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Proposed Terminology Changes to Facilitate the Analysis of MedDRA[®]-Coded Data

This article is the continuation of a discussion about the utility of the Medical Dictionary for Regulatory Activities (MedDRA) in the analysis of adverse event data. This topic was initiated by the Biometry Subgroup of the German Association of Research-Based Pharmaceutical Companies. They pointed out issues within the MedDRA terminology that physicians and scientists are facing in safety and statistical analysis. These issues include multiaxiality in standard adverse event tabulation; lack of connection between laboratory results and disease/diagnosis, between patient social back-

ground and disease classification; and more. Similar issues have been brought to the attention of the MedDRA Maintenance and Support Services Organization by MedDRA subscribers. In response to subscribers' requests, the MedDRA Maintenance and Support Services Organization conducted a feasibility study on potential modifications to MedDRA's hierarchy terms to better facilitate analytical requirements while considering the potential impacts of these changes on users of MedDRA. Changes to the MedDRA terminology were proposed and discussed.

INTRODUCTION

In International Conference on Harmonisation (ICH) regions, Medical Dictionary for Regulatory Activities (MedDRA[®]) is the standard terminology for medical information sharing regarding pharmaceuticals and other regulated medical products. Within the pharmaceutical industry, MedDRA is used to index, report, analyze, and present patient data during the entire cycle of drug development (excluding preclinical studies), which includes both clinical trials and postmarketing surveillance.

The development of MedDRA is driven by subscribers' change requests, which allows the terminology to keep pace with advances in medicine as well as current drug development needs. The role of the MedDRA Maintenance and Support Services Organization (MSSO) is to review and implement changes to MedDRA terminology. In addition, the MSSO conducts ad hoc reviews based on information received from the user community to improve MedDRA. For example, in response to the need for a standardized analytical approach to identify cases in safety analysis, the MSSO and the Council for International Organizations of Medical Sciences have joined together in an expert working group to

develop Standardized MedDRA Queries (SMQs). SMQs are groupings of terms from one or more MedDRA System Organ Classes (SOCs) that relate to a defined medical condition or area of interest. They are intended to aid in case identification.

Since MedDRA's initial release in March 1999, many companies, organizations, and regulators have converted their databases to MedDRA from their previous terminologies. Coding with MedDRA is guided by the ICH-endorsed "MedDRA Term Selection: Points to Consider" document (1). In the past few years, the focus of MedDRA users has transferred from coding to data retrieval and analysis for the purpose of risk assessment, product labeling, and safety signal detection. More and more attention is paid to MedDRA hierarchical groupings at the High Level Term (HLT), High Level Group Term (HLGT), and SOC levels in statistical analysis. Subscriber feedback indicated that some areas in the MedDRA hierarchy may need to be modified to improve MedDRA's capability to support reporting and statistical analysis.

A feasibility study conducted by the MSSO on the possibility of modifications to MedDRA hierarchy terms (i.e., HLTs and HLGTs) resulted in the following proposed changes:

- Limiting the use of Not Elsewhere Classified (NEC) in term names
- Applying secondary links from terms in SOC *Investigations* to SOC terms that classify disorders
- Applying secondary links from terms in SOC *Social circumstances* to SOC terms that classify disorders
- Breaking some multiaxiality at HLT and HLGT levels
- Allowing congenital terms and their acquired counterparts to be grouped under the same HLT
- Reassigning the primary SOC of postprocedural terms from SOC *Injury, poisoning and procedural complications* to the SOC of the disease manifestation site
- Grouping hyper- and hypometabolic disorders consistently at the HLT level

HIERARCHY RULES IN MedDRA

To better understand the proposed changes, current MedDRA hierarchy rules are reviewed. These rules are defined for the development and maintenance of the MedDRA terminology (2).

MedDRA HIERARCHY LEVEL DEFINITION

A Preferred Term (PT) is defined as the preferred descriptor for a single medical concept that is internationally recognized. A Lowest Level Term (LLT) is linked to a PT and is a synonym or subelement of its PT. HLTs, HLGs, and SOC terms are grouping terms used for analysis.

The ICH “MedDRA Term Selection: Points to Consider” document states that the reporter’s words should be linked to the closest LLT for specific events, diagnoses, signs, symptoms, syndromes, investigative tests, and surgical and medical procedures. Within MedDRA hierarchy, PTs are grouped together at the HLT level based on their common etiology, anatomical location, pathology, or pathophysiology. Similarly, HLTs are further grouped to create even broader groupings at the HLGT level. HLGs are assembled under SOC terms.

The different scope of groupings within the MedDRA hierarchy structure allows users to perform frequency analysis or case retrieval at any chosen level (e.g., PT, HLT, HLGT, or SOC). Using headache as an example, a highly specific frequency analysis or case retrieval can be done at the PT level, such as PT *Migraine with aura*; a

broader scope of the same type of analysis can be done at the HLT level, such as HLT *Migraine headaches*, which has nine subordinate PTs that represent migraine headaches; a very general search can be obtained at the HLGT level, such as HLGT *Headaches*, which has two subordinate HLTs (HLT *Headaches NEC* and HLT *Migraine headaches*) and 22 headache PTs.

