MedDRA: Safety Data Analysis and SMQs

MedDRA was developed under the auspices of the International Council for Harmonisation 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 six ICH parties (EU, EFPIA, MHLW, JPMA, FDA, PhRMA), the Medicines and Healthcare products Regulatory Agency (MHRA) of the UK, Health Canada, and the WHO (as Observer).
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Course Overview

• In this course, we will cover:
  – MedDRA overview
  – MedDRA Data Retrieval and Presentation: Points to Consider document
  – Developing queries using MedDRA
  – Examples and hands-on exercises
Course Overview (cont)

In this course, we will cover (cont):
- SMQ background and definition
- SMQs development status
- SMQ data characteristics
- SMQ testing and production maintenance
- SMQ versioning
- SMQ applications
- Customized searches

MedDRA Overview
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.

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
Marketing Applications
Publications
Prescribing Information
Advertising
Regulatory Status

• FDA, US
  – Used in several databases including FAERS (drugs and biologics), VAERS (vaccines), and CAERS (foods, dietary supplements, cosmetics)
  – Electronic submission required for study data and postmarketing reports (uses ICH standards)
• MHLW/PMDA, Japan
  – Mandatory use in electronic reporting

Regulatory Status (cont)

• EC, Europe
  – 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
Regulatory Status (cont)

• EC, Europe (cont)
  – Used throughout Summary of Product Characteristics (labeling)
  – Pharmacovigilance legislation covers suspected adverse reactions from:
    • Use inside and outside terms of marketing authorization
    • Overdose, misuse, abuse, and medication errors
    • Occupational exposures

Regulatory Status (cont)

• ICH M4E Guideline on Common Technical Document
  – Recommended in adverse event summary tables

• Health Canada, Canada
  – Used in Canada Vigilance database
  – Recommended terminology for adverse reaction reporting and Product Monograph (labeling)
  – Electronic reporting requires current version of MedDRA
Regulatory Status (cont)

- CFDA, China
  - Implementing ICH standards
    - M4 Common Technical Document (February 2018)
    - Clinical trial SUSARs use electronic reporting [E2B(R3)] and MedDRA (May 2018)
    - Postmarketing ICSRs may use E2B(R3) and MedDRA (July 2019)

Scope of MedDRA

- Medical conditions
- Indications
- Investigations (tests, results)
- Medical and surgical procedures
- Medical, social, family history
- Medication errors
- Product quality issues
- Device-related issues
- Product use issues
- Pharmacogenetic terms
- Toxicologic issues
- Standardized queries
- Not a drug dictionary
- Not an equipment, device, diagnostic product dictionary
- Patient demographic terms
- Clinical trial study design terms
- Frequency qualifiers
- Numerical values for results
- Severity descriptors
MedDRA Structure

System Organ Class (SOC) (27)
- High Level Group Term (HLGT) (337)
- High Level Term (HLT) (1,737)
- Preferred Term (PT) (23,088)
- Lowest Level Term (LLT) (78,808)

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
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
- 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
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*
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

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/](https://tools.meddra.org/wbb/)

- Features
  - Both require MedDRA ID and password
  - View/search MedDRA and SMQs
  - Support for all MedDRA languages
  - Language specific interface
  - Ability to export search results and Research Bin to local file system
Browser Demonstration
SOC View

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

MedDRA Data Retrieval and Presentation: PTC (cont)

- Developed by a working group of the ICH Management Committee
- Updated twice yearly with each MedDRA release
- Available on MedDRA and JMO websites
  - English and Japanese
  - Word (“clean” and “redlined”), PDF, HTML formats
  - “Redlined” document identifies changes made from previous to current release of document
ICH M1 Points to Consider
Working Group (PtC WG)

- Regulators and industry from EU, US, and Japan
  - Health Canada
  - MSSO
  - JMO
  - WHO (Observer)

