Module 4: Medical (MedDRA) Coding

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1. Introduction to MedDRA

Started in the 1600s, Great Britain implemented the practice of the London Bills of Mortality, a medical coding system that assigned a number to a cadaver to describe the cause of death. The objective was to detect the onset of plague epidemics.

The International Statistic Institute standardized the approach in 1893 as the Bertillon Classification, which was rapidly adopted by several countries. The World Health Organization (WHO) issued a global reference document coding all diseases, injuries and deaths in 1949 and published the Manual of the International Classification of Diseases (ICD), Injuries and Causes of Death, nicknamed today the ICD system. Originally practiced on a volunteer basis, the use of medical coding became mandatory in the United States (US) in 1996, when the government passed the Health Insurance Portability and Accountability Act calling for total privacy of patients' information.

In the late 1990s, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) developed Medical Dictionary for Regulatory Activities (MedDRA), a rich and highly specific standardized medical terminology to facilitate sharing of regulatory information internationally for medical products used by humans. ICH's powerful tool, MedDRA is available to all for use in the registration, documentation and safety monitoring of medical products both before and after a product has been authorized for sale. Products covered by the scope of MedDRA include pharmaceuticals, biologics, vaccines and drug device combination products. Today, its growing use worldwide by regulatory authorities, pharmaceutical companies, clinical research organizations and health care professionals allows better global protection of patient health.

MedDRA is a clinically validated international medical terminology dictionary (and thesaurus) used by regulatory authorities in the pharmaceutical industry during the regulatory process, from pre-marketing to post marketing activities, and for data entry, retrieval, evaluation, and presentation. In addition, it is the adverse event classification dictionary endorsed by the ICH.

Originally available in English and Japanese, MedDRA is now also translated into Chinese, Czech, Dutch, French, German, Hungarian, Italian, Portuguese and Spanish. MedDRA is widely used internationally, including in the US, European Union (EU), and Japan.

Safety databases can contain several thousands of adverse reactions. Pharmaceutical companies as well as regulatory authorities are entering adverse reaction reports received by them in safety databases. Coding data to a standard set of MedDRA terms allows Health Authorities and the biopharmaceutical industry to more readily exchange and analyze data related to the safe use of medical products:

- Retrieve (provides statistical database)
- Present and Harmonize (various kinds of data)
- Analyze (evaluate patterns and research the quality of health care)
- Communicate (mitigate and plan for future heath care needs)

This helps them to assess the number and types of adverse reactions reported with different medicinal products. Evaluation of aggregate reports helps to understand the causal association between medicinal products and adverse reactions which are not known earlier. Therefore safety databases are searched frequently for signal generation as well as signal confirmation.

Good quality of data helps in early identification of adverse reactions. An important factor that increases the efficiency of signal detection is consistency of the adverse reaction terms. However, there can be several discrepancies in the data entry of adverse reaction terms. These differences can be in the choice of terminologies for similar adverse events or different spellings.

In some instances, where the number of cases is low or if there are some cases where confounding factors are present, it may not be possible to establish the causal association if all cases could not be retrieved. In order to retrieve all cases of anemia, person searching the database should be aware of all the possible terms that have been used for coding anemia and all such possible terms should be used as search criteria. This is a cumbersome job and almost impossible to carry out. Thus, use of different terms for the same adverse reactions decreases efficiency of the database to identify adverse reactions associated with a medicinal product.

Searching of databases can provide appropriate results only when adverse reactions reported in individual case safety reports (ICSRs) have been entered uniformly in the database. Although reporters will continue to use different terms for similar adverse reactions, consistency in the choice of terms can be ensured at the time of data entry. This is achieved by coding adverse reaction terms using standardized terminologies to ensure uniform entry in the database. Such uniform data entry facilitates efficient retrieval; evaluations and presentation of data when data need to be retrieved for generating case series for signal confirmation.

