What Medical Writers Need to Know About MedDRA

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Overview

• MedDRA background
• Scope of MedDRA (vocabulary)
• Structure and characteristics (grammar)
• Evolution of MedDRA
• Key aspects of the *Data Retrieval and Presentation: Points to Consider* document
• Standardised MedDRA Queries (SMQs)
• Exercises (“how to speak MedDRA”)

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*MedDRA*
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.
Product Lifecycle: Where MedDRA is Spoken

Preclinical Testing → Clinical Phase I → Clinical Phase II → Clinical Phase III → Marketed Product

Regulatory Authority and Industry Databases
Individual Case Safety Reports and Safety Summaries

Clinical Study Reports
Investigators’ Brochures
Core Company Safety Information
Marketing Applications
Publications
Prescribing Information
Advertising
Regulatory Status In EU

- EudraVigilance database
  - Clinical trial SUSARs (Suspected Unexpected Serious Adverse Reactions)
  - Post-authorization Individual Case Safety Reports (ICSRs)
  - Requires current version of MedDRA or the one previous to it
- Good pharmacovigilance practices (GVP) specifically mention MedDRA
- Pharmacovigilance legislation covers suspected adverse reactions from:
  - Use inside and outside terms of marketing authorization
  - Overdose, misuse, abuse, and medication errors
  - Occupational exposures
- Used in interface between EudraVigilance and EU Risk Management Plan
- Used throughout Summary of Product Characteristics
- ICH M4E Guideline on Common Technical Document
  - Recommended in adverse event summary tables
Scope of MedDRA

**In**
- Medical conditions
- Indications
- Investigations (tests, results)
- Medical and surgical procedures
- Medical, social, family history
- Medication errors
- Product quality issues
- Device-related issues
- Pharmacogenetic terms
- Toxicologic issues
- Standardized queries

**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) (1,721)
Preferred Term (PT) (21,345)
Lowest Level Term (LLT) (74,229)
MedDRA

Lowest Level Term

Synonyms, lexical variants, sub-elements

**SOC** = Cardiac disorders

**HLGT** = Cardiac arrhythmias

**HLT** = Rate and rhythm disorders NEC

**PT** = Arrhythmia

**LLT**
- Arrhythmia NOS
- Arrhythmia
- LLT (Non-current)
- Other specified cardiac dysrhythmias

Not all LLTs shown
Codes and Languages

10019211

Cefaleia
Portuguese

Hoofdpijn
Dutch

Headache
English

Céphalée
French

Bolest hlavy
Czech

頭痛
Chinese

Kopfschmerz
German

Fejfájás
Hungarian

Cefalea
Italian

Cefalea
Spanish

Electronic Submission
• 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
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
- All PTs assigned a primary SOC
  - Determines which SOC will represent a PT during cumulative data outputs
  - Prevents “double counting”
  - Supports standardized data presentation
  - Pre-defined allocations should not be changed by users
SOC = Respiratory, thoracic and mediastinal disorders (Secondary SOC)

HLGT = Respiratory tract infections

HLT = Viral upper respiratory tract infections

PT = Influenza

SOC = Infections and infestations (Primary SOC)

HLGT = Viral infectious disorders

HLT = Influenza viral infections
Rules for Primary SOC Allocation

- PTs represented in only one SOC are automatically assigned that SOC as primary
- 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
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*
MedDRA Maintenance

- MedDRA is a user-responsive terminology
- Users may submit change requests (CRs) to the MSSO for consideration
  - Each organization: up to 100 CRs per month
  - For simple changes (PT and LLT levels), notification of final disposition within 7-10 working days
  - Complex changes above PT level received all year round. Posted for users’ comments mid-year.
- Twice yearly official updates
  - 1 March X.0 release (Complex and simple changes)
  - 1 September X.1 release (Simple changes only)
Evolution of MedDRA: 27th System Organ Class

• MedDRA Management Board endorsed creation of an additional (27th) SOC

• To accommodate non-clinical/non-patient concepts covering issues related to medical products
  – Important because they may affect patient safety

• Will include product quality issues
  – Existing HLGT *Product quality issues*
  – Supplemented by new terms relating to manufacturing quality system issues and distribution issues

• Planned implementation date March 2016 (MedDRA Version 19.0)
Evolution of MedDRA (cont)

