLGT Cardiac failure in its entirety, so including all its subordinate PTs that are represented in the database. Variations on this type of search include the use of MedDRA's multiaxiality, so that PTs with secondary linkages to a particular SOC would be identified and included in the search

as appropriate. Each of these approaches may be used, but the distinction from a SSC is that here the search is limited to the database under review – the list of PTs produced is not generated from the whole of MedDRA and the search cannot be applied to another database or at other times.

Database searches may be constructed with varying degrees of sensitivity and specificity. A highly sensitive search has the objective of finding all reports of adverse events that could conceivably be associated with a particular medical condition. It may include diagnoses, syndromes, signs, symptoms and laboratory and clinical investigation findings. On the other hand, a highly specific search looks only for cases recorded in a particular way, perhaps in accordance with a specified definition. It is more likely to be limited to event terms representing the precise condition, rather than including all the associated symptoms, signs and investigations.

The richness and complexity of MedDRA allow accurate recording of safety data and flexibility in searching databases. However, these features also bring potential problems. It is certainly the case with MedDRA that many database searches can be performed using primary SOC location of terms without difficulty, provided that there is an understanding of MedDRA's rules and conventions. Examples of these might be searches for terms representing alopecia, dental disorders or refractive errors. On the other hand, there are several potential traps for the unwary that may usefully be presented here, with the objective of improving confidence that a search will produce the results required.

2. MedDRA Complexity Contributing to Difficulties in Searching

2.1 Multiple Locations of Relevant Terms Within a Single System Organ Class (SOC): Recognition of Appropriate Group Terms

The appropriate grouping of MedDRA PTs under HLTs and HLGTs is a valuable aid to data retrieval. However, the user may be misled into thinking that group terms are more inclusive than is actually the case. An example of how the complexity of MedDRA may lead to difficulties for the unprepared when performing database searches can be seen when constructing a sensitive search for cases of depression. We would correctly anticipate that all the relevant terms (apart from overdose) might be found in the Psychiatric disorders SOC for their primary location. However, we would be wrong in thinking that they are all included under the HLGT Depressed mood disorders and disturbances. There are possibly relevant PTs under a number of other HLGTs as well: HLGT Manic and bipolar mood disorders and disturbances: e.g. PT Bipolar I disorder; HLGT Suicidal and self-injurious behaviours NEC (not elsewhere classified), e.g. PTs Suicide attempt, Suicidal ideation; HLGT Mood disorders and disturbances NEC, e.g. PT Crying; HLGT Disturbances in

Table III. Example of the Medical Dictionary for Regulatory Activities (MedDRA) multiaxial structure

Hierarchical level	Primary location	Secondary location	Secondary location
System Organ Class	Gastrointestinal disorders	Cardiac disorders	Hepatobiliary disorders
High Level Group Term	Gastrointestinal signs and symptoms	Heart failures	Hepatic and hepatobiliary disorders
High Level Term	Abdominal findings abnormal	Heart failure signs and symptoms	Hepatobiliary signs and symptoms
Preferred Term	Ascites	Ascites	Ascites
Lowest Level Term	Ascites	Ascites	Ascites
	Ascites chylous	Ascites chylous	Ascites chylous
	Chylous ascites	Chylous ascites	Chylous ascites