Since long, the need for uniform coding using standardized terminologies has been realized. As a result, several coding dictionaries have been developed so far. These include coding symbols for a Thesaurus of Adverse Reaction terms (COSTART), world Health organization - Adverse reaction terminology – developed by Uppsala Monitoring center (WHO – ART), adverse reaction terminology dictionary developed by them Hoechest (HART), Japanese Adverse Reaction Terminology (J-ART), ICD-9 (International Classification of Diseases) and MedDRA (Medical Dictionary for Regulatory Activities).Earlier, USFDA was using COSTART whereas WHO was using WHO – ART and different dictionaries were used by industry. Nowadays, medical coding has been more or less standardized with the use of MedDRA.

MedDRA was developed under ICH, is continuously enhanced to meet the evolving needs of its users

- ICH created a governance structure to nurture and protect the integrity of MedDRA
- MedDRA is maintained by Maintenance and Support Services Organization (MSSO) and is overseen by an ICH MedDRA Management Board appointed by the ICH Steering Committee that has overall responsibility for the direction of MedDRA, and oversees all the activities of the MedDRA Maintenance and Support Services Organization
- Updates are released twice a year-in March and September
- The terminology is used throughout the regulatory process, from clinical studies to post-marketing

2. Scope of MedDRA

With the help of MedDRA terminology, one can code diseases, surgical procedures, indications, adverse reactions, symptoms, signs, diagnoses and investigations. Thus, besides coding of reports adverse events/ reactions, signs and symptoms, MedDRA terminology can also be used for coding of social, family and medical history, therapeutic indications of suspect and concomitant drugs, provisional and confirmatory diagnoses, effects of rechallenge, investigational reports and cause of death.

However, MedDRA is:

- Not a drug dictionary
- Not a product dictionary
- Patient demographics terms cannot be coded

No frequency qualifier, no severity descriptor MedDRA terminology is used for coding of medical information during all phases of clinical development and marketing.

Table -1 – Coding in MedDRA

Level of MedDRA	**Example -1**	**Example -2**	**Example – 3**	**Example – 4**	**Example -5**
LLT	Diarrhoea	Heart burn	Nausea	Gas	Stomach pain
PT	Diarrhoea	Heart burn	Nausea	Flatulence	Abdominal pain upper
HLT	Diarrhoea (excl infective)	Dyspeptic signs and symptoms	Nausea and vomiting symptoms	Flatulence, bloating and distension	Gastrointestinal and abdominal pain (excl oral and throat)
HLGT	Gastrointestina l motility and defection	Gastrointestinal signs and symtoms	Gastrointestinal signs and symtoms	Gastrointestinal signs and symtoms	Gastrointestinal signs and symtoms

	condition				
SOC	Gastrointestinal disorders	Gastrointestinal disorders	Gastrointestinal disorders	Gastrointestinal disorders	Gastrointestinal disorders

Thus, the hierarchical structure of MedDRA ensures high specificity and quicker review. Although, PT is mostly used for case retrieval and data presentation; aggregation andanalysis of data can be carried out at different levels.

Thus, in the examples provided in the Table -1, one can retrieve all cases with adverse retrieve all cases with adverse reactions of SOC gastrointestinal disorders or only the number of cases of gastrointestinal signs and symptoms. One can also specifically retrieve the cases of nausea and vomiting. Use of LLTs ensures that the reported terms are not lost in the zeal of coding. Accurate retrieval of data is possible only when data have been entered correctly. Thus, MedDRA coding should be correct to ensure appropriate retrieval of adverse reaction reports at a later date.

3. Structure of MedDRA

MedDRA is a large terminology with a pyramid like structure. Terms in MedDRA are organized in 5 levels in a hierarchical manner viz. Low Level Terms (LLT); Preferred Terms (PT); High Level Terms (HLT); High Level Group Terms (HLGT) and System Organ Class (SOCs).

SOC is the highest level of terminology and represents anatomical or physiological system, etiology or purpose. All MedDRA terms or divided in 26 categories known as SOC. As the name suggest LLTs are at the bottom of the hierarchy and include synonyms, lexical, variants and other similar representations of specified medical conditions. LLTs are used for the data entry. Reported terms including adverse reactions, events, signs, Symptoms, investigations and others as explained under the scope of MedDRA are coded using LLTs.

