CHAPTER 5

MEDICAL CODING STANDARDIZATION OF CLINICAL DATA

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Abstract

Clinical narrative data, captured as free-text descriptions of adverse events and medical histories, presents a fundamental challenge for statistical analysis known as the "Tower of Babel" problem. Without standardization, the thousands of unique ways physicians describe the same medical concept would render global safety aggregation impossible. The solution lies in Medical Coding, the process of mapping verbatim terms to standardized, internationally recognized dictionaries. This discipline relies on two primary pillars: the Medical Dictionary for Regulatory Activities (MedDRA) for coding medical conditions and adverse events, and the World Health Organization Drug Dictionary (WHO-DD) for coding concomitant medications. Mastering MedDRA requires knowing its complex five-level hierarchy and understanding the concept of multiaxiality, where a single disease may link to multiple body systems. Similarly, WHO-DD utilizes the Anatomical Therapeutic Chemical (ATC) classification system to group drugs by their active ingredients and therapeutic indications. The operational reality of coding involves a blend of algorithmic auto-encoding and expert manual review to handle ambiguity, spelling errors, and vague terminology. By applying strict coding guidelines and resolving challenges such as "splitting" versus "lumping" diagnoses, coding professionals ensure that the qualitative language of the patient is converted into the quantitative data required for signal detection and label updates.

Keywords: *MedDRA, WHO Drug Dictionary (WHO-DD), Medical Coding, Verbatim Terms, Standardized Dictionaries*

Learning Objectives

After completion of the chapter, the learners should be able to:

- Justify the necessity of medical coding in resolving the "Tower of Babel" problem inherent in free-text clinical reporting.
- Navigate the five-level hierarchy of the MedDRA dictionary to select the most appropriate Lowest Level Term (LLT) for a given verbatim description.
- Apply the concept of multiaxiality in MedDRA to ensure comprehensive data retrieval during safety analysis.
- Utilize the World Health Organization Drug Dictionary (WHO-DD) and the ATC classification system to code concomitant medications accurately.
- Solve complex coding scenarios involving ambiguity, splitting vs. lumping of diagnoses, and the handling of "Rule Out" conditions.

INTRODUCTION TO STANDARDIZED DICTIONARIES

In the vast ecosystem of a global clinical trial, data is collected from thousands of physicians, nurses, and coordinators across dozens of countries. While the Case Report Form (CRF) provides structure for numerical data (like blood pressure, age, or lab values), a significant portion of critical clinical information is captured as **free text**. When a patient reports a side effect, the investigator writes down a description in their own words. One doctor in London might record "Headache," another in New York might write "Cephalalgia," while a third in Tokyo might simply note "Head pain."

To a computer, "Headache," "Cephalalgia," and "Head pain" are three entirely distinct strings of text. If a pharmaceutical company tried to analyze safety data based on these raw descriptions, the results would be fragmented and meaningless. They would be unable to accurately count how many patients suffered from head pain because the data is effectively speaking different languages. This chaos is known as the "Tower of Babel" problem in clinical research.

The solution to this problem is **Medical Coding**. Coding is

the process of converting these disparate, free-text descriptions (known as Verbatim Terms) into standardized, internationally recognized terminology using a controlled vocabulary or "Dictionary." This process transforms qualitative, subjective descriptions into quantitative, analyzable data.

The Necessity of Standardization

The primary objective of using standardized dictionaries is **Aggregation**. Regulatory authorities like the FDA and EMA need to answer broad safety questions, such as: "Does this drug cause liver damage?" To answer this, they cannot look for every possible synonym for liver damage (e.g., "Hepatic failure," "Elevated liver enzymes," "Jaundice," "Hepatotoxicity," "Liver injury"). Instead, they rely on standardized codes that group all these related concepts under a single semantic umbrella.

Consistency Across Time and Space

Standardization ensures consistency across both time and geography. It allows data from a Phase I trial conducted in 2010 to be combined with data from a Phase III trial conducted in 2024 (Data Pooling). It allows a study in Brazil to be pooled with a study in Germany. Without this common language, the Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) the two massive documents required for drug approval could not be written.

Signal Detection

Effective coding is the bedrock of **Signal Detection**. If a new drug causes a rare but serious side effect, such as Stevens-Johnson Syndrome (SJS), early cases might be reported vaguely as "rash" or "skin peeling." If these are coded generically, the signal is diluted. If they are coded precisely to specific dictionary terms, safety physicians can run algorithms to spot the cluster of serious skin reactions early, potentially saving lives.

The Mechanism of Coding: Verbatim to Preferred

The fundamental unit of the coding process is the mapping of the **Verbatim Term** to a **Preferred Term (PT)**.

- **Verbatim Term:** This is the exact text reported by the investigator on the CRF. It captures the nuance and

specific phrasing of the clinical observation (e.g., "Severe throbbing pain in left temple").

- **Preferred Term:** This is the distinct descriptor used in the dictionary to represent a single medical concept (e.g., "Migraine").

The coding process acts as a translation layer. When a Safety Physician reviews the data, they do not look at the thousands of unique Verbatim Terms; they look at the consolidated list of Preferred Terms. This allows them to see that 50 patients had "Migraine," even if those 50 patients used 15 different ways to describe it.

The Structure of Dictionaries: Hierarchies and Granularity

A standardized dictionary is not merely a flat list of words; it is a complex, multi-dimensional database structured hierarchically. This structure resembles a tree, with broad categories at the top (the trunk) branching out into specific details at the bottom (the leaves).

