Review Article

Review Article on Use of MedDRA in Clinical Coding

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ABSTRACT

There may be severe consequences if there is misclassification of adverse events in clinical trials. For the purpose of reducing the scope for interpretation several steps are involved such as from subject adverse event experience to presentation in tablets should be possibly standardised. MedDRA is a predefined dictionary where adverse events, signs, symptoms, diseases and diagnosis and statistical analysis are categorized. It is renewed twice in a year with several advanced categories. From its initiation past 20 years MedDRA has become the common language for safety reporting in regulative context. The main strength od MedDRA is the standardised reporting crosswise various regulatory regions and languages. The advantage in this is the particulars which are offered by enormous number of items. Adverse events in maximum clinical trials are evaluated as a part of pharmacovigilance activities that are being reported using MedDRA. Coding is a process in which the universal dictionary is which is required for translating the event which is reported by the investigator into a standard term. For the hunt for safety signal frequencies and incidences of adverse events can be scrutinized once the adverse events have been accurately coded.

Keywords: Adverse events, MedDRA MSSO, WHO Adverse Reaction Terminology, MSSO, System Organ Class (SOC), High Level Group Term (HLGT), High Level Term (HLT), Preferred Term (PT), Lowest Level Term (LLT), Scope, Languages, Maintenance of MedDRA.

INTRODUCTION

For the purpose of clarifying the adverse events, historically pharmaceutical companies have used several distinct dictionaries like WHO's adverse reaction terminology, the Thesaurus of adverse reaction terms or the international classification diseases. Medical dictionary for regulatory activities MedDRA, a standard dictionary was developed by the pharmaceutical industry along with regulatory agencies in 1994. Standardised electronic submissions were the aim at the beginning. MedDRA is a pecking order with lowest level terms at the bottom, followed by preferred term and system organ class at the top (SOC). At first, events are coded with lowest level terms which are dwelled with thousands of synonyms and different spellings of preferred terms, which are exclusive medical bodies. Companies can advise new terms or alternate placing in the hierarchy but are not permitted to add new terms which will be further taken into consideration for the biannual update. To confirm in the standard summary table, whether an adverse event is counted only once, each favoured term should have individual primary SOC. But may have definite secondary one's for the assistance of data retrieval.

MedDRA

MedDRA is defined as a clinically validated international medical terminology which is used by regulated biopharmaceutical industry and by regulatory authorities. In the entire regulatory process starting from pre-marketing to post-marketing and also for data entry, retrieval evaluation and presentation, the terminology is used. In extension, it is the classification of Adverse Events approved by International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.[3] It is updated biannually, once in March which is a complex release and other update is on September which is a simple release. MedDRA is used extensively including in United States, European Unions and Japan. Its use is presently authorized in European and Japan for the purpose of safety reporting. ICH MedDRA management board inspects the activities of MedDRA MSSO. The management board consists of six ICH parties, Medicines and Health Care Products Regulatory Agency (MHRA) of UK, Health Canada and WHO (as an observer).

HISTORY OF MedDRA

Prior to ICH numerous varieties of dictionaries that code the names of diseases were utilized. For instance, Food and Drug Administration has chosen a sign to code thesaurus of adverse reaction terms as COSTART. Most frequently operated network comprises of International Classification of Diseases (ICD) and WHO Adverse Reaction Terminology (WHOART). Few institutions have implemented internal terminology[4] for their own use. Different systems that code prevents the comparing and merging of secured information and also characterized a huge difficulty on organisations that are compelled to code the information again to submit to various areas. In 1994, Council for International Organizations of Medical Sciences (CIOMS) declared that MedDRA can be used worldwide for Adverse coding. In October 1994, version 1.0 was accepted. ICH MI team was assigned for implementation of MedDRA.

Current version of MedDRA is 23.0 which is released in march 2020.

PURPOSE OF MedDRA

- Through standardization, it promotes the exchange of clinical information.
- For product evaluation, monitoring, communication, electronic record exchange and oversight, MedDRA is an important tool.[1]
- Human medical products which includes pharmaceuticals, biologics, vaccines and drug device combination products are supported by MedDRA through coding, retrieval and analysis of clinical information.

Where MedDRA is used?

- Clinical Trial phase 1, Clinical Trial phase 2, Clinical Trial phase 3, Clinical Trial phase 4.
- Clinical study reports.
- Individual case safety reports and safety summaries.
- Investigator's Broacher.
- Analysis.[5]
- Marketing Applications.
- Publication.
- Prescribing information.
- Advertising.

Why coding is needed in MedDRA?

There are different terminologies used across the globe in order to reduce the variation, coding is been established.