Exact match of the verbatim or the closest matches area searched for. Each LLT is linked to a PT which in turn is linked to one or more HLT, then HLGT and finally SOC. Thus, on selection of LLT, the complete tree from MedDRA gets selected**.**

Similar LLTs are linked to the same PT. Each PT represents a discrete medical condition. All PTs are also duplicated as LLTs. PTs associated with similar medical conditions are in turn grouped under HLTs. HLTs are grouped as clusters under some HLGTs which in turn are distributed among 26 SOCs the highest level. Table -1 provides example of coding of five different gastrointestinal adverse events. This explains how the hierarchical structure of MedDRA allows detailed as well as precise capturing of the information.

Multi-axial structure of MedDRA

MedDRA is multi-axial terminology. This means that a PT along with its subordinate LLTs may be represented in more than one SOC. Multi-axial structure of MedDRA is defined at PT level because each PT represents a discrete medical condition As one PT may be represented in more than one SOC, for each PT, there is one Primary SOC and all other SOCs are Secondary. As a rule, PTs relating to disease or signs and symptoms are assigned to the SOC that best represents the primary manifestation site, for example PT Ear paint is assigned SOC Ear and labyrinth disorder.

However, there are certain exceptions where PT may represent a Primary SOC as well as a Secondary SOC, for example malignant neoplasms of auricular cartilage represent SOC

‘Neoplasms, benign, malignant and unspecified (Including cysts and polyps)’ and SOC- ‘Ear and labyrinth disorders’. There are SOCs like ‘Congenital, familial and genetic disorders’, ‘Neoplasms, benign, malignant and unspecified (including cysts and polyps)’ and ‘Infections and infestations’, therefore some PTS can be represented in more than one SOC.

Thus, each neoplasm, or infection will also represent a specific site in the body. Several PTs from such SOCs are represented in more than one SOC. The purpose of Primary SOC is to determine which SOC will represent a PT during cumulative data outputs and thus, it is used to support consistent data presentation for reporting. Using Primary SOC allocation also reduces the risk of double counting of events in cumulative outputs. During signal detection, secondary SOCs should be used for additional scientific analysis.

Further, PTs in some SOCs only appear in that particular SOC and not in others; i.e., they are not multi-axial, although there may be a clear correlation with some other systems, these are Investigations, surgical and medical procedures and social circumstances. This aspect needs to be considered while preparing the list of search terms for developing a case series for signal confirmation.

MedDRA is standardized and its use should be uniform across the organization using it. No changes are permitted within MedDRA at subscriber level. Therefore, users should not change the allocation of terms to Primary SOC and no customization should be done at the level of subscriber.

4. Using MedDRA

Coding with MedDRA

MedDRA coding is carried out with the help of MedDRA browser. Most of these adverse reaction databases facilitate uploading of the MedDRA dictionary within the database itself. Coder type the reported term which can be a diagnosis or symptom or sign or investigation. If there is a direct match of the LLT, this is picked automatically. For instances where a direct match is not available, a list of suggested / similar terms populates and coder has to manually choose the code that is closest to the reported term.

Basic MedDRA coding conventions:

- Use most specific term available and code to the LLT with accurate hierarchy up to SOC
- Code only verbatim reported in English, other language verbatim should be coded post translation of the non-English report into English report
- Do not classify a verbatim term in a way that would change, add, or subtract from its original meaning or content
- Dictionary Services group or MedDRA change requests are initiated by client when an appropriate term is not available for coding or the hierarchy available does not seem to represent the verbatim accurately
- When the most specific term for the verbatim is not available, use a clinically equivalent term or a general term that does not misinterpret the verbatim
- Ensure that the term selected maps to appropriate SOC

Promoting accurate and consistent terms selection for coding is one of the major objectives of MSSO. This facilitates a common understanding of shared data amongst its users, thus ensuring that MedDRA remains the standardized terminology. For this purpose, MSSO invites suggestion from its users regarding. The proposed changes for each version update of MedDRA, MSSO also holds user group meetings and publishes various guidance documents, including MedDRA Term Selection: Points to Consider (MTS:PTC), Introductory Guide to MedDRA, Introductory Guide of SMQs and various mapping documents. These documents are updates regularly and are made available to the subscribers.

A unique code (8-digit number) is associated with each term of MedDRA. These codes are non-expressive, meaning that they are just the sequence of numbers without any logic. Clear guidelines should be available within the organization to ensure consistency in coding.