SOC CLASSIFICATION

There are 26 SOC terms in MedDRA. Each SOC is one of the following three types:

1. Etiology-based SOC terms, such as SOC *Congenital, familial and genetic disorders*; SOC *Infections and infestations*; and SOC *Neoplasms benign, malignant, and unspecified (incl cysts and polyps)*
2. Disease manifestation site-based SOC terms, such as SOC *Gastrointestinal disorders*
3. Supporting SOC terms, such as SOC *Investigations*, SOC *Social circumstances*, and SOC *Surgical and medical procedures*

FIVE FIXED LEVELS OF HIERARCHY

Each path in MedDRA must contain a term for every level (see path A in Figure 1). From the bottom of the hierarchy, they are LLT → PT → HLT → HLGT → SOC. Incomplete links (see paths B and C in Figure 1), which were allowed in other adverse event coding terminologies, are not permitted in MedDRA.

EACH PT IS LINKED TO AN SOC BY ONE AND ONLY ONE PATH

A PT in MedDRA is linked to an SOC through a single PT → HLT → HLGT → SOC path (see path A in Figure 1), but the PT may be linked to more than one SOC as appropriate. This rule prevents any PT from representation in more than one HLT or HLGT within an SOC (see paths D and E in Figure 1).

EACH PT HAS A PRIMARY SOC

When a PT is linked to more than one SOC, one of those SOC linkages is designated as primary. All other nonprimary SOC terms are defined as secondary SOC terms. For example, MedDRA PT *Rubinstein-Taybi syndrome* is linked to five different SOC terms. The primary SOC is SOC *Congenital, famil-*

ial and genetic disorders. The other four SOCs are secondary SOCs consisting of SOC Cardiac disorders, SOC Musculoskeletal and connective tissue disorders, SOC Nervous system disorders, and SOC Psychiatric disorders.

The primary SOC is predefined within the MedDRA structure. For any given PT, the priority list for primary SOC allocation is as follows:

1. SOC *Congenital familial and genetic disorders*
2. SOC *Neoplasms benign, malignant, and unspecified (incl cysts and polyps)*
3. SOC *Infections and infestations*
4. SOC of the disease manifestation site

This priority ranking means that if a medical concept is a congenital disorder, its primary SOC will *always* be SOC *Congenital, familial and genetic disorders* and its secondary SOC will be its site of manifestation (e.g., PT *Heart disease congenital* has a primary link to SOC *Congenital, familial and genetic disorders* and a secondary link to SOC *Cardiac disorders*). For a concept that is a congenital infection (e.g., PT *Congenital rubella infection*), the primary SOC is still SOC *Congenital, familial and genetic disorders* with secondary SOC *Infections and infestations* and SOC *Pregnancy, puerperium, and perinatal conditions* for the example used. For a noncongenital infection, SOC *Infections and infestations* is the primary SOC, and the site of manifestation SOC is the secondary.

There are a few exceptions to the rules for primary allocations. For example, cyst and polyp terms in MedDRA are primarily linked to the SOC of site manifestation, although they are also connected to SOC *Neoplasms benign, malignant, and unspecified (incl cysts and polyps)* at the same time. Also, the majority (but not all) of injury, poisoning and procedural complications terms are represented in SOC *Injury, poisoning and procedural complications* as the primary SOC. The primary SOC allocation rules enforce the standardization in adverse event reporting among all MedDRA users. Because of the one-to-one relationship between a PT and its primary SOC, the cumulative data output only lists primary paths in MedDRA to avoid double counting.

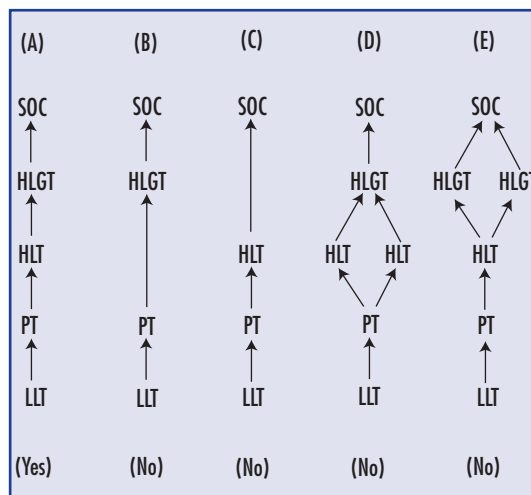


FIGURE 1

MedDRA hierarchy path.

The secondary SOC links provide alternative ways of grouping the same PT concept. For example, for the group of cor pulmonale terms (PT *Cor pulmonale*, PT *Cor pulmonale acute*, and PT *Cor pulmonale chronic*), their primary SOC is SOC *Cardiac disorders*, under which they were grouped from the cardiology standpoint. One of their secondary SOCs is SOC *Vascular disorders*, under which the terms were grouped from the point of view of the circulatory system. As a result, cor pulmonale terms can be retrieved by a query of either HLT *Right ventricular failures* (cardiac) or HLT *Pulmonary hypertensions* (vascular), depending on the interest of the analyst.