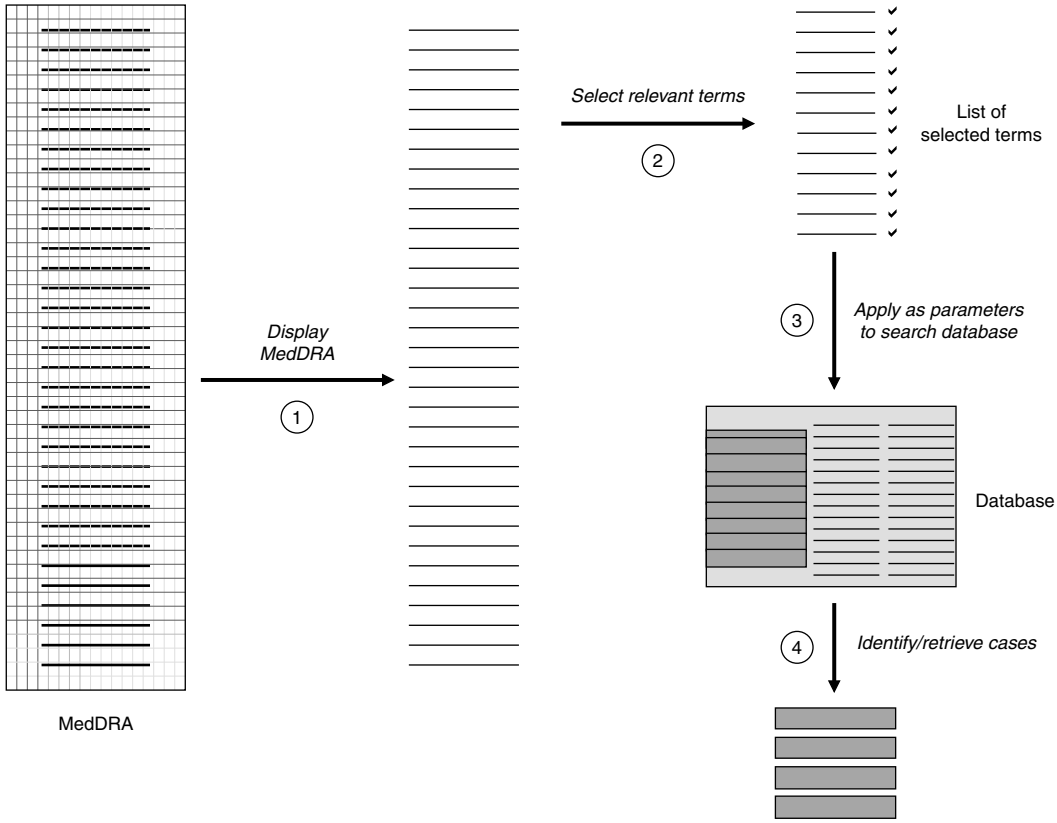

Fig. 2. Database search based on Medical Dictionary for Regulatory Activities (MedDRA) [Special Search Category].

thinking and perception, e.g. PT Morbid thoughts; HLGT Adjustment disorders (including subtypes), e.g. PT Adjustment disorder with depressed mood. Hence, it is necessary to look beyond the obvious grouped terms if all relevant cases are to be identified.

2.2 Multiple Locations of Relevant Terms Across Several SOCs: Effects on Primary SOC Searches

In keeping with the complexity of medicine, MedDRA may justifiably distribute terms relevant to a single medical condition across a number of different primary SOCs. As with the question of group terms, this might lead to a failure to identify all the requisite terms, if care is not taken. An example is provided by a sensitive search for cases relevant to cardiac failure. In this instance, if a search is carried out using only the primary location of terms, the search cannot be limited to a single SOC. The Cardiac disorders SOC contains the HLGT Heart failures, with four subordinate HLTs and some 27 PTs in their primary location. In addition, the General disorders and administration site conditions SOC ('General disorders SOC') includes the HLT Oedema NEC under the HLGT General system disorders NEC with several relevant PTs. The Respiratory, thoracic and mediastinal disorders SOC ('Respiratory SOC') contains

