Introductory Guide
MedDRA Version 19.0

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Notice to Reader

This Introductory Guide is written in English and is intended only for use with the English version of MedDRA. Additional Introductory Guides have been developed to support languages other than English and are included with their specific translation copies.

The Introductory Guide is intended for use in conjunction with the MedDRA Browsers, available with each MedDRA subscription.

Changes which are version specific or changes in documentation may be found in the What's New document. This document is included with the MedDRA release and is also posted on the MSSO Web site under Support Documentation. .

The MedDRA terminology is maintained under an ISO 9001:2008 registered quality management system.

To help readers more easily identify new and changed content within the MedDRA Introductory Guide, a list of sections with significant modifications for MedDRA Version 19.0 is provided below:

Section 6.8.1: was modified to reflect the changes to SOC *General disorders and administration site conditions* as a result of inclusion of the new SOC *Product issues*

Section 6.12.1: was modified to reflect complex changes that were implemented for MedDRA Version 19.0

Section 6.16.2: A statement related to sarcomas was modified.

Section 6.19: A section for new SOC *Product issues* was added.

Section 6.20.1: was modified to reflect complex changes that were implemented for MedDRA Version 19.0 based on DSM-V.

Acknowledgements

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1. INTRODUCTION

The Medical Dictionary for Regulatory Activities (MedDRA) Terminology is the international medical terminology developed under the auspices of the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. This guide describes the development, scope, and structure of the terminology.

1.1 BACKGROUND

Prior to the development of MedDRA, there had been no internationally accepted medical terminology for biopharmaceutical regulatory purposes. Most organizations processing regulatory data used one of the international adverse drug reaction terminologies in combination with morbidity terminology. In Europe, most of these organizations used a combination of the World Health Organization's Adverse Reaction Terminology (WHO-ART©) and the International Classification of Diseases Ninth Revision (ICD-9). In the United States, the Food and Drug Administration's (FDA) Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART©) was usually used in conjunction with Clinical Modification of ICD-9 (ICD-9-CM©). The Japanese developed their own versions of these international terminologies, Japanese Adverse Reaction Terminology (J-ART) and Medical Information System (Japan) (MEDIS). In addition, many organizations modified these terminologies to suit their needs. Established terminologies lacked specificity of terms at the data entry level, provided limited data retrieval options (e.g., too few levels in the hierarchy, or capacity to retrieve data via one axis only), and did not handle syndromes effectively. Organizations with sufficient resources developed their own "in-house" terminologies to address some or all of these deficiencies.

The use of multiple terminologies raised several problems. Using different terminologies at various stages in a product's life complicates data retrieval and analysis, making it difficult to cross-reference data. For example, safety data had frequently been classified for pre-registration clinical trials using ICD terminology and for post-marketing surveillance using J-ART, WHO-ART, or COSTART. Furthermore, using different terminologies in separate geographic regions impaired international communication and necessitated the conversion of data from one terminology to another. This data conversion had the potential to cause time delays and loss or distortion of data. In particular, these problems affected multinational pharmaceutical companies whose subsidiaries used multiple terminologies to fulfill the different data submission requirements of regulators. The use of multiple terminologies also affected communication between companies and clinical research organizations.

It became increasingly difficult to manage the information required for product registration applications and to meet the time scale requirements for data exchange between regulatory authorities and the medical product industries. These difficulties prompted an industry-wide commitment to exploit developments in communication and information technology. However, electronic communication still required a standardized data set and structure to be successful.

1.2 ADOPTION OF MEDICAL TERMINOLOGY AS AN ICH TOPIC

In October 1994, the ICH Steering Committee introduced multi-disciplinary regulatory communication initiatives to complement the ongoing safety, quality, and efficacy harmonization topics. These initiatives focused on a medical terminology for regulatory purposes (M1) and electronic standards for the transfer of regulatory information (ESTRI, M2). The ICH adopted these initiatives to recognize the increasing importance of electronic communication of regulatory data and the need for internationally agreed standards.

The aim of the ICH M1 initiative was to standardize the international medical terminology for regulatory communication. This includes communication in the registration, documentation, and safety monitoring of medical products for use in both pre- and post-marketing phases of the regulatory process. The objective was to agree on a unified medical terminology for regulatory activities that overcomes the limitations of current terminologies, is internationally accepted, and is supported by long-term maintenance. Regulators and industries benefit from such a terminology because it improves the quality, timeliness, and availability of data for analysis. The terminology also facilitates the electronic exchange of data relating to medical products and results in long-term savings in resources.

The M1 Expert Working Group (EWG) was established and was composed of representatives of the six ICH sponsors, an observer for the WHO, and the European Union acting as rapporteur. The EWG defined the “deliverables” of the initiative as a terminology of agreed content and structure (the implementable version) and an agreed maintenance framework.

1.3 DEVELOPMENT OF THE MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES (MedDRA) TERMINOLOGY

The ICH terminology was developed from a pre-existing terminology. The MEDDRA Working Party enhanced the United Kingdom MCA’s(now MHRA - Medicines and Healthcare products Regulatory Agency) medical terminology to produce MEDDRA Version 1.0. This was adopted as the basis for the new ICH terminology.

MedDRA Version 2.0 was signed off as the implementable version of the terminology at the ICH-4 conference in July 1997. A change in name and modified acronym were agreed upon at this meeting. Hence, MEDDRA is used for versions up to Version 1.5, while the implementable version (Version 2.0) and future versions are known as the MedDRA terminology.

1.4 IMPLEMENTATION OF THE TERMINOLOGY

The success of the terminology depends on its long-term maintenance and its evolution in response to medical/scientific advances and changes in the regulatory environment. This is why the MedDRA Maintenance and Support Services Organization (MSSO) is a necessary element to implementing the MedDRA terminology. The MSSO was appointed by ICH through an open competitive tender.

1.5 SCOPE OF THE TERMINOLOGY

The MedDRA terminology applies to all phases of development of medical products for human use, excluding animal toxicology. The scope of MedDRA encompasses medical, health-related, and regulatory concepts pertaining to such products. The terminology also addresses the health effects and malfunction of devices (e.g., PT *Device related infection* and PT *Device failure*). Furthermore, the terminology may also support other types of products which are regulated in at least one region such as food or cosmetics.

The categories of terms classified as “medical and health-related” for these purposes are as follows:

- signs
- symptoms
- diseases
- diagnoses
- therapeutic indications – including signs, symptoms, diseases, diagnoses, diagnosis or prophylaxis of disease, and modification of physiologic function
- names and qualitative results of investigations – e.g., increased, decreased, normal, abnormal, present, absent, positive, and negative
- medication errors and product quality terms
- surgical and medical procedures
- medical/social/family history

Although social circumstances are not usually regarded as medical terms, they fall within the “medical” scope if they are relevant to the evaluation of regulatory data (e.g., in the assessment of clinical outcome of treatment in the light of exposure to risk factors). Examples are: PT *Foreign travel*, PT *Substance use*, HLT *Tobacco use*, and HLT *Bereavement issues*. The terminology, as defined above, was developed for regulators and the regulated medical product industry. These groups can utilize the terminology for data entry, retrieval, evaluation, and presentation, and in both pre- and post-marketing phases of the regulatory process as follows:

- clinical studies
- reports of spontaneous adverse reactions and events
- regulatory submissions
- regulated product information

In consultation with the MedDRA Management Board, the terminology may be expanded in scope to accommodate additional medical/health-related and regulatory concepts that are developed based on collaborative efforts involving relevant experts. The addition of new topic areas will undergo the usual MSSO change request process.

1.6 INCLUSION OF TERMS FROM ESTABLISHED TERMINOLOGIES

The initial release of MedDRA (v2.1) in March 1999 included numeric and symbol codes from earlier terminologies in specific fields of the MedDRA files associated with term names. The codes were links from other terminologies to similar or identical terms in MedDRA and included codes from COSTART (5th Edition), WHO-ART© (3rd Quarter,

1998), ICD9, ICD9-CM, HARTS© (Release 2.2), and J-ART (1996). For example, PT *Nausea* in MedDRA has a corresponding term NAUSEA in COSTART.

MedDRA was not developed as a metathesaurus, and the hierarchies of these other terminologies are not subsets of it. Thus, data entry terms from other terminologies do not necessarily have the same PT in MedDRA as they did in their "parent" terminology. The hierarchies used for data retrieval and presentation are unique to MedDRA.

Inclusion of terms from other terminologies is restricted to those within the scope of MedDRA as defined above.

The ICH M1 Expert Working Group – who created the original version of MedDRA – included the numeric and symbol codes with the text of the terms; the codes were intended to be useful in the transition to MedDRA. Since most organizations have converted their data from older terminologies to MedDRA, and the codes have not been maintained or updated since the original release of MedDRA, the MSSO has removed them from the MedDRA files as of MedDRA v15.0.

Note that no MedDRA term names or codes have been modified or removed as a result of this action, and the structure of the MedDRA extended ASCII files has not changed.

1.7 EXCLUSION CRITERIA

The exclusion criteria used in the development of the terminology do not necessarily limit the terminology's expansion scope. Since this is a medical terminology, the following terms used in regulatory affairs are out of scope:

- Drug/product terminology (Note: The generic names of some commonly used products, such as digoxin, that are included with their associated adverse events)
- Equipment/device/diagnostic product terminology
- Study design
- Demographics (including patient sex, age, race, and religion).

As its focus is on health effects in individual patients, the following are excluded:

- Qualifiers that refer to populations rather than individual patients (e.g., rare, frequent)
- Numerical values associated with laboratory parameters are not included (e.g., serum sodium 141 mEq/L). See Section 4.9 for more details.
- Descriptors of severity are not included in the terminology. Descriptors such as "severe" and "mild" are used only when pertinent to the specificity of the term (e.g., severe vs. mild mental retardation).

2. STRUCTURAL ELEMENTS OF THE TERMINOLOGY

The MedDRA terminology was developed as a medically validated medical terminology for utilization throughout the regulatory process. The developers of the terminology designed a structure that promotes specific and comprehensive data entry and flexible data retrieval. Figure 2-1 represents the hierarchical structure of the terminology. Relationships between terms in the terminology fall into the following two categories:

2.1 EQUIVALENCE

The equivalence relationship groups synonymous terms, or equivalent terms, under Preferred Terms.

2.2 HIERARCHICAL

The hierarchy provides degrees or levels of superordination and subordination. The superordinate term is a broad grouping term applicable to each subordinate descriptor linked to it. Hierarchical levels thus represent vertical links in the terminology.

Hierarchies are an important mechanism for flexible data retrieval and for the clear presentation of data. The five-level structure of this terminology provides options for retrieving data by specific or broad groupings, according to the level of specificity required. The Lowest Level Term (LLT) level provides maximum specificity.

The terminology was not developed as a formal classification or taxonomy; each level in the hierarchy may reflect a variable degree of specificity or “granularity” from one System Organ Class to another. High Level Terms (HLTs) and High Level Group Terms (HLGTs) facilitate data retrieval and presentation by providing clinically relevant grouping of terms. Collectively, the HLT and HLGT levels are sometimes referred to as the “grouping terms” in MedDRA.

The 27 System Organ Classes (SOCs) represent parallel axes that are not mutually exclusive. This characteristic, called “multi-axiality,” allows a term to be represented in more than one SOC and to be grouped by different classifications (e.g., by etiology or manifestation site), allowing retrieval and presentation via different data sets. Grouping terms are pre-defined in the terminology and not selected on an ad hoc basis by data entry staff. Rather, the terminology is structured so that selection of a data entry term leads to automatic assignment of grouping terms higher in the hierarchy. Multi-axial links of terms are pre-assigned, ensuring comprehensive and consistent data retrieval, irrespective of which SOC is selected at data retrieval.

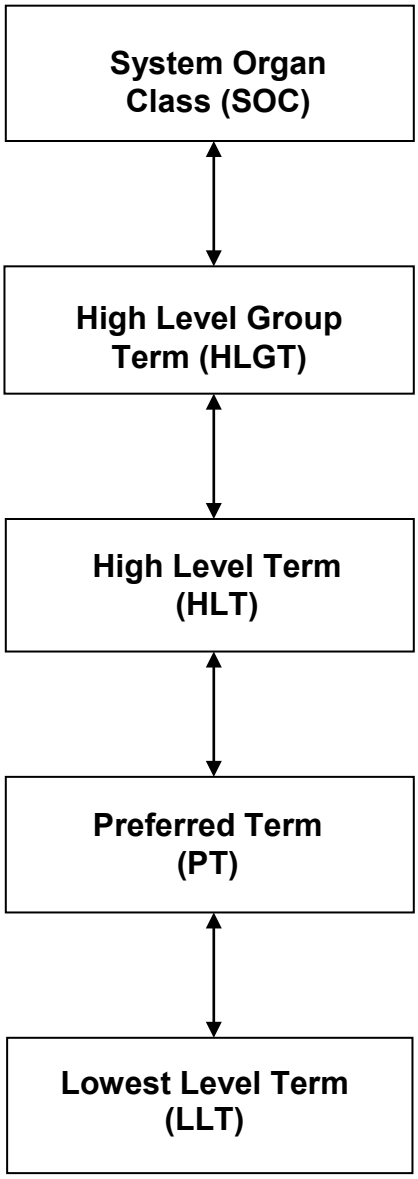

Figure 2-1. Structural Hierarchy of the MedDRA Terminology

3. LEVELS OF STRUCTURAL HIERARCHY

The levels of structural hierarchy are characterized as follows:

3.1 LOWEST LEVEL TERMS

LLTs constitute the lowest level of the terminology. Each LLT is linked to only one PT.

LLTs have any of the following relationships to their parent PT:

Synonyms: Different terms for the same concept inherent in the PT (e.g., PT *Arthritis* and its subordinate LLT *Joint inflammation*)

Lexical variants: Different word forms for the same expression. These include full names vs. abbreviations and direct vs. inverted word order (e.g., PT *Acquired immunodeficiency syndrome* and its subordinate LLT *AIDS* or PT *Biopsy tongue* and its subordinate LLT *Tongue biopsy*).

Quasi-synonyms: Quasi-synonyms are terms that are not precisely the same meaning as another term, but are treated as synonymous in a given terminology. These include site and laterality descriptions (e.g., PT *Otitis externa* and its subordinate LLT *Bilateral otitis externa*).

Sub-element: Sub-elements (of the parent PT) are represented by LLTs with more detailed information such as anatomic specificity (e.g., PT *Contusion* with LLT *Bruising of face* or LLT *Bruising of leg*).

Identical LLT: One LLT is identical to its PT for data entry purposes (e.g., PT *Dementia Alzheimer's type* and its subordinate LLT *Dementia Alzheimer's type*). In this instance, the LLT and parent PT have the same MedDRA code but appear at both levels.

Since LLTs may accommodate colloquial or culturally unique terms, every LLT may not have a unique translation in every language.

The LLT level plays an important role in facilitating the transfer of historical data because many of the terms from other terminologies incorporated, are represented at this level.

LLTs facilitate data entry and promote consistency by decreasing subjective choices made at this stage. LLTs may also be used as the basis for auto-encoding. Since LLTs may be more specific than the PT to which they are linked, users can retrieve data at the most specific level of the terminology.

LLTs carry a "current" or "non-current" flag status. Terms that are very vague, ambiguous, truncated, abbreviated, out-dated, or misspelled carry a non-current flag. These terms may derive from terminologies incorporated into MedDRA. The terminology retains LLTs with a non-current flag to preserve historical data for retrieval and analysis. The flag also allows users to implement the terminology within a database and prevent the inadvertent use of non-current LLTs in post-implementation coding.

3.2 PREFERRED TERMS

A **PT** is a distinct descriptor (single medical concept) for a symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical, or medical procedure, and medical, social, or family history characteristic.

PTs should be unambiguous and as specific and self-descriptive as possible in the context of international requirements. Therefore, eponymous terms are only used when they are recognized internationally.

The granularity/specificity of the PT level is such that clinical pathologic or etiologic qualifiers of the descriptors are represented at the PT level. For example, a variety of rhinitis and meningitis terms exist as separate entities at this level (e.g., PT *Rhinitis perennial,* PT *Rhinitis ulcerative,* PT *Rhinitis atrophic,* PT *Meningitis aseptic,* PT *Meningitis cryptococcal,* PT *Meningitis viral,* PT *Meningitis bacterial*, etc.). This level of specificity in PTs ensures that the multi-axial nature of the terminology can be maximally exploited.

There is no limit to the number of LLTs that can be linked to a PT, however, a PT must have at least one LLT linked to it. When a new PT is added to the terminology, an identical LLT is created automatically for data entry purposes.

PTs are subordinate to HLTs.

A PT must be linked to at least one SOC. A PT can be linked to as many SOCs as is appropriate. It can only be linked to each SOC via one HLT=>HLGT=>SOC route. Each PT has a primary SOC that determines under which SOC the term appears in cumulative data outputs.

3.3 HIGH LEVEL TERMS

An **HLT** is a superordinate descriptor for the PTs linked to it. It is an inclusive category which links PTs related to it by anatomy, pathology, physiology, etiology, or function. Examples of HLTs are: HLT *Bronchospasm* and *obstruction,* HLT *Mediastinal disorders,* HLT *Pulmonary oedemas*, and HLT *Upper respiratory tract neoplasms*. The terminology is not a taxonomy, so the specificity of HLTs is not uniform throughout the terminology (or between SOCs).

HLTs are intended for data retrieval and presentation purposes; they are a grouping level and are not intended to be a coding level.

HLTs are subordinate to HLGTs. An HLT must be linked to at least one SOC via an HLGT. It can only be linked to a particular SOC via one route (i.e., linked to only one HLGT per SOC). All HLTs linked to a particular HLGT will appear in every SOC to which the HLGT is linked.

