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Health informatics — Clinical particulars — Core principles for the harmonization of therapeutic indications terms and identifiers

Informatique de santé — Spécificités cliniques — Principes fondamentaux pour l'harmonisation des termes et identifiants des indications thérapeutiques

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Foreword

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This document was prepared by Technical Committee ISO/TC 215, *Health informatics,* in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 251, *Health informatics,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

The need for improved communication between health agencies, hospitals, pharmacies, pharmaceutical companies and the general public about drug safety and efficacy information requires migration from manual text entry and unstructured data that cannot be coded, to a structured data model that is interoperable across the health care ecosystem[1]. The clinical particulars conceptual class of the ISO 11615 Identification of Medicinal Products (IDMP) data model captures information about a medicinal product's indication(s), contraindication(s), undesirable effect(s) and interactions. Within this conceptual class, the Therapeutic Indication subclass captures information about the therapeutic indication for the target disease or condition for which a medicinal product is authorized, under investigation, or utilized in clinical practice. Therapeutic indications can be described using free text as presented in approved product labelling documents, and as terms and codes from standard terminologies. Consistent and accurate coding of therapeutic indication terms is needed to support a variety of processes and is found in various terminological resources and official documents, which include epidemiological and real-world databases, electronic health records and health authority reporting processes. Therefore, a key principle for terminology mapping is that maps are based on specific use cases, and stakeholders who can provide feedback on the form, content and scope of the mapping should be engaged from the beginning of and throughout the mapping exercise.

A universally accepted terminology for coding therapeutic indications does not yet exist and is not feasible due to differing international medicinal product and healthcare regulations and reporting requirements. There is a difference between the therapeutic indication of a specific medicinal product and the diseases, conditions or problems listed in an electronic health record (EHR). While most EHRs will manage a problem list and/or a list of findings and diagnoses and a medication list, it is less frequent that the indication (or indications) for each specific medication is specified for a particular patient.

In medicinal product labels, a range of authorized indications is listed, often with qualifiers (diagnostic, preventive, curative, disease-modifying) or specified patient target groups. Sometimes, diseases or conditions are explicitly listed as not being indications for a specific drug. For example, "drug x" is not indicated in von Willebrand disease, or "drug y" is contraindicated with Haemophilia A. Use of medicinal products outside the authorized indications is considered off-label.

The indication wording, and thus the related coding, is based on a highly complex process over the years-long development of a pharmaceutical product. The relationship between a medicinal product and an indication is based on evidence from clinical trials, which are often comparative in nature (e.g. placebo versus active substance, or active substance A versus active substance B). Evidence synthesis in systematic reviews is often constrained by a Patient/intervention/comparator/outcome (PICO) statement, which results in a clinical recommendation to prefer or not to prefer the use of a particular medicinal product over another intervention for a particular patient (with a specific disease or condition), aiming at a specific outcome. In a regulatory document, this information is often reduced to a statement that "this medicinal product is indicated for ….".

In regulatory documents, the relationship is specified between a particular medicinal product (with specific substance(s), dose form(s), strength(s) and pack sizes), on the one hand and the indication(s), which are often specified in a detailed form. The formulation of this detailed indication often results from strong and intricate debate between the medical department of a pharmaceutical company, medical experts and regulators. The finesse of such formulation is often difficult to catch by any of the existing terminologies. For example, the therapeutic indications for a preparation that is licensed for over-the-counter (OTC) use can be more restrictive than the indications for the same preparation when prescribed by a clinician. For example, treatment of candidiasis in pregnancy using a clotrimazole must be under the direction of a physician; an OTC preparation is not authorized for this indication.

In handbooks of pharmacology and in drug classifications, indications might be formulated at a higher level of aggregation, and substances can be aggregated to drug classes. Hence, relationships between high level indications and drug classes (rather than individual substances) can be described.

Terminologies describing drug classes (e.g. the Anatomical Therapeutic Chemical (ATC) codes, SNOMED CT®[1)], Standard Drug Groups from WHO Drug, etc.) are built using different principles and dimensions (chemical class, anatomical target, therapeutic intent, mechanism of action, molecular target site), and exhibit variable levels of granularity. The same is true for terminologies describing diseases, conditions and signs and symptoms as proxies for indications. Therefore, using different terminologies (and maps between these terminologies) to establish relationships between medicinal products/drug classes and specific indications/high level indications can be bewilderingly complex. Hence, harmonization of terminologies for therapeutic indications should account for both the specific level of regulatory listing of authorized indications for specific medicinal products, as well as the relationship between high level aggregations of indications and substances.

The most common standard terminological resources used to describe and code medicinal product indication terms are the Medical Dictionary for Regulatory Activities (MedDRA®[2)]), SNOMED CT, the International Statistical Classification of Diseases and Related Health Problems (ICD™[3)]) and Medical Subject Headings (MeSH). Mappings between these terminological resources are necessary for documentation and reporting purposes; however, the different hierarchy levels and variation in the number of terms for each resource introduce significant complexity in the creation and maintenance of terminology maps. Map usage is often restricted by the limited availability of centrally provided and approved map sets and contributes to inefficiencies and redundant manual curation by individual stakeholders for specific use cases. Creation and maintenance of comprehensive maps between clinical terminologies to support coding of indication terms will thus liberate workforce effort and enable more efficient processes, responses and comprehensive reporting.

There are safety and maintenance implications when creating and applying maps that directly impact clinical care and decision-making. Therefore, a key principle is the requirement to identify the use case for any map before creating or using mappings. For example, there is an allowable semantic shift during mapping such as for statistics and billing because of aggregation to a group level, whereas in use cases to support clinical care at the individual (patient) level, no semantic shift can be tolerated because of potential safety issues. Thus, mappings between e.g. SNOMED CT and MedDRA are semantic maps of total meaning focused on adverse events. However, additional maps between these two terminologies with use cases focused on therapeutic indications are possibly needed, so a use case will need to be developed and tested against existing maps before deciding on next steps.

This document describes use cases and principles that are applicable for creation, assessment and selection of maps specific to Therapeutic Indications. This document thus refers to and builds on the following documents regarding terminologies and mapping:

— ISO/TR 14872 on core principles for maintenance of identifiers and terms

— ISO/TR 12300 on principles of mapping between terminological systems

— ISO/TS 21564 on terminology resource map quality measures (MapQual)

1) SNOMED CT® is the registered trademark of a product supplied by the International Health Terminology Standards Organization (IHTSDO). This information is given for the convenience of users of this document and does not constitute an endorsement by ISO of the product named.

2) MedDRA is the registered trademark of a product supplied by the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) on behalf of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). This information is given for the convenience of users of this document and does not constitute an endorsement by ISO of the product named.

3) ICD™ (International Classification of Diseases) maintained by the World Health Organization is an example of a suitable product available commercially. This information is given for the convenience of users of this document and does not constitute an endorsement by ISO of this product.