THE ISOLATED SOCs

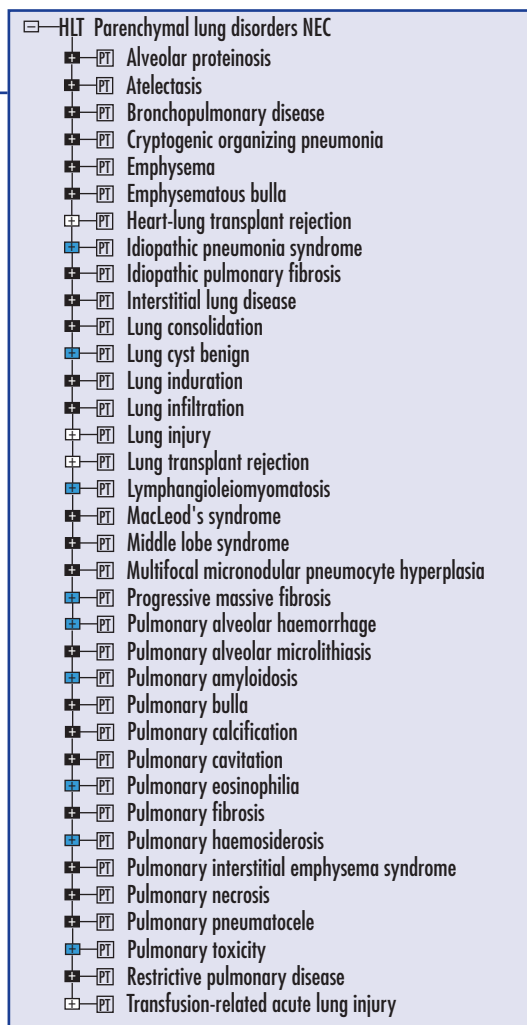
PTs in 3 of the 26 SOCs in MedDRA do not have linkages to any other SOCs. The three SOCs are SOC *Investigations*, SOC *Social circumstances*, and SOC *Surgical and medical procedures*. Under this rule, terms for investigation results (eg, laboratory test results), which are grouped under SOC *Investigations*, are not associated with their corresponding diseases. This rule was also discussed by Dr. Jürgen Kübler and coworkers from the German Association of Research-Based Pharmaceutical Companies (3).

PROPOSED TERMINOLOGY CHANGES

The MSSO has received comments and suggestions from MedDRA subscribers regarding issues or problems with the existing MedDRA hierarchy structure in statistical or safety analysis. Through many communication channels, the

FIGURE 2

Subordinate PTs under HLT Parenchymal lung disorders NEC. Black box: primary link without any additional secondary link. Blue box: primary link with additional secondary link(s). White box: secondary link.



MSSO has discussed these comments with MedDRA users and verified and validated all comments and suggestions received.

Based on subscriber inputs, the MSSO is reviewing possible changes to MedDRA's hierarchy terms (HLTs and HLGTs) to better support statistical analysis and reporting. The existing MedDRA rules and conventions, such as primary SOC allocation, are under review in this context. The potential impact of these changes on existing MedDRA-coded data is also under consideration. Next, we discuss the areas under review.

LIMITING THE USE OF NEC IN TERM NAMES

The abbreviation NEC has been widely used at the HLT and HLGT levels to serve as a catch-all grouping (essentially, "miscellaneous") for terms

that do not belong to other specific groupings. For example, HLGT *Heart failures* has four subordinate HLTs. Three of these are for signs and symptoms of heart failure, left ventricular failures, and right ventricular failures. The fourth HLT (HLT *Heart failures NEC*) is a general grouping for heart failure terms that do not belong to any of the three specific groupings. Similarly, HLGT *Headaches* is divided into a specific HLT (HLT *Migraine headaches*) and a nonspecific HLT (HLT *Headaches NEC*).

Terms in the NEC grouping are mixed concepts in general. A few NEC HLTs contain a large number of PTs, which adds complexity to data analysis. Although in some cases terms within an NEC grouping are relatively homogeneous (eg, HLT *Headaches NEC*), the abbreviation NEC does not explicitly express the type of concepts that are grouped under the HLT.

Two actions are proposed for this issue:

1. Identify and subdivide specific new HLTs from NEC HLTs having a large number of subordinate PTs. For example, HLT *Parenchymal lung disorders NEC* has 36 subordinate PTs (Figure 2). From the related PTs, a new HLT grouping for interstitial lung diseases can be created, containing the following seven PTs: PT *Alveolar proteinosis*, PT *Idiopathic pulmonary fibrosis*, PT *Interstitial lung disease*, PT *Progressive massive fibrosis*, PT *Pulmonary amyloidosis*, PT *Pulmonary fibrosis*, and PT *Pulmonary hemosiderosis*.
2. Rename the abbreviation NEC to a more intuitive and self-explanatory wording if subordinate PTs are relatively homogeneous in concept. For example, HLT *Headaches NEC* could be renamed HLT *Nonmigraine headaches*.

The MSSO will utilize the list of most frequently used SOCs (Table 1) to prioritize the efforts. Subscriber feedback received to date supports these proposals.

