

Introduction to MedDRA

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Acknowledgement

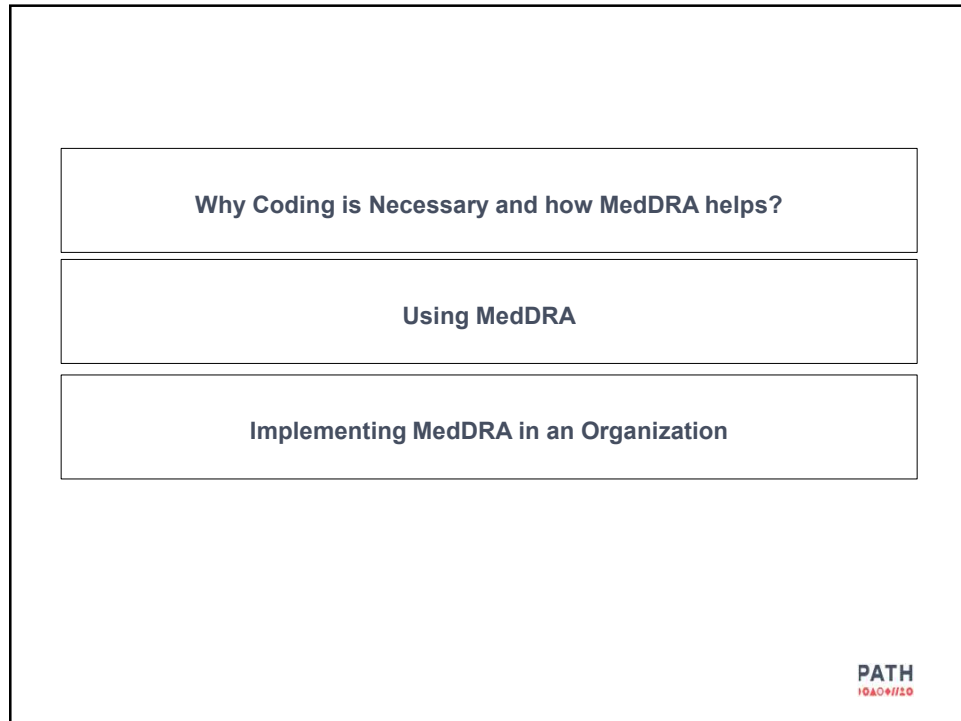
MedDRA was developed under the auspices of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH).

The activities of the MedDRA Maintenance and Support Services Organization (MSSO) are overseen by an ICH MedDRA Management Committee, which is composed of the ICH parties, the Medicines and Healthcare products Regulatory Agency (MHRA) of the UK, Health Canada, and the WHO (as Observer).

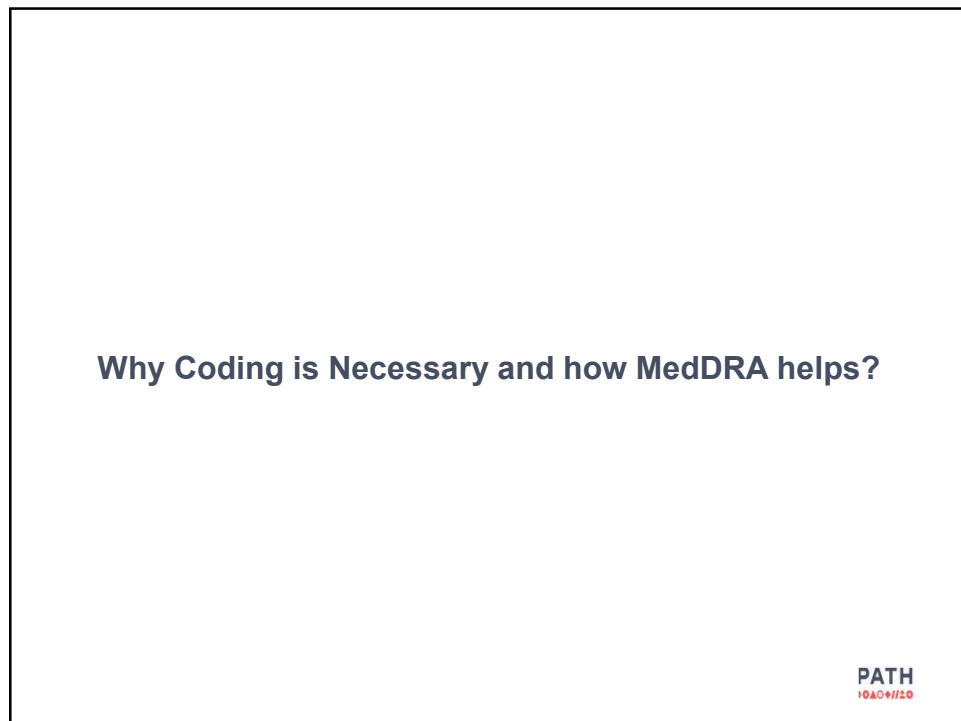
This presentation is based on the MedDRA training materials available at the MedDRA website (<https://www.meddra.org/training-materials>)