- An eight-digit numerical code is characterized with individual MedDRA terminology.
- The code does not have any expression.
- The data range can be fulfilled with the help of codes in several electronic submission categories.
- Basically, it is designated alphabetically by term which begin[3] with 10000001.However new terms are empowered consecutively.

STRUCTURE OF MedDRA

- System Organ Class (SOC)
- High Level Group Term (HLGT)
- High Level Term (HLT)
- Preferred Term (PT)
- Lowest Level Term (LLT)

System organ class

It can be defined as the maximal level of the MedDRA terminology which is notable by anatomical or physiological system, aetiology or purpose.

High level group term

It is subordinate to SOC, superordinate descriptor for one or more HLT's.

Preferred term

It embodies a single medical concept.

Lowest level term

LLT contains the least term. It is connected solely to single preferred term. It is the base level of terminology which is associated to a single PT as a synonym, lexical variant or quasi-synonym.

a) Synonyms: Variety of terminology is used for identical intrinsic ideas in preferred terms.

   For example, PT is Arthritis and for this LLT used is Joint Inflammation.

b) Lexical Variant: Distinct terms configures the matching[3] appearance. For example, PT is required Immune deficiency syndrome and LLT is AIDS.

c) Quasi synonyms: These words does not give the exact phase of other word. However, they are used as analogues. For example, PT is Otitis Externa and LLT is bilateral otitis externa.

d) Sub concept: In this, LLT constitute much comprehensive data like anatomy specificity. For example, PT is Contusion and LLT is Bruising of face.

e) Identical LLT: Sometimes LLT is similar to PT. For example, PT is Dementia Alzheimer's type and LLT is also Dementia Alzheimer's type.

LLT can lodge everyday usage words, so it may not require to translate into another language. LLT is a vital step that helps to facilitate the moving of ancient information as most of the words are included. LLT allow entering of data[1] as well as encourages stability by declining personal options. LLT can be utilized for auto encoding. Professionals can usually recover the data mostly from LLT than at PT level. It consists of current and noncurrent flag status. In noncurrent flag, words used are unclear, doubtful, cut short, old fashioned or mismarked. These are obtained from MedDRA. These flags help's the customers to develop the phraseology in the data base as well as helps to avoid accidental usage of noncurrent LLT's.

PREFERRED TERMS

It is well defined for signs and symptoms, disorders, identifying the disease, drug indications, examinations, surgery or any medical process, also history of family, medical history or social history. PT must be distinct and self-defined to achieve global standard conditions. So, while naming the PT, universally identified were used.

PT level selectively is based on pathophysiology or causes of disease are expressed.[4] For example, different meningitis words are present in this level as unique words.

PT Meningitis aseptic

PT Meningitis Cryptococcal

PT Meningitis Viral

PT Meningitis bacterial.

From this we can make sure that the representation of medical concept in multiple ways. Maximum number of LLT's may connect to PT. But a PT should consist of less than one LLT. If new PT is attached in phraseology then instinctively similar LLT is generated. PT levels is like assistant to HLT level. PT should be connected to one or more SOC. It may be associated to a SOC through HLT to HLGT then SOC way. PT terms have primary SOC which helps to identify in which collective information SOC words falls.

HIGH LEVEL TERMS

HLT is superior to PT level. It is connected to PT by anatomy and physiology, pathologically, causes and its functions. For instance, HLT Broncho spasms and obstruction and HLT Mediastinal disorders. Here, the terms used are not based on classification so, there is no specific uniformity all over the phraseology. HLT is especially used for the purpose of data recovery as well as for demonstration. This level is not used for coding instead used for grouping. HLT is like assistant to HLGT level. Every HLT should be connected to one SOC through HLGT. Every HLT should be connected to specific HLGT which can be visible in all SOC, to which HLGT is connected.[2]

HIGH LEVEL GROUP TERMS

HLGT is a miraculous caption for one or several HLT's which is associated with anatomy, physiology, pathology, aetiology or function. For example, HGLT vascular hypertensive disorders is used to link HLT's such as accelerated and malignant hypertension, HLT hypertension complications, HLT pregnancy[3] associated hypertension etc. For the purpose of data retrieval and presentation HLGT's are designed. HLGT's are abettor to SOC's. It must be associated to minimum one SOC and also to minimum one HLT i.e, the next up and down levels in the hierarchy. HLGT's can be linked to several number of SOC's where there is no limit.

SYSTEM ORGAN CLASS

For data retrieval, SOC is the crown level of hierarchy which administers the expansive concept. SOC's constitute groupings by the following:

1. Aetiology.

Example- SOC infections and infestations.

2. Manifestation site

Example- SOC gastro intestinal disorder

3. Purpose

Example-SOC surgical and medical procedure

There is an exception in the above categories which is SOC social circumstances which consist of information about the person but not the adverse event and maintains an organization for certain factors which may provide the vision into the personal issues which may have an effect on the reported event.