APPLYING SECONDARY LINKS FROM SOC INVESTIGATIONS TO DISORDER-TYPE SOCs

The MedDRA hierarchy rule states that terms for investigations (eg, laboratory tests) and investigation results in SOC *Investigations* do not have a secondary link to any other SOCs in the termi-

TABLE 1

Frequency of Reported SOCs		
SOC	Count	Percentage
General disorders and administration site conditions	110,379	13.6
Investigations	88,274	10.9
Nervous system disorders	84,362	10.4
Gastrointestinal disorders	69,189	8.5
Psychiatric disorders	54,811	6.8
Respiratory, thoracic, and mediastinal disorders	42,966	5.3
Injury, poisoning, and procedural complications	40,558	5.0
Infections and infestations	37,934	4.7
Cardiac disorders	37,594	4.6
Musculoskeletal and connective tissue disorders	36,033	4.4
Skin and subcutaneous tissue disorders	35,552	4.4
Vascular disorders	21,552	2.7
Metabolism and nutrition disorders	21,254	2.6
Blood and lymphatic system disorders	18,593	2.3
Renal and urinary disorders	18,226	2.2
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	16,146	2.0
Eye disorders	15,096	1.9
Hepatobiliary disorders	13,600	1.7
Reproductive system and breast disorders	12,553	1.5
Surgical and medical procedures	8,368	1.0
Pregnancy, puerperium, and perinatal conditions	6,736	0.8
Immune system disorders	6,430	0.8
Social circumstances	5,480	0.7
Ear and labyrinth disorders	4,026	0.5
Congenital, familial and genetic disorders	2,772	0.3
Endocrine disorders	1,953	0.2

Note: Based on published Food and Drug Administration AERS data from the first three quarters of 2004.

nology. The potential multi-axiality in SOC *Investigations* has been a long-debated topic among MedDRA users and within the MSSO. The benefit of multi-axiality is that the user would be able to retrieve disease, signs and symptoms, and associated investigation results under one SOC. There are concerns about possible uncontrolled secondary link growth for investigation results because one investigation result could be an indicator for many diseases.

To address these concerns, the MSSO proposes to

- Only link those test results that represent the diseases or diagnoses to corresponding disorder SOCs
- Make all links added as secondary

For example, PT *Blood pressure decreased* will be secondarily linked to HLT *Vascular hypotensive disorders*, for which PT *Hypotension* is grouped, but not to many other disorders that

also have hypotension (eg, shock). PT *Blood calcium decreased* will be grouped together with PT *Hypocalcemia* under HLT *Calcium decreased disorders* in SOC *Metabolism and nutrition disorders* but not to endocrine (hypoparathyroidism), renal (renal failure complication, renal tubular disease), or pancreatic disorders (acute pancreatitis), all of which may feature decreased blood calcium level. PT *HIV antibody positive* will be secondarily linked to HLT *Retroviral infections* and HLT *Acquired immunodeficiency syndromes* where PT *HIV infection* is grouped, but PT *HIV antibody negative* and PT *HIV antibody* will not be linked.

The feedback on this proposal from the MedDRA user community has been mixed. Some subscribers expressed support, and others expressed concern because they have set up their own systems within their companies to work around this well-known feature of SOC *Investigations*.

APPLYING SECONDARY LINKS FROM SOC SOCIAL CIRCUMSTANCES TO DISORDER-TYPE SOCs

SOC *Social circumstances* is one of three SOCs in MedDRA that is not multiaxial. Some concepts in SOC *Social circumstances* are closely related to concepts in other SOCs. The slight difference in wording (*addicted* vs. *addiction*) of the reported verbatim could be coded to LLTs that lead to SOCs (SOC *Social circumstances* vs. SOC *Psychiatric disorders*) that do not share multiaxial links. This situation generates some degree of confusion and inconsistency in coding and data analysis.

The rationale behind the current rule relates to an effort to differentiate social events in SOC *Social circumstances* from disease conditions in disorder SOCs, such as SOC *Psychiatric disorders*. Therefore, LLT *Addicted to drugs* is associated with PT *Drug abuser* to represent a person who has addiction as a “lifestyle issue” in SOC *Social circumstances*, whereas the slightly differently worded LLT *Addiction to drugs* (a psychiatric condition) is grouped un-

der PT *Drug dependence* in SOC *Psychiatric disorders*.

This somewhat “academic” distinction poses difficulties in practical use. The MSSO’s proposal is to allow secondary links to terms in SOC *Social circumstances* so that terms such as PT *Drug abuser* could be secondarily grouped under HLT *Substance-related disorders* together with PT *Drug dependence*.

Subscriber feedback on this one is the same as for the issue of applying secondary links from SOC *Investigations* to disorder SOCs. One side is supportive, and the other side is concerned about the proposed change.

BREAKING SOME MULTIAXIALITY AT THE HLT AND HLGTL LEVELS

Most concepts in MedDRA that express multiaxiality do so based on the PT level. Rarely, the multiaxiality occurs at HLT and HLGTL levels. For example, HLT *Mental retardations* is multiaxial to both SOC *Nervous system disorders* and SOC *Psychiatric disorders*; HLGTL *Musculoskeletal and connective tissue disorders congenital* is multiaxial to both SOC *Congenital, familial and genetic disorders* and SOC *Musculoskeletal and connective tissue disorders*.