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Benefits of Quality Data

- **Accurate and timely information** on issues that affect patient safety
- **Improved communication** among sponsors/MAH, investigators, and regulatory agencies about medicinal products
- Aids in safety **signal detection** and evaluation
- Benefits medical professionals
- Benefits patients
- **Fewer queries** for investigator and sponsor/MAH

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What is Coding?

- Taking a reported term and assigning it a standard medical term or drug name
- Drug coding
 - WHODDE (WHO Drug Dictionary Enhanced)
 - Local dictionaries
- Disease or event coding
 - MedDRA
 - WHO ICD (International Statistical Classification of Diseases and Related Health Problems)
 - SNOMED Clinical Terms

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Coding of Clinical Data

- Most data entered on Case Report Forms are "coded" in some form
- Facilitates storage, retrieval, analysis, and presentation of data
- Some coding is performed by investigators at point of data entry
 - For example, numeric codes for severity of adverse event: 1= mild, 2= moderate, etc.
- Other coding of text data is performed by the sponsor/MAH company after data collection
- Accuracy of initial coding determines accuracy of analysis

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Quality of Serious Adverse Event (SAE) Reporting in Clinical Trials

Study finds frequent errors in SAE reports to academic trial sponsors

- Event verbatim inconsistent with report: 15%
- Patient outcome not reported: 12.1%
- Investigational product not identified: 11.2%
- No causality assessment reported: 9.3%
- Event seriousness unknown: 3.6%

Study authors: *Knowledge of MedDRA basics and coding practices key to data accuracy and completeness.*

Crepin S, Villeneuve C, Merle L. Quality of serious adverse events reporting to academic sponsors of clinical trials: far from optimal. Poster at 18th Annual Meeting of French Society of Pharmacology and Therapeutics; 2014 April 22-24, Poitiers, France.

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Problems With Coding Data

- Appropriate coding requires clear initial data
- What is clear to the investigator/reporter at the point of data entry may be unclear to the sponsor/MAH at the point of data coding
- Sponsor/MAH must only code reported verbatim term; not permitted to interpret or draw information from other sources

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Problems With Coding Data (contd.)

- Example: Ambiguous information
 - Congestion (nasal, liver, sinus, pulmonary?)
 - Cramp (muscle, menstrual, abdominal?)
 - Pain (pain where?)
- Example: Ambiguous abbreviations
 - MI (myocardial infarction or mitral incompetence?)
 - GU pain (gastric ulcer pain or genito-urinary pain?)
 - Decreased BS (breath sounds, bowel sounds or blood sugar?)

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Problems With Coding Data (contd.)

- Example: Vague information
 - Patient felt “fuzzy”, “weird”, “experienced every adverse event”
- Example: Non-specific information
 - “Left wrist edema” (coded as *Peripheral edema*)

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Problems With Coding Data (contd.)

- Death, hospitalization, and disability are outcomes and are not usually considered to be adverse events
- Provide details of the underlying event, if known
- Examples:
 - “Death due to myocardial infarction” (Coded as *Myocardial infarction* with death captured as the outcome)

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Problems With Coding Data (contd.)

- Example: Ambiguous laboratory data
 - "Glucose of 40"
 - (Source of specimen - blood, urine, CSF? What units?)
 - Would have to code as *Glucose abnormal* if additional clarification is not obtained
- If using numeric values, provide units and reference range. Be specific about specimen source and diagnostic result/clinical diagnosis.