New members 2017/2018
- MFDS, Republic of Korea
- ANVISA, Brazil
- CFDA, China

Meeting 13-15 November 2017, Geneva, Switzerland

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
Quality of Source Data

• High quality data output is dependent on maintaining quality of original information reported by using consistent and appropriate term selection (Refer to MedDRA Term Selection: Points to Consider document)

• Method of conversion of data into MedDRA might impact retrieval and presentation - legacy data conversion using verbatims or coded terms

Documentation of Data Retrieval and Presentation Practices

• Organisation-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 customised 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

Organisation-Specific Data Characteristics

- Database structure (storage and use of hierarchy)
- Data storage (level of term, synonym/reported term)
- Data conversion (if applicable)
- Coding practices over time
- Limitations/restrictions (inability to view secondary SOCs)
- Term selection principles
  - More than one term selected increases counts
  - Diagnosis term only selected reduces counts
Impact of MedDRA’s Characteristics – Grouping Terms

- HLG Ts and HLTs provide clinically relevant groupings
  - HLT 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
<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>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.

<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>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 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

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*)
Multi-Axiality (cont)

• Main presentation is by Primary SOC
• Secondary SOCs used for alternate views and presentation of data

Primary SOC Analysis – SOC Infections and infestations

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v19.0)</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 v19.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOC Respiratory, thoracic and mediastinal disorders</strong></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><strong>SOC Infections and infestations</strong></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.

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### Secondary SOC Analysis – SOC Infections and infestations (cont)

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v19.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOC Renal and urinary disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT Urinary tract infection</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>SOC Ear and labyrinth disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT Ear infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>SOC Gastrointestinal disorders</strong></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
  - MedDRA Version Analysis Tool (MVAT)
- Terms used for queries should be in same version as data being queried

MedDRA Versioning (cont): Effect of PT Demotion

<table>
<thead>
<tr>
<th>MedDRA Version 18.1</th>
<th>Number of Events at PT Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic pain (PT)</td>
<td>15</td>
</tr>
<tr>
<td>Cancer pain</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MedDRA Version 19.0</th>
<th>Number of Events at PT Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic pain (no longer a PT)</td>
<td>0</td>
</tr>
<tr>
<td>Cancer pain</td>
<td>20</td>
</tr>
</tbody>
</table>
MedDRA Versioning (cont): Effect of Primary SOC Change

<table>
<thead>
<tr>
<th>MedDRA Version 18.0</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>PT Intra-abdominal haematoma</td>
<td>20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MedDRA Version 18.1</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Vascular disorders</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>SOC Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>PT Intra-abdominal haematoma</td>
<td>20</td>
</tr>
</tbody>
</table>

MedDRA Version Analysis Tool (MVAT)

- Web-based (https://tools.meddra.org/mvat)
- Free to all users
- Features
  - Version Report Generator (produces exportable report comparing any two versions)
  - Data Impact Report (identifies changes to a specific set of MedDRA terms or codes uploaded to MVAT)
  - Search Term Change (identifies changes to a single MedDRA term or code)
- User interface and report output available in all MedDRA languages
### 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>
### Adverse Event (MedDRA v18.0)

<table>
<thead>
<tr>
<th>SOC Endocrine disorders</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT Polyglandular autoimmune syndrome type I</td>
<td>2</td>
</tr>
<tr>
<td>PT Thyroid disorder</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SOC Eye disorders</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT Birdshot chorioretinopathy</td>
<td>2</td>
</tr>
<tr>
<td>PT Autoimmune uveitis</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SOC Hepatobiliary disorders</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<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>

<table>
<thead>
<tr>
<th>SOC Immune system disorders</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT Autoimmune disorder</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SOC Musculoskeletal and connective tissue disorders</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT Arthritis</td>
<td>1</td>
</tr>
<tr>
<td>PT Muscular weakness</td>
<td>2</td>
</tr>
<tr>
<td>PT Polymyalgia rheumatic</td>
<td>1</td>
</tr>
<tr>
<td>PT Rheumatoid arthritis</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SOC Skin and subcutaneous tissue disorders</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<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