Because of the different primary SOC allocation between neoplasm terms and cyst/polyp terms in MedDRA, the multiaxiality of a few HLTs and HLGTLs creates confusion in cumulative data output in which only primary links are displayed to avoid double counting. Table 2 displays an example. The HLT *Ocular neoplasms benign* is linked to both SOC *Eye disorders* and SOC *Neoplasms benign, malignant, and unspecified (incl cysts and polyps)*. The subordinate PTs are a mixture of benign neoplasm and cyst/polyp terms. As mentioned in the MedDRA hierarchy rule discussion, the primary SOC for neoplasm terms is SOC *Neoplasms benign, malignant, and unspecified (incl cysts and polyps)*, as listed in the right-hand column (see Table 2), but cyst/polyp terms have the manifestation site as their primary SOC, which is SOC *Eye disorders*, as listed in the middle column. Thus, in cumulative data output, the same HLT is linked to two SOCs with dif-

TABLE 2

Multiaxial HLT Issue in Cumulative Data Output		
Level	MedDRA Term	MedDRA Term
SOC	Eye disorders	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
HLGT	Ocular neoplasms	
HLT	Ocular neoplasms benign	
PT	Conjunctival cyst	Benign neoplasm of choroids
	Corneal cyst	Benign neoplasm of conjunctiva
		Benign neoplasm of cornea
		Benign neoplasm of eye
		Benign neoplasm of eyelid
		Benign neoplasm of lacrimal duct
		Benign neoplasm of lacrimal gland
		Benign neoplasm of optic nerve
		Benign neoplasm of orbit
		Benign neoplasm of retina
		Blepharal papilloma
		Retinal melanocytoma

ferent sets of subordinate PTs, which causes confusion and misinterpretation in statistical analysis.

There are two options to address this issue:

1. Change the primary SOC allocation rule for cyst/polyp terms from site of manifestation to SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*.
2. Break the multiaxiality of HLTs involved.

Although subscribers supported correcting the problem caused by multiaxial HLTs in primary linkage display, the feedback showed that there are objections from the users regarding option 1. Option 2 seems to be the favorable one.

ALLOWING CONGENITAL TERMS AND THEIR ACQUIRED COUNTERPARTS TO BE GROUPED UNDER THE SAME HLT

Despite the fact that all congenital terms in MedDRA are classified under SOC *Congenital, familial and genetic disorders* as their primary link-

age, they are separated hierarchically from their counterpart acquired conditions in most disease manifestation SOCs. For example, SOC *Cardiac disorders* is the manifestation site for PT *Congenital aortic valve stenosis* and PT *Aortic valve stenosis*. But, the two PTs, which represent the same pathological condition but with different etiologies, are not grouped under the same HLT in SOC *Cardiac disorders*. This increases the level of difficulty and complexity in analysis when both congenital and acquired conditions are included.

To improve MedDRA's utility in analysis, the MSSO suggests modifying the secondary groupings of congenital terms to allow them to be grouped under the same HLT with their acquired counterparts. As for the above example, it means moving the secondary link of PT *Congenital aortic valve stenosis* from HLT *Congenital cardiac valve disorders* to HLT *Aortic valvular disorders*, where PT *Aortic valve stenosis* is located. Subscriber feedback was positive on this issue.

REASSIGNING PRIMARY SOC OF POSTPROCEDURAL TERMS FROM SOC INJURY, POISONING AND PROCEDURAL COMPLICATIONS TO THE SOC OF THE DISEASE MANIFESTATION SITE

The current primary allocation for postprocedural PTs is SOC *Injury, poisoning and procedural complications*. There is inconsistency at the PT level in cumulative data output when only the primary links are considered. For example, PT *Postprocedural diarrhea* is primarily linked to SOC *Injury, poisoning and procedural complications*, and PT *Diarrhea* is primarily linked to SOC *Gastrointestinal disorders*.

In the initial ICH M1 MedDRA Expert Working Group, which developed MedDRA terminology, it was decided that postprocedural PTs would not be primarily linked to the site of manifestation because they are generally not causally linked to a drug. The intention was to separate postprocedural PTs from possible drug adverse event terms located in disorder SOCs, such as SOC *Gastrointestinal disorders*. But, the feedback from current MedDRA users indicates that the preferred approach is to make the postprocedural term primary SOC be the same as the non-procedural-related condition. The proposal would be to change the primary allocation for postprocedural terms from SOC *Injury, poisoning and procedural complications* to the SOC of the manifestation site.

GROUPING HYPER- AND HYPOMETABOLIC DISORDERS CONSISTENTLY AT THE HLT LEVEL

Inconsistent scope of HLT grouping poses a challenge in statistical data analysis. For example, in SOC *Metabolism and nutrition disorders*, calcium disorders are represented by three HLTs: HLT *Calcium increased disorders*, HLT *Calcium decreased disorders*, and HLT *Calcium metabolism disorders NEC*. On the other hand, magnesium, phosphorus, chloride, potassium, and sodium disorders are all grouped under one HLT per element, such as HLT *Magnesium metabolism disorders*. Maintaining a consistent scope for HLT groupings will make MedDRA more analysis friendly. The MSSO suggests collapsing three

calcium HLTs into one to avoid the alternative, which is to create 10 more new HLTs, many of which will have only one or two subordinate PTs. Subscribers recommended that a similar philosophy be applied to HLTs in SOC *Endocrine disorders* as well.

POTENTIAL IMPACTS TO MedDRA TERMINOLOGY

The potential impacts to MedDRA terminology for all these proposed changes are shown in Table 3 from the PT standpoint; all except one involve only grouping changes at the HLT level with the primary SOC untouched. These types of changes will have little or no impact on existing MedDRA-coded data, which are stored at the level of PT/LLT but are essential to improve the analytical performance of MedDRA. The proposal that involves reassignment of the primary SOC does require some degree of recoding for MedDRA users.

