Practical Approaches to Applying MedDRA® in Clinical Safety and Pharmacovigilance

Tutorial

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Tutorial Overview

- Overview of MedDRA
- Coding and the "MedDRA Term Selection: Points to Consider" document
- MedDRA’s application in data retrieval and analysis: the “MedDRA Data Retrieval and Presentation: Points to Consider” document
- Developing MedDRA queries
- Standardised MedDRA Queries (SMQs)
- Customized searches

Overview of MedDRA
Why MedDRA?

ICH initiative (M1)

- An international multi-lingual terminology
- Standardized communication between industry and regulators
- Support of electronic submissions
- Application throughout regulatory process for medical products
- Classification for a wide range of clinical information
- Global ICH-endorsed “Points to Consider” documents
- Global version synchronization

MedDRA Definition

MedDRA is a clinically-validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry. The terminology is used through the entire regulatory process, from pre-marketing to post-marketing, and for data entry, retrieval, evaluation, and presentation.
Applications of MedDRA in Clinical Safety and Pharmacovigilance

• Clinical trial databases (adverse events, medical & social history, investigations etc.)
• Investigator’s Brochures, Core Safety Information
• Safety summaries, Clinical Study Reports
• Individual Case Safety Reports
• Periodic Safety Update Reports
• Product Labeling

Regulatory Status

• US FDA
  ♦ Used in FDA’s Adverse Event Reporting System (AERS)
• Japanese Ministry of Health, Labour and Welfare
  ♦ Mandatory use for electronic reports
  ♦ Used in Periodic Infection and Safety Reports
  ♦ For medical devices with biological components, infections to be described with MedDRA terms
Regulatory Status (cont)

• European Union
   Clinical trials
    ▪ SUSARs (Suspected Unexpected Serious Adverse Reactions) – use MedDRA LLTs (current or previous version)
   Volume 9A (all authorized medicinal products, including OTC)
    ▪ Individual Case Safety Reports (ICSRs) – use MedDRA LLTs (current or previous version)
    ▪ For adverse reactions in Periodic Safety Update Report
    ▪ Standardised MedDRA Queries (SMQs) recommended for signal detection

Regulatory Status (cont)

• European Union (cont)
   Interface between EudraVigilance and EU Risk Management Plan
    ▪ To code indications, risks, interactions (potential and identified)
   Summary of Product Characteristics guideline
    ▪ MedDRA to be used throughout; in particular for Contraindications, Special warnings and precautions for use, and Undesirable effects sections
Regulatory Status (cont)

- ICH M4E Guideline on Common Technical Document
  - Recommended in adverse event summary tables
- Canada
  - Guidance Document for Industry - Reporting Adverse Reactions to Marketed Health Products
    - Recommended as standard for adverse reaction reports
  - Guidance for Industry - Product Monograph (labeling)
    - Preferred terminology for adverse drug reactions

Scope of MedDRA

IN
- Diseases
- Diagnoses
- Signs
- Symptoms
- Therapeutic indications
- Investigation names & qualitative results
- Medical & surgical procedures
- Medical, social, family history
- Medication errors
- Product quality, device issues
- Terms from other terminologies

OUT
- 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
MedDRA Structure

System Organ Class (SOC) (26)
High Level Group Term (HLGT) (335)
  High Level Term (HLT) (1,710)
    Preferred Term (PT) (19,086)
  Lowest Level Term (LLT) (69,019)

MedDRA Term Level Definitions

- **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 (Note: All PTs have an identical LLT)
System Organ Classes

- 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
- 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

Examples of LLTs

SOC = Cardiac disorders

HLGT = Cardiac arrhythmias

HLT = Rate and rhythm disorders NEC

PT = Arrhythmia

LLT = Arrhythmia NOS

LLT (Non-current)
Other specified cardiac dysrhythmias
Non-Current Terms

- Non-current terms are flagged at the LLT level within MedDRA
- Not recommended for continued use
- Retained within the terminology to preserve historical data for retrieval and analysis
- Terms that are vague, ambiguous, outdated, truncated, or misspelled
- Terms derived from other terminologies that do not fit MedDRA rules