Table IV. Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes

Blood and lymphatic system disorders
Cardiac disorders
Congenital, familial and genetic disorders
Ear and labyrinth disorders
Endocrine disorders
Eye disorders
Gastrointestinal disorders
General disorders and administration site conditions
Hepatobiliary disorders
Immune system disorders
Infections and infestations
Injury, poisoning and procedural complications
Investigations
Metabolism and nutrition disorders
Musculoskeletal and connective tissue disorders
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)
Nervous system disorders
Pregnancy, puerperium and perinatal conditions
Psychiatric disorders
Renal and urinary disorders
Reproductive system and breast disorders
Respiratory, thoracic and mediastinal disorders
Skin and subcutaneous tissue disorders
Social circumstances
Surgical and medical procedures
Vascular disorders

terms for various symptoms of left ventricular failure, such as Dyspnoea exertional, Orthopnoea and Nocturnal dyspnoea under the HLGT Respiratory disorders NEC, HLT Breathing abnormalities. Signs such as lung crepitation are found under the HLT Lower respiratory tract signs and symptoms. Then it is necessary to consider the Investigations SOC, HLGT Cardiac and vascular investigations (excl. enzyme tests) with relevant terms under the HLTs Cardiac function diagnostic procedures and Cardiac imaging procedures; and perhaps the HLT Heart rate and pulse investigations, in order to find cases with the PT Gallop rhythm present.

2.3 Multiple Locations of Relevant Terms Across Several SOCs: Use of Multiaxial Searching (Search by Primary and Secondary SOC Locations)

In contrast to this uni-axial (primary SOC) approach, if the database supports the MedDRA data model, it is possible to perform multiaxial searching. As mentioned above, this will show PTs in their primary as well as secondary locations and this is a considerable aid to comprehensive retrieval of terms relevant to a particular medical condition. An example where MedDRA splits similar conditions into different locations is afforded by the case of the PT Eyelid oedema. This has as its primary SOC Eye disorders. However, the PT Periorbital oedema has its primary location in the Skin and subcutaneous tissue disorders SOC ('Skin SOC'). Both PTs have secondary linkages to the other SOC, as well as to the Immune system disorders SOC. Hence, a database capable of multiaxial searches would identify cases including either condition from any of these SOCs.

If we consider the search for heart failure outlined above, looking in the Cardiac disorders SOC, HLGT heart failures would find additionally PTs such as Ascites (secondary linkage from the Gastrointestinal disorders SOC), Hepatic congestion (from the Hepatobiliary disorders SOC), Oedema peripheral (from the General disorders SOC), and Pulmonary congestion (from the Respiratory SOC). However, dyspnoeas are present in a separate location under the Cardiac SOC, namely under the HLT Dyspnoeas, under the HLGT Cardiac disorder signs and symptoms. Hence, limiting the search to the contents of the HLGT Heart failures might again lead to a failure to identify cases. It would also be necessary to search the Investigations SOC, as terms in this SOC have no secondary linkages.

Thus, we may conclude that it is not sufficient that a multiaxial search is performed. While this may help to find terms that might otherwise have been missed, being located primarily in SOCs that