Health informatics — Clinical particulars — Core principles for the harmonization of therapeutic indications terms and identifiers

1 Scope

The objective of this document is to establish common principles for the creation, assessment, selection and maintenance of maps between terminological resources used to describe and code IDMP therapeutic indications for investigational and medicinal products, medical devices, combination products, biologics and companion diagnostics. Core maintenance principles, such as reliability, reproducibility and quality assurance of the maps for future indication terminology use, are also discussed. The intended audience for this document includes:

a) Global regulators, pharmaceutical/biopharmaceutical companies, Clinical Research Organizations (CROs) and universities/scientific institutes involved in the development, authorization and marketing of medicinal products

b) Implementers of IDMP seeking more information about coding of Therapeutic Indications

c) Healthcare providers

d) Standards Organizations

e) Implementers and software vendors developing and implementing terminology map sets

f) Patients

2 Normative references

There are no normative references in this document.

3 Terms, definitions and abbreviated terms

3.1 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1.1
comorbidity
concurrent condition or co-infection described as part of the indication

3.1.2
electronic health record
EHR
repository of information regarding the health status of a subject of care, in computer processable form

[SOURCE: ISO/TR 20514:2005, 2.11, modified]

3.1.3
electronic health record system
EHR system
system for recording, retrieving and manipulating information in electronic health record

3.1.4
individual map
map
cross map
index from one term to another, sometimes using rules that allow translation from one representation to another indicating degree of equivalence

Note 1 to entry: Entry in a map which indicates how to translate from an individual source concept to a target concept. The term map is often used to indicate a table of individual map entries. It is for this reason that the individual and map tables are being differentiated.

Note 2 to entry: The use of this term is often used in ways which are confusing. It is essential to always make it clear whether you are referring to an individual map or a map table (or set).

Note 3 to entry: In SNOMED CT, each individual map is represented as a row or group of rows in a map Reference Set. It links a single map source concept code (e.g. SNOMED CT Concept ID) to one or more codes in a map target (e.g. ICD Code).

Note 4 to entry: A map is often computable and is the outcome of the mapping process.

[SOURCE: ISO/TR 12300:2014, 2.1.9]

3.1.5
maintenance organization
formal and recognized group or legal business entity involved in the direct or indirect provision of terminology services such as the creation, reconciliation, maintenance and distribution of IDMP controlled vocabularies

[SOURCE: ISO/TR 14872:2019, 3.7]

3.1.6
mapping
process of defining a relationship between concepts in one coding system to concepts in another coding system, in accordance with a documented rationale, for a given purpose

Note 1 to entry: Quality mapping will produce a usable map table, be a reproducible and understandable process.

[SOURCE: ISO/TR 12300:2014, 2.1.12]

3.1.7
map set
map table
map reference set
group of individual maps used to convert a range of entries from source to target code system

[SOURCE: ISO/TR 12300:2014, 2.1.11]

3.1.8
real-world data
RWD
data collected in a non-experimental, non-virtual situation

[SOURCE: ISO/TR 21934-1:2021, 3.9]

3.1.9
structured product labelling
SPL
document markup standard that specifies the structure and semantics of the content of authorized published information that accompanies any medicine licensed by a medicines licensing authority

[SOURCE: Reference [10]]

3.1.10
target population
type of patients or consumers for which the indication of a medicinal product is authorized or is under investigation

[SOURCE: ISO 11615:2017, 3.1.81]

3.1.11
term
linguistic representation of a concept

Note 1 to entry: A term can contain symbols and have variants, e.g. different forms of spelling

[SOURCE: ISO/TR 12300:2014, 2.2.8]

3.1.12
terminology
structured, human readable and machine-readable representation of concepts

Note 1 to entry: This includes the relationship of the terminology to the specifications for organizing, communicating and interpreting such a set of concepts.

[SOURCE: ISO/TS 23541-1:2021, 3.1.5, modified — Note added.]

3.1.13
therapeutic indication
definition of the target disease or condition for which the Medicinal Product is authorized or under investigation

[SOURCE: ISO 11615:2017, 3.1.82]

3.1.14
vocabulary
terminological dictionary which contains designations and definitions from one or more domains or subjects

[SOURCE: ISO 1087:2019, 3.7.5, modified]

3.1.15
off-label
prescribing of a medicinal product for an unapproved/unauthorized indication when a health care provider determines that it is medically appropriate for their patient

3.2 Abbreviated terms

ADR	Adverse Drug Reaction
CT	Clinical Trials
ERP	Enterprise resource planning
ICSR	Individual Case Safety Report
PSUR	Periodic Safety Update Reports

PV Pharmacovigilance

RIM Regulatory Information Management

4 Terminologies used for the coding of Therapeutic Indications

4.1 General

The following terminologies are commonly used in various jurisdictions and are required by regulatory agencies for coding medicinal product therapeutic indications.

4.2 SNOMED CT

SNOMED CT is a comprehensive, multilingual clinical healthcare terminology, used in more than eighty countries. It is a resource with comprehensive, scientifically validated clinical content that enables consistent representation of clinical content in electronic health records and is mapped to other international standards. SNOMED CT is owned, administered and developed by SNOMED International, a not-for-profit organization.

The primary purpose of SNOMED CT is to encode the meanings that are used in health information and to support the effective clinical recording of data with the aim of improving patient care. SNOMED CT provides the core general terminology for electronic health records. SNOMED CT provides for consistent information interchange and is fundamental to an interoperable electronic health record. It allows a consistent way to index, store, retrieve and aggregate clinical data across specialties and sites of care. SNOMED CT is used to represent Medical Condition in Structured Product Labelling to facilitate informed decision-making and support long-term patient care. Thus, it is the required terminology for the coding of indications reported to, e.g. the U.S. FDA[14].

4.3 MedDRA

The Medical Dictionary for Regulatory Activities (MedDRA), which is owned by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and maintained and distributed by the MedDRA Maintenance and Support Services Organization (MSSO) and the Japanese Maintenance Organization (JMO), is an international standardized terminology used to exchange regulatory information on medical products in both pre- and post-authorization phases. In developing and continuously maintaining MedDRA, the ICH endeavours to provide a single standardized international, multi-lingual medical terminology which can be used for regulatory communication and evaluation of data pertaining to medicinal products for human use. As a result, MedDRA is designed for use in the registration, documentation and safety monitoring of medicinal products through all phases of the development cycle (i.e. from clinical trials to post-marketing surveillance). Furthermore, MedDRA supports ICH electronic communication within the ICH's Electronic Common Technical Document (eCTD) and the E2B Individual Case Safety Report. [15] MedDRA is the required terminology for the coding of indications for EMA[16].

4.4 ICD

The International Statistical Classification of Diseases and Related Health Problems (ICD) is a global standard classification for reporting diseases and health conditions that is developed and maintained by the World Health Organization (WHO). It is used worldwide in systems such as patient registries, insurance claims systems, mortality and morbidity statistics, and patient health records. ICD is the foundation for the identification of health trends and statistics globally, and the international standard for reporting diseases and health conditions. It is the diagnostic classification standard for all clinical and research purposes. ICD defines the universe of diseases, disorders, injuries and other related health conditions, listed in a comprehensive, hierarchical fashion[17].