#### Adverse Event (MedDRA v18.0) | No. of cases
--- | ---
SOC Immune system disorders | 
HLGT Autoimmune disorders | 30
PT Autoimmune disorder | 4
PT Autoimmune myocarditis | 4
PT Autoimmune neutropenia | 5
PT Biliary cirrhosis primary | 3
PT Birdshot chorioretinopathy | 2
PT Evans syndrome | 1
PT Polyglandular autoimmune syndrome type I | 2
PT Polymyalgia rheumatica | 1
PT Rheumatoid arthritis | 3
PT Autoimmune uveitis | 3
PT Vitiligo | 2

---

### General Queries and Retrieval

- Document search strategy
- Highlight overall distribution of ADRs/AEs
- Identify areas for in-depth analysis (focused searches)
Overview by Primary SOC

- Use Internationally Agreed Order of SOCs when applicable, e.g., the EU 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
# Primary SOC Output Listing Example

<table>
<thead>
<tr>
<th>SOC Nervous system disorders</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLGT Mental impairment disorders</td>
<td></td>
</tr>
<tr>
<td>HLT Mental impairment (excl dementia and memory loss)</td>
<td>1</td>
</tr>
<tr>
<td>PT Disturbance in attention</td>
<td></td>
</tr>
<tr>
<td>HLGT Movement disorders (incl Parkinsonism)</td>
<td></td>
</tr>
<tr>
<td>HLT Dyskinesias and movement disorders NEC</td>
<td>2</td>
</tr>
<tr>
<td>PT Psychomotor hyperactivity</td>
<td></td>
</tr>
<tr>
<td>HLT Tremor (excl congenital)</td>
<td>3</td>
</tr>
<tr>
<td>PT Tremor</td>
<td></td>
</tr>
<tr>
<td>HLGT Neurological disorders NEC</td>
<td></td>
</tr>
<tr>
<td>HLT Disturbances in consciousness NEC</td>
<td>1</td>
</tr>
<tr>
<td>PT Somnolence</td>
<td></td>
</tr>
<tr>
<td>HLT Neurological signs and symptoms NEC</td>
<td></td>
</tr>
<tr>
<td>PT Dizziness</td>
<td>1</td>
</tr>
</tbody>
</table>

---

# 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
Secondary SOC Output
Listing Example

Programming a List of PTs in Primary and Secondary SOC Locations

SOC Eye disorders
HLGT Vision disorders
  HLT Visual pathway disorders
    PT Chiasma syndrome
    PT Optic nerve compression (primary SOC location)
    PT Optic nerve disorder (primary SOC location)
    PT Optic neuropathy (primary SOC location)
    PT Toxic optic neuropathy (primary SOC location)
    PT Visual cortex atrophy
    PT Visual pathway disorder

3 of 7 PTs are primary to SOC Nervous system disorders

Example as of MedDRA Version 19.0

Use of MedDRA at FDA

Acknowledgement: Dr. Chuck Cooper, Office of Translational Sciences, CDER, FDA
Use of MedDRA at EMA

MedDRA embedded

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

Higher level of hierarchy

SMQs

Screening at PT

MedDRA

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
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 DOTSSS!)

- Diagnosis/disease terms
- Support SOCs (Other...)
- Signs & symptoms
- Social circumstances
- Operations (Surgical and medical procedures)
- Tests (Investigations)
Example and Hands-on Exercises

Example Cardiac Arrhythmias
Example – Cardiac Arrhythmias

- Obvious starting point – HLGT Cardiac arrhythmias ("Top-down" search)
- Also use "Arrhythmia" terms as starting point of "Bottom-up" search
- What about non-multi-axial SOCs?