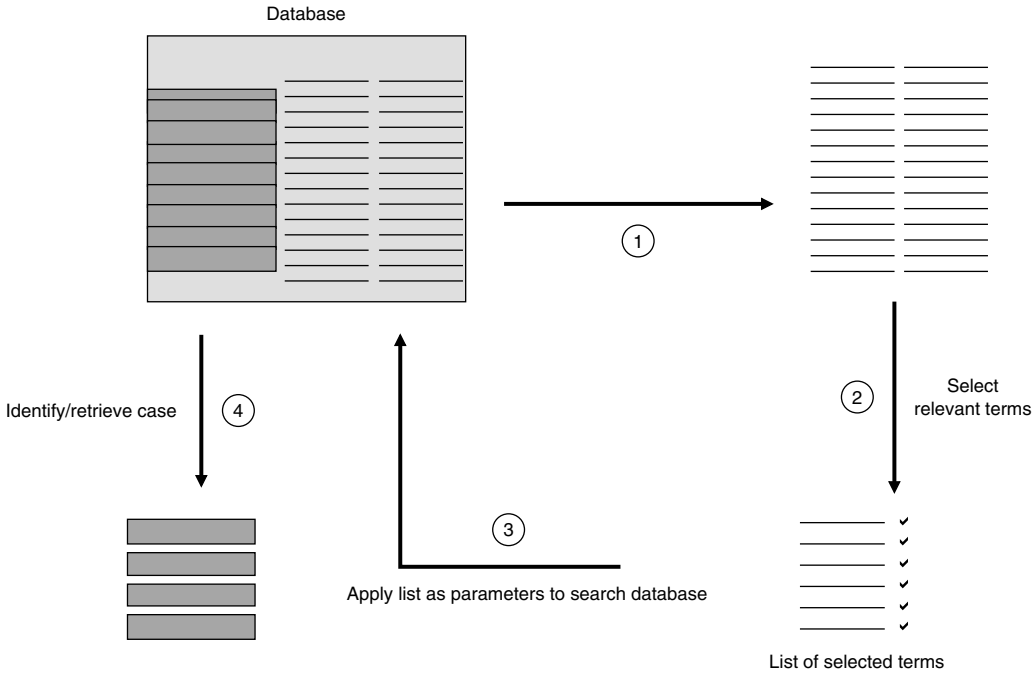

Fig. 3. Database search based on terms in the safety database.

had not been anticipated, it is still necessary to carefully consider the entire contents of the main SOCs under review in order to find all the relevant terms.

3. Incomplete Multiaxial Linkages

There are many instances where MedDRA's multiaxial linkages appear to be incomplete. Therefore, a multiaxial search based on a single SOC might identify some, but not all of the relevant terms with primary locations in other SOCs. To return to the example of a search for cardiac failure, a multiaxial search based on the Cardiac disorders SOC would find cases recorded with the PT Lung crepitation (primary location Respiratory SOC), but would not find cases recorded with the PTs Crackles lung, or Rales: these do not have secondary linkages from the Respiratory to the Cardiac disorders SOC. Similarly, while the PTs Oedema peripheral and Oedema NOS (not otherwise specified) have secondary linkages from the General disorders SOC to the Cardiac disorders SOC, the PT Pitting oedema has no such secondary linkages.

Hence, the problem that may arise from the assignment of similar conditions to very disparate locations in MedDRA is only partially resolved by the use of multiaxial searching. Another example is afforded by the PT Pneumonitis NOS, which appears under the HLGT Lower respiratory tract disorders (excl. obstruction and infection), in the Respiratory SOC. It has no secondary linkages. However, the PT Pneumonia NOS has a primary location in the Infections and infestations SOC, with secondary links to the Respiratory SOC. A multiaxial search based on the Respiratory SOC would find both terms. A multiaxial search based

on the Infections SOC would not identify Pneumonitis NOS.

An interesting example of diverse locations for similar conditions is seen for flushing. The LLT Menopausal hot flushes has a PT Menopausal symptoms. The primary SOC is Reproductive system and breast disorders ('Reproductive SOC'), with no secondary linkages. The LLT Hot flushes, however has as its PT Hot flushes NOS, primary SOC Vascular disorders, no secondary linkages. The LLT Vasodilatation, with a PT of the same name, is located in the Vascular SOC also, but this time with secondary links to the Skin SOC. The LLT Vasodilation, with its PT Vasodilation procedure, is located in the Surgical and medical procedures SOC, again with no secondary linkages. Finding all the cases associated with flushing would appear to be difficult.

While incomplete multiaxial linkages in MedDRA abound, some further examples may help illustrate the nature of the problem. As described in section 6, there is a splitting of locations between clinical conditions and investigations, and there are no secondary linkages for the Investigations SOC. Hence, the PT Glucose urine present is situated in the Investigations SOC, under the HLGT Renal and urinary tract investigations and urinalyses, HLT Urinalysis NEC. However, the PT Glycosuria is located in the Renal SOC, under the HLGT Urinary tract signs and symptoms, HLT Urinary abnormalities – with no secondary linkages. Hence, it might be missed in a multiaxial search looking at effects on glucose metabolism, which would focus on the Metabolism and nutrition disorders SOC. The same consideration applies to the PTs Bilirubinuria, Ketonuria and Pyuria, all of which are present in the same location in the Renal and urinary tract disorders SOC without secondary linkages. Myoglobinuria, on the other hand, has a primary location in the Renal SOC, with secondary linkages to the Musculoskeletal and the Cardiac disorders SOCs.