MedDRA Codes

- Each MedDRA term assigned an 8-digit numeric code
- The code is non-expressive
- Codes can fulfill a data field in various electronic submission types (e.g., E2B)
- Initially assigned alphabetically by term starting with 10000001
  - New terms are assigned sequentially
- Supplemental terms are assigned codes
A Multi-Axial Terminology

• Multi-axial = the representation of a medical concept in multiple SOCs
  ◦ Allows grouping by different classifications
  ◦ Allows retrieval and presentation via different data sets

• Purpose of Primary SOC
  ◦ Determines which SOC will represent a PT during cumulative data outputs
  ◦ Is used to support consistent data presentation for reporting to regulators

A Multi-Axial Terminology (cont)

SOC = Respiratory, thoracic and mediastinal disorders

HLG = Respiratory tract infections

HLT = Viral upper respiratory tract infections

PT = Influenza

SOC = Infections and infestations

HLGT = Viral infectious disorders

HLT = Influenza viral infections
A Multi-Axial Terminology (cont)

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

- Investigations
- Surgical and medical procedures
- Social circumstances

Rules for Primary SOC Allocation

- 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
  - **Exception:** Cysts and polyps have prime manifestation site SOC 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:

1\textsuperscript{st}: Congenital, familial and genetic disorders

2\textsuperscript{nd}: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

3\textsuperscript{rd}: Infections and infestations

MedDRA Maintenance

- MedDRA is a user responsive terminology
- Subscribers may submit change requests to the MSSO for consideration
  - Core and basic subscribers: 100 change requests (CRs) per month
  - For simple changes (PT and LLT levels), notification of supplemental change within 7-10 working days
  - Weekly supplemental changes posted on MSSO Web site
  - Complex changes above PT level received all year round. Posted for subscribers’ comments mid-year.
MedDRA Maintenance (cont)

- Twice yearly official updates
  - 1 September X.1 release (Simple changes only)
  - 1 March X.0 release (Complex and simple changes)

MSSO’s MedDRA Browsers

- MedDRA Desktop Browser
  - Download from MSSO Web site
  - View/search MedDRA and SMQs
  - Export functionality

- MedDRA Web-Based Browser
  - https://www.meddrabrowser.org/dsnavigator/
  - Requires specific user ID and password
  - Access to all MedDRA versions in English and available EU languages (and Chinese, if subscribed)
  - View/search MedDRA and SMQs
  - Export functionality
Browser Demonstration

SOC View and Search

Coding with MedDRA

Overview of “MedDRA Term Selection: Points to Consider” Document
MedDRA Term Selection: 
Points to Consider (MTS:PTC)

• An ICH-endorsed guide for MedDRA users
• Developed to promote medically accurate and consistent use of MedDRA in exchange of data (ultimately, for “medically meaningful” retrieval and analysis)

MedDRA Term Selection: PTC (cont)

• Developed by a working group of the ICH Steering Committee
  ♦ Regulators and industry representatives
  ♦ EU, Japan, USA
  ♦ Canadian observer, MSSO, JMO
• Current version available on MedDRA MSSO Website (http://www.meddrarmsso.com/subscriber_library_ptc.asp)
MedDRA Term Selection: PTC (cont)

- In some cases with more than one option for selecting terms, a “preferred option” is identified but this does not limit MedDRA users to applying that option. Organizations should be consistent in their choice of option.
- Section 4.1 – Versioning (Appendix)
  - 4.1.1 Versioning methodologies
  - 4.1.2 Timing of version implementation

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
FDA-Defined 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)

Acknowledgement: Dr. Toni Piazza-Hepp, Office of Surveillance and Epidemiology, CDER

FDA-Defined Coding Errors (cont)

• “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 anemia” coded as unspecified anemia
  • Example: “Rash subsequently diagnosed as Stevens Johnson syndrome” coded as rash

Acknowledgement: Dr. Toni Piazza-Hepp, Office of Surveillance and Epidemiology, CDER
Term Selection Points

• Definitive 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 Infection
• Modification of Pre-existing Conditions
• Exposures During Pregnancy and Breast Feeding
• Congenital Terms
• Neoplasms
• Medical and Surgical Procedures