Example – Cardiac Arrhythmias (cont)

- SOC *Investigations*
  - PTs subordinate to HLT *ECG investigations* and HLT *Heart rate and pulse investigations* should be reviewed
    - Example: PT *Heart rate irregular*
**Example – Cardiac Arrhythmias (cont)**

- **SOC Surgical and medical procedures**
  Important to review:
  - PTs subordinate to HLT *Cardiac device therapeutic procedures*:
    - Example: PT *Implantable defibrillator insertion*
  - PTs subordinate to HLT *Cardiac therapeutic procedures NEC*:
    - Example: PT *Cardioversion*

*Note: Pacemaker and other cardiac therapeutic procedure terms were not included in SMQ *Cardiac arrhythmias*.

---

**Example – Cardiac Arrhythmias (cont)**

- Because arrhythmias may produce various signs and symptoms, you may wish to review PTs subordinate to the following HLTs:
  - HLT *Disturbances in consciousness NEC*
  - HLT *Neurological signs and symptoms NEC*
  - HLT *Cardiac disorders NEC*
  - HLT *Cardiac signs and symptoms NEC*
  - HLT *Dyspnoeas*
Example – Cardiac Arrhythmias (cont)

- Lastly...
  - PTs subordinate to HLT *Death and sudden death* (under SOC *General disorders and administration site conditions*) should be reviewed
  - Example: PT *Cardiac death*
Exercise

Topic: Cardiac failure
• Build a query with a set of PTs relevant to this condition
• Consider:
  – Diagnosis terms
  – Signs and symptoms
  – Investigations
  – Surgical and medical procedures
  – Other….
• Can you identify cases of interest in a dataset?

Query Development
Exercises

Alcoholic liver disease  Falls
Hypoglycemia          Obesity
Depression             Prostate cancer
Osteonecrosis          Parkinsonism
Abuse liability        Hearing loss

• Before starting
  – Develop a definition of the condition
  – Develop inclusion/exclusion criteria (etiologies and risk factors are typically excluded)
• Note the main SOCs, HLGTs and HLTs used in your query, as well as examples of specific PTs
Developing Queries – Lessons Learned

- MedDRA is a potentially powerful tool for data retrieval, BUT it requires:
  - Solid medical knowledge
  - Solid MedDRA knowledge
- Size and complexity of MedDRA overcome lack of specificity of other terminologies, but may require a more “creative” approach to data retrieval
- WELL WORTH THE EFFORT to develop, share, and store in-house queries

Standardised MedDRA Queries (SMQs)
Standardised MedDRA Queries (SMQs)

- Collaboration between CIOMS (Council for International Organizations of Medical Sciences) and ICH (MSSO)
- Groupings of terms from one or more MedDRA SOCs 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

SMQ Development and Oversight

- CIOMS SMQ Working Group
  - Senior scientists (as members or observers) from several drug regulatory authorities and other organizations
  - Senior scientists from many pharmaceutical companies
  - MSSO and JMO
- ICH Advisory Panel
  - Representatives from industry and regulators from the three ICH regions, MHRA, Health Canada and WHO (as an observer)
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

SMQs in Production - Examples

• As of Version 21.0, a total of 103 level 1 SMQs in production

- Agranulocytosis
- Anaphylactic reaction
- Cerebrovascular disorders
- Convulsions
- 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
- Systemic lupus erythematosus
SMQ Data Characteristics

- MedDRA term inclusion
- SMQ naming convention
- Broad/narrow
- Algorithms
- Hierarchy
- SMQ status/term status within an SMQ
- Term versioning in an SMQ
- Text data included in SMQ
MedDRA Term Inclusion

- SMQs are constructed at MedDRA PT level
- LLTs that are subordinate to an included PT are also included

SMQ Naming Convention

- SMQ titles have “(SMQ)” appended to the end to ensure there is no name conflict with existing MedDRA terms
- E.g., “Agranulocytosis (SMQ)”
- Each SMQ has a unique 8-digit code starting with “2”
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

