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Adverse Event and Drug Coding in Clinical Research

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Introduction

Investigators, study coordinators, and other site personnel who record adverse event and other safety-related data are more likely to enter useful data if they have a basic understanding of how their data will be coded.

The capture and reporting of data for safety monitoring in clinical research involves the use of diverse terminologies, such as SNOMED CT, ICD-9/10, COSTART, WHO-ART, MedDRA and WHO-DD for coding observations, diagnoses and events. The purpose of these terminologies ranges from categorizing adverse events to concomitant medications to diagnoses to procedures, all of which have safety implications. Accurate, complete and consistent coding ensures that the necessary data is available for detecting and assessing safety issues. This article will focus on the two most commonly used terminologies: MedDRA and WHO-DD.

MedDRA

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) holds the intellectual property rights (ownership) of the Medical Dictionary for Regulatory Activities ("MedDRA"). The MedDRA Maintenance and Support Services Organization (MSSO) maintains the dictionary.

MedDRA is defined as:

> A medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products. (MedDRA MSSO)

An adverse event is:

> Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (ICG E6: Guidance for Good Clinical Practice)

The regulatory requirements for the investigator reporting adverse events to the study sponsors are:

> An investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately. (21 CFR 312.64)

The sponsor must also report promptly any adverse events to the U.S. Food and Drug Administration (FDA). (21CFR312.32) The FDA has issued guidance suggesting the adoption and use of one standardized coding terminology (e.g., MedDRA) in both premarketed and postmarketed studies. (Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005)

MedDRA employs a five-level hierarchy of terminology, as shown in Table 1. Ideally, research sites report adverse events using the correct Lowest Level Term, or a term that can be clearly coded into a Lowest Level Term. For example, "aching knee" can be coded as "joint pain." However, it is not clear that "knee sensitive to touch" has the same meaning, so a data query is required for clarification.

Table 1. MedDRA Terminology Hierarchy (Version 14.1)

Level	Abbreviation	Number of Codes	Example
System Organ Class	SOC	26	Musculoskeletal and connective tissue disorders
High Level Group Term	HLGT	335	Joint disorders
High Level Term	HLT	1,710	Joint-related signs and symptoms
Preferred Term	PT	19,294	Arthralgia
Lowest Level Term	LLT	69,524	Joint pain

Proper coding is complete. For example, if an investigator reports a sign or symptom of "gold," which is not in the MedDRA database, the report should not be ignored. Instead, the sponsor should send a data query to the investigator asking for clarification.

Proper coding is accurate. Investigator's reports can be confusing or ambiguous, e.g., the term "COLD" might mean "common cold," "Chronic Obstructive Lung Disease," "feels cold," or something else entirely. The coding guidelines for a study should advise whether one of these interpretations should be used (given the context of the study), or whether a data query should be sent to the investigator asking for clarification. As the study progresses, the coding guidelines should evolve to reflect issues that arise.

Accuracy does not permit assumptions based on the symptoms reported. For example, an investigator might report the symptoms of polydipsia, blood sugar increased, and polyuria, but the coder should classify these symptoms individually and not combine these into a report of "PT: Diabetes mellitus."

Accuracy requires knowledge of the coding terminology. For example, if an investigator reports a symptom "macroglossia," the coder might assume the best choice would be the exact match found in MedDRA of "PT: Macroglossia" (enlarged tongue). However, "PT: Macroglossia" is under the broader category "HLT: Tongue disorders, congenital." Unless a neonate is involved, medications do not cause congenital disorders, so a different code is required: "PT: Acquired macroglossia," which is in the "HLT: Tongue disorders" group. In another example, if the investigator reports "Convulsions upon drug withdrawal," the symptom could be coded as "LLT: Convulsions," However, "LLT: Drug withdrawal convulsions" is more accurate and conveys the correct medical concept.