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What is MedDRA?

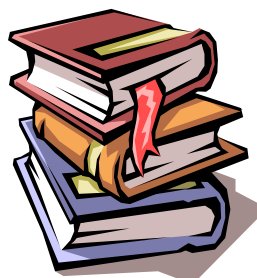
Med = Medical

D = Dictionary for

R = Regulatory

A = Activities

MedDRA is a clinically-validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry.



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MedDRA's Purpose

- Facilitate the exchange of clinical information through **standardization**
- Important tool for product **evaluation, monitoring, communication, electronic records exchange**, and **oversight**
- Supports **coding** (data entry) and **retrieval** and **analysis** of clinical information about human medical products including pharmaceuticals, biologics, vaccines, and drug-device combination products

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Key Features of MedDRA

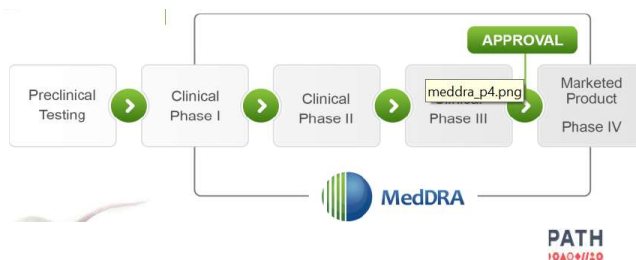
- Standardized terminology
- International scope – currently available in 14 languages
- Managed by Maintenance and Support Services Organization (MSSO) and updated bi-annually
- Structure facilitates data entry, analysis, reporting, and electronic communication
- Large terminology with > 81,000 terms at lowest level - allows greater specificity
- Used to classify a wide range of information associated with the use of pharmaceuticals and vaccines.

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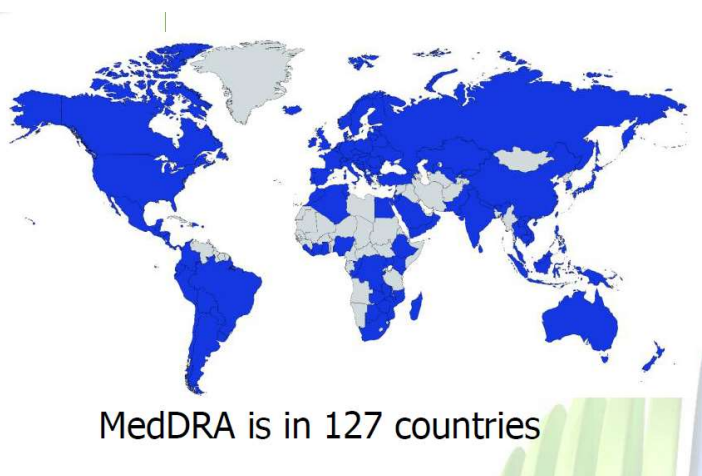
Where MedDRA is Used

- ✓ Regulatory Authority and Industry Databases
- ✓ Individual Case Safety Reports and Safety Summaries
- ✓ Clinical Study Reports
- ✓ Investigators' Brochures
- ✓ Core Company Safety Information (CCSI)
- ✓ Marketing Applications
- ✓ Prescribing Information
- ✓ Publications
- ✓ Advertising



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Where MedDRA is Used



Currently available in **14 languages** (Portuguese, Chinese, Czech, Dutch, English, French, German, Hungarian, Italian, Japanese, Korean, Portuguese, Russian, and Spanish)

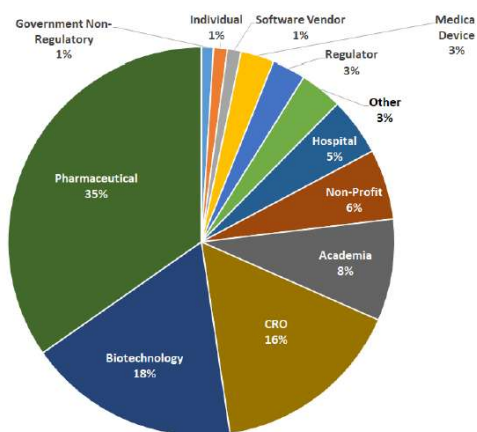
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Where MedDRA is Used