Narrow vs. Broad Example

SMQ Lactic acidosis

Definition
Lactic acidosis is a form of high anion gap metabolic acidosis. Intrinsically, cardiac contractility may be depressed, but nototropism function can be normal because of catecholamine release. Peripheral arterial vasodilation 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 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 variables to 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
    - Dialysis membrane reaction
    - Kounis syndrome
    - Procedural shock
    - Shock
    - Shock symptom
    - 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/Ur ticaria, etc.</th>
<th>Category D – Cardiovascular/Hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory failure</td>
<td>Allergic oedema</td>
<td>Blood pressure decreased</td>
</tr>
<tr>
<td>Asthma</td>
<td>Angioedema</td>
<td>Blood pressure diastolic decreased</td>
</tr>
<tr>
<td>Bronchial oedema</td>
<td>Erythema</td>
<td>Blood pressure 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 may develop as 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

SMQ Status/Term Status

- Each SMQ has a status (Active/Inactive)
- Similar in concept to MedDRA currency
- Terms assigned to an SMQ also have a status flag
  - Once a term is added to an SMQ, it will always be included in the SMQ but the status may be inactive
Term Versioning in an SMQ

- Each term included in an SMQ has version fields
  - Term addition – version of MedDRA when the term was added to the SMQ
  - Term last modified – version of MedDRA when a change was made to the term in the SMQ (e.g. status, scope)
- Allows user to know the maintenance history of the SMQ

Text Data Included in SMQ

- 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 use of SMQs
  - Details of individual SMQs
  - Notes for implementation and/or expectation of results
- Production SMQ Spreadsheet
  - SMQs and included terms, SMQ summary
- Original CIOMS Working Group documentation

Browser Demonstration
SMQ View
How to “Run” SMQs

- IT perspective of SMQs = stored queries
- Code at LLT level; most organizations store coded data as LLTs
- SMQ ASCII files include PTs and LLTs
- Load SMQs into a query tool; run query against coded MedDRA terms in safety or clinical trial database for “Hits”
- Use SMQ options, if applicable
  - Narrow/broad search
  - Algorithms
  - Hierarchy

How to “Run” SMQs (cont)
Exercise

Topic: Acute renal failure

• Run SMQ *Acute renal failure* (broad search)
• Can you identify cases of interest in a dataset?

---

SMQ Narrow Search Results Example

Asthma/bronchospasm (SMQ) Cases – Narrow Search
(since 1-JAN-2008)

<table>
<thead>
<tr>
<th>ID</th>
<th>MedDRA_PT</th>
<th>REPORT_VERBATIM</th>
<th>DATE_CREATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>045</td>
<td>Asthma</td>
<td>Asthma attack</td>
<td>01-APR-2008</td>
</tr>
<tr>
<td>053</td>
<td>Asthma</td>
<td>Severe asthma</td>
<td>10-JUN-2008</td>
</tr>
<tr>
<td>060</td>
<td>Asthma exercise induced</td>
<td>Asthma when exercising</td>
<td>30-MAY-2008</td>
</tr>
<tr>
<td>091</td>
<td>Bronchospasm</td>
<td>Spasms, bronchial</td>
<td>12-AUG-2008</td>
</tr>
<tr>
<td>074</td>
<td>Bronchospasm</td>
<td>Bronchoconstriction</td>
<td>03-JUL-2008</td>
</tr>
<tr>
<td>100</td>
<td>Bronchial hyperreactivity</td>
<td>Airways hyperreactive</td>
<td>20-SEP-2008</td>
</tr>
<tr>
<td>069</td>
<td>Bronchial hyperreactivity</td>
<td>Reactive airways disease</td>
<td>21-JUN-2008</td>
</tr>
</tbody>
</table>
SMQ Broad Search Results Example

Asthma/bronchospasm (SMQ) Cases – Broad Search
(since 1-JAN-2008)