- New HLGT Product use issues in SOC Injury, poisoning and procedural complications
  - Overdoses, underdoses, misuse, off label use now grouped in one SOC with HLGT Medication errors
  - SMQ Medication errors planned for MedDRA v19.0 in March
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
- Recommended to be used as basis for individual organization’s own coding conventions
Always Select a Lowest Level Term
Select Only Current LLT's

• 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 LLT's only
  – Non-current terms for legacy conversion/historical purposes
Autoencoder Pitfalls

• Inappropriate terms may be selected by autoencoder
• Review all autoencoding carefully
  – “Allergic to CAT scan” autoencoded as:
    LLT *Allergic to cats*
  – “Myocardial infarction in the fall of 2000” autoencoded as:
    LLT *Myocardial infarction*
    LLT *Fall*
FDA-Defined Coding Errors

- Missed Concepts
  - Example: “The patient took drug X and developed alopecia, increased LFTs and pancreatitis”. Manufacturer only codes alopecia and increased LFTs (missed concept of pancreatitis)

- “Soft Coding”
  - 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
Exercises
What Terms to Select?

- Retinal disease from HIV with near total blindness (R and L)
  Retinal damage?
  Retinal disorder?
  HIV disease?
  Blindness?
  HIV retinopathy?
  Blindness both eyes?
What Term to Select?

• The patient’s renal function was measured every six months instead of on the monthly schedule recommended in the label for the drug
  Renal function test?
  Renal function test abnormal?
  Drug monitoring procedure incorrectly performed?
• Unintentional overdose due to dispensing error
  Overdose?
  Accidental overdose?
  Medication error?
  Incorrect dose administered?
  Drug dispensing error?
MedDRA Data Retrieval and Presentation: Points to Consider
MedDRA Data Retrieval and Presentation: Points to Consider

• 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
• Developed by a working group of the ICH Steering Committee
  – Regulators and industry representatives from EU, Japan, and USA
  – Canadian and Korean regulatory authorities
  – WHO
  – MSSO and JMO

• Updated twice yearly with each MedDRA release

• Available on MedDRA and JMO websites
  – English and Japanese
  – Variety of file formats for ease of viewing and editing
  – Summary of Changes document
Data Retrieval PTC
Points Addressed

• General Principles
  – Quality of Source Data
  – Documentation of Data Retrieval and Presentation Practices
  – Do Not Alter MedDRA
  – Organisation-Specific Data Characteristics
  – Characteristics of MedDRA that Impact Data Retrieval and Analysis
  – MedDRA Versioning

• General Queries and Retrieval
• Standardised MedDRA Queries
• Customised Searches
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
Exercises
### What’s the Frequency? Condition vs. Test Result

<table>
<thead>
<tr>
<th>Reported event (% subjects)</th>
<th>Other terminology</th>
<th>MedDRA Version 18.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coded term (% subjects)</td>
<td>Body System/SOC (% subjects)</td>
</tr>
<tr>
<td>Hyperglycaemia (4.1)</td>
<td>Hyperglycaemia (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 glucoses (0.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# What’s the Problem with My Drug?

## Adverse Event (MedDRA v18.0)

<table>
<thead>
<tr>
<th>Adverse Event</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 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.
### Adverse Event (MedDRA v18.0)

<table>
<thead>
<tr>
<th>Adverse Event</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.
### Using Grouping Terms

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v18.0)</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
What Has Happened to My Data?

<table>
<thead>
<tr>
<th>MedDRA Version 17.1</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Skin and subcutaneous tissue disorders</td>
<td>20</td>
</tr>
<tr>
<td>PT Dry gangrene</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MedDRA Version 18.0</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Skin and subcutaneous tissue disorders</td>
<td>0</td>
</tr>
<tr>
<td>SOC Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>PT Dry gangrene</td>
<td>20</td>
</tr>
</tbody>
</table>
• Use Internationally Agreed Order of SOCs when applicable, e.g., the EU Summary of Product Characteristics (SPC) guideline
  – See MedDRA Introductory Guide, ASCII files
• Consider use of HLTs and HLGTs
• Line listings, tables, graphs
• Benefits - Broad overview, PTs displayed only once
• Limitations - Incomplete groupings due to SOC allocation rules, lengthy output
Primary SOC Graphical Display Example