Term Selection Points (cont)

• Investigations
• Medication/Administration Errors and Accidental Exposures
• Transmission of Infectious Agent via Medicinal 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
# Diagnoses and Provisional Diagnoses

## Diagnoses and Provisional Diagnoses (cont)

<table>
<thead>
<tr>
<th>SINGLE DIAGNOSIS</th>
<th>DEFINITIVE DIAGNOSIS</th>
<th>PROVISIONAL DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DEFINITIVE DIAGNOSIS</strong></td>
<td>Single diagnosis without signs and symptoms</td>
<td>Single provisional diagnosis without signs and symptoms</td>
</tr>
<tr>
<td>• Diagnosis (only possible option)</td>
<td>• Provisional diagnosis (only possible option)</td>
<td></td>
</tr>
<tr>
<td><strong>PROVISIONAL DIAGNOSIS</strong></td>
<td>Example: &quot;Myocardial infarction&quot; (\rightarrow) select &quot;Myocardial infarction&quot;</td>
<td>Example: &quot;Possible myocardial infarction&quot; (\rightarrow) select &quot;Myocardial infarction&quot; (select term as if definitive diagnosis)</td>
</tr>
</tbody>
</table>

Similar principles apply for multiple diagnoses.

---

<table>
<thead>
<tr>
<th>SINGLE DIAGNOSIS</th>
<th>DEFINITIVE DIAGNOSIS</th>
<th>PROVISIONAL DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DEFINITIVE DIAGNOSIS</strong></td>
<td>Single diagnosis with signs/symptoms</td>
<td>Single provisional diagnosis with signs/symptoms</td>
</tr>
<tr>
<td>• Preferred: Diagnosis only</td>
<td>• Preferred: Provisional diagnosis and signs/symptoms</td>
<td></td>
</tr>
<tr>
<td><strong>PROVISIONAL DIAGNOSIS</strong></td>
<td>Example: &quot;Anaphylactic reaction with rash, dyspnea, hypotension, and laryngospasm&quot; (\rightarrow) select &quot;Anaphylactic reaction&quot;</td>
<td>Example: “Possible myocardial infarction with chest pain, dyspnea, diaphoresis” (\rightarrow) select &quot;Myocardial infarction&quot; “Chest pain”, “Dyspnea”, and “Diaphoresis”</td>
</tr>
</tbody>
</table>

Similar principles apply for multiple diagnoses.
Diagnoses and Provisional Diagnoses (cont)

**SINGLE DIAGNOSIS**

<table>
<thead>
<tr>
<th>DEFINITIVE DIAGNOSIS</th>
<th>PROVISIONAL DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single diagnosis with signs/symptoms</td>
<td>Single provisional diagnosis with signs/symptoms</td>
</tr>
<tr>
<td>• Alternate: Diagnosis and signs/symptoms</td>
<td>• Alternate: Signs/symptoms only (as provisional diagnosis may change)</td>
</tr>
</tbody>
</table>

Example: "Anaphylactic reaction with rash, dyspnea, hypotension, and laryngospasm" → select "Anaphylactic reaction", "Rash", "Dyspnea", "Hypotension", and "Laryngospasm"

Example: "Possible myocardial infarction with chest pain, dyspnea, diaphoresis" → select "Chest pain", "Dyspnea", and "Diaphoresis"

Similar principles apply for multiple diagnoses

Investigation vs. Medical Condition

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT Selected</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>Hypoglycemia</td>
<td>LLT Hypoglycemia links to SOC Metabolism and nutrition disorders</td>
</tr>
<tr>
<td>Decreased glucose</td>
<td>Glucose decreased</td>
<td>LLT Glucose decreased links to SOC Investigations</td>
</tr>
</tbody>
</table>
Medication Errors and Product Quality Issues

- Important to capture; may have clinical consequences

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT(s) Selected</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient was administered wrong drug and experienced hypotension</td>
<td>Wrong drug administered Hypotension</td>
<td>Medication error with clinical consequences</td>
</tr>
<tr>
<td>Sterile lumbar puncture kit received in broken packaging (sterility compromised)</td>
<td>Product sterile packaging disrupted</td>
<td>Product quality issue without clinical consequences</td>
</tr>
</tbody>
</table>