3.4 HIGH LEVEL GROUP TERMS

An **HLGT** is a superordinate descriptor for one or more HLTs related by anatomy, pathology, physiology, etiology, or function. For example, HLGT *Vascular hypertensive disorders* is used to link the following HLTs: HLT *Accelerated and malignant hypertension,* HLT *Hypertension complications,* HLT *Portal hypertensions,* HLT *Pregnancy associated hypertension,* HLT *Pulmonary hypertensions,* HLT *Renal hypertensions,* HLT *Vascular hypertensive disorders* NEC, and HLT *Endocrine* and *metabolic secondary hypertension*.

HLGTs are intended for data retrieval and presentation purposes. HLGTs group HLTs to aid retrieval by broader concepts.

HLGTs are subordinate to SOCs. An HLGT must be linked to at least one SOC and to at least one HLT (the next levels up and down in the hierarchy, respectively).

There is no limit to the number of SOCs to which an HLGT can be linked.

3.5 SYSTEM ORGAN CLASS

A **SOC** is the highest level of the hierarchy that provides the broadest concept for data retrieval. SOCs comprise groupings by:

- Etiology (e.g., SOC *Infections and infestations*)
- Manifestation site (e.g., SOC *Gastrointestinal disorders*)
- Purpose (e.g., SOC *Surgical and medical procedures*)

The exception from the above categories is SOC *Social circumstances* which contains information about the person, not the adverse event and provides a grouping for those factors that may give insight into personal issues that could have an effect on the event being reported.

A SOC is related directly (superordinated) to at least one HLGT with no restriction on the number of links to HLGTs.

To avoid “double counting” while retrieving information from all SOCs, each PT is assigned a primary SOC. This is required because PTs can be represented in more than one SOC (multi-axiality). It prevents an individual PT from being displayed more than once in cumulative SOC-by-SOC data outputs, which would result in over-counting of terms. All PTs in MedDRA are assigned a primary SOC that determines the SOC in which the term is displayed in these outputs. This property does not prevent display and counting of the term in any of the SOCs in which it is represented for data retrieval purposes that do not involve all SOCs.

The following rules are used for the allocation of the primary SOC:

- PTs that are only represented in one SOC are automatically assigned that SOC as primary.

- PTs relating to diseases or signs and symptoms are assigned to the prime manifestation site SOC with the following exceptions:

  - Terms for congenital and hereditary anomalies are assigned to SOC *Congenital, familial and genetic disorders* as the primary SOC.
  - Terms for neoplasms are assigned to SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)* as primary SOC. This does not apply to cyst and polyp terms. These terms have as their primary SOC the manifestation site SOC. For example, PT *Aural polyp* has SOC *Ear and labyrinth disorders* as its primary SOC and SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)* as its secondary SOC.
  - Terms for infections are assigned to SOC *Infections and infestations* as the primary SOC.

If a PT links to more than one of these three "exceptions" SOCs, the following priority is used to determine the primary SOC:

- SOC *Congenital, familial and genetic disorders*
- SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*
- SOC *Infections and infestations.*

As an example, PT *Congenital teratoma* is linked to SOC *Congenital, familial and genetic disorders* as the primary SOC with a secondary link to SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*.

The decision was made during the development of MedDRA to abrogate the general rule of manifestation site (rather than etiology) when determining the primary SOC allocation for neoplasms, congenital abnormalities, and infections. This was done to facilitate signal identification, since all PTs relating to such categories are grouped together on routine cumulative data outputs.

Other considerations for primary SOC allocation are as follows:

- Not all SOCs in MedDRA express multi-axiality. Terms contained within SOC *Investigations*, SOC *Social circumstances*, and SOC *Surgical and medical procedures* reside within those SOCs and nowhere else in the terminology because they lack multi-axial linkages.
- The <u>majority</u> (but not all) of injury, poisoning and procedural complications terms are represented in SOC *Injury, poisoning and procedural complications* as the primary SOC.
- Application, implant, and injection site reactions are assigned the primary SOC *General disorders and administration site conditions*, while infections at these sites have the primary SOC *Infections and infestations*.

The Alphabetical Listing of MedDRA SOCs is presented in Table 3-1 (in English). Presented in Table 3-2 are the MedDRA SOCs listed in the internationally agreed order.

The original MedDRA Expert Working Group determined there is not a standard alphabetic order of SOCs due to the multi-lingual nature of MedDRA. As a result, they developed the international order to facilitate consistency irrespective of language or alphabet.

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

Table 3-1. The MedDRA Terminology SOC List – Alphabetical Listing

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

Table 3-2. The MedDRA Terminology SOC List – Internationally Agreed Order

3.6 STANDARDISED MedDRA QUERY (SMQ)

Standardised MedDRA Queries (SMQs) are groupings of MedDRA terms, ordinarily at the Preferred Term (PT) level that relate to a defined medical condition or area of interest. SMQs are intended to aid in the identification and retrieval of potentially relevant individual case safety reports. The included terms may relate to signs,

symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data, etc. The only Lowest Level Terms (LLTs) represented in an SMQ are those that link to a PT used in the SMQ; all others are excluded.

For detailed information about the SMQs, please refer to the Introductory Guide for Standardised MedDRA Queries (SMQs), which is a separate document. It can be found along with the other supporting documentation with this release.

4. RULES AND CONVENTIONS ADOPTED IN THE TERMINOLOGY (INCLUDING PRESENTATION AND FORMATTING OF TERMS)

This section, and sections 5 and 6 contain the rules and conventions used in the terminology. Each rule holds true in the majority of cases, but many rules will have exceptions. Some of those exceptions are listed within each rule, however, it is not possible to notate all exceptions. MedDRA is a medical terminology not a taxonomy and medically must be balanced, pragmatic, reflect actual medical practice, and have consideration for how different cultures interpret specific terms.

4.1 SPELLING

Terminology spelling consistently follows *Dorland's Illustrated Medical Dictionary (30th edition)*© , Dorland's online and standard medical literature for all medical terms. Nonmedical terms included in the terminology follow *Merriam-Webster® English Dictionary*.

Use of the hyphen is consistent with its most prevalent use in *Dorland's Illustrated Medical Dictionary* and standard medical literature. "Non" in a word will always be used with a hyphen unless it is a term not found in Dorland's but is accepted in the *Merriam-Webster English Dictionary* as one word (e.g., nontoxic, nonspecific, noninvasive, nondependent, nonmedical, nonproductive, noncompliance, nondominant, etc).

In accordance with *Dorland's Illustrated Medical Dictionary*, "post" terms are separated by a space with the following exceptions: hyphenated terms include "post-traumatic," "postero-lateral," and "post-term." Single word terms include forms of "postabortal," "postpartum," "postmature," "postmenopausal," "postmastoid," "postvaccinal," "postvaccinial," "postnasal," "postauricular," "postictal," "postmastectomy," and "postnatal."

British spellings are used at the PT level and above. At the LLT level, both the British spelling and the American spelling counterpart of the same term are included (e.g., LLT *Diarrhoea* and LLT *Diarrhea* under PT *Diarrhoea*). Misspelled terms that come from inherited terminologies are flagged as non-current.

4.2 ABBREVIATIONS

In general, abbreviations are excluded from levels above LLT. Exceptions to this rule are: 1) when including the full term makes the phrase very long (over 100 characters); and 2) when the term has a well-established abbreviation. Below are some examples:

CDC Centers for Disease Control (USA)

CNS central nervous system

CSF cerebrospinal fluid

ECG electrocardiogram

The following abbreviation is limited to the HLT and HLGT levels (with the exception of a few non-current LLTs)**:**

NEC not elsewhere classified

The following abbreviation is limited to the LLT level:

NOS not otherwise specified

Abbreviation letters are not punctuated by full stops (periods). Abbreviations or acronyms that may represent different meanings in the various ICH regions are excluded from the terminology to prevent ambiguity. Abbreviations and acronyms exhibiting multiple interpretations in standard text books of acronyms are generally not accepted for addition into the terminology. However, an acronym will be added, despite multiple interpretations, at the LLT level for its most common usage worldwide e.g.,LLT *CVA* for Cerebrovascular accident and LLT *Raised LFTs* for Raised liver function tests.

Based upon advice from the MedDRA Expert Panel, the majority of abbreviated virus LLTs (and related terms without abbreviations and a qualifier), which can be interpreted as either an investigation or infection terms such as LLT *HAV*, LLT *HBV,* and LLT *Hepatitis B virus,* are non-current. As of MedDRA 12.1, the MSSO will refrain from adding new abbreviated terms without the qualifier of “test” or “infection.”

The chemical elements are represented in MedDRA with their official chemical symbols on LLT level such as “Cl” for chloride and “Cu” for copper.

4.3 CAPITALIZATION

Most of the terminology is presented in lower case letters. Upper case letters are used only for the initial letter in each term, with the exception of proper names (e.g., PT *Non-Hodgkin’s lymphoma*), and components of microorganism taxonomic names and abbreviations.

Terminologies, dictionaries, and thesauri traditionally use a mixture of lower and upper case letters to indicate the correct orthography of terms. However, organizations have complete flexibility regarding how they implement term case in their databases. Upper case terms can be used exclusively if desired.

4.4 PUNCTUATION

Apostrophes are used in proper names (e.g., PT *Gilbert’s syndrome*).

Diacritical marks, for example the French “accent aigu” or “é,” (e.g., PT *Guillain-Barre syndrome*) are excluded from the English version of the terminology.

4.5 SINGLE WORD *VS*. MULTIPLE WORD TERMS

Each LLT or PT represents a single concept, but the concept may be expressed in one or more words.

Terms describing two or more concepts were “inherited” from other terminologies (e.g., LLT *Nausea vomiting and diarrhoea*). These compound terms are linked as LLTs to the PT that denotes the primary or most clinically relevant effect. For example, the term *Nausea vomiting and diarrhoea* is an LLT linked to PT *Vomiting*. Additionally, this term has been flagged non-current.

4.6 WORD ORDER

In general, the PT, HLT, HLGT, and SOC levels use natural language word order which means the term is expressed in the way it is generally spoken (e.g., PT *Myocardial infarction*, not *Infarction myocardial).* The exception is when reversing the words in a PT facilitates grouping of similar terms for alphabetical display in SOC hierarchies. For example: PT *Meningitis aseptic,* PT *Meningitis chemical,* PT *Meningitis eosinophilic,* and PT *Meningitis toxoplasmal.*

4.7 MedDRA CODES

In contrast to the typical use of the word "code" in the regulatory milieu, within MedDRA, the "code" refers to the eight-digit number assigned to each term and is not to be confused with the text string of the term itself. Each term in MedDRA has a unique non-expressive code. Non-expressive, in this context, means that no information can be derived from the digits within the code (e.g., SOC assigned level within the hierarchy, etc.). A code is assigned to all terms across all categories. Initially, the codes were assigned in alphabetical order starting with 10000001. New terms added to the terminology are assigned the next sequential number. Previously used MedDRA codes are usually not reused for new terms, however, in some circumstances, when terms are renamed (e.g., the correction of misspellings), codes may be reused.

4.8 BODY SITE CONSIDERATIONS IN MedDRA

Abdominal wall – In general, the abdominal wall is classified in MedDRA as a gastrointestinal structure.

Cardiac and vascular anomalies – Certain congenital anomalies include both cardiac and vascular components; these terms are linked to HLT *Congenital cardiovascular disorders NEC* (with HLGT *Congenital cardiac disorders* linking it to SOC *Cardiac disorders*).

Chest wall - The chest wall is classified as a musculoskeletal structure. In general, terms related to the chest wall are linked to SOC *Musculoskeletal and connective tissue disorders*.

Eyelid - The eyelid is classified as a structure of the eye. In general, terms related to the eyelid are primarily linked to SOC *Eye disorders* and secondarily to SOC *Skin and subcutaneous tissue disorders*.

Pharynx and diaphragm - The pharynx and diaphragm are classified in MedDRA as respiratory structures.

Pinna - The pinna, including the ear lobe, is considered part of the ear and has a primary link to SOC *Ear and labyrinth disorders*.

4.9 NUMERICAL VALUES

Some MedDRA LLTs contain numerical values associated with certain clinical parameters (e.g., LLT *Foetal growth retardation, unspecified, 1,500-1,749 grams*); usually these are terms incorporated from other terminologies, and are flagged non-current since they do not fit MedDRA rules. Numerical values associated with laboratory parameters are also excluded (e.g., serum sodium 141 mEq/L).

Numerals may be incorporated into LLTs and PTs when they are part of a name or inherent to the concept (e.g., PT *5-alpha-reductase deficiency*).

4.10 AGGRAVATION OF UNDERLYING CONDITIONS

The majority of terms expressing "aggravated" concepts (e.g., LLT *Allergy aggravated*) have been inherited from other terminologies. As a result of the modified term review, several similar concepts were added in MedDRA Version 9.1. However, in the future the MSSO will add new terms containing "aggravated," "worsen/-ed/-ing," or "exacerbated," only if they demonstrate medical significance.

4.11 NOS AND NEC TERMS

Terms including "NOS" (not otherwise specified) are a common feature of medical terminologies used within drug regulatory affairs. In MedDRA, "NOS" terms are only found on the LLT level and are meant to represent concepts for which no further specific information is available (e.g., during coding of adverse events). Terms carrying "NOS" reflect nonspecific terms and can only be interpreted with reference to other terms specified in the terminology. The specified concept is not a constant throughout this terminology (e.g., it may relate to acute vs. chronic conditions, body site, or infective organism). For coding, users should employ the most specific term available (e.g., LLT *Cluster headaches* vs. LLT *Headache NOS*). At the direction of the MedDRA MSSO Management Board, as of MedDRA Version 6.1, no additional "NOS" terms will be accepted into the terminology. Additionally, all "NOS" terms previously existing at the PT level have been demoted to the LLT level in the terminology.

Similarly, "NEC" (not elsewhere classified) is a standard abbreviation used to denote groupings of miscellaneous terms that do not readily fit into other hierarchical classifications within a particular SOC. The "NEC" designation is used only with HLTs and HLGTs for grouping purposes. For example, HLT *Bladder disorders NEC* includes a diverse range of PTs including PT *Bladder stenosis,* PT *Bladder granuloma* and PT *Bladder telangiectasia*. All "NEC" terms previously existing at the PT level have been demoted to the LLT level and flagged non-current.

4.12 GENDER SPECIFIC TERMS

In general, gender specific terms are not included in MedDRA because patient gender is traditionally considered a database variable. However, a special case has been made for instances in which the gender of the patient makes the concept clinically distinct as for certain breast and reproductive tract disorders (e.g., PT *Breast cancer*

male and PT *Breast cancer female*). In general, there is also a corresponding gender-neutral term (PT *Breast cancer*).

4.13 HIERARCHY NAMING CONVENTIONS

Plurality

Terms at the HLT and HLGT levels are normally in the plural form since they are groupings of medical concepts (e.g., HLT *Malignant hepatobiliary neoplasms*). Generally, terms at the PT and LLT levels are in the singular form since they are not groupings of medical concepts.

Use of Adjectives

The adjective form, e.g., “cardiac” or “hepatic” is used whenever possible instead of the noun (e.g., “heart” or “liver”). The exceptions are when there is a naming conflict (i.e., two terms at different levels that could potentially be represented by the same text string) or when the term is not normally stated as such in common practice. For example, “heart attack” is normally used in common practice rather than “cardiac attack.”

“Excl” and “Incl”

In order to be consistent with the conventions for the grouping terms, the standard use of terms with “including” or “excluding” are represented as the following:

1. “excl” represents excluding,” “except,” and “excl.”
2. “incl” represents including and “incl.”

“Signs and symptoms;” “infections and inflammations”

In the text of terms where such phrases are used, the word order is “signs and symptoms” and “infections and inflammations.”

Benign and malignant

Generally, words “benign” and “malignant” are placed at the end of the text strings in SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)* and at the beginning of the text strings in other SOCs. This convention provides information as to which SOC and HLGT the term belongs to by reading its name only.

Congenital

Generally, the word “congenital” is placed at the end of the text string in SOC *Congenital, familial and genetic disorders* and at the beginning of the term in other SOCs. This convention provides information as to which SOC and HLGT the term belongs by only reading its text string. The term “congenital” has been used to describe any condition present at birth, whether genetically inherited or occurring in utero.

Disorder, disease, and disturbance

In MedDRA, the concept of “disturbance” is subordinate to “disease” which is subordinate to “disorder.” “Disorder” is generally used in the HLT, HLGT, and SOC levels since it is more of a general term (e.g., HLGT *Gallbladder disorders*). As an exception, “disease” is sometimes used at the HLT level when this is the most common

way of stating the concept e.g., HLT *Parkinson's disease and parkinsonism*. "Parkinson's disease" is the most common way of stating the term, not "Parkinson's disorder."

"Disturbance" is synonymous with "disorder" and will be only added if that is the preferred wording for a concept. If a "disorder" term exists at the PT/LLT level, the "disturbance" concept will no longer be added.

5. PT AND LLT NAMING CONVENTIONS

5.1 GENERAL WORD USAGE

Alcohols: Single word names are used for alcohols (e.g., "ethanol," not "ethyl alcohol"). The symbol –OH is spelled out (e.g., LLT *17-hydroxycorticosteroid activity*).

Anastomosis: This is classified as a surgical procedure and is single-axial linked to SOC *Surgical and medical procedures*. Alternative terms are used to describe related disorders outside of the surgical realm.