We may conclude that, although linkages of MedDRA terms to secondary locations are widespread and constitute a useful feature, they cannot be relied upon to comprehensively identify terms located in SOCs that are not otherwise explored in a search.

4. Non-Intuitive Locations

An example will serve to illustrate the problem of incomplete secondary linkages, coupled with another potential source for errors in searching: the non-intuitive location of some PTs in MedDRA. Constructing a search for angioedema might begin with the Skin and subcutaneous tissue disorders SOC, HLGT Angioedema and urticaria, HLT Angioedemas. All PTs with primary locations in this HLT would be expected to be relevant to the search. These comprise Angioneurotic oedema, Angioneurotic oedema aggravated, Circumoral oedema, Periorbital oedema, and Face oedema. By including PTs with secondary linkages to this HLT, we would find additionally cases with the following PTs: Eyelid oedema; Tongue oedema; Small bowel angioedema; Hereditary angioedema; Laryngeal oedema; Laryngotracheal oedema; and Oedema mouth.

However, some relevant PTs do not have secondary linkages to the Skin and subcutaneous disorders SOC, and might be missed unless the search was widened to include the respective SOCs: the PT Localised oedema has LLTs under it that include Oedema uvula, Oedema auricular and Oedema abdomen NOS. Its primary location is in the General disorders SOC, and while it has secondary linkages to Cardiac SOC and Metabolism and nutrition SOC, it has no linkages to the Skin SOC. Likewise, the PT Allergic oedema NOS (Primary location in the Immune SOC) has a secondary link to General disorders SOC, but not to the Skin SOC.

It might be even less likely that the following PTs would be found, unless their location had been previously ascertained by specifically searching MedDRA for terms containing the word 'swelling': Swelling NOS; Local swelling; Peripheral swelling. These have no secondary linkages and

are located in the Musculoskeletal and connective tissue disorders SOC, under the HLGT Musculoskeletal and connective tissue disorders NEC, and the HLT Soft tissue disorders NEC. Such a location would not intuitively include terms that are relevant to angioedema. The problem is relevant also to the previous search for heart failure. The LLT Ankle swelling has as its PT Joint swelling, HLT Joint related signs and symptoms, HLGT Joint disorders in the Musculoskeletal disorders SOC. There are no secondary linkages to the Cardiac SOC (nor to any other).

Thus, it may be seen that in some instances, the placement of terms in MedDRA, while not being incorrect, is not intuitive and does not help in using the terminology for purposes of searching databases. Probably the only sure remedy for this problem is the expansion of secondary linkages, and in some instances, changes in the assignment for primary SOC location.

5. Obscure Nomenclature

In some instances, terms have been selected as PTs that may not be widely recognised, in preference to LLTs that are universally known. Thus, Chromaturia has been allocated as the PT for the LLT Urine discolouration, Allergic granulomatous angiitis as the PT for the LLT Churg Strauss syndrome, Ochlophobia for Fear of crowded places, Azotaemia for Uraemia (although Uraemia odour is a PT), Dysphemia for stammer (although there is a PT Stammering aggravated), and Basedow's disease for Exophthalmic goitre (although there are separate PTs for Goitre and for Exophthalmos NOS. While all these may be technically and medically correct, they do not assist in the identification of cases by those who are not experts in the respective disciplines. Again, the only real remedy for this problem is to revert to the use of the most widely recognised name for a condition as the PT.

6. MedDRA Rules and Difficulties in Searching Databases

A number of rules and conventions in MedDRA have profound effects on strategies to be adopted for searching databases and could result in errors in data retrieval if the individual is not familiar with them. Some of the rules relevant to the location of terms are summarised in table V. The most important of these rules involves the lack of multiaxial linkages between the Investigations SOC and any other SOC. This requires that even multiaxial searches should usually include an exploration of the Investigations SOC in addition to other relevant SOCs if cases are not to be missed.