<table>
<thead>
<tr>
<th>SOC</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear</td>
<td>1.9</td>
</tr>
<tr>
<td>Eye</td>
<td>1.3</td>
</tr>
<tr>
<td>Gastr</td>
<td>13.2</td>
</tr>
<tr>
<td>Genrl</td>
<td>3.7</td>
</tr>
<tr>
<td>ImmUN</td>
<td>0.3</td>
</tr>
<tr>
<td>Infec</td>
<td>12.8</td>
</tr>
<tr>
<td>Inj&amp;P</td>
<td>1.5</td>
</tr>
<tr>
<td>Inv</td>
<td>3.0</td>
</tr>
<tr>
<td>Metab</td>
<td>1.5</td>
</tr>
<tr>
<td>Musc</td>
<td>1.9</td>
</tr>
<tr>
<td>Nerv</td>
<td>10.7</td>
</tr>
<tr>
<td>Preg</td>
<td>0.3</td>
</tr>
<tr>
<td>Psych</td>
<td>0.6</td>
</tr>
<tr>
<td>Repro</td>
<td>1.5</td>
</tr>
<tr>
<td>Resp</td>
<td>8.8</td>
</tr>
<tr>
<td>Skin</td>
<td>3.0</td>
</tr>
<tr>
<td>Surg</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Relative frequency of any event (%)
Focused Searches

Useful when further investigating concepts of interest

- Secondary SOC assignments
  - Programming required if database does not allow automated output by secondary SOC
  - Benefits - more comprehensive view of medically related events
  - Limitations - display by primary and secondary SOC could lead to double counting

- Grouping terms (HLGT/HLT)

- SMQ

- Customized search
  - Modified SMQ
  - Ad hoc query
Exercise
### How Many Cases of Autoimmune Diseases?

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v18.0)</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOC Blood and lymphatic system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>PT Anaemia</td>
<td>5</td>
</tr>
<tr>
<td>PT Autoimmune neutropenia</td>
<td>5</td>
</tr>
<tr>
<td>PT Evans syndrome</td>
<td>1</td>
</tr>
<tr>
<td>PT Platelet anisocytosis</td>
<td>1</td>
</tr>
<tr>
<td>PT Platelet toxicity</td>
<td>2</td>
</tr>
<tr>
<td><strong>SOC Cardiac disorders</strong></td>
<td></td>
</tr>
<tr>
<td>PT Autoimmune myocarditis</td>
<td>4</td>
</tr>
<tr>
<td>PT Myocardial infarction</td>
<td>1</td>
</tr>
<tr>
<td>PT Myocarditis</td>
<td>2</td>
</tr>
</tbody>
</table>
How Many Cases of Autoimmune Diseases? (cont)

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v18.0)</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOC Endocrine disorders</strong></td>
<td></td>
</tr>
<tr>
<td>PT Polyglandular autoimmune syndrome type I</td>
<td>2</td>
</tr>
<tr>
<td>PT Thyroid disorder</td>
<td>1</td>
</tr>
<tr>
<td><strong>SOC Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td>PT Birdshot chorioretinopathy</td>
<td>2</td>
</tr>
<tr>
<td>PT Autoimmune uveitis</td>
<td>3</td>
</tr>
<tr>
<td><strong>SOC Hepatobiliary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>PT Biliary cirrhosis primary</td>
<td>3</td>
</tr>
<tr>
<td>PT Hepatitis toxic</td>
<td>1</td>
</tr>
<tr>
<td>PT Hepatocellular injury</td>
<td>1</td>
</tr>
</tbody>
</table>
### How Many Cases of Autoimmune Diseases? (cont)

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v18.0)</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Immune system disorders</td>
<td></td>
</tr>
<tr>
<td>PT Autoimmune disorder</td>
<td>4</td>
</tr>
<tr>
<td>SOC Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>PT Arthritis</td>
<td>1</td>
</tr>
<tr>
<td>PT Muscular weakness</td>
<td>2</td>
</tr>
<tr>
<td>PT Polymyalgia rheumatica</td>
<td>1</td>
</tr>
<tr>
<td>PT Rheumatoid arthritis</td>
<td>3</td>
</tr>
<tr>
<td>SOC Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>PT Alopecia</td>
<td>1</td>
</tr>
<tr>
<td>PT Skin haemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>PT Vitiligo</td>
<td>2</td>
</tr>
</tbody>
</table>
### Secondary SOC Analysis and Use of a Grouping Term