As of Dec 2020

- 6,800 Subscribing organizations (MSSO+JMO)
- 127 Countries



MedDRA Users Profile

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Scope of Terminology

- **Therapeutic indications** – including signs, symptoms, diseases, diagnoses, diagnosis or prophylaxis of disease, and modification of physiologic function
- Names and qualitative results of **investigations** – e.g., increased, decreased, normal, abnormal, present, absent, positive, and negative
- **Medication errors** and **product quality terms**
- Surgical and medical **procedures**
- Medical/social/family **history**

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Out of Scope of Terminology

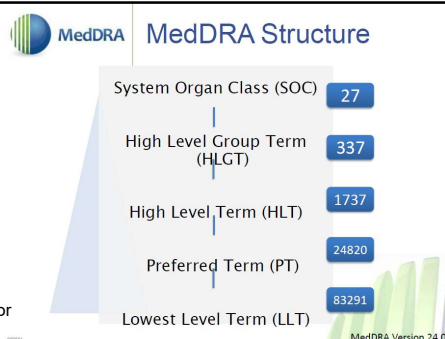
- Not a drug dictionary
- Patient demographic terms
- Clinical trial study design terms
- Frequency qualifiers
- Numerical values for results
- Severity descriptors
- Not an equipment, device, diagnostic product dictionary

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MedDRA Structure

- **SOC - Highest level of the terminology**, and distinguished by anatomical or physiological system, etiology, or purpose
- HLGT - Subordinate to SOC, superordinate descriptor for one or more HLTs
- HLT - Subordinate to HLGT, superordinate descriptor for one or more PTs
- **PT - Represents a single medical concept**
- **LLT - Lowest level of the terminology, related to a single PT as a synonym, lexical variant, or quasi synonym**

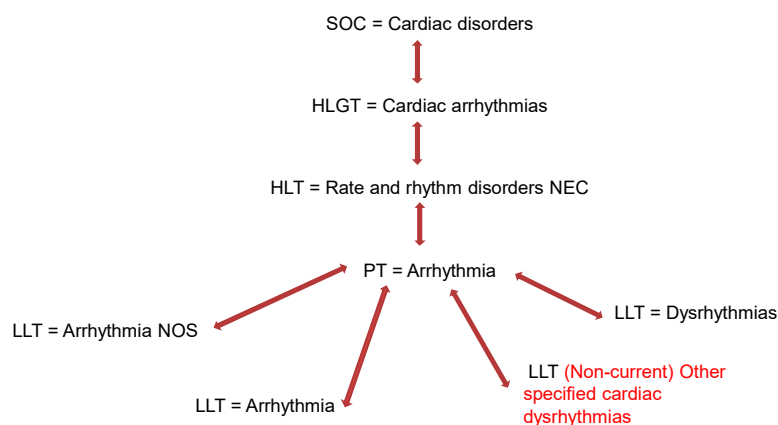


1.Synonyms Different terms for the same descriptor same concept e.g.: PT Arthritis LLT Joint Inflammation
2.Lexical variants Different word forms for the same expression e.g., PT Biopsy tongue LLT Tongue biopsy
3.Quasi-synonym Terms that are not precisely the same meaning as another term but are treated as synonymous. E.g., PT Otitis externa LLT Bilateral otitis externa.

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Five Layers of MedDRA



Non-Current Terms

- Flagged at the LLT level in MedDRA
- Not recommended for continued use
- Retained to preserve historical data for retrieval and analysis

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System Organ Classes (27)

- Blood and lymphatic system disorders
- Cardiac disorders
- Congenital, familial and genetic disorders
- Ear and labyrinth disorders
- Endocrine disorders
- Eye disorders
- Gastrointestinal disorders
- General disorders and administration site conditions
- Hepatobiliary disorders
- Immune system disorders
- Infections and infestations
- Injury, poisoning and procedural complications
- Investigations
- Metabolism and nutrition disorders
- Musculoskeletal and connective tissue disorders
- Neoplasms benign, malignant and unspecified (incl cysts and polyps)
- Nervous system disorders
- Pregnancy, puerperium and perinatal conditions
- Product issues
- Psychiatric disorders
- Renal and urinary disorders
- Reproductive system and breast disorders
- Respiratory, thoracic and mediastinal disorders
- Skin and subcutaneous tissue disorders
- Social circumstances
- Surgical and medical procedures
- Vascular disorders

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MedDRA Codes

- Each MedDRA term assigned an 8-digit numeric code starting with “1”
- The code is non-expressive
- Codes can fulfill a data field in various electronic submission types (e.g., E2B)
- New terms are assigned sequentially
- The code is assigned to the translated term in each MedDRA language.