The convention that is applied is that laboratory and investigation findings are located in the Investigations SOC, whereas the corresponding clinical conditions are to be found in the SOC describing the respective anatomical or pathophysiological entity. For example, the PT Blood sodium decreased is present in the Investigations SOC, while the PT Hyponatraemia is found in the Metabolism and nutrition disorders SOC. Similarly, the PT for Electrocardiogram PR interval prolonged is in the Investigations SOC, while Atrioventricular block first degree is in the Cardiac disorders SOC.

However, sometimes the distinctions become blurred and PTs appear in diverse locations de-

Table V. Special search categories in Medical Dictionary for Regulatory Activities (MedDRA) version 5.1

Anaphylaxis
Arrest (cardiac)
Blood dyscrasias/bone marrow depression
Cardiac ischaemia
Haemorrhage
Hypersensitivity reactions
Oedema
Pain
Pre-malignant lesions
Secondary immunocompromised state
Thrombosis
Upper GI bleeding/perforation
Vasculitis

GI = gastrointestinal.

pending on seemingly trivial differences in assignment of terms at the time of coding the original report. For example, Liver function tests NOS abnormal is a PT in the Investigations SOC. Its 19 subordinate LLTs include: Abnormal liver function tests; Deranged liver function tests; Elevated liver enzyme levels; Liver enzyme abnormal; and Hepatic enzymes increased. On the other hand, cases coded with LLTs such as Impaired liver function, Hepatic function abnormal, or Hepatic dysfunction NOS would be automatically allocated to the Hepatobiliary disorders SOC, with the PT Hepatic function abnormal NOS. Likewise, the LLTs Renal function abnormal and Kidney dysfunction are assigned the PT Renal impairment NOS under the Renal and urinary disorders SOC, whereas the LLTs Renal function tests NOS abnormal and Function tests multiple kidney abnormal are located under the PT Renal function tests NOS abnormal in the Investigations SOC.

Other SOCs that do not obviously have relevance to drug safety and that have no secondary linkages may also contain terms that could in fact be pertinent to safety. For example, the Surgical and medical procedures SOC contains PTs such as Cardiac pacemaker insertion (could be relevant if looking for cases with arrhythmia or heart block), Cataract extraction (maybe important if looking at ophthalmological adverse events), and Antidepressant therapy (relevant to a search for depression). Searching this SOC may be advisable for comprehensive review of a safety issue, for example.

Other instances are present in the Social circumstances SOC, this again having no secondary linkages. Thus, the PTs Aborted pregnancy, Hearing disability, Paralytic disability, or Walking disability might have been used to code adverse events. There is a need for care in the use of terms when coding adverse event data in order to avoid these problems. While these points are covered in the relevant guidelines,[3] databases could still contain adverse events coded inappropriately in the past using terms from the Social circumstances SOC.

Another MedDRA rule that may lead to incomplete data retrieval is the requirement that there is only one hierarchical route for a PT within a SOC. Thus, a PT may only be present under one HLT and one HLGT within any single SOC. An example where this might be problematic is for increased blood alkaline phosphatase, with the PT Blood alkaline phosphatase NOS increased. Increases in alkaline phosphatase could result from a variety of pathologies, including intestinal, hepatic and bone disease. According to the MedDRA rule, it cannot be present under more than one of the respective group terms in the Investigations SOC. Hence, the PT is located under none of them. Instead, it is found under the HLT Tissue enzyme analyses NEC, below the HLGT Enzyme investigations NEC. It is not present alongside abnormal liver function tests under the HLT Liver function analyses, HLGT Hepatobiliary investigations. While the approach taken may be rational, it does not help in finding relevant cases.