In addition, the International Classification of Primary Care (ICPC) is accepted within the WHO Family of International Classifications (FIC) as a classification for primary care or general practice. ICPC, 2nd edition (ICPC-2) classifies patient data and clinical activity in the domains of General/Family Practice and primary

care; it allows classification of the patient's reason for encounter (RFE), the problems/diagnosis managed, interventions, and the ordering of these data in an episode of care structure[18].

Since the diagnosis and interventions assigned by the healthcare provider and coded with ICD and ICPC are related to the indications of a pharmaceutical product, mappings between disease terms within these classifications to those used for coding the therapeutic indications are useful in the healthcare domain.

4.5 MeSH

The Medical Subject Headings (MeSH) thesaurus is a controlled and hierarchically organized vocabulary produced by the National Library of Medicine (NLM). It is used for indexing, cataloguing, and searching of biomedical and health-related information. The usage of appropriate descriptors from NLM's Medical Subject Headings (MeSH)-controlled vocabulary thesaurus or terms from another vocabulary, such as SNOMED CT, that has been mapped to MeSH within the Unified Medical Language System (UMLS) Metathesaurus, is required when posting the primary disease or condition being studied in a clinical trial at clinicaltrials.gov[19][20].

5 Use Cases for Coding of Therapeutic Indications

5.1 General

Medicinal product therapeutic indications are initially proposed for clinical trials and can be further detailed and refined for regulatory submissions, and, if successful, will be included in product labels as part of the marketing authorization process. Details of the indications are recorded and exchanged as text and codes, via regulator and pharmaceutical company systems. Once authorized for distribution, the medicinal products enter the supply chain along with the authorized indication information. This information can then be used within the healthcare domain, including during the prescribing, dispensing, administering cycle, with data stored and processed in clinical support systems, medicinal product dictionaries and electronic health records. If adverse reactions to a medication are encountered, indication information can be sent back to regulators and pharmaceutical companies in reports as part of the pharmacovigilance process. Indication data are also be used as part of the reimbursement process and for pharmaco-epidemiological or other statistical analyses. A high-level view of the flow of indication data is shown in Figure 1. This section describes some of the use cases for indications and the need for harmonization of indication-related data.

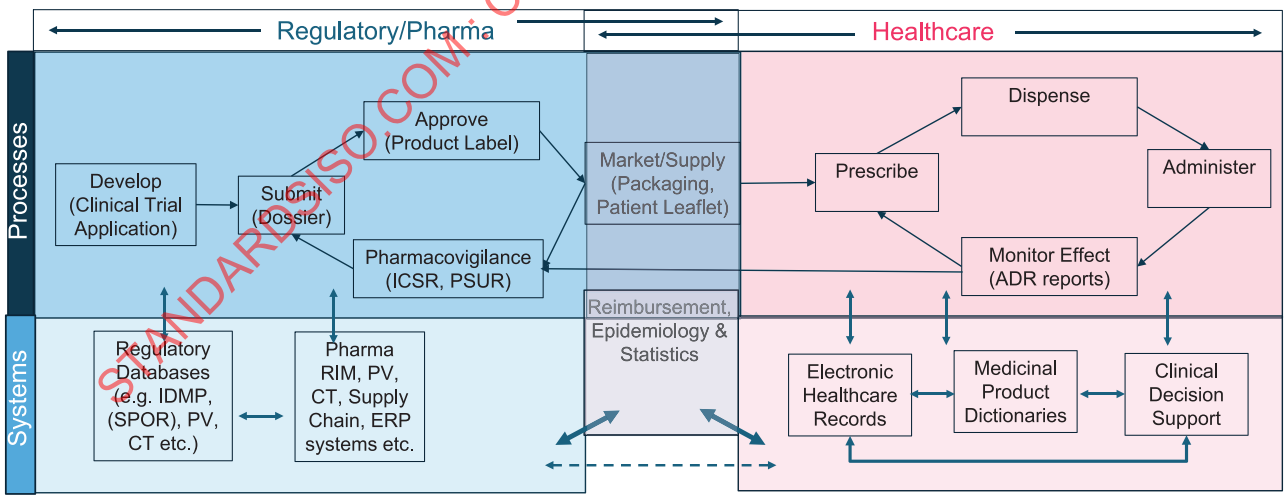

Figure 1 — Processes & Systems Involving Product Indication Data Across Regulatory & Healthcare4

5.2 IDMP data exchange between global regulators and bio/pharmaceutical companies during regulatory processes

5.2.1 Clinical Trials (Medicinal Product Development Lifecycle)

During the development lifecycle of a medicinal product, clinical trials must be conducted to prove the safety and efficacy of the medicine, and indications must be submitted by the pharmaceutical company to the regulator as part of the clinical trial application process (e.g. clinical trial application (CTA) in Europe, Investigational new drug (IND) application for the US). Clinical trials for the same medicinal product are often conducted in multiple countries. Requirements for the description of the indication text and how it is coded vary between regions, so the indication data for the same medicinal product can be recorded differently between regions. The availability of maps between terminologies would facilitate exchange of this data between regions.

5.2.2 Regulatory Submission and Coded Labelling Information

After the successful completion of clinical trials, a regulatory submission for authorization of the medicinal product can be submitted to the regulator. The data submitted will include details of the therapeutic indication(s) to be approved/authorized and to be included in the product label as well as coding of the indication terms.

According to health authority guidance for labelling documents used as the basis for information to health care professionals and patients, therapeutic indications should be clearly stated to reflect in which disease/condition and target population the benefit-risk balance was established to be positive.

Nevertheless, defining the therapeutic indication is quite complex and requires a multidimensional analysis of aspects that influence the benefit/risk assessment with respect to the interpretation of wording in different therapeutic areas. The therapeutic indication is the primary information on the use of a medicine, and it should clearly state the disease/condition and population that a medicine is intended to treat. Examples of such areas of common interest refer to the description of the target population, the severity of the disease, the aim of the treatment (diagnostic indication, prevention, or treatment), the place of the medicinal product in the therapy, the use in combination therapy, as well as the consistency of wording within and across therapeutic areas.

Study data standards describe principles for the exchange of clinical and nonclinical research data between computer systems and provide a framework for the organization of study data. For example, the Clinical Data Interchange Standards Consortium-Study Data Tabulation Model (CDISC-SDTM) provides a standard for organizing and formatting data to streamline processes in collection, management, analysis and reporting. CDISC SDTM is a required standard in certain regulatory regions (i.e. US, Japan) and promotes the use of common dictionaries to be utilized across clinical studies adverse events, concomitant medications, procedures, indications, study drug names, and medical history. More specifically, SDTM requires SNOMED CT to identify the medical condition or problem that the investigational product in a clinical study is intended to affect (treat, diagnose or prevent, i.e. the indication)[21].