Preferred Term Code		English		Spanish		Japanese
10022000	=	Influenza	=	Influenza	=	インフルエンザ
10047470	=	Viral myocarditis	=	Miocarditis virica	=	ウイルス性心筋炎
10027599	=	Migraine	=	Migraña	=	片頭痛

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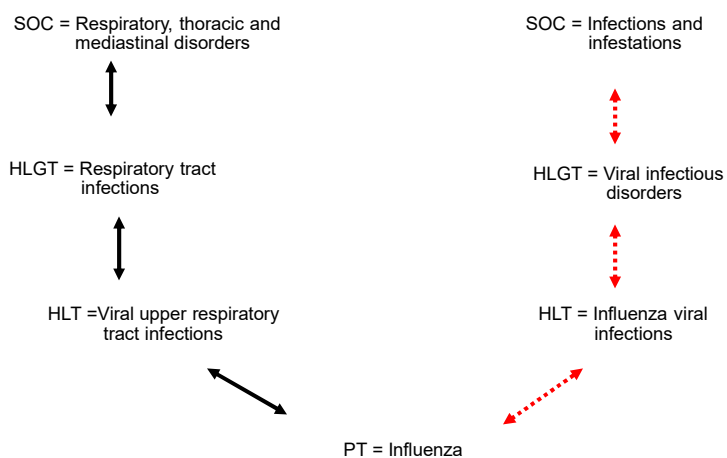
A Multi-Axial Terminology

- Multi-axial = the representation of a medical concept in multiple SOC's
- All PTs assigned a primary SOC
- Determines which SOC will represent a PT during cumulative data outputs
- Supports standardized data presentation

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Example: Multi-Axial Terminology



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A Multi-Axial Terminology (contd.)

PTs in the following SOC **only** appear in that particular SOC and not in others, i.e., they are not multi-axial

- ☐ Investigations
- ☐ Surgical and medical procedures
- ☐ Social circumstances

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Using MedDRA

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MSSO's MedDRA Browsers

- Each require MedDRA ID and password
- View/search MedDRA and SMQs
- Support for all MedDRA languages
- Language specific interface
- Export search results

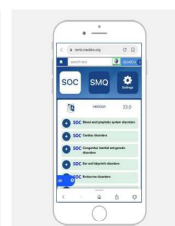


MSSO's MedDRA Browsers



MedDRA Desktop Browser (MDB)
Download MDB and release files from MedDRA website

MedDRA Web-Based Browser (WBB)
<https://tools.meddra.org/wbb/>



Mobile MedDRA Browser

<https://mmb.meddra.org>

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Making the Most of MedDRA

To take advantage of MedDRA's richness and specificity, the source data should be

- Clear
 - Concise
 - Complete
 - Accurate
-
- Be specific if necessary - MedDRA can handle multiple specific medical concepts:
 - Headache - more than 50 types, including cluster, sinus, migraine, lumbar puncture headache
 - Organisms - down to species level e.g. *Staphylococcus aureus*

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What are Company Specific Coding Conventions?

- Written guidelines for coding with MedDRA in your organization
- Support accuracy and consistency
- Could include instructions on how to complete data fields for adverse events, medical history etc. on paper or electronic CRFs
- Could include general principles of how to record text-based information as well as specific instructions for particular therapeutic areas

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Why Do We Need Coding Conventions?