7. Inadequacies of Special Search Categories

SSCs are collections of PTs that have been assembled from across various SOCs by searching the whole of MedDRA. The SSCs that are included in version 5.1 of MedDRA are shown in table IV. The intention of having SSCs is that they provide reproducible searches that can be applied to any safety database. However, the utility of the existing SSCs is limited not only by their small number, but also by lack of clarity about the criteria that were applied in their construction. Thus, for example, the Haemorrhage SSC appears to be quite extensive, with more than 300 PTs and it includes many terms for bleeding, and for conditions leading to a tendency to bleed. It includes terms for unusual conditions, such as Rift Valley fever and Omsk haemorrhagic fever. Inexplicably however, it does not include Thrombocytopenia, Platelet

count decreased, or Coagulation time NOS prolonged, although Bleeding time prolonged and Bleeding time abnormal are present. It also contains PTs such as Anastomotic ulcer perforation, Duodenal ulcer perforation and Thrombosed varicose vein; the SSC Hypersensitivity reactions is more restricted, comprising just 32 PTs. It does not include many terms that might be expected to be identified in a search for hypersensitivity reactions, such as various terms for allergies like the PTs Allergic bronchitis, Allergy test positive, Allergy to vaccine, Alveolitis allergic, or certain terms suggesting angioedema, such as Laryngeal oedema or any of the PTs for urticaria.

An example of the unreliability of existing MedDRA SSCs is seen with the Upper GI bleeding/perforation SSC, which omits such terms as Mallory-Weiss syndrome, Oesophageal varices haemorrhage, Gastric haemorrhage, Gastric varices haemorrhage and Gastritis atrophic haemorrhagic, while including the PTs Ileal perforation, Ileal ulcer, Small intestinal ulcer NOS and Small intestinal perforation NOS, which are perhaps not strictly relevant to the upper gastrointestinal tract. The inclusion of these latter terms highlights the difficulty of agreeing the content of a SSC in the absence of a clear definition of its scope and purpose.

At the time of writing, the MedDRA MSSO has requested subscribers to MedDRA to review the content of existing SSCs, to suggest any necessary changes, and to propose new categories. It seems likely, therefore that there will be improvements and expansions to the SSCs in the future.

8. Errors in Data Presentation

It is important to adjust for the effects of multiaxiality if data are being presented using primary and secondary term locations. If a PT associated with a single case appears under more than one SOC, it may be counted more than once, giving an inflated result. Hence, the output from the database should either be limited to the primary SOC location of terms, or a filter must be applied to ensure that each case is counted only once.

9. Discussion

MedDRA was intended as a replacement for existing terminologies that exhibited certain failings and to bring benefits of standardisation that would support electronic exchange of safety data. It is perhaps inevitable with any new product that is as complex as MedDRA that there are initial errors that require amendments and improvement. It is likely over the coming year that there will be increasing use of MedDRA by regulatory authorities, pharmaceutical companies and others and it remains to be seen whether the potential pitfalls described in this paper are a real problem.

Under some circumstances, failure to identify one or two cases relevant to a particular adverse reaction to a drug might not be important. Thus, whether there are 100 or 110 cases of liver failure in association with the use of a drug may not be of critical importance to its safety profile. In many of the examples presented in this paper, there is the likelihood that the terms involved would only be seldom used in any particular database. In addition, one might envisage that in some situations, the cases that are already identified may be sufficient to establish a signal, even if every relevant case is not found. However, it could also happen that these 'missing' reports would tip a series of cases over a threshold when evaluating the signal. Perhaps the biggest problem would result from a lack of recognition that a search had not produced the result that was intended.

Practices for recording case information in safety databases differ within the pharmacovigilance community. This diversity has not been remedied by the existing guidelines on term selection,[3] which indicate that all of the following approaches are acceptable. Thus, some organisations (perhaps the majority) enter terms for each diagnosis, as well as all symptoms, signs and investigation findings. Others record only the prin-

cipal diagnosis, if stated by the reporter of the adverse event, as well as any associated manifestations that are inconsistent with that diagnosis, holding the remaining information as a narrative rather than as coded terms. Some organisations record the diagnoses, where given, as the adverse event term, and enter the signs, symptoms and investigations in a separate field as 'co-manifestations'. The impact of missing cases when searching a safety database is affected by the approach used in data entry. If a single term (the diagnosis) is the only record representing each case, missing this term leads to loss of the entire case to the search result. On the other hand, if each case is represented by the several terms as reported (diagnosis, symptoms, etc.), and one of the terms is not identified, there remains the possibility of retrieving the case with the remaining terms.