5.2.2.1 Coded Labelling Information

Maps between the terminologies commonly used for coding therapeutic indications within each domain, i.e. SNOMED CT in the clinical space, MedDRA for safety reporting, and ICD in the healthcare domain, enable the transformation of unstructured information, e.g. in labelling documents, to structured (coded) information. In this way, by making that data interoperable, further use cases can be supported, from the tracking of off-label usage to identification of unmet medical needs.

5.2.2.2 Use Case: Structured Electronic Product Information

Clinical particulars such as indications and contra-indications are key for enabling clinical decision support systems to be able to use product information and the patient's health records to alert the prescriber or dispenser to potential issues or harm with the chosen medicines for a specific patient.

Structured electronic product information (ePI) enables the easy checking of product information for products concerning the same substances and linkage to other systems.

Online repositories of product information and linkage to this data through use of barcodes on packaging will enable patients to benefit from the latest information for their medicines and translations of this information into other languages.

Certain health authorities have implemented or have current initiatives to structure electronic product information. These initiatives have leveraged data standards to structure and code medicinal product information that includes therapeutic indications. For example, in 2005 the U.S. FDA implemented HL7 Structured Product Labeling to structure and code medicinal product information[22] (i.e. ePI). In 2019, Health Canada initiated their transition to a structured XML format for their product monograph templates also utilizing HL7 SPL.[23] The European Medicines Agency (EMA) have also initiated an ePI initiative utilizing HL7 Fast Healthcare Interoperability Resources (FHIR), which also lends itself to the coding of medicinal product information to include therapeutic indications.[24] Of note, U.S. FDA and Health Canada have identified SNOMED CT as the terminology for the identification of therapeutic indications whereby EMA has identified MedDRA. This introduces an additional use case in the application of the general principles identified within this document for additional mapping between SNOMED CT and MedDRA beyond the pharmacovigilance use case.

5.2.2.3 Clinical Decision Support

Clinical decision support systems use indication information extensively. Firstly, they provide this information “as data” – to allow a clinician to look up the set of medications that can be used to treat a particular condition. For example, a clinician might know that "alpha-blocker medication” can be used to relieve chronic urinary retention in men with benign prostatic hyperplasia; the Clinical Decision Support (CDS) can list the products that have this indication (e.g. alfuzosin, tamsulosin) rather than other indications (such as treatment of hypertension – terazosin).

Secondly, CDS use indication information to provide accurate dosage checking. Some medicinal products have quite different dosage regiments depending on indication. For example, for phosphate binding in renal failure, an antacid containing aluminium hydroxide can be used in a dosage of up to 20 capsules per day (in 5 divided doses), but when used as an antacid, the maximum dosage is only 5 capsules per day. (Another example, penicillamine is used to treat rheumatoid arthritis and for Wilson’s disease at different dosage regimens.)

Thirdly, CDS use diagnosis information in decision rules, as one of the patient characteristics to determine the appropriate usage of a medicine. For example, if a patient has rheumatoid arthritis, this is a risk factor that will be part of the consideration to prescribe gastric protection for a non-steroidal anti-inflammatory drug (NSAID).

As an additional consideration, contra-indications are a special subgroup referring to diseases, which when present, prohibit the use of that medicine in this patient.

A standard terminological resource for indication terms in a machine-readable format allows users with clinical decision support tools, electronic health records (EHRs), registries, and electronic prescribing systems to rapidly search and sort product information. A fully automated health information exchange system requires the ability to uniquely define and identify clinical particulars within an automated health information exchange system and the adoption of internationally accepted data standards (i.e. ISO IDMP) and message exchange standards such as Health Level Seven (HL7) Fast Healthcare Interoperability Resources (FHIR). The application of data and message exchange standards enables the inclusion of machine-readable data elements for the electronic exchange of clinical particulars for health care providers, patients, and relevant regulated and healthcare product information use cases. This will greatly enhance users' ability to automatically search and sort product information, which allows for patients, healthcare professionals (HCPs), and providers to support a more robust electronic health records, electronic prescribing systems, and an array of clinical decision support systems and tools at their disposal.

5.2.3 Clinical protocol

The standardization of the representation of therapeutic indications based on information in the EHR along with drug information enables the users to retrieve and analyse information for clinical review and audit. This also allows the re-use of clinical data for additional statistical purposes where required.

A clinical protocol describes the processes and procedures directing the conduct and analysis of a clinical study. Currently there is no internationally harmonized standard template for the format and content of the clinical protocol document to support consistency across sponsors and exchange of protocol information. This lack of harmonization contributes to inefficiencies and difficulties in reviewing and assessing clinical protocols by regulators, sponsors, ethical oversight bodies, investigators, and other stakeholders. The standardization of the representation of therapeutic indications based on information in the EHR along with drug information enables the users to retrieve and analyse information for clinical review and audit. This also allows the re-use of clinical data for additional statistical purposes where required.

The ICH is an organization comprised of regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceuticals and develop ICH guidelines. ICH established a formal working group, M11: Clinical electronic Structured Harmonized Protocol (CeSHarP).[25] CeSHarP describes the general design principles, format, and structure of the protocol for the broad adoption of an internationally harmonized clinical protocol supported by electronic content structured for exchange. All steps within the conduct of a study are within scope (e.g. trial design, investigator on-boarding, study setup, study reporting, and review). Identification and coding of indications within a clinical protocol is paramount and relevant to the primary/secondary objectives, study design, subject selection (e.g. inclusion/exclusion criteria), concurrent medications and overall study treatment(s) methodology.

The core principles identified within this document are fully in line with the global identification of indications to support an internationally harmonized clinical protocol exchange; SDOs engaged in the global identification of indications (e.g. SNOMED CT) are relevant stakeholders in the promotion of an internationally harmonized structured and electronic clinical protocol.

5.2.4 Risk Management

Structured content of an electronic risk management plan (eRMP) following the ICH E2E guideline allows linking of indications, contra-indications, and the monitoring of studies linked to study registries including pre-authorization safety concerns and those that are part of the of the pharmacovigilance plan.

For valid and trustworthy secondary use of health data from electronic health records and telematic messages (e.g. lab and imagery results, referral and discharge letters), terminologies of both the clinical world and the research world should be the same or adequately mapped.

Off-label use must be documented and the indication of this off-label use should be clearly specified. Safety issues in these uncommon and non-regulated situations should be identified. It is also possible that such off-label uses hint at new uses of well-known drugs, requiring new trials to corroborate the suggested new indication.

One special form of indication for medicinal products is symptom relief for side effects of other medicines, called cascade therapy. In principle, this form of prescribing should be avoided. In large databases at population level, prescription sequence analysis could signal unknown side-effects.

The scientific evaluation of the risk-benefit balance of the medicinal product included in the PSUR (Periodic Safety Update Reports) are based on all available data, including data from clinical trials and real-world data in unauthorized indications and populations.

Post-authorization studies are classified as safety studies when their main aim for initiating the study includes a number of objectives, e.g. to assess patterns of drug utilization that add knowledge regarding the safety of the medicinal product or the effectiveness of a risk management measure (e.g. collection of information on indication, off-label use, dosage, co-medication or medication errors in clinical practice that can influence safety, as well as studies that provide an estimate of the public health impact of any safety concern).