MedDRA versions

MedDRA dictionary is updated two times in a year, in March and September with inputs from subscribers. While coding for ICRs, only one version of MedDRA should be used to code all relevant data elements of one ICSR. The version that should be used is always the last one released by the maintenance organization. Sponsors should make necessary arrangements to update the new version of MedDRA dictionary within 60 day of its release. Thus, for March release, MedDRA version is updated on the first Monday of April and September release, MedDRA version is updated on the first Monday of October.

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 in MedDRA, ensuring comprehensive and consistent data retrieval, irrespective of which SOC is selected at data retrieval. According to MedDRA 21.1:

- SOC – 27
- HLGT – 337
- HLT – 1737
- PT – 23088

LLT – 78808MedDRA ver 22.0 is available since 01 March 2019.

It should be noted that EU regulatory authorities, EMEA and MHRA upload the new version of MedDRA in their database on first Monday of the next month of the release. If a company transmits a report where coding has been done with new version of MedDra by regulatory

authority, such a report shall be rejected by regulators. MedDRA has been translated into several languages. Translations of MedDRA facilitate specificity of the LLT captured.

Although there is no regulatory requirement mandating recording of all data with new versions of MedDRA, as a good practice, all organizations using MedDRA should review if direct matches of verbatim are available with new versions and the availability of medically better terms.

Accessing MedDRA

MedDRA can be accessed by subscribing to it. MedDRA license is organization specific and needs to be renewed annually. MedDRa subscription is of various types as mentioned below. The eligibility for different types of subscriptions is determined on the basis of intended purpose of use, type of organization as well as total annual revenues of the organization. Different types of MedDRA subscription are:

- Basic for non-profit and teaching organizations
- Core-for pharma companies, cost of subscription varies depending on the total annualrevenues of the organization

System Developer-for organizations that develop software products that utilize MedDRA. Such a license specifically authenticates the user company for testing the terminology with their developed product and not for classification analysis or communication of data.

Regulatory authorities are eligible for free access to MedDRA and its all translations. Special license – very small companies based in European Economic Area with annual turnover of less than 10 million Euros are eligible to use MedDRA within EV-WEB free of cost.

Service providers CRO or BPO processing the cases cannot procure MedDRA license for multiple pharmaceutical companies. Each company is required to procure its own specific license.

MedDRA is distributed in sets of flat extended ASCII delimited files. There is a different set of files for each available language. Translations of certain languages like Chinese, Hungarian and Czech are distributed in UTF-8 format.

MedDRA is compatible with most of the operating systems and does not have any specific hardware or software requirements. All software applications commonly used by the pharmaceutical industry, for example Oracle, MS SQL server and MS Access, can either load MedDRA directly or through a load utility.

Limitations of MedDRA

Although MedDRA is one of the best coding dictionaries available today, and is used by most of the regulatory authorities yet it has some limitations as listed below :

MedDRA generally does not include term qualifiers for example frequent or rare, but for few exceptions for example frequent bowel movements. Considering that the reported terms frequently include qualifiers, therefore, direct coding will not be possible for reported terms that contain qualifiers.

MedDRA coding does not reflect severity of the disease, i.e. mild and severe although there are exceptions; for example severe acute respiratory syndrome, severe mental retardation, mild mental retardation and moderate mental retardation.

In MedDRA there is minimal reference to demographic terms, for example those related to gender or race or age. These terms are included only in those conditions where these terminologies area a component of a well-defined medical condition, for example floppy infant, infantile spasm, elderly primigravida, breast cancer male. The HLT infancy, childhood and adolescence psychiatric disorders NEC includes several LLT and PT terms related to this particular age group.

Attempts are being made to overcome these limitations. One of the solutions can be using MedDRA with a database that captures patient demographics, disease severity and numerical values independently of MedDRA itself, thereby facilitating subgroup analysis.