Cervical (neck) and Cervix (uterus): In general, the word "cervical" is used to identify the neck location whereas "cervix" is used to identify the uterine location. When a "cervical" term refers to the uterus, it carries the qualifier of "uterine" to differentiate it from cervical spine conditions. Exceptions to this latter convention are concepts that could only relate to the uterine location (e.g., PT *Cervical dysplasia*) and thus require no further qualification.

Dilation and Dilatation: Standard medical definitions of "dilation" and "dilatation" indicate that they are synonyms. The MSSO recognizes that there are some common usages in certain cultures for these types of terms. However, for purposes of distinction in MedDRA, the term "dilation" is considered a procedure and the term "dilatation" is considered a disorder. The word "procedure" is normally added to "dilation," e.g., PT *Stomach dilation procedure* to make it self-explanatory. An exception to this convention is PT *Uterine dilation and curettage,* since it is recognized as a procedure without the addition of the qualifying word.

Drainage (surgical/procedural term) and Discharge (non-surgical secretion term): "Drainage" is a term used as a procedure (systematic withdrawal of fluids), whereas "discharge" and "secretion" are terms used for the excretion of liquids from the body. "Drainage" terms that fall outside of the realm of surgical procedures are considered exceptions and dealt with by using the word "discharge." These terms are linked appropriately based on their particular meaning (e.g., PT *Post procedural discharge* links to SOC *Injury, poisoning and procedural complications*). In addition, all surgical terms retain "drainage" and link to SOC *Surgical and medical procedures*. Finally, if a term can be either a surgical procedure or a non-surgical term, then both the "term+drainage" (PT *Post procedural drainage* linked to SOC *Surgical and medical procedures*) and the "term+discharge" (PT *Post procedural discharge* linked to SOC *Injury, poisoning and procedural complications*) are present in the terminology and linked as indicated above. The MSSO recognizes that there are some common usages in certain cultures for these types of terms that may not be reflected by this MedDRA rule. Subscribers are advised to make clear which concept applies – surgical, non-surgical, or both – when submitting Change Requests.

Failure and Insufficiency: In MedDRA, for the major body systems of cardiac, hepatic, pulmonary, and renal, the words "failure" and "insufficiency" are used synonymously. In SOC *Cardiac disorders,* SOC *Hepatobiliary disorders,* SOC *Renal and urinary disorders, and* SOC *Respiratory, thoracic and mediastinal disorders,* the "failure" term is generally at the PT level and the "insufficiency" term is at the LLT level (e.g., PT *Cardiac failure* and *LLT Cardiac insufficiency*).
Interpretations of the words "failure" and "insufficiency" can be problematic; some users may interpret the concepts as synonymous while others interpret them as similar, but differing in severity (with "insufficiency" being less severe than "failure"). In order to reconcile this, MSSO decided to make the terms essentially synonyms for the major body systems as described above. The MSSO realizes this means that many subscribers will have a different interpretation of these words than MedDRA's, but MSSO found this was the most practical solution for consistency in the terminology.

Gangrene Terms: Terms with "gangrene" or "gangrenous" have a primary link to SOC *Infections and infestations,* except those specifically representative of a noninfective concept (e.g. PT *Dry gangrene*).

Drug Product Names: Generic drug names are used (e.g., "digoxin," not "Lanoxin®") but only appear in MedDRA because they give further clarification to their parent PT (e.g., PT *Toxicity to various agents*) in the early days of the terminology.

Greek Letters: Greek letters are spelled out ("alpha," not "α;" "beta," not "β").

Eponymous Terms: Eponymous terms are only used if recognized internationally (e.g., LLT *Paul Bunnell test* linked to PT *Mononucleosis heterophile test*).

Lesion: .Lesion terms may be considered for inclusion in MedDRA when the word "lesion" is part of a medical concept, e.g., PT *Glomerulonephritis minimal lesion* or a well documented medical concept, e.g., LLT *Brain lesion.* However, the term will not be added when adding a broad "lesion" term only adds an additional imprecise term to existing "disorder" concepts, e.g., "renal lesion," when one could use for coding the existing LLT *Renal disorder* under *PT Renal disorder*.

Lump (non-neoplastic): For MedDRA terms, the word "lump" is not considered neoplastic. Terms with "lump" are linked primarily to the SOC that represents the site of manifestation.

Mass (non-neoplastic): For MedDRA terms the word "mass" is not considered neoplastic. Terms with "mass" are linked primarily to the SOC that represents the site of manifestation. "Mass" terms which have no inherent anatomic site (e.g., PT *Mass*) are linked as primary to SOC *General disorders and administration site conditions*.

Tumor (neoplastic): Terms containing the word "tumo(u)r" are considered neoplastic. PTs that represent tumors are linked primarily to SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*. The secondary link is to the site of

manifestation when identified. If malignancy is not specified in a tumor term, it is linked to an HLT that contains the wording " …malignancy unspecified."

Congenital and Acquired: For conditions or diseases existing in both congenital and acquired forms, the following convention is applied: the more common form of the condition/disease is represented at the PT level without adding a qualifier of either "congenital" or "acquired." For example, hypothyroidism is more commonly acquired than congenital; therefore, the unqualified term is at the PT level (PT *Hypothyroidism*). The less common form of the condition or disease will also be at the PT level but with a qualifier added. Using again the example of hypothyroidism, the less common congenital form has the qualifier "congenital" at the PT level (PT *Congenital hypothyroidism*). The addition of qualified LLTs under the non qualified PT term is limited in MedDRA. The qualified LLTs will only be added in instances where the likelihood of occurrence of congenital and acquired condition is close to being the same. The alignment of existing affected terms along the lines described above (i.e., the "acquired," "congenital," and unqualified terms) has already been carried out in MedDRA Version 8.0. The subscriber Change Request process will drive the remainder of alignments of possible term sets.

Polyp Terms: The existing unqualified polyp terms in MedDRA (e.g., PT *Gastric polyps*) currently default to a benign classification within SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*. Newly accepted polyp terms will not include a qualifier of "benign." Polyps are secondarily linked to SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)* and primarily linked to the appropriate site of manifestation SOC. Polyp terms with the qualifier of "malignant" will no longer be added to MedDRA. Instead, it is recommended that subscribers use available "malignant neoplasm" terms for their coding needs.

Death: Death terms are in SOC *General disorders and administration site conditions* and may have additional secondary links to related site or etiology SOCs. For example, PT *Death* is only linked to SOC *General disorders and administration site conditions*, while PT *Death neonatal* is linked primarily to SOC *General disorders and administration site conditions* and secondarily to SOC *Pregnancy, puerperium and perinatal conditions.*
Foetal and maternal death terms are linked primarily to SOC *Pregnancy, puerperium and perinatal conditions* as they are considered a special population.
"Death of a relative" is considered a social issue, and terms will be found linked only to SOC *Social circumstances*.
"Cell death" is considered an exception and is linked primarily to SOC *Metabolism and nutrition disorders* because it is an event on a cellular, not organism, level.

Occlusion and obstruction: In general, whenever referring to blood vessels, stents, shunts, and catheters, the word "occlusion" is used at the PT level (PT *Hepatic artery occlusion*). The word "obstruction" is generally used in association with non-vascular terms, such as the gastrointestinal tract or respiratory system (e.g., PT *Colonic obstruction* and PT *Tracheal obstruction*).

Injury and damage: Injury and damage concepts were discussed by a MedDRA Expert Panel which resulted in new guidelines for MedDRA. Based on this, injury and damage terms in MedDRA are considered generally as synonymous. Injury or damage to a major organ that has a low probability for a traumatic causality will be placed primary to the site of manifestation, unless causality ”due to accident” is the more obvious or the most probable. In this case, the term will be linked primary to SOC *Injury, poisoning and procedural complications*. Following this guidance some liver injury terms were re-aligned. PT *Cholestatic liver injury*, PT *Mixed liver injury*, and PT *Liver injury* are considered non-traumatic and are primarily linked to SOC *Hepatobiliary disorders* while PT *Traumatic liver injury* is primarily linked to SOC *Injury, poisoning and procedural complications*.

Intestine and Intestinal: Terms with a combination of small/large and intestine/intestinal refer to the anatomical site and not the severity of concepts, e.g., PT *Small intestinal haemorrhage* and PT *Large intestine polyp* refer to the site of haemorrhage and polyp respectively and not the severity of the two events.

Spine and Spinal: For the purposes of MedDRA, spine and spinal terms are considered synonymous with vertebral and spinal column concepts rather than with the spinal cord, unless "spinal" clearly represents a neurological concept such as PT *Spinal claudication*.

5.2 GENERAL SEARCH STRATEGIES

Single-axial SOC search: SOC *Investigations*, SOC *Social circumstances*, and SOC *Surgical and medical procedures* are single-axial SOCs. The terms in these SOCs are only represented in these SOCs, i.e., they do not have links to any other SOCs in MedDRA. If a search of MedDRA-coded data is to include laboratory test results, social issues, or therapeutic procedures, these individual SOCs should be represented in the query. For example, increased blood glucose is associated with diabetes mellitus; however, PT *Diabetes mellitus* is represented in SOC *Metabolism and nutrition disorders* and SOC *Endocrine disorders*, whereas PT *Blood glucose increased* is represented only in SOC *Investigations*. (Please refer to Section 6 - System Organ Classes - for additional information.)

6. SYSTEM ORGAN CLASSES

Explanatory Notes

Explanatory notes are provided for each SOC and cover its structure and the basis for classification (e.g., anatomic, pathologic, or etiologic). These notes provide guidance on use of the terminology to ensure effective and comprehensive data retrieval.

The total number of unique terms at each level of the MedDRA heiarchy can be found in the latest version of the MedDRA Distribution File Format Document

6.1 BLOOD AND LYMPHATIC SYSTEM DISORDERS

6.1.1 Basis for Classification

The terms within this SOC are primarily divided pathologically at the HLGT level. At the HLT level, terms are further subdivided by etiology and pathology wherever possible. For example, HLGT *Haemolyses and related conditions* consists of HLTs that group together hemolytic PTs with common etiology (e.g., HLT *Anaemias haemolytic immune*). HLTs concerning spleen, lymphatic, and reticuloendothelial system disorders are divided on an anatomic basis. Finally, HLTs concerning hematologic neoplasms have been classified according to histologic criteria.

Some HLTs are meant to address a relevant group of related pathologic conditions, such as HLT *Eosinophilic disorders*, which shares a place under HLGT *White blood cell disorders* with other HLTs mostly related (though not always) to blood peripheral findings.

6.1.2 Conventions and Exceptions

The representation of hematologic neoplasms is identical to the hierarchy developed for the same terms within SOC *Neoplasms benign and malignant (incl cysts and polyps).* Lymphoma classification in MedDRA at the PT level and above follows the Revised European-American Lymphoma (R.E.A.L.) Classification. The Working Formulation classification is limited to the LLT level.

All lymphatic system-related disorders have their primary link to SOC *Blood and lymphatic system disorders* except infective and congenital disorders. (Lymphoma terms do not follow this convention).

6.1.3 Search Strategies

If a search is intended to cover an overall classification of anemias, then in addition to HLGT *Anaemias nonhaemolytic and marrow depression*, both HLGT *Haemoglobinopathies* and HLGT *Haemolyses and related conditions* should also be considered. In a similar situation, when looking for a general view of “bleeding diatheses,” consider searching under HLGT *Coagulopathies and bleeding diatheses (excl thrombocytopenic)*, and HLGT *Platelet disorders* (especially HLT *Thrombocytopenias*).

6.2 CARDIAC DISORDERS

6.2.1 Basis for Classification

The division of HLGTs within this SOC has been done partly on an anatomic basis (endocardial, myocardial and pericardial disorders, coronary artery disorders, and valve disorders) and partly by pathophysiology (neoplasms, arrhythmias, cardiac failure, congenital cardiac disorders, and cardiac signs and symptoms). HLTs are grouped by pathophysiology, with the exception of valve disorders, which are grouped anatomically by the valve affected.

6.2.2 Conventions and Exceptions

All congenital cardiac disorders are placed within HLGT *Congenital cardiac disorders*. Thus, HLGT *Cardiac valve disorders* contains only those cardiac valve disorders that are not specified as congenital.

Certain congenital anomalies include both cardiac and vascular components. These terms have been linked to HLT *Congenital cardiovascular disorders NEC* (with HLGT *Congenital cardiac disorders* linking it to SOC *Cardiac disorders*).

Electrocardiogram (ECG) results are not included in SOC *Cardiac disorders*; they are grouped in HLT *ECG Investigations* within SOC *Investigations*.

Auscultatory abnormalities are grouped in HLT *Cardiac auscultatory investigations* under HLGT *Cardiac and vascular investigations (excl enzyme tests)* in SOC *Investigations.*

For the major body systems of cardiac, hepatic, pulmonary, and renal, the terms “failure” and “insufficiency” are used synonymously. In SOC *Cardiac disorders*, the “failure” term is at the PT level and the “insufficiency” term is at the LLT level (e.g., PT *Cardiac failure* and LLT *Cardiac insufficiency*).

6.3 CONGENITAL, FAMILIAL AND GENETIC DISORDERS

6.3.1 Basis for Classification

The terms within this SOC are primarily divided anatomically at the HLGT level. Where possible, these divisions at the HLGT level reflect the system organ classes used in MedDRA as a whole (e.g., HLGT *Hepatobiliary disorders congenital* and HLGT *Endocrine disorders congenital are the names of SOCs with "congenital" added*). Exceptions to this are HLGT *Chromosomal abnormalities and abnormal gene carriers*, HLGT *Congenital and hereditary disorders NEC,* and HLGT *Cytoplasmic disorders congenital*. At the HLT level, terms are further subdivided by anatomy wherever possible (e.g., HLT *Thyroid disorders congenital*). For those HLGTs that cannot be divided by anatomy (e.g., HLGT *Metabolic and nutritional disorders congenital*), PTs are grouped in HLTs by disease process (e.g., HLT *Inborn errors of bilirubin metabolism*) or, in the case of HLGT *Infections and infestations congenital*, by class of organism (e.g., HLT *Bacterial infections congenital*).

6.3.2 Conventions and Exceptions

In MedDRA, the term "congenital" is used to describe any condition present at birth, whether genetically inherited or occurring in utero.

Most MedDRA terms representing congenital, familial, and genetic disorders have manifestations in more than one system or organ class. Since a term can only appear in one HLT within a SOC, the HLT for these terms has been selected according to the most clinically significant manifestation of that disorder. Additionally these terms typically have SOC *Congenital, familial and genetic disorders* as their primary SOC. However, they will have links to secondary SOCs as usual in the multi-axial structure. For example, PT *Congenital HIV infection* links to four SOCs: SOC *Congenital, familial and genetic disorders* (primary), SOC *Pregnancy, puerperium and perinatal conditions*, SOC *Immune system disorders*, and SOC *Infections and infestations*.

For conditions or diseases existing in both congenital and acquired forms, the following convention is applied: the more common form of the condition/disease is represented at the PT level without adding a qualifier of either "congenital" or "acquired." For example, hypothyroidism is more commonly acquired than congenital; therefore, the unqualified term is at the PT level (PT *Hypothyroidism*). The less common form of the condition or disease will also be at the PT level but with a qualifier added. Using again the example of hypothyroidism, the less common congenital form has the qualifier "congenital" at the PT level (PT *Congenital hypothyroidism*). The addition of qualified LLTs under the non qualified PT term is limited in MedDRA. The qualified LLTs will only be added in instances where the likelihood of occurrence of congenital and acquired condition is close to being the same. Alignment of existing affected terms along the lines described above (i.e., the "acquired," "congenital," and unqualified terms) has already been carried out in MedDRA Version 8.0. The subscriber Change Request process will drive the remainder of alignments of possible term sets.

6.4 EAR AND LABYRINTH DISORDERS

6.4.1 Basis for Classification

The terms within this SOC are primarily divided at the HLGT level by anatomic site (external, middle, and inner ear). At the HLT level, terms are further subdivided anatomically, but the disease process may also be reflected at this level (e.g., HLT *Middle ear infections and inflammations*). Congenital problems are grouped in HLGT *Congenital ear disorders (excl deafness*), which is subdivided into HLTs by anatomic criteria. Non-site specific terms are linked to HLGT *Hearing disorders*.

6.4.2 Conventions and Exceptions

The PTs for neoplasms appear in the appropriate HLT by anatomic site (e.g., PT *Benign middle ear neoplasm* appears in HLT *Middle ear disorders NEC*).

Infections and inflammations are grouped at the HLT level in the HLGT *External ear disorders (excl congenital)*, HLGT *Middle ear disorders (excl congenital)*, and HLGT *Inner ear and VIIIth cranial nerve disorders*.

The pinna, which includes the ear lobe, is considered part of the ear structure and is primarily linked to SOC *Ear and labyrinth disorders*.

6.5 ENDOCRINE DISORDERS

6.5.1 Basis for Classification

Endocrine disorders are classified using two general approaches. The first approach groups HLTs specific to the dysfunction of a specific endocrine gland under an HLGT specific to that gland. For example, HLGT *Adrenal gland disorders* is superordinated to HLT *Adrenal cortical hyperfunctions,* HLT *Adrenal cortical hypofunctions,* HLT *Adrenal gland disorders NEC,* HLT *Adrenal medulla disorders,* and HLT *Adrenal neoplasms.*

HLT *Adrenal gland disorders NEC* contains terms relating to adrenal gland infections, injuries, and congenital disorders. These terms have secondary links to SOC *Endocrine disorders.*

The second type of classification includes HLGTs that group disorders affecting multiple endocrine glands, such as HLGT *Endocrine and glandular disorders NEC* and HLGT *Neoplastic and ectopic endocrinopathies.*

Within HLGT *Endocrine and glandular disorders NEC*, HLT *Endocrine disorders NEC* includes congenital and myopathic disorders with primary links to their respective SOCs. HLT *Polyglandular endocrine disorders* contains terms for conditions involving multiple endocrine glands.