In prescription event monitoring (PEM), a follow-up questionnaire can be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information, e.g. patient demographics, indication for treatment, duration of therapy (including start date), dosage, clinical events, and reasons for discontinuation. PEM tends to be used as a method to study safety just after product launch, and there is the opportunity to collect more detailed information on adverse events from a large number of physicians and/or patients.

A signal in pharmacovigilance is about information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action. A signal often relates to all medicinal products containing the same active substance, including combination products. Certain signals might only be relevant for a particular medicinal product or in a specific indication, strength, pharmaceutical form, or route of administration, whereas some signals might apply to a whole class of medicinal products.

5.3 Pharmacovigilance

5.3.1 General

Adverse effects experienced after taking a medication can be reported in various ways and by different stakeholders. A component of an adverse event report is the indication for which the suspect drug was taken. If an adverse effect occurs in a healthcare facility, it can be reported by a healthcare professional and utilize data from within the healthcare system, e.g. the EHR. Although the indication(s) in the EHR might have been derived from the original term(s) as approved by the regulator, the format in which it is coded can differ. Alternatively, the adverse event can be reported where access to the clinical record details is not available, e.g. by a patient directly to a receiving person or system, in which case details might be described in less precise terms (e.g. lay terms) or can be prompted by the receiver or system (e.g. reporting app), potentially leading to a different level of detail and possibly different coding tools.

Key pharmacovigilance concepts in an electronic health record (SNOMED CT) must be mapped to MedDRA for the purpose of adverse event reporting to regulatory authorities, or for epidemiological research, etc. Vice versa, these same key terms coded in MedDRA representing adverse events, warnings, and other regulatory information could be mapped to SNOMED CT so that the information is available in the patient's record to aid in clinical decision making.

MedDRA terms used for adverse events, warnings, and other regulatory information in product labelling can be mapped to ICD so that concepts in an electronic health record or decision support system can be available at the point of care when prescribing, dispensing, or administering the product.

A cross-map between SNOMED CT and MedDRA should commence with an understanding of the strengths and limitations of each vocabulary. Two independent maps (MedDRA to SNOMED CT) and (SNOMED CT to MedDRA) have been derived from frequently used, as well as key pharmacovigilance MedDRA terms (about 7,400 key pharmacovigilance terms) identified by the European Medicines Agency and the UK's Medicines & Healthcare products Regulatory Agency (MHRA) as part of the WEB-RADR-2[26] and WEB-RADR[27] projects. The maps are intended to facilitate the exchange of data between regulatory databases (which use MedDRA) and healthcare databases/EHRs (which use SNOMED CT). In one use case, key pharmacovigilance concepts coded in SNOMED CT in an electronic health record (EHR) could be converted to MedDRA for the purpose of adverse event reporting to regulatory authorities or for the purposes of epidemiological research. In the opposite direction, these same key terms coded in MedDRA representing adverse events, warnings, and other regulatory information could be converted into SNOMED CT so that the information is available in the patient's record to aid in clinical decision-making. Mappings between SNOMED CT and MedDRA are semantic maps of total meaning focused on adverse events. Additional mapping of therapeutic indications is dependent on the context of the use case as it requires testing against existing maps to determine if it is fit for purpose for the use case(s).

5.3.2 Clinical information in the EHR supporting regulation for Pharmacovigilance

Globally, there is increasing uptake of electronic health records to describe the care of individuals including the prescribing of medicinal products. The data in EHRs is becoming more reliable, supported by using standard terminologies, standardized templates for capturing information, and links to decision support,

and protocols. Therefore, there is now an opportunity to re-use that clinical data for pharmacovigilance as required by regulators rather than from separate systems for data collection.

To facilitate this movement of data from EHR systems to regulation requires maps, since those terminologies used in clinical care and regulation are not the same e.g. SNOMED CT used in the EHR, and MedDRA required by regulation.

5.3.3 Identify potentially inappropriate prescribing/off-label use

Potentially inappropriate prescribing can be identified in field studies and in administrative databases with explicit criteria. The rules take the form of: IF THEN BECAUSE, where under IF the condition for triggering an alert is mentioned (e.g. the presence of an obsolete medicinal product in the medication list, or the presence of a contra-indication, or possible interactions). Under THEN, a specific warning can be generated, presenting the problem to the prescriber, and possibly alternatives for the prescription. BECAUSE can list the reasons why this warning is triggered.

From 3 selected internationally validated lists of explicit criteria of potentially inappropriate prescribing, a total of 650 criteria were entered (n = 282 from European Union (7)-PIM (2015), n = 201 from Beers (2015) and n = 167 from the STOPP/START list (2014) in a repository). From all 650 criteria, 36,1 % required clinical information, from which 17,8 % requested disease information only, and 18,3 % required additional information (indication, history of diseases, laboratory results or severity of diseases). This additional information can be automatically retrieved from high quality clinical care systems, provided correct coding is used[28].

5.4 Registries

Terminologies used by different registries covering the same disease need to be linked to each other. The mapping of medical terms, diagnoses and adverse events across different registries using standard terminologies helps many stakeholders with different requirements. For example, safety evaluations of medicines for rare diseases with small populations benefit from the exchange of data between multiple registries from different jurisdictions (e.g. Europe and US).

Traditional drug utilization research can provide data on exposure of populations to medicinal products or pharmaco-therapeutic groups. It is of great interest to be able to split these exposed populations by indication of the targeted drugs, when more than one clinically and quantitively important indication for these drugs exist. Populations using the same drug for different indications will have different risk profiles and safety issues.

6 Mapping principles specific to therapeutic indications

6.1 Maps between Terminologies

6.1.1 General

Maps are developed in accordance with a documented rationale, for a given purpose and as a result, there can be different maps between the same pair of code systems to meet different use cases. A simple map is a 1:1 relationship between a source terminology to a selected target code of a terminology, i.e. between concepts with similar meaning, e.g. SNOMED CT to ICD-Oncology. A complex map is regarded as a rule-based map in that it includes multiple map groups and map advice, e.g., SNOMED CT to ICD-10.

6.1.2 Mapping Prerequisites

Prior to embarking on the process of creating a map, the following are key principles that shall be considered.

— Individual, non-standardized mappings shall be avoided whenever possible and instead maps used that are provided by standards organizations, e.g. MedDRA Maintenance and Support Services Organization (MSSO), SNOMED International and the World Health Organization (WHO), i.e. those between SNOMED

CT and ICD and SNOMED CT and MedDRA should be used. Furthermore, maps between terminologies might be needed in both directions depending on the use case, as they can differ for each direction.

— Due to safety and maintenance implications when creating and applying maps that directly impact clinical care and decision-making, use cases for any map shall be identified before creating or using mappings. For example, there is an allowable semantic shift during mapping such as for statistics and billing because of aggregation to a group level, whereas in use cases to support clinical care at the individual (patient) level, no semantic shift shall be tolerated because of potential safety issues.