Use of MedDRA in signal Detection

While evolution of MedDRA as a standardized terminology facilitates data presentation and retrieval, there were concerns that detection of new adverse reactions may get delayed due to the split coding of signs, symptoms and investigations. It is worthwhile mentioning again that investigations are linked to a different SOC, Thus, attempts were made to develop standard tools to assist in the retrieval of data in such a manner so as to facilitate

identification of new adverse reactions. Considering the limitations of MedDRA, these tools identify groups of terms that can be used to generate case series for signal generation and confirmation. These tools included Special Search Categories, MedDRA Analytical Grouping, Special Search Queries and SMQs. Today, SMQs have become the standard tool for data retrieval, through it is worthwhile to learn about previous tools also.

5. Standardized MedDRA Queries

Standardized MedDRA Queries (SMQs)

SMQs are groupings of MedDRA terms that relate to a defined medical condition or area of interest. SMQs are used as standard tools to assist in the identification and retrieval of safety data. These groupings help is data exploration and retrieval by assisting in the formulation of a "case definition", thus, facilitating an early detection of syndromes / medical conditions which can otherwise get masked by split coding of individual adverse events, signs, symptoms or laboratory abnormalities. Terms included in SMQs are either one of the following – signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data, etc related to the medical condition of interest. Usually SMQs include MedDRA terms at PT level.

MedDRA SSCs were intended for a similar purpose. However, after several years of MedDRA use, both the regulatory authorities and biopharmaceutical industry concluded that SSCs did not adequately address the need. Therefore, SMQs are being developed to better address the need for standardization of data retrieval queries.

Designing of the Contents of SMQs

CIOMS and MSSO have been working together on developing an extensive set of SMQs. The terms used in SMQs are usually at the PT level. Only Lowest Level Terms (LLTs) represented in an SMQ are those that link to a PT used in the SMQ; all other are excluded. Introductory guide for SMQs can be downloaded from MSSO website. It explains basic concepts of SMQs and also incorporates the definitions, inclusion and exclusion criteria, hierarchy (if applicable), and algorithm (if applicable) for each SMQ. Each SMQ comes with an accompanying documentation of how individual SMQs were developed and defined. This includes Notes on implementation and /or expectation of query results and list of references for the specific SMQ.

SMQs may have a mixture of very specific terms and less specific terms that are consistent with a description of the overall clinical syndrome associated with a particular adverse event and drug exposure. Some SMQs are a straightforward collection of terms; others must be

designed to accommodate combinations of terms from more than one group. To address these varied aspects, SMQs may have certain specific design features.

Special Features of SMQs

These are intended to improve the quality of query result by increasing the specificity and reducing the noise level. They are optional, thus users can use an SMQ as a list of MedDRA terms with any special features. Special features include Narrow vs Broad searches; Algorithmic search, and Hierarchies. A narrow approach accommodates those instances in which a user may need to identify cases that are highly likely to represent the condition of interest. Thus, a narrow approach yields specificity. On the other hand, broad approaches includes those instances in which a user seeks to identify all possible cases, including some that may prove to be of little or no interest on closer inspection. A “broad” search includes both the “narrow” terms and the additional “board” terms, often of a less specific nature.

Thus, although broad search is less specific, it is more sensitive.

An algorithm is a defined combination of selected terms used for selection of cases, better case identification with high specificity as well as high sensitivity. Application of the algorithm is most helpful when it is expected that a large number of cases will be retrieved by broad scope terms; these algorithms are expected to reduce the need for manual sorting of the cases of interest. An algorithmic SMQ is designed to reduce the “noise” level among broad terms. Not all SMQs have an algorithm. For those SMQs that do have an algorithm, each algorithm is unique and needs to be implemented individually.

Potential Utility and limitations of SMQs

SMQs are a useful search and data retrieval tool and can ensure infirmity and reproducibility of search strategies and results. With the help of SMQs MedDRA terms for specific medical conditions can be pre-defined in the protocol or risk management plan to facilitate an early identification of the medical condition of interest. It must be remembered that role of the SMQs is limited to retrieval of the case reports for evaluating potential safety signals.

Individual case report evaluation is needed to answer specific safety questions. Further, in spite of the ongoing international efforts to develop this standardized tool, there are no regulatory implications or requirements for the use of SMQs.

6. MedDRA Version 22.0 (SUMMARY OF CHANGES)

SUMMARY OF IMPACT ON THE TERMINOLOGY

The tables below (Tables 6-1 through 6-3) summarize the impact on MedDRA in Version 22.0. These tables are intended only as a reference.