The impact of differences in methods of database implementation needs to be assessed and recognition should be given to the diverse ways in which MedDRA has been implemented by different subscribers, so that common approaches to searching can still be achieved. In order to understand the safety data that have been generated by a search using MedDRA, it is necessary to know what method of searching has been employed and what degree of sensitivity has been applied. Perhaps 'good retrieval practices' would dictate that searches should be performed in more than one way (for example, by using both an SSC and direct selection of terms from a database), and that results of searches should be accompanied by a record of the method of searching, the sensitivity of the search, the version of MedDRA used, and of the way that MedDRA has been implemented in the database. There is a need for consensus guidelines on the optimal methods for data retrieval that would incorporate some or all of these considerations.

Recognising some of the uncertainties attaching to using MedDRA for data retrieval, the Council for International Organisations of Medical Science has set up a working group to establish new standard searches (in effect, SSCs) for MedDRA.[8] It is to be hoped that these searches will be created for a wide variety of the more important adverse reactions, will be accompanied by guidance for their use, and that these will gain acceptance by regulators and industry alike.

None of the issues that have been mentioned in this paper are irremediable in respect of MedDRA itself. A thorough review of the terminology from the perspective of data retrieval would doubtless identify other examples that could be problematic. Missing linkages can be rectified, names of group terms can be made more transparent, idiosyncratic location of terms can be changed. There are two possible approaches to these deficiencies that might be applied: correction of errors identified *ad hoc* by users, or systematic review of the terminology by the MSSO or other body. Certainly, it is appropriate that users provide feedback to the MSSO on errors, inconsistencies and omissions that are relevant to data retrieval. In this respect, feedback that is actively sought by the MSSO, for example on existing SSCs, may be a useful stimulus for improvement. However, subscribers may be reluctant to do this if the feedback constitutes a 'change request'. These change requests are part of the paid services in MedDRA and are commonly used by subscribers to seek the necessary addition of new terms to MedDRA; highlighting difficulties with data retrieval may limit the other changes available to the user. Alternatively (or additionally), a review group could be established to specifically examine MedDRA from the perspective of data retrieval and data base searches.

The effective use of MedDRA requires that users understand a considerable amount of medicine as well as the terminology structure and conventions. Inappropriate selection of terms for coding may lead to severe difficulties in data retrieval and the generation of spurious results. Lack of awareness of the MedDRA structure and limitations in knowledge of medical concepts are similarly likely to result in loss of (or failure to find) important data in the course of database searching. Hence, suita-

ble training is likely to be critical to the effective use of MedDRA in pharmacovigilance and this needs to cover more than just the mechanics of coding and data entry.

10. Conclusions

As presently constructed, MedDRA has several advantages over other terminologies used in the drug safety environment. However, there are some difficulties that may arise in the course of searching databases and examples of these have been described above. They may be addressed at the level of the individual user, by suitable training and experience, as well as by the user reporting to the MSSO/JMO any deficiencies that have been detected so that suitable corrections may be made. Other remedies may include the production of regulatory and other guidance on the implementation and use of MedDRA so that variability may be minimised. Further systematic review of MedDRA from the perspective of deficiencies in linkages or of term placement is needed. The generation of standardised, well-defined, validated searches that may be used 'off the shelf' will also help optimise the use of the terminology, particularly where the same search may need to be performed repeatedly on multiple data sets. Until these enhancements are widely available, MedDRA users would be well-advised to take great care when searching a safety database to ensure that cases are not inadvertently missed.

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