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v18.0)</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Immune system disorders</td>
<td></td>
</tr>
<tr>
<td>HLGT Autoimmune disorders</td>
<td>30</td>
</tr>
<tr>
<td>PT Autoimmune disorder</td>
<td>4</td>
</tr>
<tr>
<td>PT Autoimmune myocarditis</td>
<td>4</td>
</tr>
<tr>
<td>PT Autoimmune neutropenia</td>
<td>5</td>
</tr>
<tr>
<td>PT Biliary cirrhosis primary</td>
<td>3</td>
</tr>
<tr>
<td>PT Birdshot chorioretinopathy</td>
<td>2</td>
</tr>
<tr>
<td>PT Evans syndrome</td>
<td>1</td>
</tr>
<tr>
<td>PT Polyglandular autoimmune syndrome type I</td>
<td>2</td>
</tr>
<tr>
<td>PT Polymyalgia rheumatica</td>
<td>1</td>
</tr>
<tr>
<td>PT Rheumatoid arthritis</td>
<td>3</td>
</tr>
<tr>
<td>PT Autoimmune uveitis</td>
<td>3</td>
</tr>
<tr>
<td>PT Vitiligo</td>
<td>2</td>
</tr>
</tbody>
</table>
Use of MedDRA at EMA

### MedDRA embedded

**Acknowledgement:** Dr. Aniello Santoro, EMA
Use of MedDRA at EMA: Impact of Multi-axiality

Signal: Cardiac toxicity – Drug A

- Analysis at SOC Cardiac disorders level
  - Primary SOC assignments:
    - Total number of cases: 122
- If secondary SOC assignments included:
  - Total number of cases: 249
  - 14 additional PTs
  - Assess if additional PTs (cases) are of relevance

Acknowledgement: Dr. Aniello Santoro, EMA
Developing Queries Using MedDRA
What is a Query?

Clinical Trial Database
Safety Database

Case
LLT1
LLT2
LLT3

Query
SMQ
PT
LLT
LLT
LLT 1
PT
LLT
LLT
LLT

"Hit"
Query Strategy Tips

- Define the condition
- Develop inclusion/exclusion criteria
- Good browser is key component
- Search “non multi-axial” and “other/support” SOCs
- Search a term’s “neighbors”, including secondary locations
- Use grouping terms where applicable
- Avoid using LLTs (Exception: species information at LLT level in SOC *Infections and infestations*)
- Store for future use
- Review for impact of new MedDRA versions
Complete the Circle
(Connect the DOTSSSS!)
Building a Query Exercise
Standardised MedDRA Queries (SMQs)
Standardised MedDRA Queries (SMQs)

- Result of cooperative effort between CIOMS (Council for International Organizations of Medical Sciences) 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
SMQs in Production - Examples

- As of Version 18.0, a total of 98 in production
  - Agranulocytosis
  - Anaphylactic reaction
  - Cerebrovascular disorders
  - Convulsions
  - Depression and suicide/self-injury
  - Hepatic disorders
  - Hypersensitivity
  - Ischaemic heart disease
  - Lack of efficacy/effect
  - Osteonecrosis
  - Peripheral neuropathy
  - Pregnancy and neonatal topics
  - Pseudomembranous colitis
  - Rhabdomyolysis/myopathy
  - Severe cutaneous adverse reactions
  - Systemic lupus erythematosus
SMQ Lactic acidosis

Definition
Lactic acidosis is a form of high anion gap metabolic acidosis - Intrinsic cardiac contractility may be depressed, but inotropic function can be normal because of catecholamine release. Peripheral arterial vasodilatation and central vasoconstriction can be present - Central nervous system function is depressed, with headache, lethargy, stupor, and, in some cases, even coma. Glucose intolerance 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 dyspnea, stupor or coma, vomiting, drowsiness, 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 confirmed 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 verbatims to terms of an older terminology or other coding conventions).
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)
• ICSR coding at LLT level, analysis at PT level (medical concept):
  ✓ It may be important to conduct analysis at higher level of hierarchy: SOC, HLGT, HLT
    - When doing so, impact of axial and non multi-axial SOCs needs to be taken into
      account: relevant PTs in more than 1 SOC
  ✓ It may be important to conduct analysis at SMQ level to maximise likelihood
      that all terms related to a specific medical condition of interest are identified