Table 6-1 Summary of Impact on SOCs, HLGTs, HLTs

Level	Change request action	Net change	Ver 21.1	Ver 22.0
SOC	Total SOCs	0	27	27
HLGT	New HLGTs	2	0	2
	Merged HLGTs	2	0	2
	Total HLGTs	0	337	337
HLGT	New HLTs	6	0	6
	Merged HLTs	6	0	6
	Total HLTs	0	1,737	1,737

Table 6-2 Summary of Impact on PTs and LLTs

Level	Change request action	Ver 21.1		Ver 22.0
PT	New PTs	347		327
	Promoted PTs	19		42
	Demoted PTs	65		50
	Net change	301		319
	Total PTs	23,389		23,708
LLTs changes				
LLTs	Currency status	Net change	V 21.1	V 22.0
	Current Terms	748	70,229	70,977
	Non-current Terms	7	9278	9,285
	Total terms	755	79,507	80,262

Table 6-3 Summary of Impact on SMQs

Level	Net change	Ver 21.1	Ver 22.0
Level 1	1	103	104
Level 2	0	82	82
Level 3	0	20	20
Level 4	0	16	16
Level 5	0	2	2

7. Other Common Coding Methods

7.1 COMMON TOXICITY CRITERIA ADVERSE EVENETS (CTCAE)

CTCAE is a descriptive terminology of adverse events that also includes grading of adverse events of anticancer therapies. The Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) developed original common Toxicity Criteria (CTC) in 1983 to assist the documentation and analysis of adverse effects of chemotherapy. CTCAE serves to facilitate the evolution of new therapies, treatment modalities, and supportive measures so to standardize reporting of Adverse Events across groups and modalities without regards to chronicity. Besides containing the list of commonly encountered adverse event terms, CTCAE is also accompanied by a grading (Severity) scale for each adverse event.

The first version of CTCAE was released in 1983 with 50 terms. CTCAE v 4.0 includes 764 adverse event terms and 26 'other, specify options for reporting text terms not listed in CTCAE. Each AE term is associated with a 5 point severity scale. Definitions of each grade are provided in the enclose table. Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than 5 options for grade selection. Grading of AEs is based on how they impact Activities of Daily Living (ADL). Instrumental ADL is limited in Grade 2, instrumental ADL refer to preparing meals, shopping for groceries or cloths, using the telephone, managing money, etc. AEs limiting self-care ADL are graded as severe or Grade 3; self-care ADL includes bathing dressing and undressing, feeding self, using the toilet, taking medications and not bed-ridden. Refer to Table 2: Grading of CTC AEs for details.

Table -2- Grading in CTC AE

Grade 1	Mild, Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate, minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated, disabling; limiting self care ADL
Grade 4	Life –threatening consequences, urgent intervention indicated

Grade 5	Death related to AE

Mapping of CTCAE with MedDRA

Initially CTCAE was mapped with MedDRA to facilitate consistency in the retrieval of data. Documents mapping CTC v2.0 and CTCAE v3.0 are available on the CTEP web site. CTCAE v3.0 has been mapped to MEdDRA version 11.0. There is no mechanism to incorporate the mapping of different grades of CTCAE terms. To facilitate the understanding of the coders and reviewers, the convention followed for mapping is described in the document "CTC v3.0 to MedDRA v 11.0 mapping: Conventions and Notes. " Many CTCAE terms represent multiple concepts, for example CTCAE term – Extra pyramidal / involuntary movement/ restlessness and Fatigue /Asthenia / Lethargy / Malaise. In MedDRA such a concept represents multiple concepts. Therefore, these terms are mapped to a single concept of MedDRA which is considered to be the most important or closest clinically relevant concept. One must go through the mapping documents so as to understand the basis of mapping which will be useful while retrieving the data for developing a case series or aggregate data analysis.

Version4.0 of CTCAE is MedDRA v 12.0 compatible at the adverse event terms level where each CTCAE term is a MedDRA LLT.