— Create a pilot map as proof of concept

6.1.3 Required Processes

During the creation of a map, a documented mapping process shall outline a clear workflow tied to a methodology; such methodologies include dual independent review or mapper-reviewer workflow, such as:

1. A set of agreed use cases to inform the scope of the map
2. Agreement for local or national modifications
3. An agreed quality assurance process
4. Education and training on source and target terminologies, tooling, methodologies
5. Competencies and skillsets for mappers
6. Knowledge of sources and target terminologies

   Understand and explain the purpose of the map
7. Understand the way in which the map will be utilized (end user experience)
8. Understand and be able to apply the structure, content and relationships for the source and target terminology
9. Understand the process to maintain and publish the map
10. End-user feedback methodology
11. Technical validation
12. Governance, maintenance
13. Agreed format for publication and distribution
14. Agreed timelines
15. Resource plan
16. Funding

6.2 Therapeutic Indications - Mapping best practice principles and conventions

When creating a map, the mapping team will require a set of mapping conventions (rules) focused on ensuring a consistent approach resulting in a stable quality product that is fit for purpose.

Source and target of the map must be identified.

NOTE Experience indicates that a bi-directional map must be considered as two separate artifacts and created separately.

Examples of established principles:

— When mapping from (e.g.) SNOMED CT (source) to ICD-10 (target) there are many coding rules that need to be considered to produce accurate, consistent, and reproducible maps, which should be outlined in a document and be easily accessible by the mapping specialist.

— Where possible, the Mapping Principles should be referenced.

EXAMPLE 1

https://apps.who.int/classifications/apps/icd/icd10training/ICD-10%20training/Start/index.html

EXAMPLE 2

MAPPED FOLLOWING WHO GUIDANCE

The map advice MAPPED FOLLOWING WHO GUIDANCE is utilized when assigning an ICD-10 target based on conventions and assumptions in WHO Guidance.

Fracture of skull (disorder), 71642004

S02,90 Fracture of skull and facial bones, part unspecified closed

MAPPED FOLLOWING WHO GUIDANCE

POSSIBLE REQUIREMENT FOR AN EXTERNAL CAUSE CODE

The use of the supplementary fifth character 0 closed, or 1 open, to indicate whether a fracture is open or closed. WHO guidance is that if a fracture is not indicated as closed or open then it should be classified as closed. By adding the map advice MAPPED FOLLOWING WHO GUIDANCE it is clear to the end user the ICD-10 coding conventions have been adhered to.

EXAMPLE 3

POSSIBLE REQUIREMENT FOR MORPHOLOGY CODE

All source concepts representing neoplastic disorders in code ranges (C00-D48) will be mapped according to this principle. Morphology mapping with ICD-O is out of scope for the map. An advice note will be recorded by the Map Specialist to denote a morphology code, in case it is required for completeness.

Primary malignant neoplasm of bone (disorder), 93725000

C41,9 Malignant neoplasm: Bone and articular cartilage, unspecified

POSSIBLE REQUIREMENT FOR MORPHOLOGY CODE

EXAMPLE 4

THIS IS AN EXTERNAL CAUSE CODE FOR USE IN A SECONDARY POSITION

An external cause code from Chapter XX is used with a code from another chapter, to add to the detail captured by the diagnosis code by giving the reason for the condition, especially in situations where the diagnosis code specifies to “use an additional external cause code.” The external cause code should always be sequenced AFTER the disease chapter code in a secondary position.

An exception to this rule is when a SNOMED Concept (source) is described as an ‘Event’ and maps to only one external cause code. In this instance the map advice THIS IS AN EXTERNAL CAUSE CODE FOR USE IN A SECONDARY POSITION should be added to identify both the need to record a diagnosis code and that sequencing rules apply.

Accident caused by splinter (event), 218065002

W45 Foreign body or object entering through skin

THIS IS AN EXTERNAL CAUSE CODE FOR USE IN A SECONDARY POSITION

POSSIBLE REQUIREMENT FOR PLACE OF OCCURRENCE

6.3 General mapping guidance

6.3.1 General

A Mapping Principles and Conventions document should also contain general mapping guidance to assist the Mapping Specialist.

For example, in the MedDRA (source) to SNOMED CT (target) map high level guidance is documented.

A. MedDRA groups its terms in a five-level hierarchy. The Preferred Term (PT) level represents single medical concepts, and the Lowest Level Term (LLT) level represents synonyms, lexical variants, and sub elements. SNOMED CT structure uses concepts as Fully Specified Names (FSN's) with several descriptions available (synonyms).

B. Check the SNOMED CT concepts and the MedDRA terms against the hierarchical placement to determine if the concepts/terms are equivalent. For example,
10050713 Vitamin D is an LLT in MedDRA and is assigned to the SOC of investigations, and so is a test name. A direct lexical match to Vitamin D in SNOMED CT finds Vitamin D is a substance. Further review indicates the MedDRA (source) LLT Vitamin D should be mapped instead to SNOMED CT (target) 83729008 Vitamin D measurement (procedure).

C. Any concepts or terms that are not an Exact Match are flagged as unmappable. This identifies relevant concepts in either terminology that might be missing and are required to provide a more complete mapping. The addition of any new content is discussed by the relevant terminology organization.

More details on the conventions followed to map MedDRA to SNOMED CT and SNOMED CT to MedDRA can be found here: Mapping Conventions document[29].

6.3.2 Mapping of national and regional terms

Where regional or national terms are used to describe therapeutic indications rather than a standardized terminology, any maps that are developed should be based on criteria and guidance set out in this document including full maintenance and updates. In undertaking this work, the user should consider the sharing between jurisdictions and therefore the consequences of developing a local map. From a safety perspective and the support of interoperability, local mapping solutions should be avoided where possible when data is meant to be exchanged across jurisdictions.

6.3.3 Regulatory agencies

6.3.3.1 Therapeutic Indications EU – EMA

Jurisdictional regulatory guidelines propose some key principles that can be applied to facilitate a consistent approach when deciding on the wording of the therapeutic indication. Also, they clarify the regulatory framework surrounding the assessment of applications for the therapeutic indication, provide guidance of such a wording that can be applied across therapeutic areas to foster consistency and improve clarity in the understanding of the wording of the indications for stakeholders. See for example EMA/CHMP/483022/2019 guideline for Assessors of Centralized Applications. Based on the proposed principles, a list of examples is provided in A.2.

As part of the electronic submission of information for authorized medicinal products, the authorized therapeutic indications should be provided using the MedDRA dictionary for coding. For each indication, the following information should be provided: the MedDRA version selected for coding, the MedDRA level selected for coding, and the selected MedDRA code.