HLGT *Endocrine disorders of gonadal function* includes HLTs covering male disorders, female disorders, and gender unspecified disorders as well as disorders occurring at puberty. Many of the terms here are primarily linked to the body system SOC that is affected, with secondary links to SOC *Endocrine disorders*.

6.5.2 Conventions and Exceptions

There are two separate HLGTs that relate to diabetes: HLGT *Glucose metabolism disorders (incl diabetes mellitus)*, with HLTs for diabetes mellitus and both hypo- and hyperglycemic conditions; and HLGT *Diabetic complications*, which subdivides the complications of the disease anatomically. These two HLGTs are multi-axial and are also linked to SOC *Metabolism and nutrition disorders*.

Pancreatic endocrine disorders are linked primarily to SOC *Endocrine disorders*, whereas pancreatic exocrine disorders are linked primarily to SOC *Gastrointestinal disorders*. If the term does not distinguish between endocrine and exocrine, then the primary link defaults to SOC *Gastrointestinal disorders* (e.g., PT *Pancreatic disorder*).

6.6 EYE DISORDERS

6.6.1 Basis for Classification

SOC *Eye disorders* is subdivided along pathophysiologic and anatomic lines. The primary ordering of the HLGTs is according to pathophysiology, e.g., HLGT *Ocular infections, irritations and inflammations* and HLGT *Ocular neoplasms*. Both pathophysiology and anatomy are used to approach the classification of other HLGTs, which are disorders occurring in specific tissues of the eye, e.g., structural change, deposit, or degeneration of the anterior portion of the eye, or vascular disorder and hemorrhage of retina, choroids, or vitreous. HLGTs using pathophysiology for organization are subdivided using anatomically classified HLTs. For example, under HLGT *Ocular injuries* is HLT *Corneal injuries*. In HLGTs using the pathophysiologic and anatomic organization, HLTs are also further classified anatomically. Eyelid, lash, and lacrimal disorders are included in this SOC under the appropriate pathophysiologic HLGTs.

HLGT *Congenital eye disorders (excl glaucoma)* is inclusive of all congenital eye disorders with the exception of glaucoma. HLT *Congenital glaucomas* is located under a separate HLGT, namely, HLGT *Glaucoma and ocular hypertension*. All congenital eye terms have a secondary linkage to SOC *Eye disorders.*

HLGT *Eye disorders NEC contains* a mixture of HLTs based on both anatomy and etiology (e.g., HLT *Corneal disorders NEC*). This HLGT contains those medical concepts that are of an unspecified nature as well as those terms related to eye structures that do not fall within the HLGT classification scheme.

HLGT *Vision disorders* is segmented primarily by pathophysiology and contains terms that describe the etiology of visual disorders, such as HLT *Amblyopic vision impairment,* HLT *Refractive and accommodative disorders,* HLT *Colour blindness (incl acquired),* and HLT *Blindness (excl colour blindness)*.

HLGT *Ocular neoplasms* is subdivided pathophysiologically according to tumor type.

Note that there are hierarchical classifications in other SOCs that include terms of relevance to ophthalmologic concepts. Such terms merit consideration when designing search strategies and data retrieval and analysis criteria for terms pertaining to eye disorders. Examples include:

- SOC *Nervous system disorders*: HLGT *Neurological disorders of the eye*;
- SOC *Surgical and medical procedures*: HLGT *Eye therapeutic procedures*;
- SOC *General disorders and administration site conditions*: HLT *Eye complications associated with device*;
- SOC *Injury, poisoning and procedural complications*: HLT *Eye and ear procedural complications;*
- SOC *Investigations*: HLT *Ophthalmic function diagnostic procedures*, HLT *Ophthalmic histopathology and imaging procedures*, PT *Ophthalmological examination abnormal (*under HLT *Physical examination procedures and organ system status*).

6.6.2 Conventions and Exceptions

PT *Blindness* is linked to HLGT *Vision disorders*. To make a distinction between blindness as a disability and blindness as a medical disorder, PT *Sight disability* is linked to SOC *Social circumstances* (blindness as a disability) and PT *Blindness* is linked to SOC *Eye disorders* (blindness as a medical disorder) and to SOC *Nervous system disorders* .

The eyelid is classified as a structure of the eye. In general, terms related to the eyelid are primarily linked to SOC *Eye Disorders* and secondarily to SOC *Skin and subcutaneous tissue disorders*.

6.7 GASTROINTESTINAL DISORDERS

6.7.1 Basis for Classification

There are three principles for classification in this SOC. Terms are gathered at the HLGT level by a mix of disease process, etiology, and pathologic groupings (e.g., HLGT *Abdominal hernias and other abdominal wall conditions,* HLGT *Gastrointestinal infections*, and HLGT *Gastrointestinal ulceration and perforation*). These HLGTs are subdivided into HLTs by anatomic site or subtypes of the disease process. For instance, HLGT *Gastrointestinal infections* contains HLTs based on anatomic site (anal and rectal, intestinal, esophageal, etc.), but HLGT *Gastrointestinal motility and defaecation conditions* has HLTs reflecting the disease process (e.g., HLT Gastrointestinal dyskinetic disorders). Neoplasm terms are linked to HLGT *Benign neoplasms gastrointestinal* and to HLGT *Malignant and unspecified neoplasms gastrointestinal NEC*. The remaining HLGTs are based on anatomic site (HLGT *Oral soft tissue conditions*) with HLTs denoting further anatomic specificity (HLT *Cleft lip and cleft palate disorders*), disease process (HLT *Stomatitis and ulceration*), or a combination of both (HLT *Oral soft tissue pain and paraesthesia*).

6.7.2 Conventions and Exceptions

HLGT Gastrointestinal infections and HLGT *Gastrointestinal inflammatory conditions* are separate HLGTs in SOC *Gastrointestinal disorders*. In other SOCs, inflammatory and infectious conditions are often within a single HLGT (e.g., HLGT *Ocular infections, irritations and inflammations* in SOC *Eye disorders*). Pancreatic endocrine disorders are linked primarily to SOC *Endocrine disorders*. Pancreatic exocrine disorders are linked primarily to SOC *Gastrointestinal disorders*. If the term does not distinguish between endocrine and exocrine, then the primary link defaults to SOC *Gastrointestinal disorders* (e.g., PT *Pancreatic disorder*).

“Perineum” terms may be linked to several SOCs including SOC *Reproductive system and breast disorders* and SOC *Pregnancy, puerperium and perinatal conditions*. Newly added “perineum” terms resulting from Change Requests are linked to their most appropriate classification on a case-by-case basis.

6.8 GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS

6.8.1 Basis for Classification

This SOC contains terms that do not readily fit into the hierarchy of any one SOC or are nonspecific disorders that impact several body systems or sites. HLGTs within it are divided by etiology (therapeutic and non-therapeutic effects and administration site reactions) or pathology (fatal outcomes and tissue conditions). The HLTs within each HLGT are mainly divided by disease process. Exceptions are HLGT *Administration site reactions*, which is divided by type of administration - (application, implant, and injection site); and HLGT *Therapeutic and nontherapeutic effects (excl toxicity)*, which is grouped by type of effect (e.g., HLT *Interactions* and HLT *Therapeutic and nontherapeutic responses*). HLT *Therapeutic and nontherapeutic responses* is a broad HLT intended to capture terms in MedDRA that cannot be placed in any other specific HLT grouping (e.g., PT *Drug effect decreased* and PT *Drug ineffective*). Terms related to specific drugs, drug related issue, specific site of manifestation or specific condition will be placed according to the established placement rules in MedDRA (e.g., PT *Oestrogenic effect* is mapped only to site of manifestation in HLT *Endocrine abnormalities of gonadal function NEC).*

In MedDRA Version 19.0, grouping terms relating to product quality issues and device issues have been moved from this SOC to the new SOC *Product issues* which was created to accommodate non-clinical/non-patient related concepts. Specifically, HLGT *Product quality issues* with its five subordinate HLTs (HLT *Product contamination and sterility issues*, HLT *Product label issues*, HLT *Product packaging issues*, HLT *Product physical issues*, and HLT *Product quality issues NEC)* has been merged with new HLGT *Product quality, supply, distribution, manufacturing and quality system issues* in SOC *Product issues.* Additionally, HLGT *Device issues* has been moved to SOC *Product issues* with all its eight subordinate HLTs (HLT *Device computer issues*, HLT *Device electrical issues*, HLT *Device incompatibility issues*, HLT *Device information output issues*, HLT *Device issues NEC*, HLT *Device malfunction events NEC*, HLT *Device operational issues NEC*, and HLT *Device physical property and chemical issues).*

6.8.2 Conventions and Exceptions

Representing PTs in SOC *General disorders and administration site conditions* in each potential secondary SOC would create an inordinately large number of multi-axial links. Therefore, most of the PTs in this SOC are primarily linked to SOC *General disorders and administration site conditions*, and have limited representation in secondary SOCs (e.g., PT *Injection site atrophy* is primarily to SOC *General disorders and administration site conditions* and secondarily only to SOC *Injury, poisoning and procedural complications*). There are a number of PTs in this SOC that are non-multi-axial due to their general nature (e.g., PT *Fatigue,* PT *Malaise,* and PT *Discomfort*).

LLT *High temperature* is in SOC *General disorders and administration site conditions*. Although the concept should appear in SOC *Investigations* by convention (i.e., it could

be interpreted as a measured parameter), it is most frequently used as an expression for fever (PT *Pyrexia)*. Thus, this term is represented in SOC *General disorders and administration site conditions*.

HLGT *Complications associated with device* is used to capture patient reactions that occur during the use of a medical device (may or may not be directly attributable to the use of the device) and events that are a direct consequence of use of the medical device.

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6.9 HEPATOBILIARY DISORDERS

6.9.1 Basis for Classification

The terms in this SOC are grouped under four HLGTs. Three of these HLGTs are grouped by anatomic location and are subdivided into HLTs reflecting the etiology or disease process. For example, HLGT *Bile duct disorders* includes HLT *Bile duct infections and inflammations,* HLT *Obstructive bile duct disorders (excl neoplasms)*, and HLT *Structural and other bile duct disorders*. The remaining HLGT is HLGT *Hepatobiliary neoplasms*, distinguishing between benign and malignant neoplasms and neoplasms with unspecified characteristics at the HLT level.

Two spellings, “hepato-biliary” and “hepatobiliary,” are used frequently in practice. MedDRA uses “hepatobiliary,” following *Dorland’s Illustrated Medical Dictionary*.

For the major body systems of cardiac, hepatic, pulmonary, and renal, the terms “failure” and “insufficiency” are used synonymously. In SOC *Hepatobiliary disorders*, the “failure” term is at the PT level and the “insufficiency” term is at the LLT level (e.g., PT *Hepatic failure* and LLT *Hepatic insufficiency*).

6.10 IMMUNE SYSTEM DISORDERS

6.10.1 Basis for Classification

The terms within this SOC are divided by disease process. The HLGTs are HLGT *Allergic conditions,* HLGT *Autoimmune disorders,* HLGT *Immune disorders NEC*, and HLGT *Immunodeficiency syndromes*. Further sub-classification at the HLT level is by pathologic groupings, with some anatomically based subdivision as in the case of HLGT *Autoimmune disorders*.

6.10.2 Conventions and Exceptions

Only very well defined secondary immunodeficiencies have been included under HLT *Immunodeficiency disorders NEC*. The link of all possible immunodeficiencies under this HLT would result in too large a group for analytical purposes.

The concept of transplant rejection is recognized as an effect of the immune system; therefore, related terms have SOC *Immune disorders* as the primary link with the site of manifestation as a secondary link.

Due to the systemic nature of SOC *Immune system disorders*, multi-axial terms are especially frequent. For instance, conditions related to the group of "connective tissue disorders" are found under HLGT *Autoimmune disorders* as well as in SOC *Musculoskeletal and connective tissue disorders* (in HLGT *Connective tissue disorders (excl congenital)*), with still a possible third link in the related anatomic SOCs (generally the primary link). For instance, PT *Lupus vasculitis* has the following links:

PT	HLT	HLGT	SOC	Link
Lupus vasculitis	**Vasculitides NEC**	**Vascular inflammations**	**Vascular disorders**	**Primary**
	Lupus erythematosus (incl subtypes)	Connective tissue disorders (excl congenital)	Musculoskeletal and connective tissue disorders	Secondary
	Lupus erythematosus and associated conditions	Autoimmune disorders	Immune system disorders	Secondary

Table 6-1. Sample of Exceptions and Conventions in SOC Immune System Disorders

Other pathologic groupings within SOC *Immune system disorders,* in which a similar multi-axial richness can be found, are transplant rejection terms (that are also in SOC *Injury, poisoning and procedural complications* linked to HLGT *Procedural related injuries and complications NEC)*. Transplant terms are also linked to their respective anatomic site SOCs. HLT *Vasculitides* has its counterpart in SOC *Vascular disorders* grouping terms (see HLGT *Vascular inflammations*); terms linked to this HLT are also found in the associated anatomic SOCs.

6.11 INFECTIONS AND INFESTATIONS

6.11.1 Basis for Classification

SOC *Infections and infestations* were developed to provide a unique location for infectious disorders and related conditions. The organization of this SOC at the HLGT level is based on broad, commonly used taxonomic classifications of pathogens (e.g., HLGT *Bacterial infectious disorders,* HLGT *Fungal infectious disorders*, and HLGT *Ectoparasitic disorders*). At the HLT level, these groups are further sub-classified by genus in most cases for bacterial, protozoal, fungal, and viral disorders (e.g., HLT *Candida infections*).

One general HLGT, HLGT *Infections - pathogen unspecified* is used to group together infections by anatomic location rather than pathogen class. The HLTs under this HLGT are named according to general anatomic location, such as HLT *Bone and joint infections*. However, diseases of specific anatomic locations caused by specified pathogens are classified under the name of the pathogen, and not under the corresponding anatomic location in this HLGT.

6.11.2 Conventions and Exceptions

Most PTs in SOC *Infections and infestations* are primarily linked to this SOC. Exceptions are PTs that have a primary link to either SOC *Congenital, familial and genetic disorders* or SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*. For these terms, the link to SOC *Infections and infestations* is secondary. Additionally, PTs under HLT *Inflammatory disorders following infection* within HLGT *Ancillary infectious topics* may also have a secondary link to SOC *Infections and infestations*. This HLGT does not include PTs representing infections or infestations but instead includes PTs that are very closely related such as PT Infectious disease carrier; it also has terms representing types of infectious transmission (e.g., PT *Air-borne transmission*) or inflammatory conditions following an infection (e.g., PT *Rheumatic fever*).

Terms ending with “-itis” are linked to SOC Infections and infestations only if they most frequently represent infectious conditions (PT *Tonsillitis*). Those terms that most frequently represent inflammatory conditions (e.g., PT *Bursitis*) are linked only to their corresponding site of manifestation SOCs.

In general, pathogen genus is represented at the HLT level (e.g., HLT *Mycoplasma infections*). The PT level generally combines genus and anatomic site of infection in a single term (e.g., PT *Pharyngitis mycoplasmal*), Genus, anatomic site, and species are designated in a single term at the LLT level (e.g., LLT *Mycoplasma pneumoniae pharyngitis*).

When the concepts of “sepsis” and “septic(a)emia” are paired in the terminology, the “sepsis” terms are PTs and the corresponding “septic(a)emia” terms are LLTs.

Terms with “gangrene” or “gangrenous” have a primary link to SOC Infections and infestations, except those specifically representative of a noninfective concept (e.g. PT *Dry gangrene*).

Within SOC *Infections and infestations,* PT level “cellulitis” terms are linked to the appropriate bacterial infection HLTs rather than the site of manifestation HLTs.

6.11.3 Search Strategies

For a search of opportunistic infections, the underlying disease, drug class, and other aspects possibly relevant to the question should be considered when selecting terms from MedDRA. For example, the most likely pathogen or the body site affected may differ depending on the cause of immunosuppression (e.g., HIV infection, solid organ transplant, hematopoietic stem cell transplant, malignancy, chemotherapy, TNF-alfa blockers, etc.), geographical region, and calendar year/decade (due to changes of prominence of pathogens over time). As a starting point, SOC *Infections and infestations* should be reviewed multi-axially.

For a narrow (specific) search, it may suffice to restrict the search to certain terms in SOC Infections and infestations

If taking a broad approach, all terms in SOC *Infections and infestations* may be included in the search, including terms not indicating the causative agent (e.g., PT *Pneumonia* or PT *Sepsis*). Additionally, relevant terms may be found in SOC *Investigations*, such as laboratory abnormality terms in HLGT *Microbiology and serology investigations*.

Additional terms may be relevant for inclusion for specific conditions as in the following examples:

For an underlying HIV infection, many PTs containing "HIV," "AIDS," "CD4," or "T-lymphocyte" may be added, plus PT Immune reconstitution syndrome.

For an underlying solid organ transplant or hematopoietic stem cell transplant, certain PTs containing "transplant" or "graft" may be relevant.

For an underlying malignancy, SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)* may be reviewed; certain PTs indicating neutropenia and resulting complications secondary to chemotherapy may be added to the search.

6.12 INJURY, POISONING AND PROCEDURAL COMPLICATIONS

6.12.1 Basis for Classification

This SOC provides a grouping for those medical concepts where an injury, poisoning, procedural, or device complication factor is significant in the medical event being reported.