- Differences in medical aptitude of coders
- Consistency concerns (many more “choices” to manually code terms in MedDRA compared to older terminologies)
- Even with an autoencoder, may still need manual coding

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MedDRA Support Documentation

ICH-endorsed guides for MedDRA users

- ❖ MedDRA Term Selection: Points to Consider (MTS:PTC)
- ❖ MedDRA Data Retrieval and Presentation: Points to Consider (DRP:PTC)

Recommended to be used as the basis for individual organizations' coding and retrieval conventions

- Developed by a working group of the ICH Steering Committee
 - Regulators and industry representatives
 - EU, Japan, USA
 - Canadian observer, MSSO, JMO
- Updated twice yearly with each MedDRA release
- Available on MSSO, JMO, and ICH Web sites
 - Variety of file formats for ease of viewing and editing
 - Summary of Changes document

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MedDRA Term Selection: Points to Consider (MTS:PTC)

- MedDRA Term Selection: Points to Consider (MTS:PTC)
 - Provides term selection advice for industry and regulatory purposes
 - Objective is to promote accurate and consistent term selection to facilitate a common understanding of shared data
 - Complete versions available in English, Japanese, Chinese, Korean and Spanish



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MTS:PTC Content - General Term Selection Principles

- Quality of Source Data
- Quality Assurance
- Do Not Alter MedDRA
- Always Select a Lowest Level Term
- Select Only Current Lowest Level Terms
- When to Request a Term
- Use of Medical Judgment in Term Selection
- Selecting More than One Term
- Check the Hierarchy
- Select Terms for All Reported Information, Do Not
- Add Information



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MTS:PTC Content - Term Selection Points

- Diagnoses and Provisional Diagnoses with or without Signs and Symptoms
- Death and Other Patient Outcomes
- Suicide and Self-Harm
- Conflicting/Ambiguous/Vague Information
- Combination Terms
- Age vs. Event Specificity
- Body Site vs. Event Specificity
- Location Specific vs. Microorganism Specific Information
- Modification of Pre-existing Conditions
- Exposures During Pregnancy and Breast Feeding
- Congenital Terms
- Neoplasms
- Medical and Surgical Procedures
- Investigations

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MTS:PTC Content - Term Selection Points (contd.)

- Medication/Administration Errors, Accidental Exposures and Occupational Exposures
- Misuse, Abuse and Addiction
- Transmission of Infectious Agent via Product
- Overdose, Toxicity and Poisoning
- Device-related Terms
- Drug Interactions
- No Adverse Effect and "Normal" Terms
- Unexpected Therapeutic Effect
- Modification of Effect
- Social Circumstances
- Medical and Social History
- Indication for Product Use
- Off Label Use
- Product Quality Issues

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Term Selection Points (Sample)

- Always Select a Lowest Level Term
- Lowest Level Term that most accurately reflects the reported verbatim information should be selected
- Degree of specificity may be challenging
 - Example: "Abscess on face" select "Facial abscess," not simply "Abscess"
- Select current LLTs only
 - Non-current terms for legacy conversion/historical purposes
- Select terms for every AE reported, regardless of causal association
- Select terms for device-related events, product quality issues, medication errors, medical and social history, investigations and indications as appropriate

Reported Information	MedDRA Coding Term (LLT)
Throbbing above temple Aching all over head Pulsing pain in head Really bad headache Headache	Headache
Infection in lungs	Lung infection
Patient took Drug A instead of Drug B and experienced hypertension	Wrong drug administered Hypertension

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Term Selection Points (Sample) (contd.)

Primary SOC

- PTs for diseases, signs and symptoms are assigned to prime manifestation site SOC
- Congenital and hereditary anomalies terms have SOC *Congenital, familial and genetic disorders* as Primary SOC
- Neoplasms terms have SOC *Neoplasms benign, malignant and unspecified* (incl cysts and polyps) as Primary SOC
- Infections and infestations terms have SOC *Infections and infestations* as Primary SOC

Primary SOC Priority

- If a PT links to more than one of the exceptions, the following priority will be used to determine primary SOC:
 - 1st: Congenital, familial and genetic disorders
 - 2nd: Neoplasms benign, malignant and unspecified (incl cysts and polyps)
 - 3rd: Infections and infestations

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Term Selection Points (Sample) (contd.)