Overview of “MedDRA Data Retrieval and Presentation: Points to Consider” Document
MedDRA Data Retrieval and Presentation: Points to Consider

- An ICH-Endorsed Guide for MedDRA users on Data Output
- Developed by an ICH Expert Working Group
- Provides data retrieval and presentation options for industry or regulatory purposes
- Objective is to promote understanding of implications that various options for data retrieval have on accuracy and consistency of final output

Data Retrieval PTC Points Addressed

- General Principles
  - Quality of Source Data
  - Documentation of Data Retrieval and Presentation Practices
  - Do Not Alter MedDRA
  - Organization-Specific Data Characteristics
  - Characteristics of MedDRA that Impact Data Retrieval and Analysis
  - MedDRA Versioning
- General Queries and Retrieval
- Standardised MedDRA Queries
- Customized Searches
Documentation of Data Retrieval and Presentation Practices

- Organization-specific guidelines
  - Consistent with Points to Consider documents
  - Coding conventions
  - Data retrieval and output strategies (including SMQs)
  - Quality assurance procedures
  - MedDRA version used for search
  - Search strategy methods
  - Version update processes
  - Processes for customized MedDRA queries

Do Not Alter MedDRA

- MedDRA is a standardized terminology with a pre-defined term hierarchy
- Users must not make *ad hoc* structural alterations, including changing the primary SOC allocation
- If terms are incorrectly placed, submit a change request to the MSSO
Impact of MedDRA’s Characteristics – Grouping Terms

• HLGTs and HLTs provide clinically relevant groupings
  • HLGT Cardiac arrhythmias
    • HLT Cardiac conduction disorders
    • HLT Rate and rhythm disorders NEC
    • HLT Supraventricular arrhythmias
    • HLT Ventricular arrhythmias and cardiac arrest

Impact of MedDRA’s Characteristics – Grouping Terms (cont)

• Caution - ensure all terms are relevant to output
  • HLT Vascular tests NEC (incl blood pressure)
    • PT Blood pressure decreased
    • PT Blood pressure increased
• Caution - related PTs in different locations in SOC
  • HLT Bullous conditions
    • PT Stevens-Johnson syndrome
  • HLT Exfoliative conditions
    • PT Dermatitis exfoliative
## Which Level? – SOC Investigations

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v14.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Investigations</td>
<td>13 (29.5%)</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>PT Aspartate aminotransferase increased</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>PT Alanine aminotransferase increased</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>PT Gamma-glutamyltransferase increased</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>PT Blood creatine phosphokinase increased</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>PT Blood alkaline phosphatase increased</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Blood glucose increased</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PT Blood lactate dehydrogenase increased</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Lipase increased</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT White blood cell count decreased</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Blood amylase increased</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Faecal fat increased</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Patients may have more than one event reported

---

## Which Level? – SOC Investigations (cont)

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v14.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Investigations</td>
<td>13 (29.5%)</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>PT Blood pressure increased</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Blood urea increased</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Occult blood positive</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Liver function test abnormal</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Monocyte count decreased</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Protein urine present</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Patients may have more than one event reported
### Which Level? – SOC Investigations (cont)

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v14.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Investigations</td>
<td>13 (29.5%)</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>HLT Liver function analyses</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>HLT Tissue enzyme analyses NEC</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>HLT Digestive enzymes</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>HLT White blood cell analyses</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>HLT Skeletal and cardiac muscle analyses</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>HLT Carbohydrate tolerance analyses (incl diabetes)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HLT Faecal analyses NEC</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HLT Vascular tests NEC (incl blood pressure)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>HLT Renal function analyses</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>HLT Urinalysis NEC</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Patients may have more than one event reported.