Terms that represent events directly attributed to trauma, poisoning, and procedural complications are primarily linked to SOC *Injury, poisoning and procedural complications,* with the exception of terms related to birth trauma such as PT *Facial nerve injury due to birth trauma*, which is primary to SOC *Pregnancy, puerperium and perinatal conditions*. Bone fractures, which in most cases are attributed to trauma, are primary to this SOC, whereas pathologic and osteoporotic fractures are primary to SOC *Musculoskeletal and connective tissue*. Terms in HLT *Poisoning and toxicity* under HLGT *Exposures, chemical injuries and poisoning* are generally primarily linked to this SOC, except when the body system is identified by the text string of the term. In these cases, the SOC representing the site of manifestation is primary. An example of this is "toxic nephropathy," which could be an adverse event due to an external agent or to an internal organ condition. (PT *Nephropathy toxic* is linked primarily to SOC *Renal and urinary disorders* and secondarily to SOC *Injury, poisoning and procedural complications*.)

Injury and damage concepts were discussed by a MedDRA Expert Panel which resulted in new guidelines for MedDRA. Based on this, injury and damage terms in MedDRA are considered generally as synonymous. Injury or damage to a major organ that has a low probability for a traumatic causality will be placed primary to the site of manifestation, unless causality "due to accident" is the more obvious or the most probable. In this case, the term will be linked primary to SOC *Injury, poisoning and procedural complications*. Following this guidance some liver injury terms were re-aligned. PT *Cholestatic liver injury*, PT *Mixed liver injury*, and PT *Liver injury* are considered non-traumatic and are primarily linked to SOC *Hepatobiliary disorders* while PT *Traumatic liver injury* is primarily linked to SOC *Injury, poisoning and procedural complications*.

A distinction has been made between exposure "to" versus exposure "via" terms (e.g., PT *Exposure to body fluid* and PT *Exposure via body fluid*) because this distinction is relevant to the representation of different exposure concepts and is of particular significance to toxicologic elements of pharmacovigilance. While the difference between "via" and "to" may appear subtle, the "via" terms indicate the vehicle by which the patient is exposed whereas "to" concepts identify the specific agent of exposure. For example, PT *Exposure to body fluid* might be used to code medical history, when it may not be known whether the body fluid was infectious or contained some other harmful element. The "via" terms are meant to be used in combination with one or more additional term(s), for example, to code the agent of exposure, such as LLT *Hepatitis B*, and any resulting clinical consequences, such as LLT *Jaundice*.

HLGT *Procedural related injuries and complications NEC* groups terms related to surgical and medical therapeutic procedures. The HLTs are mainly grouped

anatomically, but there are also procedure-specific term groupings such as HLT *Induced abortion complications* and HLT *Anaesthetic complications*.

HLGT *Administration site reactions* is a multi-axial HLGT. It is primarily linked to SOC *General disorders and administration site conditions*. This HLGT is also linked (secondarily) to SOC *Injury, poisoning and procedural complications* for the purpose of providing a common SOC linkage with surgical and medical treatment types of procedural complications that are typically found only in this SOC. HLGT *Administration site reactions* is sub-grouped into HLT *Application and instillation site reactions*, HLT *Implant and catheter site reactions*, HLT *Injection site reactions,* HLT *Infusion site reactions,* HLT *Vaccination site reactions* and HLT *Administration site reactions NEC*.

Medical practitioners frequently use the words “poisoning” and “toxicity” interchangeably. Based upon this common usage of the words, a distinction is not made between poisoning and toxicity in MedDRA. Instead, these types of terms are both grouped under HLT *Poisoning and toxicity*.

HLGT *Medication errors* is *further divided into* HLT groupings based on the type of medication errors. The subordinate HLTs are HLT *Maladministrations,* HLT *Medication monitoring errors,* HLT *Accidental exposures to product,* HLT *Medication errors NEC, and HLT Intercepted medication errors*. The latter HLT was added in MedDRA Version 19.0 to facilitate the coding and retrieval of intercepted medication errors. They represent a distinct category of medication errors and refer to situations where an error occurred but was identified and intercepted before reaching the patient.

A new HLGT *Product use issues* was added for MedDRA Version 18.0. It is further divided into HLT groupings of related product use concepts (misuse, off label use, overdoses, and underdoses) in one location to facilitate coding and retrieval, based on the type of product use issues without the need for additional multi-axial links. The subordinate HLTs are:

- HLT *Off label uses* accommodates specific off label use concepts such as PT *Off label use*.
- HLT *Overdoses NEC* accommodates overdose concepts that are not necessarily maladministrations such as PT *Intentional overdose* and PT *Prescribed overdose*. HLT Overdoses NEC replaced HLT Overdoses.
- HLT *Product use issues NEC* accommodates a mix of misuse, intentional use, and other non-specific use concepts. This new HLT will have two new PT concepts in addition to existing non-specific use PTs:

  – PT *Product use issue* accommodates non-specific product use concepts that are not specifically identified as medication errors, off label use, misuse etc.

  – PT *Intentional product use issue accommodates* use issue concepts that are known to be intentional but are not specifically identified as being misuse or off label use.

- HLT *Underdoses NEC* accommodates underdose concepts that are not necessarily maladministrations such as PT *Intentional underdose* and PT *Prescribed underdose.*

6.12.2 Conventions and Exceptions

HLGT *Bone and joint injuries* is an exception to the general organization of this SOC. This HLGT is not aligned anatomically under HLGT *Injuries NEC* in the way that the other body systems are grouped. This has been done for two reasons: 1) the skeletal system is frequently and significantly impacted by traumatic injuries; and 2) this additional level of classification allows a better linking to SOC *Musculoskeletal and connective tissue disorders*.

Most terms representing chemical injuries are only in this SOC, while many of the other injury terms are multi-axial with a secondary linkage to their respective site of manifestation.

Although terms for acute alcohol intoxication or poisoning are found in this SOC, the concept of ”alcoholism” is represented in SOC *Psychiatric disorders* as PT *Alcoholism*.

6.13 INVESTIGATIONS

6.13.1 Basis for Classification

The most significant characteristics of SOC *Investigations* are: 1) its content (i.e., investigations, not conditions); and 2) its single-axial nature. For MedDRA, an "investigation" is a clinical laboratory test concept (including biopsies), radiologic test concept, physical examination parameter, and physiologic test concept (e.g., pulmonary function test).

Only PTs representing investigation procedures and qualitative results (e.g., PT *Blood sodium decreased*, PT *Blood glucose normal*) appear in SOC *Investigations*. Terms representing conditions (e.g., hyperglycemia) or mixed concepts of conditions with an investigation are excluded from this SOC and can be found in the respective "disorder" SOCs (e.g., PT *Hyperosmolar state*, PT *Haemosiderosis*, PT *Orthostatic proteinuria*, and PT *Renal glycosuria*).

Terms in SOC *Investigations* are present only in this SOC and in no other SOC (i.e., SOC *Investigations* is single-axial). Therefore, it is important that queries of MedDRA-coded data encompass terms from both the "disorder" SOCs (e.g., PT *Thrombocytopenia* in SOC *Blood and lymphatic system disorders*) as well as the supporting investigation concepts in SOC *Investigations* (e.g., PT *Platelet count decreased*) since one cannot exploit multi-axial links to bridge these types of terms.

Several classification approaches to HLGTs are used in this SOC:

- Some HLGTs group investigations according to body system or according to the clinical discipline commonly specializing in a particular body system (e.g., HLGT *Skin investigations*, HLGT *Gastrointestinal investigations*, and HLGT *Haematology investigations (incl blood groups)*).
- Other HLGTs group (by type of substance, or by type of procedure) those analyses or investigations that do not fit readily into a single body system (e.g., HLGT *Water, electrolyte and mineral investigations*, HLGT *Lipid analyses*, HLGT *Toxicology and therapeutic drug monitoring, HLGT Cytogenetic investigations*, and HLGT *Physical examination and organ system status topics*).
- Three HLGTs include terms for investigations which are not classified elsewhere:
  - HLGT *Enzyme investigations NEC* groups tests that are commonly used to identify abnormalities in several body systems (e.g., HLT *Tissue enzyme analyses NEC* contains alkaline phosphatase tests for bone or liver disorders, while HLT *Skeletal and cardiac muscle analyses* contains creatine kinase isoenzyme terms related to heart, skeletal muscle, and brain tissue).
  - HLGT *Investigations, imaging and histopathology procedures NEC* includes terms describing laboratory test interference as well as terms covering unspecified laboratory investigations and imaging, and pathology procedures without a specified site.

- HLGT *Protein and chemistry analyses NEC* includes specific protein analyses that are not usually associated with single system disorders (e.g., albumin tests and turbidity tests) as well as renin and angiotensin tests.

- HLGT *Foetal and neonatal investigations* groups all fetal and neonatal investigations and procedures. It includes HLTs for diagnostic, histopathologic, and imaging procedures.
- HLT *Physical examination procedures and organ system status*, linked to HLGT *Physical examination and organ system status topics*, includes parameters measured (e.g., body temperature and body weight), and conditions found (e.g., abnormal prostate examination and hypophonesis) during physical examination.

HLTs in this SOC are generally self-explanatory. They are based on a variety of approaches:

- Some HLTs group diagnostic procedures (e.g., HLT *Cardiac function diagnostic procedures*), imaging procedures (e.g., HLT *Gastrointestinal and abdominal imaging procedures*), or pathology procedures (e.g., HLT *Musculoskeletal and soft tissue histopathology procedures*). Note, however, that some of the diagnostic procedure HLTs include imaging procedures (e.g., HLT *Ophthalmic function diagnostic procedures* includes PT *Angiogram retina*).
- For some HLTs, anatomic site or tissue type is used for grouping (e.g., HLT *Adrenal cortex tests*, HLT *Cerebrospinal fluid tests (excl microbiology)*). In such instances diagnostic, imaging, or histopathology procedures may be included within one HLT (e.g., HLT *Urinary tract function analyses NEC*).
- Other HLTs group tests of related analytes or parameters (e.g., HLT *Lysosomal enzyme analyses*, HLT *Water and electrolyte analyses NEC*, HLT *Platelet analyses*, HLT *Fungus identification and serology*).
- The following are some additional specific characteristics of SOC *Investigations*:
  - **Diaphragm and mediastinum –** Diaphragm pathology procedures and mediastinal pathology procedures are found in HLT *Respiratory tract and thoracic histopathology procedures* under HLGT *Respiratory and pulmonary investigations (excl blood gases)*.
  - **Gastrin –** Gastrin tests are included in HLT *Gastrointestinal, pancreatic and APUD hormone analyses* in HLGT *Endocrine investigations (incl sex hormones)*.
  - **Laparoscopy –** PT *Laparoscopy* appears within HLT *Gastrointestinal and abdominal imaging procedures* under HLGT *Gastrointestinal investigations.*
  - **Lymph nodes -** Lymph node scans and lymph gland histopathology procedures are included in HLT *Bone marrow and immune tissue imaging procedures* and HLT *Bone marrow and immune tissue histopathology procedures* in HLGT *Haematology investigations (incl blood groups)*.
  - **Red blood cell sedimentation rate –** PT *Red blood cell sedimentation rate* is found within HLT *Haematological analyses NEC*.

- **Urea –** Tests for urea are linked to HLGT *Renal and urinary tract investigations and urinalyses,* either within HLT *Renal function analyses* or HLT *Urinalysis NEC*.

Where possible, PTs in this SOC are those included in IUPAC, LOINC®, and IFCC standards. However, in some cases, texts of terms from these standard terminologies are not the commonly used wording by practitioners. In these instances, the text strings used in MedDRA are the ones more commonly used in practice. In some cases, natural language has been used in preference to technical correctness to avoid confusion (e.g., PT *Activated partial thromboplastin time* instead of the IUPAC term "Coagulation, surface induced"). Vitamins are represented by their common names rather than by the chemical names used in IUPAC.

6.13.2 Conventions and Exceptions

The qualifier "increased" in MedDRA terms refers to changes from normal state to high, from low to normal, from low to high, and from low normal to high normal. Similar considerations apply to results that are "decreased." MedDRA investigation terms use the qualifiers of "low" and "high" at the LLT level only; these LLTs with "low" and "high" are linked to PTs with qualifiers of "decreased" and "increased" respectively. Additionally, qualifiers "low/decreased" and "high/increased" in SOC *Investigations* are considered synonyms.

"High and "low" terms in MedDRA are generally considered to be laboratory/investigation type of terms and are found in the SOC *Investigations.* Exceptions to this rule are as follows:

- LLT *Blood pressure high* and LLT *Low blood pressure* are linked to PT *Hypertension* or PT *Hypotension*; these PTs are in SOC *Vascular disorders*.
- PTs representing "low grade" neoplasms are linked to SOC *Neoplasm benign, malignant and unspecified (including cysts and polyps)* (e.g., PT *Astrocytoma, low grade*).
- PT *Sputum decreased* and PT *Sputum increased* are in SOC *Respiratory, thoracic and mediastinal disorders*. This is because these terms commonly express a medical condition rather than an investigation finding.
- LLT *High temperature* is in SOC *General disorders and administration site conditions*. Although the concept should appear in SOC *Investigations* by convention (i.e., it could be interpreted as a measured parameter), it is most frequently used as an expression for fever (PT *Pyrexia*); thus, this term is in SOC *General disorders and administration site conditions.*

The qualifier "abnormal" in a MedDRA term represents a situation where the "direction" (i.e., increased or decreased) of the abnormal result is not specified. Other qualifiers used in SOC *Investigations* are "normal," "present," or "absent" for descriptive laboratory tests (e.g., PT *Blood urine absent*), "positive" or "negative" for qualitative tests (e.g., PT *Pregnancy test positive*), "prolonged," or "shortened" for tests measured in time (e.g., LLT *APTT prolonged*), and "toxic," "therapeutic," or "subtherapeutic" for drug level monitoring tests (e.g., PT *Drug level below therapeutic*). An unqualified term (e.g., PT

Oxygen saturation, PT *pH urine*) may be used to point to an actual value in a separate database field. Terms containing the prefixes “hyper-” and “hypo-” (e.g., PT *Hypercholesterolaemia*, PT *Hyponatraemia*) are found in their respective “disorder” SOCs and not in SOC *Investigations*.

If an analyte is not normally present in a specimen, the PT describing that abnormality may be used in some cases (e.g., PT *Glucose urine present*).

For specimen identification, the noun form of the specimen name is used (“urine cortisol,” not “urinary cortisol”) in SOC *Investigations*.

As of MedDRA Version 7.0, there has been a change to the MSSO convention for adding terms to SOC *Investigations*. Blood is no longer the default/assumed specimen when a Change Request does not specify the specimen type. In the future, newly added terms will include the specimen type if it is medically significant. When new terms without specimen type are added as PTs, any corresponding existing terms with specimen type will be demoted to LLT and linked to this new term. As an example, LLT *Blood opiates increased* is linked to PT *Opiates positive*.

For non-laboratory procedures (e.g., radiology), anatomic site replaces specimen type in the term and is stated in the text string.

It is important to consider the “incl” and “excl” aspects of any given term when navigating through the hierarchy. For example, enzyme tests that are excluded from HLGT *Cardiac and vascular investigations (excl enzyme tests)* and HLGT *Musculoskeletal and soft tissue investigations (excl enzyme tests)* are found under HLGT *Enzyme investigations NEC*. Reproductive system related hormone analyses are located under HLGT *Endocrine investigations (incl sex hormones*). Blood gas tests that are excluded from HLGT *Respiratory and pulmonary investigations (excl blood gases)* are grouped under HLGT *Metabolic, nutritional and blood gas investigations*.

Generally, the descriptors “direct” and “indirect” are used only at the LLT level; one exception is the placement of Coombs direct/indirect tests at the PT level (e.g., PT *Coombs indirect test negative*).

The “-gram” form of a term is considered a type of record of findings (e.g., PT *Audiogram*) and is generally found at the PT level. The corresponding “-graphy” terms are usually found as LLTs linked to their corresponding “-gram” terms (e.g., LLT *Left ventriculography* linked to PT *Cardiac ventriculogram left*).

6.13.3 Term Placement Guidelines (set forth in the first Blue Ribbon Panel in 2003)

In most cases microbiology and serology investigations use general “serology” terms at the LLT level. The same general rule applies to DNA tests. Specimen types are not differentiated at the PT level unless they have clinically different interpretations. Requested terms of antibody, IgG, IgM, of microorganisms are added at the LLT level under a PT “genus + qualified or unqualified test” term.

Uncommon organisms have serology and DNA tests at the LLT level under a general PT (e.g., LLT *Babesia serology negative* is linked to PT *Parasitic blood test negative*)..

For requested “culture” terms, only specimen terms of blood, CSF, urine, or stool for bacterial, fungal, and viral type investigations will remain at the PT level. Other specimen terms will be represented at the LLT level. For example, LLT *Culture bone positive* is linked to PT *Culture positive*.

The microorganism DNA tests (e.g. bacterial DNA test, viral DNA test positive, fungal DNA test positive) are generally not represented at the PT level. They are represented as LLTs under unqualified or test positive PTs such as LLT*Bacterial DNA test positive* under PT *Bacterial test positive ,* LLT *Fungal DNA test positive under PT Fungal test positive.* The type of organism is also listed at the LLT level. For example, LLT *Pneumocystis carinii DNA test positive* is linked to PT *Pneumocystis test positive*.

For hormone, mono- or oligosaccharides, amino acid, oligopeptides, or metal element analysis, specimen types are not differentiated at the PT level unless they have clinically different interpretations. Whether or not the specimen type will be represented at the LLT level is determined by clinical significance.