Proper coding is consistent. For example, if an investigator reports a symptom of "hearing less than before,'' the study guidelines might specify that it always be coded as "LLT: Hearing decreased," but never "LLT: Hearing loss."

WHO-DD

The Uppsala Monitoring Centre maintains the World Health Organization's Drug Dictionary ("WHO-DD"), which can be used to identify concomitant medications.

A variety of product types are included in the dictionary, such as the following:

- Conventional medicinal products
- Vaccines
- Biologics
- Herbal remedies
- Homeopathics
- Generic names
- Group categories

The WHO-DD is organized based on Anatomical Therapeutic Chemical (ATC) Classifications. Each medicinal product is classified according to the primary organ or system on which it acts and its chemical, pharmacological and therapeutic properties. Table 2 gives an example of how Paracetamol is classified in the ATC system:

Table 2. ATC Structure for Paracetamol (Acetaminophen)

Level	Code	Classification
Level 1 Main Group	N	Nervous System
Level 2: Therapeutic Main Group	N02	Analgesics
Level 3: Chemical/Pharmacological/ Therapeutic subdivision	N02B	Other Analgesics and Antipyretics
Level 4: Chemical/Pharmacological/ Therapeutic subgroups	NO2BE	Anilides
Level 5: Chemical Substance – WHO-DD Drug Name	00020001001	See Drug Codes below

Unlike MedDRA codes, which consist of abbreviations and words, WHO-DD Drug Codes) consist of 11 digits, which have intrinsic meanings as shown in Table 3:

Table 3. WHO-DD Drug Code for Paracetamol (00020001001)

Classification	Digits	Code	Meaning
Drug Record Number (DRECNO)	1 to 6	000200	The active ingredient or unique combination of active ingredients
Sequence 1 (seq 1)	7 to 8	01	The salt or the ester of the active ingredient in a single ingredient product
Sequence 2 (seq 2)	9 to 11	001	The trade names and, in some cases, a synonym for a generic name. Value 001 identifies the name of the generic drug record number level, the preferred name. In single ingredient drug record numbers, Value 001 will also be the substance name. For multiple-ingredient drug record numbers, Value 001 will be the trade name of the first product with that combination of ingredients.

In Table 4, the DRECNO (first six digits of the Drug Code) remains the same because the base substance is the same in each product. Sequence 1 (seq 1) reflects the different salts and esters of the base product. Sequence 2 (seq 2) identifies trade names and, in some cases, a synonym to a generic name. The entry with seq 2 value 001 identifies the basic generic drug, the preferred name. In single-ingredient drug record numbers, this entry also identifies the substance name. For multiple-ingredient drug record numbers, it identifies the

trade name of the first product with that combination of ingredients. Seq 2 values above 001 are assigned chronologically.

Table 4. Components of the Drug Code

DRECNO	Seq 1	Seq 2	Product Name	Ingredients
000174	01	001	Phenytoin	Phenytoin
000174	01	002	Difhydan	Phenytoin
000174	02	001	Phenytoin sodium	Phenytoin sodium
000174	02	002	Dilantin	Phenytoin sodium
000174	03	001	Phenytoin calcium	Phenytoin calcium

In addition to an ATC Classification and Drug Code, the Uppsala Monitoring Centre also assigns a unique Medicinal Product ID (MP_ID) to each medicinal product. For example, the Medicinal Product ID of Zomig is 64641, when marketed (by AstraZeneca) in Denmark and consisting of 2.5 mg of zolmitriptan with the name specifier of Rapimelt tongue-soluble tablets. In other words, every combination of strength, form and country of manufacture receives a unique Medicinal Product ID. Medicinal Product IDs do not have inherent meaning like Drug Codes.

Conclusion

Effective data analysis requires that the aggregated data accurately reflect all the actual observations and events. Investigators, study coordinators, and other site personnel who record adverse event and related data protect subject safety and save everyone time by providing the medical coders with data that is accurate, complete and consistent.

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