### Granularity

<table>
<thead>
<tr>
<th>Other Terminology Preferred Terms</th>
<th>No. of Events</th>
<th>MedDRA Version 14.0 Preferred Terms</th>
<th>No. of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>INFECTION</td>
<td>15</td>
<td>Upper respiratory tract infection</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nasopharyngitis</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infection</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower respiratory tract infection</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin infection</td>
<td>1</td>
</tr>
</tbody>
</table>
Multi-Axiality

- Primary SOC allocation rules affect the way data are distributed across the terminology
- Impact on frequencies of medical condition of interest should be considered
- Example: for hepatic abnormality search in SOC Hepatobiliary disorders, SOC Investigations (laboratory test terms), SOC Surgical and medical procedures (e.g., PT Liver transplant)
- Main presentation is by Primary SOC; secondary SOCs used for alternate views

<table>
<thead>
<tr>
<th>Reported event (% subjects)</th>
<th>Other terminology</th>
<th>MedDRA Version 14.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coded term (% subjects)</td>
<td>Body System/SOC (% subjects)</td>
</tr>
<tr>
<td>Hyperglycemia (4.1)</td>
<td>Hyperglycemia (10.5)</td>
<td>Metabolism and nutritional disorders (10.5)</td>
</tr>
<tr>
<td>Increased blood sugar (2.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose increased (2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose was high (1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increasing glucose (0.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Primary SOC Analysis – SOC Infections and infestations

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v14.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Infections and infestations</td>
<td>14 (31.8%)</td>
<td>4 (26.7%)</td>
</tr>
<tr>
<td>PT Upper respiratory tract infection</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>PT Sinusitis</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>PT Urinary tract infection</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>PT Ear infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Viral infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Bronchitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Influenza</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Localised infection</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PT Lower respiratory tract infection</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Pneumonia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Tooth abscess</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Patients may have more than one event reported

### Secondary SOC Analysis – SOC Infections and infestations

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v14.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT Upper respiratory tract infection</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>PT Sinusitis</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>PT Bronchitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Influenza</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Lower respiratory tract infection</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Pneumonia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>SOC Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT Viral infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Localised infection</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Patients may have more than one event reported
### Secondary SOC Analysis – SOC Infections and infestations (cont)

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v14.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT Urinary tract infection</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>SOC Ear and labyrinth disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT Ear infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>SOC Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT Tooth abscess</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Patients may have more than one event reported

---

### MedDRA Versioning

- **MedDRA is updated twice a year**
  - 1 March X.0 release (all levels)
  - 1 September X.1 release (LLT and PT levels only)
- **Version used in data retrieval and presentation should be documented**
- **Resources:**
  - “What’s New” document
  - Version report
- **Terms used for queries should be in same version as data being queried**
MedDRA Versioning (cont) - Effect of Primary SOC Change

<table>
<thead>
<tr>
<th>MedDRA Version 13.1</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Injury, poisoning and procedural complications</td>
<td>20</td>
</tr>
<tr>
<td>PT Retinal scar</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MedDRA Version 14.0</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Injury, poisoning and procedural complications</td>
<td>0</td>
</tr>
<tr>
<td>SOC Eye disorders</td>
<td>20</td>
</tr>
<tr>
<td>PT Retinal scar</td>
<td></td>
</tr>
</tbody>
</table>

Developing Queries Using MedDRA
General Principles

- Define the medical condition
- Develop inclusion/exclusion criteria
- Know your data, e.g., how specific coding conventions impact retrieval strategy
- Good browser is key component
  - Flexible search capabilities
  - Ability to view secondary SOC assignments

Query Strategy Tips

- ALWAYS search the “non-multi-axial” SOCs
- Consider searching the “support” SOCs
- Use “Top-down” and “Bottom-up” searches
- Use multi-axial links
- Use grouping terms; exclude non-relevant PTs
- Avoid using LLTs in queries
  - Exception: for infections, specific species information is found at the LLT level
Additional Points About Query Development

- Periodically review queries to determine possible impact of new MedDRA versions, e.g., PT term demotion, LLT currency changes, renaming of HLT/HLGTs, remapping of terms, etc.
- Set aside enough time – a thorough, well-constructed query takes time, but it is well worth the effort
- Recycle! If a query worked for one product, it could be applicable to others

Connect the DOTSSS!