The best practice guidance EMA/245789/2015[30] on coding of indications in the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD) aimed at clarifying the current selection of MedDRA codes for authorized indications using the data structure in the XEVMPD in relation to the ones defined in the ISO 11615 standard to achieve a consistent way of coding. A further aim was to reinforce the existing guidance for selecting MedDRA codes for the coding of authorized indications. The core principle of

indication coding (in the context of Art. 57 product submission) is to capture the most detailed and complete MedDRA LLT (Lowest Level Term) code, based on the indication text in section 4.1 of the SmPC, following a set of principles. This set of principles is defined in the EMA/245789/2015 guidance together with examples that illustrate the principles.

The EU IDMP IG[16] for the submission of data on medicinal products makes use of the ISO 11615 standard allowing the coding of further structured details related to indication, such as populations specifics (e.g. age, age range, gender, race) and other therapy specifics (e.g. second line treatment, co-treatment) related to the approved therapeutic indication.

According to the guide, the coding of the authorized indication(s) as disease, symptom or procedure as reflected in Section 4.1 of XX Therapeutic Indications of the corresponding SmPC or another regulatory document will be specified. The chosen MedDRA term should be as specific as possible, with the aim to capture the most detailed level of information presented in the indication section. To achieve a greater specificity of the coded term, the guidance recommends the selection of the MedDRA term that accounts for as much information as possible, such as:

— Both the disease and its cause as provided in the SmPC, (e.g. 'Osteoporosis steroid induced')

— Aspects of 'Disease status specification' (e.g. Pancreatic adenocarcinoma metastatic)

— Details related to the target population (e.g. 'Osteoporosis postmenopausal')

— Timing/duration (e.g. 'Hepatitis chronic persistent')

To clarify the separation between 'Indication as Disease/Symptom/Procedure' as described in ISO 11615 and 'Comorbidity/concurrent disease', where the indication text states: "Treatment of pancreatic insufficiency in patients with cystic fibrosis", then 'pancreatic insufficiency' must be included as indication, whereas 'cystic fibrosis' represents the 'Comorbidity/concurrent conditions' aspect of the indication.

Careful consideration of the drug's mechanism of action and impact on the disease is required when assessing whether the diseases mentioned in the indication text are considered as 'comorbidity' or whether they constitute the therapeutic indication. Treatment of typical signs and symptoms of a disease can represent treatment of the disease. Looking at an example where indication states: "For the treatment of hyperglycaemia in type II diabetes", it should be considered that treatment of hyperglycaemia (i.e. achieving normoglycaemia) is the goal of all antidiabetic treatment, and type II diabetes should therefore be considered as the indication for treatment and not a concurrent disease. See the EU IG for more details and examples.

Therapeutic intent, the reason behind the choice of a therapy and the context in which a given approach should be used, is another important aspect and there are other requirements as well with respect to various electronic mapping of drug indications. For example, an active ingredient can have two distinct indications, which differ solely on dosage strength. In progressing toward a practice of precision medicine, there is a need to capture and structure therapeutic intent for computational reuse, thus enabling more sophisticated decision-support tools and a possible mechanism for computer-aided drug repurposing.

6.3.3.2 Therapeutic Indications U.S. FDA

The primary role of the INDICATIONS AND USAGE section of structured product labelling is to enable health care practitioners to readily identify appropriate therapies for patients by clearly communicating the drug's approved indication(s). Among other information, the INDICATIONS AND USAGE section states the disease or condition, or manifestation or symptoms thereof, for which the drug is approved, as well as whether the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of that disease or condition, including relief of symptoms[31].

Furthermore, the disease, condition, or manifestation should be included in the indication using high-level terms that are clinically relevant and scientifically valid (e.g. asthma, diabetes mellitus, pain). Although the U.S. FDA does not endorse any resource for terms used to describe diseases, conditions, or symptoms, all terminology should be well understood and easily recognizable by health care practitioners.

6.3.3.3 Therapeutic Indications – Further implementations by health authorities

Due to these differing regulations and reporting requirements between various regulatory agencies, as well as those terminologies and classifications used within the healthcare sector, the use of one standard terminological resource for indication terms is not feasible. Therefore, maps between these terminological resources are necessary for documentation and reporting, to aid clinical decisions, and to answer the need for improved communication between health agencies, hospitals, pharmacies, pharmaceutical companies, and the public about drug safety. See Annex A for examples of regional implementations of IDMP Therapeutic Indications.

Annex A
(informative)

Implementations of the IDMP Therapeutic Indications Data Model

A.1 IDMP Therapeutic Indications Data Models

In the context of ISO 11615, indications for which medicinal products are approved and authorized are captured in the Clinical Particulars information model, as shown in Figure A.1, allowing regions to further refine the requirements and business rules during the implementation.

Figures A.2 and A.3 show how the indications have been realized by HL7 FHIR MedicinalProductDefinition and ClinicalUseIssue resources.

Figure A.4 shows how indications are captured by POCP_RM060100UV within HL7 v3 architecture.