For therapeutic drug monitoring analyses, there will be no further expansion of drug classes at this time.

For narcotic drugs, specimen types are not differentiated at the PT level unless they have clinically different interpretations.

6.14 METABOLISM AND NUTRITION DISORDERS

6.14.1 Basis for Classification

There are three broad approaches to group terms at the HLGT level in this SOC. The first type groups HLTs into HLGTs that describe disorders in the handling of specific substances by the body (e.g., HLGT *Purine and pyrimidine metabolism disorders,* HLGT *Inborn errors of metabolism*, and HLGT *Lipid metabolism disorders*).

A second type of grouping assembles HLGTs describing conditions associated with nutritional disorders in general (e.g., HLGT *Appetite and general nutritional disorders*, HLGT *Vitamin related disorders*).

The third type of HLGT covers medical conditions that may not be associated with a specific metabolic or nutritional pathogenesis (e.g., HLGT *Acid-base disorders*, HLGT *Electrolyte and fluid balance conditions*).

6.14.2 Conventions and Exceptions

Due to the multiplicity of etiologies and effects of many imbalances and disorders, most of these conditions have been assembled within HLT *Metabolic disorders NEC* under HLGT *Metabolism disorders NEC*. It should be noted that there are two separate HLGTs that relate to diabetes: HLGT *Glucose metabolism disorders (incl diabetes mellitus)* and HLGT *Diabetic complications.*

6.15 MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS

6.15.1 Basis for Classification

SOC *Musculoskeletal and connective tissue disorders* is classified at the HLGT level by tissue type such as bone, muscle, and connective tissue or by disease entity such as neoplasms, congenital disorders, and deformities. HLGT *Musculoskeletal and connective tissue disorders NEC* is a general grouping category. Subordinate to this HLGT, HLT *Musculoskeletal and connective tissue signs and symptoms NEC* categorizes terms that are not classified elsewhere in this SOC.

Infection terms can be found in one of four HLGTs. Three of them include: HLT *Bone and joint infections (excl arthritis)* is linked to HLGT *Bone disorders (excl congenital and fractures)*, HLT *Infectious arthritis* is linked to HLGT *Joint disorders*, and HLT *Muscle infections and inflammations* is linked to HLGT *Muscle disorders*. In addition to these three HLTs, other infections in this SOC are grouped in HLT *Musculoskeletal and connective tissue infections and inflammations NEC* under the general grouping HLGT *Musculoskeletal and connective tissue disorders NEC.*

HLGT *Musculoskeletal and connective tissue neoplasms* has HLTs to categorize neoplasms as benign, malignant, or either unspecified or premalignant.

6.15.2 Conventions and Exceptions

HLGT *Fractures* is closely aligned with HLGT *Bone and joint injuries* in SOC *Injury, poisoning and procedural complications*. Terms that are directly attributed to trauma, poisoning, and procedural complications are primarily linked to SOC *Injury, poisoning and procedural* complications. For example, bone fractures, which in most cases are attributed to trauma, are primary to SOC *Injury, poisoning and procedural complications*, whereas pathologic and osteoporotic fractures are primary to SOC *Musculoskeletal and connective tissue*.

HLT *Soft tissue disorders NEC* provides a grouping for those general soft tissue terms that cannot be linked to other specific body system organ classes.

6.16 NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)

6.16.1 Basis for Classification

This SOC is classified anatomically, with pathologic sub-classifications for staging of both benign and malignant neoplasms. The reference for PT names is the PDQ (*Physicians Data Query*) *Terminology Guide*, a publication of the United States National Cancer Institute, except in the area of non-Hodgkin's lymphomas where the nosology developed by the International Lymphoma Study Group [NL Harris, ES Jaffe, H Stein, PM Banks, JK Chan, ML Cleary, G Delsol, C De Wolf- Peeters, B Falini, and KC Gatter. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994, 84: 1361-1392] supersedes the PDQ terminology. Several legacy classifications for lymphomas were incorporated into LLTs.

Lymphoma classification in MedDRA at the PT level and above follows the Revised European-American Lymphoma (R.E.A.L) Classification; the *Working Formulation* classification is limited to the LLT level.

For cysts and polyps, the primary linkage is to the site of manifestation with secondary linkage to SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*. All other neoplasm terms have a primary linkage to this SOC with secondary linkages to the site of manifestation.

At the present time, the words "cancer" and "carcinoma" are used synonymously within the anatomically classified HLGTs at the PT and LLT levels of the MedDRA hierarchy, even though it is recognized that there is a distinction between such concepts. In addition to the terms that relate to classifications by stage of therapy, there has been an attempt to include PTs to capture terms that are less specific and do not provide staging information (e.g., PT *Breast cancer*).

Breast neoplasms HLGTs make a distinction between male and female malignant neoplasms. This is one of the few instances in MedDRA where a distinction is made for gender.

Primary site malignant neoplasms that have metastasized are qualified by the word "metastatic" (e.g., PT *Bone cancer metastatic* represents a primary malignant neoplasm of bone which has metastasized to a site elsewhere in the body). Neoplastic lesions at secondary sites are qualified by the phrase "metastases to" (e.g., PT *Metastases to gallbladder* represents a malignant neoplasm from somewhere in the body that has established a metastatic focus in the gallbladder).

6.16.2 Conventions and Exceptions

Terms that represent non-neoplastic conditions, that may be associated with neoplastic conditions (e.g., PT *Tumour ulceration*) are found in HLT *Oncologic complications and emergencies*.

Sarcomas are classified outside the strict anatomic classification due to the ubiquitous nature of these neoplasms.

Malignant melanomas which do not specify an anatomical site, by convention are classified as skin melanomas, which is the most prevalent location. For this reason, PT *Malignant melanoma* links to HLT *Skin melanomas (excl ocular).* When staging for a malignant neoplasm is included in the text string, the naming convention of "site/malignancy/stage" is maintained as much as possible in this SOC.

Terms for staging information are not included for malignancies for which therapy is not stage-dependent.

HLGT *Neoplasm related morbidities* contains terms for disorders specifically related to oncologic complications and emergencies. Some, but not all, PTs in HLT *Oncologic complications and emergencies* and HLT *Paraneoplastic syndromes NEC* that are specific to sites of manifestation have primary links to that site with SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps) as a secondary link.*

HLGT *Metastases* contains terms for both specific site involvement and unknown or unspecified sites. The specific site terms generally have a primary link to SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)* and a secondary link to the site of manifestation SOC.

"Metastatic" terms (e.g., PT *Ovarian cancer metastatic*) are present at the PT level in MedDRA and are distinct from other PTs indicating a "stage IV" of malignancy. This has been done because metastasis can occur at different stages of disease and is not exclusively associated with stage IV, thus a linkage of "metastatic" terms to "stage IV" terms would not always be appropriate.

"High" and "low" terms in MedDRA are generally considered to be laboratory/investigation type of terms and are found in SOC *Investigations*. An exception to this rule is PTs representing "low grade" neoplasms which are linked to SOC *Neoplasm benign, malignant and unspecified (incl cysts and polyps)* (e.g., PT *Astrocytoma, low grade*).

The existing unqualified polyp terms in MedDRA (e.g. PT *Gastric polyps*) currently default to a benign classification. Newly accepted polyp terms do not include a qualifier of "benign." Polyps are secondarily linked to SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*, and primarily linked to the appropriate site of manifestation SOC. Within SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*, polyp terms are linked to HLTs that represent the benign form rather than the malignant/unspecified form. Polyp terms with the qualifier of "malignant" will no longer be added to MedDRA. Instead, it is recommended that subscribers use available "malignant neoplasm" terms for their coding needs.

6.17 NERVOUS SYSTEM DISORDERS

6.17.1 Basis for Classification

Neurologic disorders are classified using three broad approaches at the HLGT level: anatomic groupings, groupings based on etiology, and pathophysiologic groupings. HLGTs containing disorders classified anatomically are represented by HLGT *Spinal cord and nerve root disorders* and HLGT *Cranial nerve disorders (excl neoplasms)*. Examples of etiologic classification are HLGT *Congenital and peripartum neurological conditions* and HLGT *Central nervous system infections and inflammations*. Pathophysiologic classification is exemplified by HLGT *Demyelinating disorders and* HLGT *Peripheral neuropathies*.

In MedDRA, signs and symptoms uniquely associated with disorders are generally included as HLGTs covering those disorders. However, neurologic signs and symptoms that could be associated with a variety of disorders are classified under HLGT *Neurological disorders NEC*, e.g., HLT *Abnormal reflexes*.

6.17.2 Conventions and Exceptions

HLT *Optic nerve disorders NEC* is included under HLGT *Cranial nerve disorders (excl neoplasms)* rather than under HLGT *Neurological disorders of the eye*. HLT *Pupillary signs* is included under HLGT *Neurological disorders NEC*.

Headaches have their own HLGT and are not included under HLGT *Neurological disorders NEC*.

HLT *Hereditary muscle disorders* is linked to HLGT *Congenital and peripartum neurological conditions* rather than to HLGT *Neuromuscular disorders*.

HLT *Coma states* is linked to HLGT *Neurological disorders NEC*.

6.18 PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS

6.18.1 Basis for Classification

Disorders are grouped in a variety of ways in this SOC to distinguish between maternal, fetal, and neonatal disorders, and to delineate disorders according to the timeline of pregnancy (e.g., labor, delivery, postpartum, etc.). Examples of this type are HLGT *Maternal complications of labour and delivery* and HLGT *Postpartum and puerperal disorders*. Others are classified at the HLGT level according to anatomy (e.g., HLGT *Placental, amniotic and cavity disorders (excl haemorrhages)*). Other HLGTs are classified to differentiate maternal and fetal disorders (e.g., HLGT *Foetal complications* and HLGT *Maternal complications of pregnancy*).

6.18.2 Conventions and Exceptions

This SOC includes terms that represent both normal and high-risk conditions related to pregnancy that are not complications or adverse events (e.g., PT *Twin pregnancy* or PT *Elderly primigravida*). These are classified in HLGT *Pregnancy, labour, delivery and postpartum conditions*.

Abnormalities of fetal presentation, which could be considered both a maternal and fetal complication, have been classified under HLGT *Foetal complications* in HLT *Foetal position and presentation abnormalities*.

HLGT *Neonatal and perinatal conditions* represents the only specific “pediatric” grouping within the terminology. Terms for other pediatric conditions are dispersed amid terms for adult conditions.

Terms relating to fetal and neonatal issues are generally primarily linked to the site of manifestation SOC with a secondary link to this SOC. Terms involving fetal exposure to drugs and other substances (e.g., tobacco) have a primary link to SOC Injury, poisoning and procedural complications and a secondary link to SOC *Pregnancy, puerperium and perinatal conditions.*

For terms related to “abortion,” the following are points of note:

- Both “spontaneous” and “not specified” abortions are single-axial terms linked to SOC *Pregnancy, puerperium and perinatal conditions*.
- All “induced” forms of abortion are linked only to SOC Surgical and medical procedures.
- Complications of induced abortion are primarily linked to HLT *Induced abortion complications* (under HLGT *Procedural related injuries and complications NEC* in SOC *Injury, poisoning and procedural complications*).
- Complications of both “spontaneous” and “not specified” abortions are primarily linked to HLT *Abortion related conditions and complications* (under *HLGT Abortions and stillbirth* in SOC *Pregnancy, puerperium and perinatal conditions*).

When searching for terms describing toxic exposures related to pregnancy, delivery, lactation and other circumstances potentially impacting the fetus or newborn, the user

may need to consider selected PTs in certain HLTs in this SOC (including, but possibly not limited to, HLT *Foetal conditions due to maternal conditions* and HLT *Newborn complications NEC*) as well as various “exposure” concepts located in SOC *Injury, poisoning and procedural complications* (e.g., terms linked to HLGT *Exposures, chemical injuries and poisoning*).

“Perineum” terms may be linked to several SOCs including SOC *Reproductive system and breast disorders* and SOC *Pregnancy, puerperium and perinatal conditions*. New “perineum” terms resulting from Change Requests are linked to their most appropriate classification on a case-by-case basis.

Most “death” terms are linked primarily to SOC *General disorders and administration site conditions*. Fetal and maternal death terms are linked primarily to SOC *Pregnancy, puerperium and perinatal conditions* as they are considered a special population.

However, PT *Death neonatal* is linked primarily to SOC *General disorders and administration site conditions* and secondarily to SOC *Pregnancy, puerperium and perinatal conditions.*

6.19 PRODUCT ISSUES

6.19.1 Basis for Classification

The MedDRA Management Board endorsed the recommendation of the Blue Ribbon Panel on the scope of MedDRA (April 2014) for the addition of a 27th SOC to MedDRA to accommodate non-clinical/non-patient related concepts pertaining to products. These concepts are important from regulatory and public health perspectives as they may affect patient safety. This SOC *Product issues* has been added in MedDRA Version 19.0 and includes terms relevant for issues with product quality, devices, manufacturing quality systems, product supply and distribution, and counterfeit products. One of the goals of incorporating product quality terms into MedDRA is to support the recording of product quality issues and any associated adverse events using a single terminology. It is envisaged that the product quality terms, including those relating to manufacturing and distribution, may be used to report product defects to regulatory authorities and may also be used in organizations' internal databases to track and trend quality issues or deviations.

SOC *Product issues* contains two HLGTs: HLGT *Device issues* and HLGT *Product quality, supply, distribution, manufacturing and quality system issues.* HLGT *Device issues* has been moved from SOC *General disorders and administration site conditions* with all its eight subordinate HLTs (HLT *Device computer issues*, HLT *Device electrical issues*, HLT *Device incompatibility issues*, HLT *Device information output issues*, HLT *Device issues NEC*, HLT *Device malfunction events NEC*, HLT *Device operational issues NEC*, and HLT *Device physical property and chemical issues).*

HLGT *Product quality, supply, distribution, manufacturing and quality system issues* contains five product quality HLTs which have been moved from SOC *General disorders and administration site conditions* (HLT *Product contamination and sterility issues*, HLT *Product label issues*, HLT *Product packaging issues*, HLT *Product physical issues*, and HLT *Product quality issues NEC*). In addition, this HLGT contains eight HLTs which have been added in MedDRA Version 19.0 to cover issues relating to counterfeit products, manufacturing quality, and supply and distribution*:* HLT *Counterfeit, falsified and substandard products*, HLT *Manufacturing facilities and equipment issues*, HLT *Manufacturing issues NEC*, HLT *Manufacturing laboratory controls issues*, HLT *Manufacturing materials issues*, HLT *Manufacturing production issues*, HLT *Product distribution and storage issues*, and HLT *Product supply and availability issues.*

6.19.2 Conventions and Exceptions

This SOC is focused on issues related to products rather than clinical or patient related concepts and, therefore, the majority of terms are single-axial and have no need for multi-axial links to other patient related "disorder" SOCs. However, product terms that also denote a patient related issue express multi-axiality to preserve the link to patient safety. For example, PT *Transmission of an infectious agent via product* is linked to

primary SOC *Infections and infestations* and has a secondary link to SOC *Product issues*.

Device terms are event based, not device type based. Therefore, the MedDRA term name will generally not include the specific type of device. However, exceptions may be made for generic types of devices and device components (in widespread use) such as stents, pumps, catheters, needles, and syringes.

HLT *Manufacturing laboratory controls issues* is intended to cover issues with various laboratory tests conducted during the manufacturing process, including stability testing.

HLT *Product distribution and storage issues* is intended to cover issues with the storage of products by manufacturers, distributors, wholesalers, etc. In contrast, product storage issues by end-users such as healthcare professionals, patients, and consumers are considered to be medication errors and are represented by appropriate medication error terms in SOC *Injury, poisoning and procedural complications*.

HLT *Product supply and availability issues* is distinct from distribution, shipping and storage concepts and is intended to cover concepts such as supply chain interruption, product not available on formulary, product withdrawn from market, etc.

6.20 PSYCHIATRIC DISORDERS

6.20.1 Basis for Classification

The primary guideline used for the classification of psychiatric disorders is the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-V)©* published by the American Psychiatric Association. Associated symptoms are grouped at the HLGT levels according to the classification scheme suggested by the DSM-V. The disorders specifically named by DSM-V, or those in the vocabulary that are very closely related disorders, are placed together in the appropriate HLT. Signs and symptoms uniquely associated with disorders under an HLGT are grouped at the HLT level. For example, HLGT *Depressed mood disorders and disturbances* includes an HLT for the DSM-V listed *Depressive disorders*, and another HLT for *Mood alterations with depressive symptoms*, which includes the depression-related symptoms which would not meet the DSM-V criteria for a diagnosis.

For MedDRA Version 19.0, HLGT *Somatoform and factitious disorders* was replaced with new HLGT *Somatic symptom and related disorders.* Similarly, HLT *Somatoform disorders*, HLT *Mental retardations* and HLT *Paraphilias* were also replaced by HLT *Somatic symptom disorders*, HLT *Intellectual disabilities* and HLT *Paraphilias and paraphilic disorders* respectively due to changes in how these concepts are referenced in DSM-V.

Signs and symptoms that are applicable to multiple DSM-V classifications are grouped under the general HLGT *Mood disorders and disturbances NEC* and HLGT *Psychiatric and behavioural symptoms NEC.*

Terms that have a basis in a central nervous system disorder are linked primarily to SOC *Nervous system disorders* and secondarily to SOC *Psychiatric disorders*. For example, PT *Dementia Alzheimer's type* has a primary link to SOC *Nervous disorders* and a secondary link to SOC *Psychiatric disorders*.