7.2 Systematized Nomenclature of Medicine- clinical Terms (SNOMED-CT)

As the name itself indicates, SNOMED-CT is a comprehensive clinical terminology. It was originally created by the College of American Pathologists (CAP). Since April 2007, it is owned, maintained, and distributed by the International Health Terminology Standards Development Organization (IHTSDO) which is a non-profit associated in Denmark. In 2003, SNOMED was selected as the standard terminology for electronic medical records in the United States. As MedDRA is the standard terminology for the coding of adverse drug reactions. There are plans to map MedDRA to SNOMED in the near future via the National Library of Medicine Unified Medical Language System (UMLS).

7.3 WHO Drug Dictionary Enhanced (WHO-DD)

Reports of adverse drug reactions may include several co-suspect drugs as well as medicinal products that have been co-administered along with the suspect drug. It is important to collect information about co-suspects and co-administered medicinal products. In order to

appropriately evaluate drug interactions, information about these products may be available as trade names and searching for active ingredient, dosage, formulations etc may be time consuming and tedious process. Therefore, WHO Drug Dictionary Enhanced has been developed to facilitate data entry of the information about co-suspects and coadministered products, code them and facilitate retrieval of data when required.

It is a comprehensive dictionary of medicinal product information as it includes trade names of medicinal products, their active ingredients and therapeutic use. This dictionary also contains information about the country in which the product is marked as well as its dosage form and strength.

This dictionary directly matches the medicinal products co-administered with the suspect drug. It can also be used to group medicinal products of similar class together. Further, for a particular active ingredient, one can code all formulations of the active ingredient under one head and can code all formulations of the active ingredient under one head and can also sub-group the formulations with a specific salt or ester form together, for example morphine sulfate or morphine tartrate or simply as morphine. Thus, it translates a drug name to useful information, which is used for coding and analysis of drug safety data both before and after marketing.

It is licensed, maintained and regularly updates by World Health Organization's (WHO) Uppsala Monitoring Center (UMC). It includes trade names of tens of thousands of marketed products. It is used by pharmaceutical companies, clinical research organization and drug regulatory authorities for indentifying drug names, their active ingredients and therapeutic uses. All entries are coded with the Anatomical Therapeutic and Chemical (ATC) classification as well coding system of WHO Drug Dictionary Enhanced.

Majority of the entries in WHO Drug Dictionary Enhanced refer to the prescription – only products. In addition it also includes some over-the-counter (OTC) products. Biotech and blood products, diagnostic substances and contrast media are also entered in this dictionary. UMC has also introduced a special Herbal Dictionary which codes the drugs of natural origin. This dictionary is developed as a separate product from WHO Drug Dictionary Enhanced, although it follows the same structure and general principles. Herbal dictionary contains trade

names of the herbal remedies together with the active ingredients in the form of herbal plants. All products in the WHO herbal dictionary are coded with herbal ATC classification.

UMC has entered in collaboration with IMS Health. Prior to this collaboration, the dictionary was called WHO drug Dictionary, and after this collaboration, it is called WHO Drug Dictionary Enhanced. New WHO drug Dictionary Enhanced contains data from the IMS Health data. It is produced in the same formats and with the same principles as previous WHO drug Dictionary. This collaboration has resulted in an increase the coverage in a larger number of countries and to get fast access to information about the launch of new products.

The hierarchical structure of WHO Drug Dictionary Enhanced allows easy and flexible dataretrieval, aggregation and the analysis of data at different levels of precision as per the level of information available. Thus, one may search with the name of the formulation of the active ingredient with specific salt/ester and may as well incorporate the additional information available in form of dosage, strength etc.

WHO dictionary facilitates searching as:

- Chemical and therapeutic groupings – using the WHO drug record number system and the ATC classification for the main indication for which a medicinal product is used. ATC itself is a hierarchy with five levels.
- Ingredient / combination of ingredients level.
- Pharmaceutical product level – combination of ingredients, form and strength
- Medicinal product level referring to the named product marketed and sold in a particular country.

Other benefits offered by WHO Drug Dictionary Enhanced include consistent and up-to-date information entry. Like MedDRA, WHO Drug Dictionary Enhanced is available in software – independent electronic format for easy implementation in the user systems.