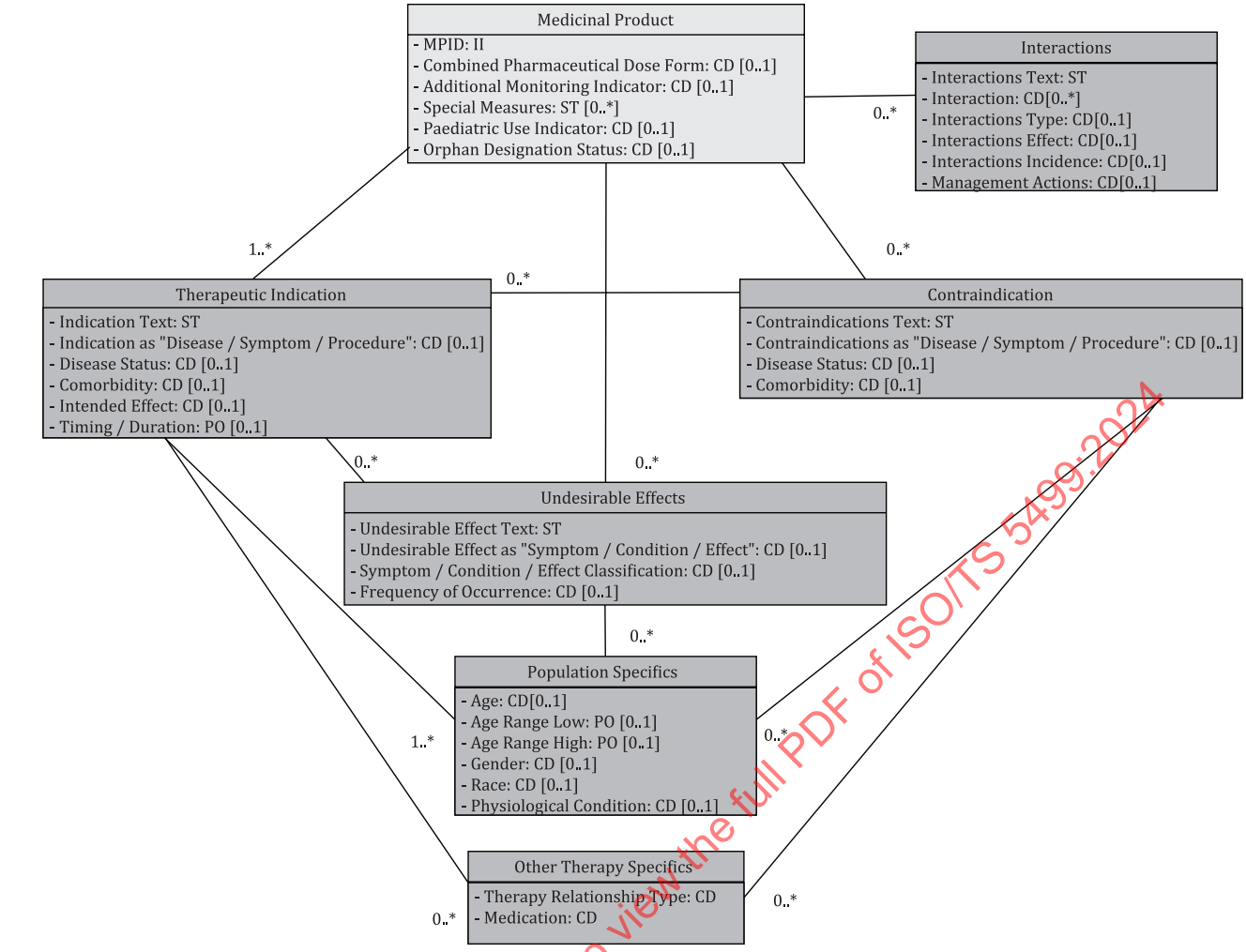

Figure A.1 — Clinical particulars section detailed description diagram (SOURCE: ISO 11615:2017, 9.9.2.1)

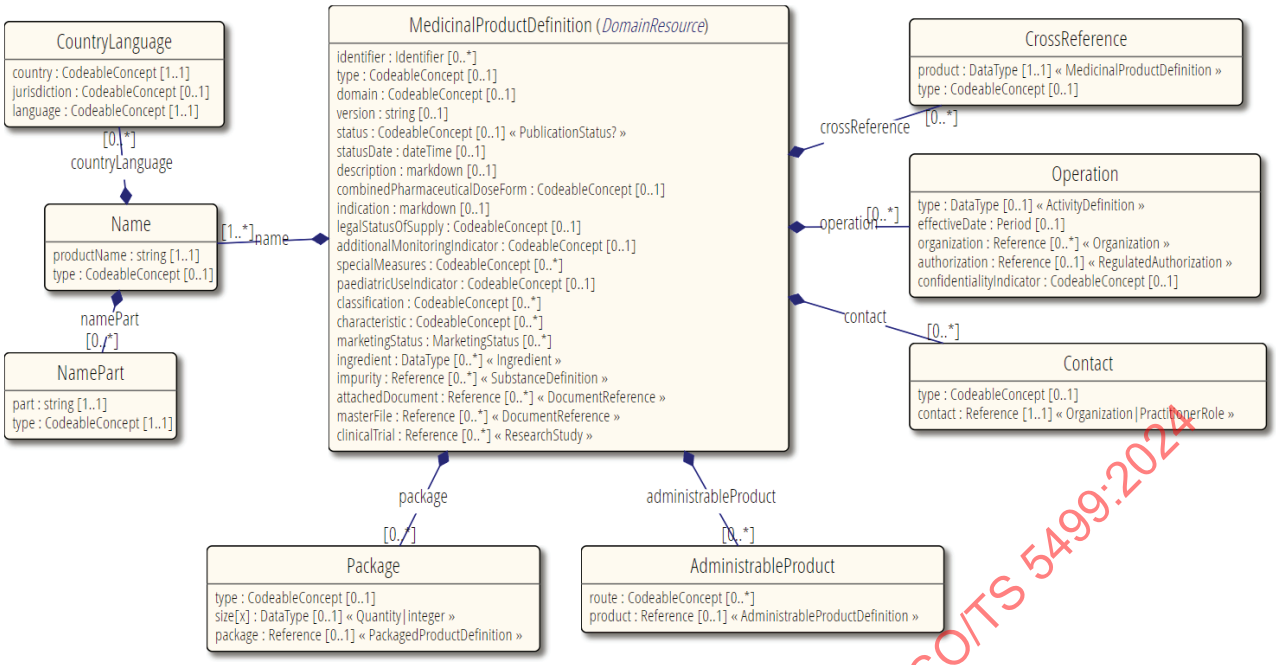

Figure A.2 — Detailed definition of a medicinal product as per FHIR MedicinalProductDefinition Resource (SOURCE: Reference [32])

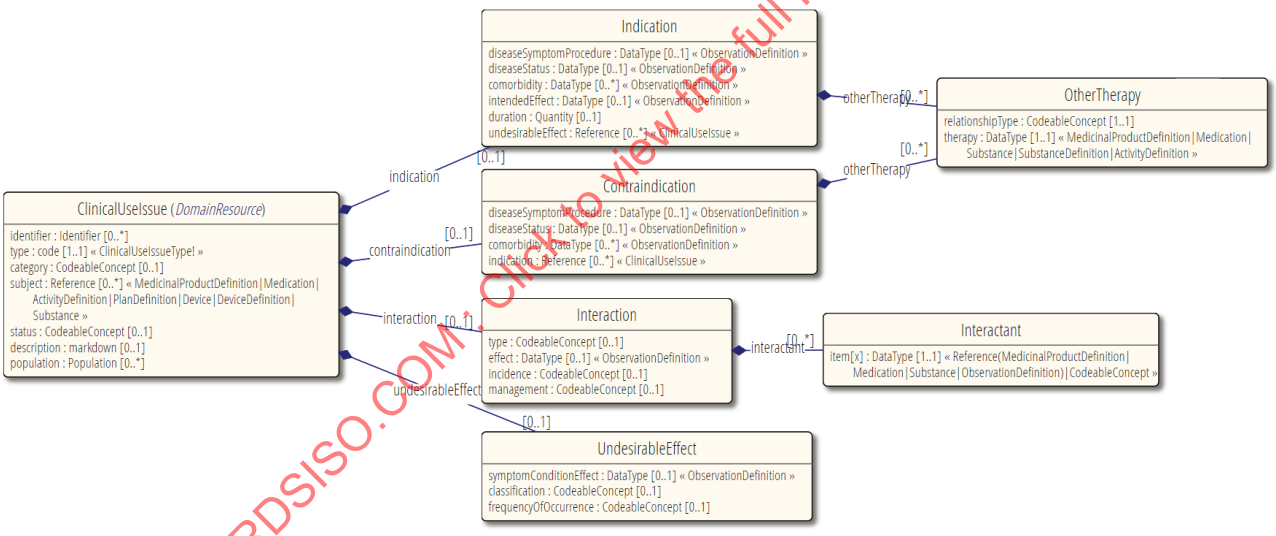

Figure A.3 — Representation of definitional facts about the potential use of a medication, device or procedure as defined by the ClinicalUseIssue FHIR resource (SOURCE: Reference [33])