SUBSCRIBER SURVEY RESULTS

Enlightened by the hierarchy feasibility study, the MSSO conducted a terminology survey within a selected group of subscribers. The purpose of the survey was to obtain more user input on issues related to the feasibility study and MedDRA terminology in general. In December 2004, there were 29 individuals from 22 companies who received an email from the MSSO asking for their participation. Among them, 22 (representing 15 companies) agreed to participate. The survey questions were sent out in January 2005. The MSSO received 12 responses from 12 companies by March 2005. The survey was composed of three sections with general and open-ended questions, which gave the responder the opportunity to comment freely. Section 1 was about MedDRA hierarchy regarding the appropriate size, scope, and name of the groupings and the use of NEC specifically. Section 2 was on multiaxiality: multiaxiality at the level beyond PT and benefits and disadvantages of having three isolated SOCs. Section 3 contained miscellaneous questions on topics such as the acceptable volume of changes per release, MSSO's communication with subscribers, train-

TABLE 3

The Potential Impact of Suggested Changes to MedDRA		
Proposal	PT-HLT Linkage Change	Primary SOC Change
Reducing the use of Not Elsewhere Classified (NEC) in term names	Yes	No
Applying secondary links from SOC Investigations to SOCs that classify disorders	Yes	No
Applying secondary links from SOC Social circumstances to SOCs that classify disorders	Yes	No
Breaking some multiaxiality at the HLT and HLGT levels	Yes	No
Allowing congenital terms and their acquired counterparts to be grouped under the same HLT	Yes	No
Reassigning the primary SOC of postprocedural terms from SOC Injury, poisoning and procedural complications to the SOC of the disease manifestation site	No	Yes
Grouping hyper- and hypometabolic disorders consistently at the HLT level	Yes	No

ing, MedDRA's role in labeling, method of implementing feasibility study results, and the top three changes that the subscriber would like to make to MedDRA.

Although it is a small pool of responders, there was adequate representation of the types of reaction from subscribers. In general, there are three kinds of responses:

1. Active: proposing recommendation for possible changes to the terminology
2. No opinion: either because of irrelevance of the question to their work or lack of understanding of the imposed question
3. Object: do not want any changes made to MedDRA

Next is a detailed summary of subscriber responses:

SECTION 1: MedDRA HIERARCHY

Subscribers are generally comfortable with the current hierarchy structure. It is understood that certain groupings at the HLT and HLGT levels are large because of the nature of the MedDRA terminology. From the user's point of view, the large-size group is acceptable as long as the subordinate concepts are closely related. Setting an arbitrary size seems inappropriate. To subscribers, the NEC type of grouping is necessary, but they would like the wording to be more

intuitive than the abbreviation NEC. A few participants stated that they only use PTs and SOCs in analysis, not HLT- or HLGT-level terms.

SECTION 2: MULTIAXIALITY

The survey indicated that the majority of MedDRA users rely on primary paths for both reporting and analysis. The usage of secondary links is limited. There is a sense of confusion about secondary links, and some subscribers indicated that applying secondary groupings during analysis is complex and confusing. Multiaxiality at the HLT and HLGT levels is generally not favored among responders. Half of the responding group agreed that granting a secondary link from SOC *Investigations* and SOC *Social circumstances* to the disorder SOCs would be useful and beneficial. When asked if the multiaxiality should be removed from MedDRA, all except one desired to keep the multiaxiality feature; a few pointed out that secondary links are helpful in safety searches.

SECTION 3: MISCELLANEOUS

Regarding the tolerable percentage of changes in MedDRA for one release, 10% seemed to be acceptable. But, overall, users wanted minimal or no impact on their work, as declared by one responder that any changes to LLTs that have

not been used in their database are fine. When asked about the preferred implementation approach for changes resulting from the MedDRA hierarchy feasibility study, the majority would like to view a complete list of changes with a schedule for the incremental implementation plan. A few requested one-time implementation of all changes.

With respect to MedDRA's role in product labeling, most participants agreed that MedDRA will play an important role in this area. The most diverse answers related to the question about the top three changes that subscribers would like to make to MedDRA. The answers are listed in Table 4. All responders not only acknowledged the importance of providing MedDRA training in the workplace but also expressed the difficulties of doing so. The most favorable communication channel is the MSSO's Web site and the "MedDRA Term Selection: Points to Consider" document.

SUMMARY

In the feasibility study, several changes to MedDRA's structure were proposed. We believe that these modifications will indeed strengthen MedDRA in aiding safety and statistical data analysis. The proposed changes are in agreement with the results of the subscriber survey conducted in support of this study. Although a few subscribers suggested eliminating NEC groupings, the majority of MedDRA users acknowledged that this type of "miscellaneous" grouping is needed for the classification in the terminology. Limiting the use of the abbreviation NEC in HLT and HLGT names provides intuitive insight for statisticians and other analysts about subordinate concepts. Reducing the number of PTs under each NEC HLT encourages the maintenance organization to create new HLTs on specific topics so that the hierarchical groupings in MedDRA become more self-explanatory. Allowing multiaxiality in SOC *Investigations* and SOC *Social circumstances* is the first step toward grouping disease/diagnosis together with supporting information, such as laboratory test results, which helps in overall analysis. Breaking multiaxiality of certain HLT/HLGTs

and adjustment of primary SOCs for postprocedural terms improves the quality of cumulative data presentation.