Reporting a Specific Diagnosis

- Where possible, report the most important medical event or specific diagnosis rather than individual signs and symptoms
- Can provide provisional diagnosis e.g., "possible", "presumed", "rule out"
- Accuracy is important in preventing dilution of safety signals or generating false signals

SIGNS and SYMPTOMS	DIAGNOSIS
Chest pain, dyspnea, diaphoresis, ECG changes	Myocardial infarction

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Unqualified Test Name Term List

- MSSO developed and maintains list of unqualified test name terms
 - These terms (e.g., PT *Blood glucose*) should never be reported as AEs
 - Intended for use in E2B test name field only

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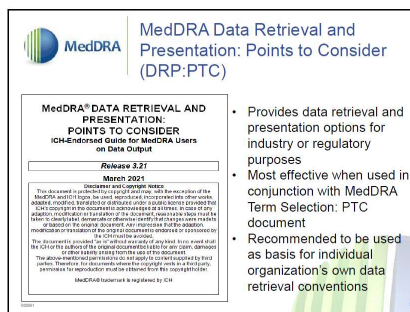
Standardised MedDRA Queries (SMQs)

- Groupings of terms from one or more MedDRA SOC's related to medical condition or area of interest
- Terms relate to signs/symptoms, diagnoses, syndromes, physical findings, laboratory and other test data, etc.
- Intended to aid in case identification
- As of Version 24.0, a total of 108 level 1 SMQs in production

EXAMPLES

•Agranulocytosis
 •Anaphylactic reaction
 •Central nervous system vascular disorders
 •Convulsions
 •COVID-19
 •Depression and suicide/self-injury
 •Hepatic disorders
 •Hypersensitivity
 •Ischaemic heart disease
 •Lack of efficacy/effect
 •Medication errors
 •Osteonecrosis
 •Peripheral neuropathy
 •Pregnancy and neonatal topics

•Pseudomembranous colitis
 •Rhabdomyolysis/myopathy
 •Severe cutaneous adverse reactions
 •Shock
 •Systemic lupus erythematosus



- Provides data retrieval and presentation options for industry or regulatory purposes
- Most effective when used in conjunction with MedDRA Term Selection: PTC document
- Recommended to be used as basis for individual organization's own data retrieval conventions

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Quality of Source Data, Quality Assurance

- Quality of original information impacts quality of output
- Obtain clarification of data
- Can be optimized by careful design of data collection forms and proper training of staff
- Organizations' coding guidelines should be consistent with MTS:PTC
- Review of term selection by qualified individuals
- Human oversight of automated coding results
 - Example: "Allergic to CAT scan" auto encoded as: *Allergic to cats*

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Important Coding Errors

- Missed Concepts
 - All medical concepts described after the product is taken should be coded
 - Example: “*The patient took drug X and developed alopecia, increased LFTs and pancreatitis*”. Manufacturer only codes alopecia and increased LFTs (missed concept of pancreatitis)
 - Example: “*The patient took drug X and developed interstitial nephritis which later deteriorated into renal failure*”. Manufacturer only codes interstitial nephritis (missed renal failure concept)

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Important Coding Errors (contd.)

“Soft Coding”

- Selecting a term which is both less specific and less severe than another MedDRA term is “soft coding”
- Example: “*Liver failure*” coded as hepatotoxicity or increased LFTs
- Example: “*Aplastic anaemia*” coded as unspecified anaemia
- Example: “*Rash subsequently diagnosed as Stevens Johnson syndrome*” coded as rash

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Implementing MedDRA in an Organization

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Governance Structure for MedDRA

ICH MedDRA Management Committee appointed by the ICH Assembly to provide oversight of MedDRA related activities and the Maintenance and Support Services Organization (MSSO)

Management Committee and MSSO Relationship

- ICH owns MedDRA
- ICH MedDRA Management Committee
 - Contracts with MSSO to maintain it
 - Has oversight of all operations of the MSSO
- Meets regularly with MSSO
- Sets subscription rates
- Approves developmental plans and services
- Membership includes ICH regulatory authorities and industry associations

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MedDRA Subscriptions

- To use MedDRA, you must obtain a subscription
- MedDRA subscriptions are enterprise subscriptions
 - All parts of the organization can use the same subscription
 - No limit to the number of users within an organization
- Subscription grants access to MedDRA for one year
- There are four types of MedDRA subscriptions

MedDRA 2021 Subscription Rates are available on MedDRA MSSO website
<https://www.meddra.org/subscription-rates>



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Types of MedDRA Subscriptions