Each PT is accredited with the primary SOC in order to ward off double counting in the process of retrieving information from all SOC's. This is necessary as PT's can be characterized in more than one SOC. This process prohibits a particular PT from being visible more than a time in aggregate SOC-by-SOC data outputs[5] that outcomes the over counting of terms. A primary SOC is designated to all PT's in MedDRA which regulates the SOC in which the term s displayed in the outputs.

For the allocation of primary SOC the following rules are utilized:

- PT's which are only characterized in single SOC are undoubtedly accredited that particular SOC as primary.
- There are some exceptions where the PT's are associated to diseases or science and symptoms and attached to the prime manifestation site SOC.

  (1) For congenital and hereditary anomalies are authorized to SOC's Congenital, familiar and genetic disorders as primary SOC.

  (2) For Neoplasms, terms are designated to SOC neoplasm benign, malignant and unspecified (include cysts and polyps) as primary SOC. These terms have their individual primary SOC, the manifestation site SOC.

  (3) For infections, terms are assigned to SOC infections and infestation as primary SOC.

For suppose if there is linkage of PT to several of the above exception SOC's, then the priority mentioned below is used to regulate primary SOC.

(a) SOC congenital, familiar and genetic disorders.

(b) SOC neoplasms benign, malignant and unspecified.

(c) SOC infections and infestations.

For example, PT congenital teratoma is linked to SOC congenital, familiar and genetic disorder as primary SOC alongside secondary link to SOC neoplasm benign, malignant and unspecified.

During the development of MedDRA, this decision was taken place to abolish the manifestation site rule when regulating the primary SOC allotment for neoplasms, congenital abnormalities and infections. This was performed to aid in signal detection, as all PT's relating to

those categories are organized together on regular aggregate data outputs.

Other considerations for primary SOC allocation are as follows:

- All SOC's in MedDRA do not explicit multi-axiality. Some terms like terms which enclose within SOC investigations, SOC social circumstances and SOC surgical and medical procedures dwell within those SOC's and nowhere additional in the terminology as they have inadequate multi-axial linkages.
- Maximum number of injuries, poisoning and procedural complications terms are expressed which are characterized in SOC injury, poisoning and procedural complications as primary SOC.
- Primary SOC is assigned with application, implant and injection site reaction Infestations at general disorders and administration site condition have primary SOC infections and infestations[1].

The Alphabetical Listing of MedDRA SOCs is presented below in the internationally agreed order.

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 (includes 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*
SOC *Infections and infestations*
SOC *Neoplasms benign, malignant and unspecified (include 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*

The MedDRA Terminology SOC List – Internationally Agreed Order

Scope of MedDRA

IN	OUT
• Pharmacogenetic terms • Medical conditions • Medical and surgical procedures • Indications • Investigations • Product quality issues • Device related issues • Medical, social, family history • Medication errors • Product use issues • Toxicological issues • Standardized queries	• Not a drug dictionary • Not an equipment, device, diagnostic product dictionary • Clinical trial • Study design terms • Patient demographic terms • Numerical values for results • Frequency qualifiers • Severity descriptors

LANGUAGES OF MedDRA

Formerly MedDRA is accessible only in two languages, English and Japanese. But now it is accessible in several languages. They are:

1. Dutch
2. Portuguese
3. French
4. German
5. Hungarian
6. Cezch
7. Italian
8. Spanish
9. Russian
10. Korean
11. Chinese

MAINTENANCE OF MedDRA

Maintenance and Support Services Organization (MSSO) governs MedDRA. The intellectual property rights of MedDRA is maintained by International Federation Pharmaceutical Manufacturers and Association (IFPMA) which is a trustee of International Conference on Harmonization (ICH) Steering Committee. As per the request[2] of the subscriber, MedDRA is updated by MSSO. For example, for the inclusion of an advanced medical concept which is about to be in MedDRA or for the modification of current concept.

CONCLUSION

By all counts, and with proven results, it is MedDRA is a clinically accepted worldwide pharmaceutical mechanisation used to control by a pharmaceutical industry by administrative unit. Standardization across regulatory regions and languages is certainly welcome. With nonstop regularity, it assists the interchange of clinical information and avail one self of clinical trial phases and also in post marketing surveillance studies. It gives clear cut information about total diseases or surgery conditions from System Organ Class (SOC) to Lowest Level Term (LLT). This leads to development of high potential dictionary which is available in 13 different languages. Likewise, the constant evaluation of MedDRA could be considered a strength in that it can adopt to new situations. Awareness of these issues can help regulatory writers and ensure that safety reporting is as clear and transparent as possible.

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