The subscriber survey revealed MedDRA users' opinions regarding the terminology and the maintenance organization. It included potential future improvement to MedDRA, such as better classification of terms relating to infections, organisms, and sites, and the improvement opportunities in the services provided by the MSSO, such as an on-line view of the latest version of the dictionary.

DISCUSSION

MULTIAXIALITY AT THE HLT/HLGT LEVELS

Overlapping of scopes between certain SOCs provides the basis for MedDRA multiaxiality. Multiaxiality provides the opportunity to analyze a concept or a group of concepts from different angles, such as etiology versus site of manifestation and pathological classification versus anatomical classification. MedDRA hierarchy rules define multiaxiality as occurring at three different levels:

1. PT level, meaning a PT is linked to two or more HLTs in different SOCs, such as PT *Rubinstein-Taybi syndrome*, which is linked to three HLTs
2. HLT level, meaning an HLT is linked to two or more HLGTs in different SOCs, such as HLT *Mental retardations*, which is linked to two HLGTs
3. HLGT level, meaning an HLGT is linked to two or more SOCs, such as HLGT *Musculoskeletal and connective tissue disorders congenital*, which is linked to two SOCs

Multiaxiality at the HLT and HLGT levels has posed challenges in data analysis and the maintenance of MedDRA. Difficulties and confusion caused by some multiaxial HLT/HLGTs in cumulative data presentation are shown in Table 2. Multiaxial HLT/HLGTs also limit the linkages that the MSSO may apply to certain newly added PTs. As an example, because of the rule that a PT can only be linked to an SOC through one HLT and one HLGT route, PT *Congenital osteodystrophy* cannot be linked to HLT *Metabolic bone disorders* in SOC *Musculoskeletal and connective tissue disorders* because it is linked to HLT

TABLE 4

Subscribers' Wish List	
ID	Wished Change
1	Ability to load the supplemental changes into the MSSO browser
2	An online view of the latest version of the dictionary
3	A simple list of all new supplemental terms (in alphabetical order) updated on a regular basis until incorporated in the next release
4	More general terms to deal with real data (eg, spontaneous reporting in Pharmacovigilance), for which precise medical conditions are not always specified, but meaningful classification is needed (eg, "strange feelings")
5	Better classification of terms relating to infections, organisms, and sites
6	Multiaxiality for SOC Investigations and SOC Surgical and medical procedures would be beneficial
7	Change version updates to once per year
8	Increase development of SMQs
9	We do not always agree with the decisions regarding a change in MedDRA as put forward by the MSSO. Can this process be more transparent?
10	Eliminate SMQs
11	Move all unique concepts to the PT level and just have synonyms and lexical variants at the LLT level
12	Make the three isolated SOCs multiaxial
13	Allow multiple linkages in a single SOC
14	Add a field to the database to indicate the version (or date) the term was added to MedDRA
15	Make the change control rules more strenuous to avoid multiple changes to a given term over successive releases
16	Make MedDRA required in all ICH regions for both postmarketing surveillance and clinical study coding
17	Include medical device codes utilized by regulatory agencies

Non-site-specific bone disorders congenital, which is multiaxial to both SOC *Musculoskeletal and connective tissue disorders* and SOC *Congenital, familial and genetic disorders*. Thus, the multiaxiality of HLT *Non-site-specific bone disorders congenital* makes it difficult for the maintenance organization to assign the most appropriate linkage for PT *Congenital osteodystrophy* in SOC *Musculoskeletal and connective tissue disorders*.

In MedDRA, PT is the level for a single medical concept. It is also the level at which primary and secondary linkages are differentiated. The accurate linkages for a PT concept shall be based on its medical definition and clinical manifestation and should not be restricted by multiaxiality at higher levels. Therefore, we believe that it would be beneficial to limit multiaxiality only to PT concepts and break all multiaxiality at the HLT and HLGT levels.

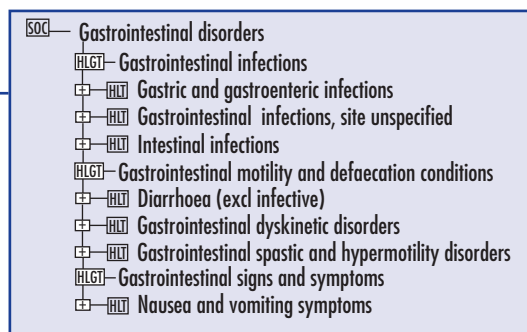
MULTIAXIALITY IN SOC INVESTIGATIONS

Multiaxiality in SOC Investigations is one of the most frequently discussed topics within the user community and the MSSO. In the proposed revision (March 2005) to the guideline on Summary of Product Characteristics from the European Medicines Agency, it is recommended that "As a general rule, any ADR should be assigned to the most relevant SOC related to the target organ. For example, 'Liver function test abnormal' should be assigned to the SOC 'Hepatobiliary disorders' rather than to the SOC 'Investigations'" (4).