Grouping for Analysis

The hierarchy allows researchers to analyze data at different levels of granularity. For detailed signal detection, they might look at the specific Preferred Term level (e.g., "Viral Pneumonia"). However, for a high-level safety summary in a drug label, they might aggregate data at a higher level, such as the "System Organ Class" (e.g., "Infections and Infestations").

This hierarchical structure ensures that no safety signal is lost. If a drug causes various types of eye problems (blurred vision, eye pain, redness), looking at each term individually might show insignificant numbers. But grouping them under the "Eye Disorders" system might reveal a statistically significant trend that warrants a warning on the package insert.

The Two Pillars: MedDRA and WHO-DD

While there have been many medical dictionaries in the past (such as COSTART or ICD-9), the modern biopharmaceutical industry relies almost exclusively on two global standards:

1. **MedDRA (Medical Dictionary for Regulatory Activities):** This is the mandatory standard for coding

medical history, adverse events, and medical procedures. It is maintained by the **MSSO** (Maintenance and Support Services Organization) and is required for regulatory submissions in the US, Europe, and Japan. MedDRA is updated twice a year (March and September) to include new medical concepts (e.g., "COVID-19" was added rapidly in 2020).

2. **WHO-DD (World Health Organization Drug Dictionary):** This is the global standard for coding concomitant medications. It is maintained by the **Uppsala Monitoring Centre (UMC)**. It allows sponsors to categorize the various drugs patients are taking (e.g., grouping "Tylenol," "Panadol," and "Calpol" under the active ingredient "Paracetamol" and the therapeutic class "Analgesics").

Operational Coding: Auto-Encoding vs. Manual Coding

In practice, the volume of data in clinical trials is too vast to code entirely by hand. Modern coding tools (often integrated into the EDC system) use **Auto-Encoding** algorithms.

The Auto-Encoding Process

The system compares the Verbatim Term against the dictionary. If an exact match is found (e.g., the doctor wrote "Nausea" and "Nausea" exists in the dictionary), the system assigns the code automatically. Sophisticated systems also use a "Synonym List" a sponsor-specific list of previously coded terms. If "Head pain" was coded to "Headache" in a previous study, the system remembers this and auto-codes it next time.

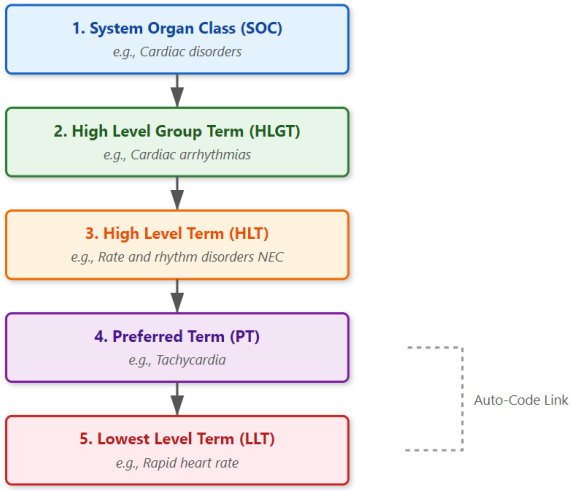

Figure 5.1: The MedDRA Five-Level Hierarchy

Manual Coding and Queries

If the Verbatim Term is ambiguous, misspelled, or uses non-standard abbreviations (e.g., "Pt had N/V" or "Pink pill"), the system cannot code it. It sends the term to a "Coding Queue" for **Manual Coding**. A trained Medical Coder must then interpret the text.

- *Ambiguity:* If a term is too vague (e.g., "Chest trouble"), the coder cannot assume it is "Chest Pain" or "Pneumonia." They must raise a **Coding Query** to the site asking for clarification.
- *Guidelines:* To ensure consistency, coders follow strict "Coding Guidelines" (e.g., "Always code to the diagnosis, not the symptom, if the diagnosis is known"). This prevents one coder from choosing "Fever" while another chooses "Viral Infection" for the same event.

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MEDDRA (MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES)

STRUCTURE AND USAGE

Among the various tools used in clinical research, few are as ubiquitous or as critical as the **Medical Dictionary for Regulatory Activities**, commonly known as **MedDRA**. Before the 1990s, the lack of a unified international terminology meant that a "heart attack" might be coded differently in Europe than in the United States, making global safety comparisons nearly impossible. To resolve this, the International Council for Harmonisation (ICH) developed MedDRA as a single, standardized medical terminology to be used throughout the regulatory lifecycle of a medical product from pre-marketing clinical trials to post-marketing pharmacovigilance.

Table 5.1: MedDRA Hierarchy Structure

Level	Name	Definition/Usage	Example Term
Level 1	System Organ Class (SOC)	Highest level grouping by anatomy/etiology.	*Cardiac disorders*
Level 2	High Level Group Term (HLGT)	Broad grouping of related conditions.	*Cardiac arrhythmias*
Level 3	High Level Term (HLT)	Grouping by anatomy, pathology, or physiology.	*Rate and rhythm disorders NEC*
Level 4	Preferred Term (PT)	Distinct medical concept (Primary level for Signal Detection).	*Tachycardia*
Level 5	Lowest Level Term (LLT)	Verbatim synonym or lexical variant selected by coder.	*Rapid heart rate*