• Challenge: strike the correct balance
  ✓ Too narrowly focused search (specificity): exclude events of potential relevance
  ✓ Too broad search (sensitivity): difficult to identify a trend or signal that may require further analysis (incl. case review)
**Signal of Lactic Acidosis - PT vs. SMQ**

<table>
<thead>
<tr>
<th>Active Substances</th>
<th>SOC</th>
<th>HLGTs</th>
<th>HLTS</th>
<th>SMQ Broad</th>
<th>SMQ Narrow</th>
<th>PTs</th>
<th>Tot EV</th>
<th>PRR (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug A</td>
<td>Metab</td>
<td>Acid-Base Disorders</td>
<td>Metabolic Acidoses (Excl Diabetic Acidoses)</td>
<td>Hyperglyc/New Onset Diabetic Acidosis</td>
<td>Lactic Acidosis</td>
<td>Lactic Acidosis</td>
<td>63</td>
<td>13.74</td>
</tr>
</tbody>
</table>

**SMQ Lactic acidosis (Broad search)**

<table>
<thead>
<tr>
<th>PT</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidosis</td>
<td>2</td>
</tr>
<tr>
<td>Anion gap increased</td>
<td>1</td>
</tr>
<tr>
<td>Blood bicarbonate abnormal</td>
<td>1</td>
</tr>
<tr>
<td>Blood bicarbonate decreased</td>
<td>6</td>
</tr>
<tr>
<td>Blood gases abnormal</td>
<td>1</td>
</tr>
<tr>
<td>Blood lactic acid increased</td>
<td>27</td>
</tr>
<tr>
<td>Hyperlactacidaemia</td>
<td>22</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>63</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>18</td>
</tr>
<tr>
<td>PCO2 decreased</td>
<td>1</td>
</tr>
</tbody>
</table>

**Broad search** of SMQ identifies additional ICSRs with related **signs** and symptoms where no specific diagnosis is made. These would be missed if search only conducted with PT **Lactic acidosis**.

Acknowledgement: Dr. Aniello Santoro, EMA
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
### EMA: Use of a Modified MedDRA Query Based on an SMQ

<table>
<thead>
<tr>
<th>PT</th>
<th>N. ICSRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac arrest</td>
<td>275</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>4</td>
</tr>
<tr>
<td>Cardio-respiratory arrest</td>
<td>185</td>
</tr>
<tr>
<td>Electrocardiogram QT interval abnormal</td>
<td>1</td>
</tr>
<tr>
<td>Electrocardiogram QT prolonged</td>
<td>274</td>
</tr>
<tr>
<td>Electrocardiogram repolarisation abnormality</td>
<td>5</td>
</tr>
<tr>
<td>Electrocardiogram U-wave abnormality</td>
<td>1</td>
</tr>
<tr>
<td>Long QT syndrome</td>
<td>14</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>490</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>97</td>
</tr>
<tr>
<td>Sudden death</td>
<td>140</td>
</tr>
<tr>
<td>Syncope</td>
<td>302</td>
</tr>
<tr>
<td>Torsade de pointes</td>
<td>36</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>8</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>37</td>
</tr>
<tr>
<td>Ventricular tachyarrhythmia</td>
<td>1</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>46</td>
</tr>
</tbody>
</table>

- **Signal of QT prolongation with Drug A**: SMQ *Torsade de pointes/QT prolongation*
- **Well-known association of Drug A with hypotension and fainting**
- **May be sensible to modify SMQ and exclude PTs *Loss of consciousness* and *Syncope*, to reduce noise in data retrieval**
- **Data retrieval strategy needs to be documented**

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When an SMQ is modified, it is called modified MedDRA query based on an SMQ

Acknowledgement: Dr. Aniello Santoro, EMA
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
• In this session, we:
  – Reviewed MedDRA’s scope, structure, and characteristics
  – Reviewed key sections of the *MedDRA Data Retrieval and Presentation: Points to Consider* document
  – Reviewed Standardised MedDRA Queries
  – Discussed customized searches
  – Learnt how to speak to MedDRA
Questions?

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