- Diagnosis/disease terms
- Support SOCs (Other…)
- Signs & symptoms
- Social circumstances
- Operations (Surgical and medical procedures)
- Tests (Investigations)
Cardiac Failure Query Exercise

- Build a query with a set of PTs relevant to this condition
- Connect the DOTSSS
- Can you identify cases of interest in a dataset?

Standardised MedDRA Queries (SMQs)
Definition of SMQ

- Result of cooperative effort between CIOMS and ICH (MSSO)
- Groupings of terms from one or more MedDRA System Organ Classes (SOCs) related to defined medical condition or area of interest
- Included terms may relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data, etc., related to medical condition or area of interest
- Intended to aid in case identification

SMQ Benefits and Limitations

- Benefits
  - Application across multiple therapeutic areas
  - Reusable programming
  - 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
SMQ Development Summary

• Pre-release: tested on databases available to CIOMS Working Group members; typically, at least one company and one regulator database
• Production Phase: continue to be fine-tuned by MedDRA subscribers through the MSSO maintenance process

SMQs in Production - Examples

• As of Version 14.0, a total of 85 in production (One is inactive)
  • Agranulocytosis
  • Anaphylactic reaction
  • Cerebrovascular disorders
  • Convulsions
  • Depression and suicide/self-injury
  • Hepatic disorders
  • Ischaemic heart disease
  • Lack of efficacy/effect
  • Peripheral neuropathy
  • Pregnancy and neonatal topics
  • Pseudomembranous colitis
  • Rhabdomyolysis/myopathy
  • Severe cutaneous adverse reactions
  • Systemic lupus erythematosus
Narrow and Broad Searches

• "Narrow" scope – specificity (cases highly likely to be condition of interest)
• "Broad" scope – sensitivity (all possible cases)
• "Broad search" = All broad + all narrow terms
• MedDRA term can be broad or narrow depending on SMQ
  - Example: PT Renal failure acute
    - Narrow in Acute renal failure (SMQ)
    - Broad in Rhabdomyolysis/myopathy (SMQ)

Lactic acidosis (SMQ)

Definition:
Lactic acidosis is a form of high serum gap metabolic acidosis. Intravascular compartment may be depressed, but intracellular function can be normal because of catecholamine release. Peripherally arterial vasoconstriction and central vasoconstriction can be present. Central nervous system function is depressed, with headache, lethargy, stupor, and, in some cases, even coma. Observe tachypnea may occur. Characterized by an increase in plasma L-lactate. Acidosis is seldom significant unless blood lactate exceeds 5 mmol/L. Clinical presentation in type B lactic acidosis. Symptoms: hyperventilation or hypoxia, stupor or coma, vomiting, diarrhoea, and abdominal pain. Onset of symptoms and signs is usually rapid accompanied by deterioration in the level of consciousness.

Source:

Note:
Testing in two regulatory databases confirms that the term list is adequate; in one regulatory database, the term "acidosis" identified cases, but this may be a phenomenon of the database characteristics (coding of "acidosis" terms of an older terminology or other coding conventions).
Algorithmic SMQs

- Some SMQs are designed to utilize algorithms
- Better case identification among broad search terms may result if cases are selected by a defined combination of selected terms

Algorithmic SMQ Example

- *Anaphylactic reaction (SMQ):*
  - A case with any of the following PTs:
    - Anaphylactic reaction
    - Anaphylactic shock
    - Anaphylactic transfusion reaction
    - Anaphylactoid reaction
    - Anaphylactoid shock
    - Circulatory collapse
    - First use syndrome
    - Kounis syndrome
    - Shock
    - Type I hypersensitivity

  (Narrow search terms = Category A)
Algorithmic SMQ Example (cont)

<table>
<thead>
<tr>
<th>Category B – Upper airway/Respiratory</th>
<th>Category C – Angioedema/Urictaria, etc.</th>
<th>Category D – Cardiovascular/Hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory failure</td>
<td>Allergic oedema</td>
<td>Blood pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>decreased</td>
</tr>
<tr>
<td>Asthma</td>
<td>Angioedema</td>
<td>Blood pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diastolic decreased</td>
</tr>
<tr>
<td>Bronchial oedema</td>
<td>Erythema</td>
<td>Blood pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>systolic decreased</td>
</tr>
</tbody>
</table>