Congenital disorders such as PT *Tourette's disorder* that have a basis in SOC *Psychiatric disorders* have a primary link to SOC *Congenital, familial and genetic disorders* in accordance with MedDRA rules. These terms have secondary links to SOC *Psychiatric disorders*, as well as to the body system of manifestation.

HLGT *Sleep disorders and disturbances* includes HLTs that cover all aspects of sleep disorders. HLT *Parasomnias* contains abnormal sleep-related disturbances (e.g., PT *Abnormal dreams,* PT *Nightmare,* and PT *Somnambulism*).

Conditions associated with substance abuse (e.g., LLT *Enema abuse,* LLT *Laxative abuse* under PT *Drug abuse*, and PT *Alcoholism*) are included in SOC *Psychiatric disorders* in HLT *Substance-related disorders.*

According to DSM-V, the official psychiatric term for addiction is "substance dependence." Therefore, the word "addiction," in general, only appears at the LLT level in MedDRA.

For new "abuse" terms in MedDRA, the text string is devised to distinguish terms in SOC *Social circumstances* from those in SOC *Psychiatric disorders*. "Abuse" terms are linked to SOC *Psychiatric disorders* and kept independent of "dependence" counterparts

PTs. Terms that refer to a person, such as PT *Drug abuser*, are in SOC *Social circumstances*.

6.20.2 Conventions and Exceptions

An attempt is made to name disorders that are included in DSM-V using the conventions established by the American Psychiatric Association. However, these disorders are associated with a specific set of criteria for diagnosis, while the more general names in the existing vocabulary do not always map in a one-to-one manner. For this reason, they are all included as disorders under the same HLT.

6.21 RENAL AND URINARY DISORDERS

6.21.1 Basis for Classification

The majority of HLGTs in this SOC are based on anatomic classification (e.g., HLGT *Bladder and bladder neck disorders (excl calculi)* and HLGT *Ureteric disorders*). Further subdivision on the HLT level has PTs grouped by disease process wherever possible (e.g., HLT *Bladder infections and inflammations*, HLT *Bladder reflux conditions*), and those remaining are grouped under HLTs such as HLT *Bladder disorders NEC*.

HLGT *Genitourinary tract disorders NEC* contains terms that do not specify exact sites within the genitourinary tract. Within this HLGT, HLTs are subdivided into congenital, infectious and inflammatory, and miscellaneous categories. Where a site is specified, the terms for neoplasms and congenital disorders are gathered at the HLT level within the HLGT of the appropriate anatomic site (e.g., HLT *Renal neoplasms* in HLGT *Renal disorders (excl nephropathies)* and HLT *Ureteric disorders congenital* within HLGT *Ureteric disorders*).

Signs and symptoms in this SOC are grouped under HLGT *Urinary tract signs and symptoms*, which has three HLTs: HLT *Bladder and urethral symptoms*, HLT *Urinary abnormalities*, and HLT *Urinary tract signs and symptoms NEC*.

6.21.2 Conventions and Exceptions

HLT *Urinary abnormalities* gathers most of the “-uria” terms present in the terminology. This decision was made to avoid conflicts with respect to underlying etiology as in the case of PT *Proteinuria*, which may have several intrarenal and extrarenal etiologies The corresponding terms with the phrase or concept “in urine” (e.g., PT *Protein urine present*) are found in SOC *Investigations.*

For the major body systems of cardiac, hepatic, pulmonary, and renal, the terms “failure” and “insufficiency” are used synonymously. In SOC *Renal and urinary disorders,* the “failure” term is at the PT level and the “insufficiency” term is at the LLT level (e.g., PT *Renal failure* and LLT *Renal insufficiency*).

6.22 REPRODUCTIVE SYSTEM AND BREAST DISORDERS

6.22.1 Basis for Classification

The terms within this SOC are classified using two general approaches: anatomic and functional.

HLGTs based on anatomy (e.g., HLGT *Breast disorders* and HLGT *Penile and scrotal disorders (excl infections and inflammations)*) are subdivided mainly by disease process at the HLT level (e.g., HLT *Benign and malignant breast neoplasms*, HLT *Lactation disorders*). Signs and symptoms for the anatomic part may form an HLT (e.g., HLT *Prostatic signs, symptoms and disorders NEC* and HLT *Breast signs and symptoms*).

Other HLGTs reflect functional disorders e.g., HLGT *Sexual function and fertility disorders* and HLGT *Menopause related conditions*. HLTs are based on subtypes of functional disorder (e.g., HLT *Erection and ejaculation conditions and disorders,* HLT *Spermatogenesis and semen disorders*).

HLGT *Congenital reproductive tract and breast disorders* contains terms for conditions present at birth irrespective of whether the conditions are hereditary or acquired in utero. The HLTs allocate terms on the basis of gender (male, female, or unspecified).

Infections and inflammations are not linked to the HLGTs by anatomic location but by gender (e.g., HLGT *Female reproductive tract infections and inflammations* and HLGT *Male reproductive tract infections and inflammations*). Terms where gender is not specified are in HLT *Reproductive tract infections and inflammations NEC* within HLGT *Reproductive tract disorders NEC*.

HLGT *Reproductive tract disorders NEC* provides a broad classification for terms where gender is not specified. The HLTs include HLT *Gender disorders* and HLT *Reproductive tract disorders NEC (excl neoplasms)* as well as terms for neoplasms, infections and inflammations, and signs and symptoms.

6.22.2 Conventions and Exceptions

Unlike other anatomically based HLGTs in this SOC, which exclude terms for infections and inflammations, HLGT *Breast disorders* contains HLT *Breast infections and inflammations*.

“Perineum” terms may be linked to several SOCs including SOC *Reproductive system and breast disorders* and SOC *Pregnancy, puerperium and perinatal conditions*. New “perineum” terms resulting from Change Requests are linked to their most appropriate classification on a case-by-case basis.

For historical and practical reasons the MSSO prefers to keep the unqualified concepts for intraepithelial lesions such as LLT *High grade squamous intraepithelial lesion* under PT *Cervical dysplasia*. For areas other than cervix, the MSSO provides corresponding intraepithelial concepts upon request under the appropriate PTs such as LLT *Low grade prostatic intraepithelial neoplasia* under PT *Prostatic dysplasia* or LLT *Anal high grade squamous intraepithelial lesion* under PT *Anogenital dysplasia*.

6.23 RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS

6.23.1 Basis for Classification

HLGTs that reflect the anatomic site (e.g., HLGT *Pleural disorders*) contain HLTs based on pathologic classification (e.g., HLT *Pleural infections and inflammations,* HLT *Pneumothorax and pleural effusions NEC*). HLGTs that describe a larger anatomic site (e.g., HLGT *Upper respiratory tract disorders (excl infections)*) are further divided at the HLT level into more specific anatomic locations, disease processes, or a combination of parameters (e.g., HLT *Nasal congestion and inflammations*). Other HLGTs are based on disease processes (e.g., HLGT *Respiratory tract neoplasms*) with anatomic subdivisions as HLTs.

HLGTs may also reflect both the anatomic site and disease process (e.g., HLGT *Lower respiratory tract disorders (excl obstruction and infection)* and HLGT *Upper respiratory tract disorders (excl infections)*).

HLGT *Respiratory tract infections* contains HLTs based on infective organisms (bacterial, viral, etc.), as well as anatomic site groupings (e.g., HLT *Upper respiratory tract infections NEC*).

Specific HLGTs have been created for congenital disorders (HLGT *Congenital respiratory tract disorders*), neonates (HLGT *Neonatal respiratory disorders*), and respiratory disorders (HLGT *Respiratory disorders NEC*) which contain HLTs that are not based on anatomic sites or specific disease processes (e.g., HLT *Breathing abnormalities*).

6.23.2 Conventions and Exceptions

The title of HLGT *Lower respiratory tract disorders (excl obstruction and infection)* is self-explanatory. Infections are in a separate HLGT, but obstruction terms reside in HLT *Bronchospasm and obstruction* within HLGT *Bronchial disorders (excl neoplasms).*

HLGT *Upper respiratory tract disorders (excl infections)* is not similarly structured. Although infections are excluded in a separate HLGT, terms for obstruction may reside within the same HLGT *Upper respiratory tract disorders (excl infections)*. These PTs are in the HLTs for the appropriate anatomic site (e.g., PT *Nasal dryness* is within HLT *Nasal disorders NEC*). Terms describing obstructions may also be in other HLGTs placed by causal factors. For instance, PT *Tracheitis obstructive* is linked to HLT *Upper respiratory tract infections NEC* within HLGT *Respiratory tract infections*.

Infections have been placed in a single HLGT, namely, HLGT *Respiratory tract infections*. However, HLT *Pleural infections and inflammations* is in HLGT *Pleural disorders*.

All neoplasms are within HLGT *Respiratory tract neoplasms* with the exception of *pleural neoplasms*, which are in HLGT *Pleural disorders (*HLT *Pleural neoplasms)*.

PT *Sputum decreased* and PT *Sputum increased* are in SOC *Respiratory, thoracic and mediastinal disorders.* This is because these terms commonly express a medical condition rather than an investigation finding.

For the major body systems of cardiac, hepatic, pulmonary, and renal, the terms “failure” and “insufficiency” are used synonymously. In SOC *Respiratory, thoracic and mediastinal disorders,* the “failure” term is at the PT level and the “insufficiency” term is at the LLT level (e.g., PT *Respiratory failure* and LLT *Respiratory insufficiency*).

6.24 SKIN AND SUBCUTANEOUS TISSUE DISORDERS

6.24.1 Basis for Classification

The principal division at the HLGT level in this SOC is by pathophysiology or etiology (e.g., HLGT *Angioedema and urticaria*, HLGT *Pigmentation disorders*, and HLGT *Cutaneous neoplasms benign*). The exceptions are HLGT *Skin appendage conditions*, which is a microanatomic grouping, and HLGT *Epidermal and dermal conditions*, which groups skin conditions that do not belong to any of the other HLGTs. At the HLT level, the division is mainly pathologic.

6.24.2 Conventions and Exceptions

In general, terms related to the eyelid are primarily linked to SOC *Eye disorders* and secondarily to SOC *Skin and subcutaneous tissue disorders*.

6.25 SOCIAL CIRCUMSTANCES

6.25.1 Basis for Classification

SOC *Social circumstances* is one of the three single-axial SOCs in MedDRA. The purpose of this SOC is to provide a grouping for those factors that may give insight into personal issues that could have an effect on the event being reported. Essentially, SOC *Social circumstances* contains information about the person, not the adverse event. As an example, terms such as PT *Drug abuser* and PT *Death of relative* are found in this SOC, whereas their respective disorder terms such as LLT *Drug addiction* and PT *Death* are found in SOC *Psychiatric disorders* and SOC *General disorders and administration site conditions*, respectively.

The terms within this SOC do not fall into any anatomic or pathologic classification. The HLGTs are broad groupings of social factors (e.g., family issues, legal issues, or economic circumstances). At the HLT level, these HLGTs are further subdivided into groups of social factors with a common theme (e.g., HLGT *Family issues* is divided into HLT *Bereavement issues*, HLT *Dependents*, and HLT *Family and partner issues*).

In MedDRA, terms representing crime or action of abuse and the perpetrator of the crime or abuse are kept in a PT/LLT relationship, with crime/action of abuse at the PT level and perpetrator of the crime or abuse at the LLT level under HLT *Criminal activity* in SOC *Social circumstances* (e.g., PT *Sexual abuse* and its LLT *Sexual abuser).* Terms representing the victim of these crimes are qualified with "victim of" at the PT level under HLT *Crime victims* in SOC *Social circumstances*. Unqualified terms representing the victim are placed under the "victim of" PT as an LLT (e.g., PT *Victim of child abuse* and LLT *Maltreated child)*.

For new “abuse” terms in MedDRA, the text string is devised to distinguish terms in SOC *Social circumstances* from those in SOC *Psychiatric disorders*. "Abuse" terms are linked to SOC *Psychiatric disorders* and kept independent of “dependence” counterpart PTs. Terms that refer to a person, such as PT *Drug abuser*, are in SOC *Social circumstances*.

6.25.2 Conventions and Exceptions

HLT *Drug and chemical abuse* excludes alcohol-related terms. HLT *Alcohol product use* captures all aspects, including alcoholic, abstention, and social use. PT *Alcoholism* is found in SOC *Psychiatric disorders*.

HLGT *Legal issues* makes a distinction between being a victim of a crime and being the person who committed the crime.

PT *Blindness* is linked to HLGT *Vision disorders*. To make a distinction between blindness as a disability and blindness as a medical disorder, PT *Sight disability* is linked to SOC *Social circumstances* (blindness as a disability) and PT *Blindness* is linked to SOC *Eye disorders* (blindness as a medical disorder) and to SOC *Nervous system disorders***.** Similar terms relate to deafness (i.e*.,* PT *Deafness* is in SOC *Ear and labyrinth disorders* and PT *Hearing disability* is in SOC *Social circumstances).*

6.26 SURGICAL AND MEDICAL PROCEDURES

6.26.1 Basis for Classification

This SOC is one of the three single-axial SOCs in MedDRA. It contains only those terms that are surgical or medical procedures. There are no multi-axial links between terms in this SOC and other SOCs.

The nature of this SOC makes it more of a “support” SOC for recording case information and for developing queries. Surgical and medical procedures may occur in the treatment of an adverse event, as an associated condition related to the indication for a medical product, or as medical history. A comprehensive search strategy needs to consider that this is a single-axial SOC whose terms are not found elsewhere in the terminology.

The terms within this SOC are primarily divided by anatomic region at the HLGT level, with the exception of HLGT *Therapeutic procedures and supportive care NEC*. This HLGT groups general or miscellaneous therapeutic procedures, and HLGT *Soft tissue therapeutic procedures*, groups subordinated HLTs by tissue type.

There is a distinction between the term “abortion,” which is frequently used as a procedure term, and a disorder term such as “spontaneous abortion.” In MedDRA, the term “induced abortion” is used to identify the term as a procedure; therefore, it is in this SOC. The term “spontaneous abortion” is used as the disorder term and is in SOC *Pregnancy, puerperium and perinatal conditions*. When an abortion term is not identified as being either a procedure or a disorder, it is assumed to be a disorder term and is categorized in SOC *Pregnancy, puerperium and perinatal conditions*.

6.26.2 Conventions and Exceptions

The anatomic breakdown at HLGT level is similar to the SOC organization (represented body systems) in MedDRA, with a few exceptions where treatment of certain body systems are closely related. The result is groupings that are similar to surgical subspecialties:

- Ear, nose, and throat procedures are grouped under a single HLGT, HLGT *Head and neck therapeutic procedures*, since procedures in these areas constitute a single surgical speciality.
- Skull and vertebrae procedures are grouped with brain and spinal cord therapy.
- Muscle, tendon, cartilage fascia, and bursa operations are grouped in HLGT *Soft tissue therapeutic procedures*. However, PT *Ligament operation* is linked to HLT *Joint therapeutic procedures* in HLGT *Bone and joint therapeutic procedures*.

At the PT and LLT level, terms with the words “operation” and “surgery” are used interchangeably.

Standard medical definitions of "dilation” and "dilatation" indicate that they are synonyms. The MSSO recognizes that there are some common usages in certain cultures for these types of terms. However, for purposes of distinction in MedDRA, the

term "dilation" is considered a procedure and the term "dilatation" is considered a disorder. The word "procedure" is normally added to "dilation," e.g., PT *Stomach dilation procedure* to make it self explanatory. An exception to this convention is PT *Uterine dilation and curettage* since it is recognized as a procedure without the addition of the qualifying word.

Anastomosis is classified as a surgical procedure and is single-axial linked to SOC *Surgical and medical procedures*. Alternative terms are used to describe related disorders outside of the surgical realm.

"Drainage" is a term used as a procedure (systematic withdrawal of fluids), whereas "discharge" and "secretion" are terms used for the excretion of liquids from the body. "Drainage" terms that fall outside of the realm of surgical procedures are considered exceptions and dealt with by using the word "discharge." These terms are linked appropriately based on their particular meaning (e.g., PT *Post procedural discharge* links to SOC *Injury, poisoning and procedural complications*). In addition, all surgical terms retain "drainage" and link to SOC *Surgical and medical procedures*. Finally, if a term can be either a surgical procedure or a non-surgical term, then both the "term+drainage" (PT *Post procedural drainage* linked to SOC *Surgical and medical procedures*) and the "term+discharge" (PT *Post procedural discharge* linked to SOC *Injury, poisoning and procedural complications*) are present in the terminology and linked as indicated above. The MSSO recognizes that there are some common usages in certain cultures for these types of terms that may not be reflected by this MedDRA rule. Subscribers are advised to make clear which concept applies - surgical, non-surgical, or both - when submitting Change Requests.

Revision procedures are generally represented in MedDRA as subelement LLTs of the basic procedure concept for example LLT *Ileostomy revision* is placed under PT *Ileostomy* and LLT *Amputation revis*ion placed under PT *Amputation*.

6.27 VASCULAR DISORDERS

6.27.1 Basis for Classification

The terms within this SOC are primarily divided by pathology or clinical disease entity at the HLGT level. Most vascular disorder terms are already grouped anatomically by their representation within the anatomic "disorder" SOCs; this division allows more flexible data retrieval. At the HLT level, terms are further subdivided anatomically. Although not identical, there is a close similarity in the distribution of anatomic locations represented at the HLT level under HLGT *Arteriosclerosis, stenosis, vascular insufficiency and necrosis,* HLGT *Embolism and thrombosis,* HLGT *Vascular disorders NEC*, and HLGT *Vascular haemorrhagic disorders*.