WHO Drug Dictionary Enhanced contains a high percentage of all product names that appear as co-medication, thus increasing the likelihood of finding a direct match in the dictionary. Further, UMC in an attempt to fully meet the requirements of all users, responds quickly to requests for new entries or to other suggestions which are compatible with the fundamental

structure of WHO-DD and can potentially enhance the usefulness of the dictionary. Thus, need for manual investigations and fact-finding is reduced.

As there is less requirement for making assumptions and guesses, quality of the coded data improves by using WHO-DD. Now drugs are constantly introduced on the market in all countries of the world, and sometimes marketed formulations are modified. Therefore, WHO Drug Dictionary Enhanced is updated four times per year so as to keep track of these changes. Till March 2005, the versions of WHO Drug Dictionary have been known as Quarter 1, Quarter 2, Quarter 3 and Quarter 4. These names have referred to the Quarter during which the data has been entered into the dictionary. From a customer's perspective this has been confusing since Quarter 1 has been distributed in June etc. To avoid confusion, currently the releases are referred to as the dates of release i.e. March 1, June 1, September 1 and December 1.

8. Summary

Appropriate and consistent coding practices are must for accurate data retrieval and presentation. Therefore, coding plays a very crucial role in correct evolution of the safety of products during clinical development and after marketing. Till sometime back several dictionaries were in use, e.g. WHO-ART, COSTART, etc. Nowadays, however, the choice of dictionaries has been more or less standardized and most of the Pharmaceutical companies, regulators and academia are using WHO Drug Dictionary Enhanced for coding of medicinal products and MedDRA for coding of diagnosis, adverse events, signs, symptoms, indications, investigations, medical history and surgical procedures. Regular updating of these terminologies and involvement of users has ensured that these remain standardized terminologies in popular use.

In order to match the dynamic pace of the development of medicine, for any terminology to remain current, it is critical that the terminology is updated in response to the new developments. Regular review of these terminologies is carried out to identify and correct the errors or non-current concepts and modify it in response to the problems faced by its users or implement enhancements based on user feedback.

For appropriate coding, coders should be well-acquainted with the basic rules of coding, hierarchical structure of MedDRA, mapping conventions and limitations of coding. Coding staff can't work in isolation. Quality of coding is directly affected by the quality of data in the ICRs. Therefore, call handling teams should be advised and trained accordingly. If some information is not clear or incomplete or discrepancies are there, reporter must be followed up for clarifications and additional information.

9. Further reading & References

9.1 Further Reading

- Primary System Organ Class (SOC) allocation in MedDRA – available on website – http://meddramsso.com/public_videos.asp
- CTC v3.0 to MedDRA v 11.0 mapping : Conventions and Notes
- MSSO Introductory Guide to MedDRA
- MSSO Introductory Guide for Standardized MedDRa Queries.
- CIOMS working Group V. Current Challenges in Pharmacovigilance: Pragmatic Approaches. Geneva: WHO, 2001.

9.2 References

- Brown E.G. using MedDRA Implications for Risk Management. Drug Safety 2004;27(8):591-602.
- Common Terminology Criteria for Adverse Events (CTCAE) and common Toxicity Criteria (CTC). Available on website http://ctep.concer.gov/protocoldevelopment/electronic_applications/ ctc.html
- Klepper MJ. MedDRA- An Introduction. Available on the website http://www.rti.org/pubs/meddra_intro.pdf Accessed on 23 April 2011.
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- MSSO Introductory Guide to MedDRA version14.0 Available on the website https://meddramsso.com
- MSSO Data Quality Coding and MedDRA. Available on the website – http://meddramsso.com/punlic_training.asp
- MSSO. Introductory Guide for Standardized MedDRA Queries. Available on the website –http://meddramsso.com
- MSSO. MedDRA Data Retrieval and Presentation: Points to Consider. Available on the website – https://meddramsso.com
- SNOMED Clinical Terms (SNOMED CT). Available on websitehttp:// www.nlm.nil.gov/research/umls/Snomed/snomed_main.html
- World Health Organization welcome to the WHO Drug Dictionary Enhanced. Downloaded from the website http://www.umc-prodcts.com/graphics/2489.pdf Accessed on 23 April 2011.