- Case = A (Narrow terms)
- Or Term from Category B and term from Category C
- Or Term from either Category B or Category C plus Term from Category D

Hierarchical SMQs

- Some SMQs have been developed as a set of queries related to one another in a hierarchical relationship
- Not related to MedDRA standard hierarchy
- One or more subordinate SMQs combined to create a superordinate, more inclusive SMQ
Hierarchical SMQ Example

- Haematopoietic cytopenias
  - Haematopoietic cytopenias affecting more than one type of blood cell
  - Haematopoietic erythropenia
  - Haematopoietic leukopenia
  - Haematopoietic thrombocytopenia

Other Data Included in SMQ Files

- Description field
  - Additional information about each SMQ (from SMQ Introductory Guide)
- Source field
  - Medical references used in development/maintenance
- Development note
  - Pertinent notes for proper use
  - Description of algorithm (if applicable), and definition of categories
SMQ Files and Documents

- MedDRA distributed files unchanged by inclusion of SMQ files
- SMQ Introductory Guide
  - Recommended reading for optimal utilization of SMQs
  - Details of individual SMQs
  - Notes for implementation and/or expectation of results
- Production SMQ Spreadsheet
  - SMQs and included terms (.xls)
- “What’s New” document summarizes SMQ changes
- Original CIOMS Working Group documentation

SMQ Versioning

- It is recommended that organizations utilize the SMQs with data coded with the same version of MedDRA
  - Match the MedDRA version of the SMQ with the MedDRA version of the coded data
  - Mismatches of SMQ and MedDRA coded data could produce unexpected results
SMQ Versioning (cont)

- Examples of PTs added to SMQs in MedDRA Version 14.0:
  - PT *Metabolic cardiomyopathy* in SMQ *Cardiomyopathy*
  - PT *Arterectomy* in SMQ *Embolic and thrombotic events, arterial*
- Using version 13.1 SMQs which do not contain these PTs would fail to identify cases coded to these terms in a database using MedDRA Version 14.0

Browser Demonstration

SMQ View
SMQ Applications

How to “run” SMQs

Clinical Trial Database
Safety Database

Query

Case
LLT1
LLT2
LLT3

"Hit"

SMQ
PT
LLT
LLT
LLT
LLT
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)

- **Postmarketing**
  - 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)

SMQ Programming Example

- **Asthma/bronchospasm (SMQ):** 
  Example of code for narrow search

```sql
proc sql;
connect to oracle (user=edu001 orapw=edu001 path="@dev_edu1");
title 'Asthma/bronchospasm (SMQ) Cases – Narrow Search';
title2 'since 1-Jan-2006';
select case_number as Case_ID,
meddra_pt as MedDRA_PT,
report_verbatim,
date_created
from drug_safety_table
where (date_created >= '01-JAN-2006') and
  (meddra_pt in (select meddra_pt_name
                   from SMQ_content
                   where SMQ_name = 'Asthma/bronchospasm (SMQ)' and scope = 'narrow'))
order by case_number;
quit;
```

For broad search, omit scope
SMQ Asthma/bronchospasm - Narrow search results example

The SAS System

Asthma/bronchospasm (SMQ) Cases - Narrow Search
(since 1-Jan-2006)

<table>
<thead>
<tr>
<th>Case_ID</th>
<th>MedDRA PT</th>
<th>REPORT VERBATIM</th>
<th>DATE CREATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asthma</td>
<td>Asthma attack</td>
<td>01-JAN-2006</td>
</tr>
<tr>
<td>2</td>
<td>Asthma</td>
<td>Severe asthma</td>
<td>05-AUG-2006</td>
</tr>
<tr>
<td>3</td>
<td>Asthma exercise induced</td>
<td>Asthma when exercising</td>
<td>01-JUN-2006</td>
</tr>
<tr>
<td>4</td>
<td>Bronchospasm</td>
<td>Sputum, bronchial</td>
<td>31-MAR-2006</td>
</tr>
<tr>
<td>5</td>
<td>Bronchospasm</td>
<td>bronchoconstriction</td>
<td>23-MAY-2006</td>
</tr>
<tr>
<td>6</td>
<td>Bronchial hyperreactivity</td>
<td>Airways hyperreactive</td>
<td>14-APR-2006</td>
</tr>
<tr>
<td>7</td>
<td>Bronchial hyperreactivity</td>
<td>Reactive Airways disease</td>
<td>17-FEB-2006</td>
</tr>
</tbody>
</table>