6.27.2 Conventions and Exceptions

In general, terms related to thrombosis are primarily linked to the site of manifestation, when applicable, and are secondarily linked to SOC *Vascular disorders*.

Conditions represented in HLGT *Arteriosclerosis, stenosis, vascular insufficiency and necrosis,* and in HLGT *Embolism and thrombosis* are closely related in clinical or practical view. However, whereas the first one addresses "chronic" impairments developed progressively (such as PT *Renal arteriosclerosis*), the second one represents "acute" conditions (e.g., LLT *Renal artery embolism* or PT *Renal artery thrombosis* compared to PT *Renal artery stenosis* or PT *Renal artery arteriosclerosis*).

"High" and "low" terms in MedDRA are generally considered to be laboratory/investigation type of terms and are found in SOC *Investigations*. Exceptions to this rule are LLT *Blood pressure high* and LLT *Low blood pressure* under PT *Hypertension* and PT *Hypotension*, respectively, which are in SOC *Vascular disorders*.

APPENDIX A: ACRONYMS

A

ASCII	American Standard Code for Information Interchange

C

CIOMS	Council for International Organizations of Medical Sciences
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms

E

EWG	Expert Working Group
EXCL	Excluding, except, excl

F

FDA	Food and Drug Administration (United States)

H

HARTS	Hoechst Adverse Reaction Terminology System
HLGT	High Level Group Term
HLT	High Level Term

I

ICD-9	International Classification of Diseases – 9th Revision
ICD-9-CM	International Classification of diseases – 9th Revision Clinical Modification
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
INCL	Including, incl
IUPAC	International Union of Pure and Applied Chemistry

J

J-ART	Japanese Adverse Reaction Terminology
JPMA	Japan Pharmaceutical Manufacturer Association

L

LLT	Lowest Level Term
LOINC	Logical Observation, Identifiers, Names and Codes

M

MCA	Medicines Control Agency (United Kingdom)
MEDIS	Medical Information System (Japan)
MedDRA	Medical Dictionary for Regulatory Activities
MEDDRA	Medical Dictionary for Drug Regulatory Affairs
MHLW	Ministry of Health, Labour and Welfare (Japan)
MHRA	Medicines and Healthcare products Regulatory Agency (United Kingdom)
MSSO	Maintenance and Support Services Organization

P

PT	Preferred Term

S

SMQ	Standardised MedDRA Query
SOC	System Organ Class

W

WHO	World Health Organization
WHO-ART	World Health Organization Adverse Reaction Terminology

For a list of MedDRA term abbreviations and acronyms, please visit our Web site (http://www.meddra.org/how-to-use/support-documentation).

APPENDIX B: MedDRA CONCEPT DESCRIPTIONS

This appendix provides a list of MedDRA concept descriptions. A concept description is a description of how a concept is interpreted, used, and classified within the MedDRA terminology and is not a definition. The concept descriptions are intended to aid the consistent and accurate use of MedDRA in coding, retrieval, and analysis and to overcome the differences of medicine practice worldwide. The MSSO expects this appendix to be a working document and grow as subscribers request additional concepts to be documented.

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

A

Abuse

Abuse is the intentional, non therapeutic use of a product – over the counter or prescription - for a perceived reward or desired non-therapeutic effect including, but not limited to its psychotropic effects. Abuse may occur with a single use, sporadic use or persistent use of the product.

Acute

For use in medicine, the word means “reaching a crisis rapidly.” In some instances, an “acute” condition may be interpreted as more severe than a “chronic” one. This was considered during the processing of proposed modified terms to assure that terms expressing only severity were not included.

Addiction

Addiction is an overwhelming desire to take a drug for non-therapeutic purposes together with inability to control or stop its use despite harmful consequences. Addiction can result from a drug-induced physical dependence which may be accompanied by a withdrawal syndrome; and addiction can occur because of a compulsion to experience the drug's psychological, behavioral or physical effects.

Aggravated

From “aggravate”: To make worse, e.g., “bronchitis *aggravated* by smoking.” For the purposes of term placement in MedDRA, the use of modifiers exacerbated, aggravated and worsened is interchangeable

Application site

For the purposes of MedDRA, an application site is considered to be the surface that contacts a topical medication in the form of a cream, lotion, or patch (e.g., an estrogen hormone patch). It does not pertain to other

methods of drug delivery such as injection or infusion by catheter or other means.

Angina

"Angina" exists in MedDRA as a non current LLT because of the ambiguous nature of the term. Angina is interpreted as a variant expression for acute tonsillitis (angina tonsillaris) in certain languages. However, based on the popular usage of this term in English language for Angina pectoris, in MedDRA it is linked to PT Angina pectoris.

Arthritis/Arthrosis

In MedDRA, any inflammation of a joint is considered "arthritis." In contrast "arthrosis" is interpreted as a non-inflammatory degenerative joint disease and is linked to PT Osteoarthritis.

C

Cancer/Carcinoma

"Cancer" is a disease in which abnormal cells divide uncontrollably and can spread to other parts of the body (metastasize). "Cancer" can be one of several histologic types including those derived from epithelial tissues (carcinomas), those derived from mesenchymal tissue (sarcomas), and those arising from hematopoietic and lymphoid tissues (leukemia, lymphomas, and multiple myeloma). In the context of MedDRA, "carcinoma" and "cancer" are considered synonymous. "Carcinoma" terms are generally subordinate to "cancer" terms (e.g., LLT *Skin carcinoma* is linked to PT *Skin cancer*).

Cell marker

A cell marker is a biochemical or genetic characteristic of a cell which discriminates between different cell types.

Chronic

Of long duration; subject to a disease or habit for a long time. In some instances, a "chronic" condition may be interpreted as milder than an "acute" one. This was considered during the processing of proposed modified terms to assure that terms expressing only severity were not included.

Closure

Closure is the cap, lid, stopper or other feature which is the primary mechanism for protecting the product from spill, air etc.

Cold

For purposes of MedDRA, the mention of "cold" without addition of any prefix of feeling signifies the catarrhal disorder associated with nasopharyngitis. "Coldness" and "feeling cold," are body temperature perceptions of uncomfortably low temperature for humans.

Compounding

Compounding refers to products that are usually made by a pharmacist or physician.

Compounding issue

Compounding issue refers to quality problems associated with those products.

Coring

A small piece of the stopper is sometimes sheared off (known as coring); an example could be after a needle is inserted through the stopper of a medication vial.

Crystal formation

Crystals are symmetrically arranged formations created by the solidification of a chemical element, a compound, or a mixture found in or on the dosage form which is not normal for the product.

D

Device capture

PT *Device capturing issue* refers to a situation where a device fails capture signal input or output, or captures the wrong signal input or output.

Device use error

An act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the operator.

Diaphragm

For purposes of MedDRA, diaphragm is considered a respiratory structure.

Dispensing Error

Dispensing errors are not limited to pharmacists. It can include nurses and physicians. For example, physicians can dispense sample products in their office.

Dissolution

Dissolution is the process in which one substance is dissolved in another. Dissolution and solubility are considered synonyms in MedDRA.

Dosage

The determination and regulation of the size, frequency, and number of doses.

Dosage Form

The physical form in which a drug is produced for administration to recipient (tablets, capsules, cream etc.).

Dose

A quantity to be administered at one time, such as a specified amount of medication.

Dose Omission

Failure to administer an ordered dose. Excludes patient's refusal and clinical decision (contraindication) or other reason not to administer (e.g., patient sent for test). Hicks, R.W., Santell., JP., Cousins, D.D., and Williams, R.L. (2004) MedMARx 5th Anniversary Data Report: A chartbook of 2003 Findings and Trends 1999-2003. Rockville, MD: USP Center for the Advancement of Patient Safety).

Documented hypersensitivity to administered drug

This medication error refers to the situation when a patient is administered a drug that is documented in the patient's medical file to cause a hypersensitivity reaction in the patient. Example: Despite the fact that the patient's medical record indicated "sulfa allergy," the physician prescribed a sulfa antibiotic. Subsequently, the patient took the antibiotic and experienced hives. A related term, PT *Documented hypersensitivity to administered product*, applies to similar situations involving known hypersensitivity to other types of products, not specifically drugs.

Drug diversion

For the purposes of term selection and analysis of MedDRA-coded data, drug diversion means that a drug is diverted from legal and medically necessary uses toward illegal uses.

Drug Formulation

Refers to both active and inactive ingredients.

Duration

Includes duration of therapy/length of therapy.

E

Exacerbation

See "Aggravated." For the purposes of term placement in MedDRA, the use of modifiers exacerbated, aggravated and worsened is interchangeable

Exposure

For the purposes of MedDRA, the concept of "exposure":

- Is not limited to drugs; it can include exposure to chemicals, toxins, radiation, communicable disease, etc.

- Can occur through various pathways (via blood, direct contact, etc.)

Extension

When paired with a product or a device, an extension is a component of a device that carries the impulses from the implant site of a device to the lead.

G

Gel Formation

A product has formed into a gelatinous matter, a colloid in a more solid form than a solution which is not normal for the product.

H

High Blood Pressure

"High" and "low" terms in MedDRA are generally considered to be laboratory/investigation type of terms and are found in the SOC *Investigations.* However, because of the synonymous use of expression blood pressure high and hypertension in common usage, the LLT *Blood pressure high* is linked to PT *Hypertension* in SOC *Vascular disorders*.

Hypertension vs. Hypertonia

Hypertonia" may be synonymous for "hypertension" in some languages. However, for purposes of MedDRA, hypertonia is defined as a condition marked by an abnormal increase in muscle tension and a reduced ability of a muscle to stretch. Hence, it is placed in muscle tone disorders.

Hy's Law

Hy's law is used as an indicator for potential drug-induced liver injury. To be considered a potential "Hy's law" case, the following three components must all be met:

- Elevation of aminotransferases, e.g., alanine aminotransferase (ALT) and aspartate aminotransferase (AST), of >3x upper limit of normal (ULN)
- Alkaline phosphatase (ALP) <2x ULN
- Increase in total bilirubin ≥2x ULN

Please refer to the July 2009 FDA Guidance for Industry – "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" for additional information.

I

Inappropriate Schedule

Includes all deviations from the prescribed dosage schedule.

Issue

The word "issue" for the purpose of MedDRA is used as a general term,

which does not necessarily point to a failure or defect when paired with a product or a device.

L

Label

Label refers to display of written, printed, or graphic matter upon the container or packaging.

Labelled drug-disease interaction medication error

This medication error refers to the situation when a patient is prescribed, dispensed, or administered a drug that is documented in the drug label as having the potential to exacerbate or worsen the patient's pre-existing disease(s). Example: A patient has a medical history of having bleeding gastric ulcers. However, the patient was inadvertently prescribed and dispensed several doses of aspirin.

Labelled drug-drug interaction medication error

This medication error refers to the situation when a patient is prescribed, dispensed, or administered a drug that is documented in the drug label to cause a drug to drug interaction with the patient's existing medication(s). Example: Patient became pregnant whilst taking an antifungal drug and an oral contraceptive. This interaction is clearly stated in the product data sheet.

Labelled drug-food interaction medication error

This medication error refers to the situation when a patient is prescribed, dispensed, or administered a drug that is documented in the drug label to cause an expected adverse event with patient's consumed food. Example: Patient drank grapefruit juice whilst taking a calcium channel blocker and the calcium channel blocker is labeled for grapefruit juice interaction.

Lower gastrointestinal tract

For purposes of MedDRA the following constitute the lower gastrointestinal tract - small intestine (duodenum, jejunum, ileum) large intestine-cecum (and the vermiform appendix attached to the cecum) colon (ascending colon, transverse colon, descending colon and sigmoid flexure), rectum, and anus.

Lower respiratory tract

For purposes of MedDRA the lower respiratory tract is comprised of bronchi, bronchioles, alveoli and lungs.

M

Medication error

Medication errors are defined as any preventable event that may cause or

lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer. Such events may be related to professional practice, health care products, procedures and systems, including prescribing, order communication, product labeling, packaging and nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use.

Medication monitoring error

For the purposes of term selection and analysis of MedDRA-coded data, a medication monitoring error is an error that occurs in the process of monitoring the effect of the medication through clinical assessment and/or laboratory data. It can also refer to monitoring errors in following instructions or information pertinent to the safe use of the medication.

Misuse

Misuse is the intentional and inappropriate use of a product - over the counter or prescription - other than as prescribed or not in accordance with the authorized product information.

O

Occupational exposure

Occupational exposure encompasses the “chronic” exposure to an agent (including therapeutic products) during the normal course of one’s occupation, and could include additional scenarios in specific regulatory regions. For example, occupational exposure may additionally relate to a more acute, accidental form of exposure that occurs in the context of one’s occupation.

Off Label Use

Off label use is the intentional use of a product for a medical purpose not in accordance with the authorized product information.

Overdose

For the purposes of term selection and analysis of MedDRA-coded data, overdose is more than the maximum recommended dose (in quantity and/or concentration), i.e., an excessive dose.

P

Precipitate

Precipitate is substance separated from a solution or suspension by chemical or physical change usually as an insoluble solid which is not normal for the product.

Preparation

A medicinal substance that is ready for use (e.g., a preparation for colds). http://www.merriam-webster.com/medical/preparation

Prescribing error

Prescribing errors may be made in the hand of physicians or other healthcare professionals who have the prescription authority.

Procedure

This term relates to concepts currently in SOC *Injury, poisoning and procedural complications* under HLGT *Procedural related injuries and complications NEC* and in SOC *Surgical and medical procedures*.

Product

In the context of MedDRA, "product" can refer to various types of products intended for human use such as drugs (prescription and over the counter), biologics, vaccines, combination products, devices, nutraceuticals, dietary supplements, etc.

Product coating incomplete

Product coating incomplete refers to the outer coating of a product when it does not entirely cover the product and can appear blotchy, splattered or speckled.

Product colour issue

Product color issue is when the product color is not uniform; color has faded, or turned to a different color/shade.

Product dosage form confusion

Product dosage form confusion is a misinterpretation of the dosage form of a product which may potentially result in a medication error.

Product label confusion

Product label confusion is a misinterpretation of the appearance and/or content of a product label which may potentially result in a medication error. This may be due to similarity with another product's label or due to confusing information on a single product label.

Product name confusion

Product name confusion is a misinterpretation of the correct name of a product which may result in a medication error. This may be due to a misleading name, or due to similar-looking or sounding product names.

Product odour abnormal

A change in the normal odor of the product.

Product packaging confusion

Product packaging confusion is a misinterpretation of the appearance of a product's packaging which may potentially result in a medication error. This may be due to similarity with the appearance of another product's packaging or due to confusing appearance or presentation of a single product's packaging.

Product taste abnormal
A change in the normal taste of the product.

Product quality issues
Product quality issues are abnormalities that may be introduced during the manufacturing/labeling, packaging, shipping, handling or storage of the products.

Progression of
Movement forward; advancement. Continuously spreading or increasing in severity.

Prophylaxis of
Protective treatment for or prevention of disease. For the purposes of term placement in MedDRA, the use of modifiers “prophylaxis” and “prevention of” is interchangeable.

R

Rate
The amount of drug (dose) administered per unit of time

Recurrent
Occurring or appearing again or repeatedly**.** For the purposes of term placement in MedDRA, the modifiers “relapse” and “recurrent” are synonymous.

S

Seal
A seal refers to an outer wrap on the closure or a liner attached to the container underneath the closure to either protect the product or act as a tamper evident feature.

Sedimentation
Sedimentation is the settling of product or foreign material to the bottom of a vial/container which is not normal for the product.

Sore/soreness/sores
For purposes of MedDRA, “sore” and “soreness” terms are used for pain. “Sore” terms, unless clearly addressed to a concept e.g. LLT Bed sore linked to PT Decubitus ulcer – are mainly placed under either pain related PTs or PTs indicating inflammation. “Sores” are considered lesions of the skin or mucous membrane frequently associated with pain, inflammation etc., depending on the context.

Solubility

See the concept description for dissolution.

Strength

Refers to a concentration of active ingredient found in a particular dosage form.

Subacute

Between acute and chronic: course of a disease of moderate duration or severity. Please see definitions of “acute” and “chronic.”

T

Technique

The manner of performance, method, operation, procedure, or details (e.g., pharmaceutical technique, aseptic technique) used to prepare a product.

Tenderness

For purposes of MedDRA tenderness terms are defined as sub-elements of pain and mainly subordinated to “Pain” or to “-algia” PTs unless they clearly address a single concept (e.g., PT *Abdominal rebound tenderness*).

Thrombophlebitis

Inflammation of a vein (phlebitis) associated with thrombus formation (thrombosis). The MSSO acknowledges the international use of thrombophlebitis/phlebothrombosis/vein thrombosis interchangeably, but MedDRA recognizes them as separate unique concepts. MedDRA also makes a distinction between superficial and deep vein thrombosis. When thrombosis occurs in the lower extremity, it is often called deep venous thrombosis/thrombophlebitis (DVT); when superficial vessels are involved, it is superficial thrombosis/thrombophlebitis.

U

Underdose

For the purposes of term selection and analysis of MedDRA-coded data, underdose is the administration of less than the minimum recommended dose (in quantity and/or concentration).

Upper gastrointestinal tract

In MedDRA the following organs constitute the upper gastrointestinal tract: mouth (buccal cavity; including salivary glands, mucosa, teeth, and tongue), oesophagus and stomach which includes the cardia, fundus, body, and pylorus.

Upper respiratory tract

In MedDRA the upper respiratory tract is comprised of nose, paranasal sinuses, pharynx, larynx and trachea.

W

Worsened/worsening

See “aggravated.” For the purposes of term placement in MedDRA, the use of modifiers exacerbated, aggravated and worsened is interchangeable.