Analysts are also in favor of finding diagnosis and test results in one place of the MedDRA hierarchy. This means that terms in SOC Investigations need to have links made to disorders SOCs. Because the relationship between a diagnosis and a test value varies from one-to-one to many-to-many, the concerns about uncontrollable

FIGURE 3

HLTs containing subordinate diarrhea terms.



secondary linkages to test result terms and the subsequent increases of complexity in the terminology are strong among MedDRA subscribers. The criteria proposed by the MSSO for applying secondary links to qualifying test results is aimed at reducing this risk while allowing SOC *Investigations* terms to be multiaxial.

NEC GROUPINGS IN MedDRA

Using a meaningful name for HLTs or HLGTs is helpful for medical and statistical analysts. Because MedDRA is not a taxonomy, NEC groupings ensure that all terms in MedDRA have a place holder at their parent level. But, how can the NEC grouping name be made more meaningful without compromising the role that it plays in the hierarchy?

The two approaches suggested in the feasibility study will reduce the number of PTs subordinated to groupings with the word NEC and limit the use of NEC in HLT and HLGT term names. They do not eliminate the use of NEC in MedDRA. As acknowledged by subscribers in the survey, this type of miscellaneous holder is essential. Often, NEC groupings contain mixed types of concepts. Thus, it is recommended that some level of medical judgment be applied to accurately understand concepts in NEC groupings.

CONSISTENT SCOPE OF HLT/HLGT GROUPING

One of the proposals in the feasibility study is to group hyper- and hypometabolic disorders consistently at the HLT level. The recommended suggestion is to merge three calcium metabolic disorder HLTs into one so that the HLT scope for calcium will be consistent with that for other el-

ements in the same SOC, such as magnesium, phosphorus, chloride, potassium, and sodium. Subscriber feedback suggested applying the same philosophy of having both hyper- and hypodisorders under the same HLT to SOC *Endocrine disorders*. We believe the consistent scope of HLT or HLGT grouping should apply within the same SOC and not be mandated across SOCs. The rationale is that different SOCs in MedDRA may be classified differently (2). For example, SOC *Infections and infestations* is classified by pathogens; SOC *Metabolism and nutrition disorders* is categorized by substances, nutritional disorders, and metabolic or nutritional pathogenesis; and SOC *Endocrine disorders* is classified by each endocrine gland. Attempting to harmonize grouping between two different SOCs that follow different classifications does not seem to be appropriate.

MedDRA SPECIAL SEARCH CATEGORIES

MedDRA Special Search Categories (SSCs) are used to group PTs relevant to an issue, usually a disease or syndrome, and accommodate clinical concepts that cross SOC hierarchies (2). They permit grouping together the signs and symptoms associated with a particular disease or diagnosis [eg, *PAIN (SSC)*], which often are located in a number of SOCs.

One of the challenges in generating incident tables and frequency analysis is that some clinical signs and symptoms are dispersed in different hierarchy groups (ie, in HLTs under different HLGTs due to MedDRA hierarchy rules). For example, diarrhea terms are listed under seven different HLTs in SOC *Gastrointestinal disorders*. The seven HLTs are listed in Figure 3. Because of the MedDRA hierarchy rule that each PT is linked to an SOC by one and only one path, the current disease classification at the HLT and HLGT levels in SOC *Gastrointestinal disorders* does not allow symptom terms like diarrhea to be grouped under a single HLT without disrupting established disease groupings in the same SOC. Using the diarrhea example shown in Figure 3, grouping all diarrhea terms under a single HLT in SOC *Gastrointestinal disorders* would result in the

disruption of other existing HLT groupings, such as HLT *Gastric and gastroenteric infections*; HLT *Intestinal infections*; HLT *Gastrointestinal infections, site unspecified*; HLT *Gastrointestinal dyskinetic disorders*; and HLT *Gastrointestinal spastic and hypermotility disorders*.

SMQs—with their focused topics and more flexible retrieval options—are likely to supplant the MedDRA SSCs for case identification in safety surveillance. SMQs have narrow and broad search options and algorithms in some instances. They offer a much more sophisticated query capability than the SSCs. Given the likely prominence of SMQs in the future, a plan for what to do with SSCs is needed. We suggest redefining the purpose of the SSCs to serve as the basis for the future development of the proposed MedDRA Labeling Entities (5) and other pragmatic groupings. Subscribers are very supportive of this initiative, which greatly facilitates frequency analysis and the generation of incident tables.

MIXED OPINIONS IN THE SUBSCRIBER SURVEY

Opinions in the survey were diverse. Some subscribers wanted to extend the multiaxiality in MedDRA because it is helpful in analysis; others did not because they never use secondary groupings. Some MedDRA users welcomed changes and improvements made to the terminology, while others wanted stabilization (essentially, no changes). Some subscribers liked the SMQs and would like to see increased speed of their development; others would rather eliminate SMQs. These varied responses reflect the different views of users based on their own experiences with using MedDRA (eg, for data coding vs. data analysis). They also reflect different guidelines and conventions in coding and analysis used by companies and regulators. We recom-

mend the ICH standards for data coding and analytical purposes (2,6).

It is hoped that this article will open the dialog among MedDRA users on analytical strategies, recommendations, and approaches on MedDRA-coded data and perhaps possible improvement opportunities for the MedDRA terminology.

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