Case study at EMEA

Signal detection using SMQ

Hyperglycaemia/new onset diabetes mellitus

Based on work by:
Victoria Newbould
Nick Halsey
Stefano Cappe
Panos Tsintis
Magnus Lerch
and Patricia Mozzicato

Acknowledgement: Jim Slattery, EMEA. Slides used with permission.
EMEA Signal Detection Activities (made simple)

- All newly arrived reports are reviewed
- Disproportionality measure – Proportional Reporting Ratio (PRR) – is calculated
- If the lower confidence bound exceeds one and the total number of cases is 3 or more further investigation may be started

Question

- Although not designed primarily for detection of drug safety issues, is it likely that the SMQs will have advantages over other levels of MedDRA in early signalling of new safety problems?
Design of Study

- SMQ *Hyperglycaemia/new onset diabetes mellitus*
- An antipsychotic with known association
- Calculate PRR as function of time
- Compare with PRR from single PTs, HLT, and HLGT

Signal Detection from various Adverse Event Groups

Note: Points marked with a black dot have counts of 3 or more cases
Case Study Conclusions

• There is potential for well thought-out grouping of MedDRA categories to improve signal detection
• In this case narrow was better than broad – thus not simply a matter of amalgamating all clinically related terms
• However, both broad and narrow competed with PTs and higher levels
• In designing SMQs for signal detection we must consider ‘specificity’ to avoid increasing noise

Customized Searches
Customized Searches – Modified SMQs

• Do not modify SMQ unless there is a compelling reason – makes it non-standard
• “Modified MedDRA query based on an SMQ”
  ♦ To be used to refer to an SMQ that has been modified
  ♦ All modifications must be documented
  ♦ Version updates and maintenance are responsibility of organization that created it

Modified MedDRA Queries Based on SMQs - Examples

• Additional PTs needed
  ♦ Drug-device combination product investigated for lack of efficacy
  ♦ Document that PT Device failure has been added to SMQ Lack of efficacy/effect
• Excluding PTs
  ♦ Antipsychotic investigated for QT prolongation also has association with hypotension/fainting
  ♦ Exclude PT Syncope from SMQ Torsade de pointes/QT prolongation (broad search) to prevent “noise” in retrieval
Modified MedDRA Queries Based on SMQs – Examples (cont)

• Changing scope of SMQ term
  - Product investigated for severe cutaneous adverse reactions including potential for DRESS syndrome; specific (narrow) search result is required
  - Include PT Drug rash with eosinophilia and systemic symptoms (normally a broad search term) with the narrow search terms in SMQ Severe cutaneous adverse reactions

Customized Searches – *Ad Hoc* Queries

• Need medical knowledge
• Need knowledge of structure and characteristics of MedDRA and of your data
• Refer to the *MedDRA Data Retrieval and Presentation: Points to Consider* document for query construction tips
• Save query for future use; maintenance needed for MedDRA version changes
• Consider submitting *ad hoc* query to MSSO via change request for possible development as an SMQ
Exercise

• SMQ *Lack of efficacy/effect* often needs to be modified based on the particular characteristics of a product

• Consider how you would create a Modified MedDRA Query based on SMQ *Lack of efficacy/effect* for:
  • An inhaled bronchodilator indicated for use in asthma

• Remember to document changes!

Tutorial Summary
Tutorial Summary

• In this tutorial we have:
  • Learned about the "MedDRA Data Retrieval and Presentation: Points to Consider" document and reviewed various options for data retrieval for industry and regulatory purposes
  • Learned how to develop queries using MedDRA
  • Learned about Standardised MedDRA Queries
  • Discussed customized searches

Thank You!