- **Regulatory Authority**
 - Eligible to receive MedDRA at no charge
- **Non-Profit/Non-Commercial**
 - Eligible to receive MedDRA at no charge
 - Non-profit medical libraries, educational institutions, and direct patient care providers (i.e., hospitals for educational use)
 - In general, any organization conducting non-commercial work
- **Commercial**
 - Commercial organizations (e.g., pharmaceutical companies, CROs)
 - Rates vary based on the annual revenue (turnover) of the organization
- **System Developers**
 - Reserved for organizations that develop software products that use MedDRA
 - Use is limited to software development and MedDRA testing, not for providing MedDRA support services (e.g., coding, analysis, transmission of MedDRA coded data)



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What Do I Get with a MedDRA Subscription?

- Access to MedDRA release files
- Full features of MedDRA website
- Submit requests for changes to MedDRA
- Free training
- Help Desk
 - Global support via phone, email, online chat, social media
- Software tools
- MedDRA User Group participation



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Next Steps

- Develop your organizational implementation strategy
- Download the latest MedDRA release
- Access and use one of the MedDRA browser tools to begin coding and data analysis activities
- Consider if you already have data coded in another terminology (legacy data) that you need to convert to MedDRA



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Organizational Implementation Strategy

- No single method for all organizations
- Implementation approach depends on factors such as size of organization
- MSSO provides many tools and resources to assist implementation

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Procedures Documentation

- Documentation of procedures and processes is a best practice for all organizations
- Standard operating procedures and other relevant documents in an organization should address the use of MedDRA
 - Coding, dictionary management, MedDRA versioning, analytical processes and the use of MedDRA tools

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MedDRA Maintenance

- Users can send change requests (CRs) to MSSO for consideration
 - Organizations allowed 100 CRs/month
 - Rigorous medical review by MSSO physicians
- Two MedDRA updates/year
 - 1 March X.0 (Complex release) - *Version 24.0*
 - 1 September X.1 (Simple release)

Proactive MedDRA Maintenance

- Corrections/improvements made internally by the MSSO
- General changes suggested by users

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MedDRA: Take home Points

- ✓ *MedDRA has become the standard medical terminology for drug regulators and pharmaceutical/ vaccine/ bio-technology/ medical devices companies in the ICH region.*
- ✓ *MedDRA allows easy communications with others and is a powerful tool for public health monitoring.*
- ✓ *Availability in multiple languages makes it accessible to the widest numbers of users.*
- ✓ *After more than a decade of use, MedDRA has a wealth of experience around it with a strong maintenance program to keep it current and numerous tools to support subscribers.*

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Thank You

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Guidelines on coding of medical data

- ICH regulatory requirement– coding of reported Adverse Events and Serious Adverse Events to the MedDRA dictionary when submitting electronic reports
- FDA– anticipated MedDRA requirement but it is not yet CFR
- Our client base (“Industry Standard” ~64 pharma, OTC, biotech and device companies)
 - Code at least Adverse Events
 - Optionally code:
 - Medical History
 - Lab
 - Con-Med Indications

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Reasons to Update to a New MedDRA Version

- MedDRA is updated twice a year in March and September
- Take advantage of new terms and other improvements
- Use the same new version to summarize data from different sources that had used older versions
 - "Pooling" clinical trials for analysis
 - Post-marketing safety summaries, etc.
- Use of recent versions of MedDRA may be required or preferred by regulatory authorities
- Stay current with development partners and contract research organizations
- Harmonize use of MedDRA to optimize communication of data

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SMQ Benefits and Limitations

Benefits

- Application across multiple therapeutic areas
- Validated reusable search logic
- Standardized communication of safety information
- Consistent data retrieval
- Maintenance by MSSO/JMO

Limitations

- Do not cover all medical topics or safety issues
- Will evolve and undergo further refinement even though they have been tested during development

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SMQ Applications

Clinical trials

- Where safety profile is not fully established, use multiple SMQs on routine basis as screening tool
- Selected SMQs to evaluate previously identified issue (pre-clinical data or class effect)

Post-marketing

- Selected SMQs to retrieve cases for suspected or known safety issue
- Signal detection (multiple SMQs employed)
- Single case alerts
- Periodic reporting (aggregate cases for safety and other issues, e.g., lack of efficacy)

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