<table>
<thead>
<tr>
<th>ID</th>
<th>MedDRA_PT</th>
<th>REPORT_VERBATIM</th>
<th>DATE_CREATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>023</td>
<td>Allergic respiratory disease</td>
<td>Respiratory (allergy) disorder</td>
<td>18-FEB-2008</td>
</tr>
<tr>
<td>045</td>
<td>Asthma</td>
<td>Asthma attack</td>
<td>01-APR-2008</td>
</tr>
<tr>
<td>063</td>
<td>Asthma</td>
<td>Severe asthma</td>
<td>10-JUN-2008</td>
</tr>
<tr>
<td>060</td>
<td>Asthma exercise induced</td>
<td>Asthma when exercising</td>
<td>30-MAY-2008</td>
</tr>
<tr>
<td>016</td>
<td>Bronchial obstruction</td>
<td>Bronchial obstruct.</td>
<td>16-JAN-2008</td>
</tr>
<tr>
<td>039</td>
<td>Bronchial obstruction</td>
<td>Bronchus obstruction</td>
<td>14-MAR-2008</td>
</tr>
<tr>
<td>091</td>
<td>Bronchospasm</td>
<td>Spasms, bronchial</td>
<td>12-AUG-2008</td>
</tr>
<tr>
<td>074</td>
<td>Bronchospasm</td>
<td>Bronchoconstriction</td>
<td>03-JUL-2008</td>
</tr>
<tr>
<td>100</td>
<td>Bronchial hyperreactivity</td>
<td>Airways hyperreactive</td>
<td>20-SEP-2008</td>
</tr>
<tr>
<td>099</td>
<td>Bronchial hyperreactivity</td>
<td>Reactive Airways disease</td>
<td>21-JUN-2008</td>
</tr>
<tr>
<td>088</td>
<td>Obstructive Airways disorder</td>
<td>Obstructive Airways disorder</td>
<td>29-JUL-2008</td>
</tr>
<tr>
<td>049</td>
<td>Obstructive Airways disorder</td>
<td>Obstructed Airways dis.</td>
<td>20-APR-2008</td>
</tr>
<tr>
<td>022</td>
<td>Wheezing</td>
<td>Wheeze</td>
<td>16-FEB-2008</td>
</tr>
<tr>
<td>031</td>
<td>Wheezing</td>
<td>Wheezeles</td>
<td>02-MAR-2008</td>
</tr>
<tr>
<td>106</td>
<td>Wheezing</td>
<td>Wheezing</td>
<td>28-SEP-2008</td>
</tr>
<tr>
<td>046</td>
<td>Wheezing</td>
<td>Wheezing (acute)</td>
<td>06-APR-2008</td>
</tr>
</tbody>
</table>

SMQ Testing, Production Maintenance, and Versioning
SMQ Development Summary

- Pre-release testing by CIOMS Working Group members
  - Typically, at least one company and one regulator database
  - Cases retrieved reviewed for relevance
  - Fine-tuning of SMQ may require several iterations
  - Reviewed and approved by CIOMS WG
- Production Phase: continue to be fine-tuned through the MSSO maintenance process

SMQ Production Maintenance

- SMQ change requests
  - Considered simple change requests, part of 100 CRs/month allowed per subscriber
  - Final disposition not time limited
- MSSO reviews all new terms for inclusion in existing SMQs and reviews impact of term demotions, moves, etc. on SMQs
- CIOMS IWG reviews all SMQ change requests 18-24 months post-production
SMQ Versioning

- It is recommended that organizations use 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)

- Example of PT added to SMQs in MedDRA Version 19.0:
  - PT *End stage renal disease* in SMQ *Chronic kidney disease*
- Using version 18.1 SMQs which do not contain these PTs would fail to identify cases coded to these terms in a database using MedDRA Version 19.0
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)
Use of SMQs at FDA

Acknowledgement: Dr. Chuck Cooper, Office of Translational Sciences, CDER, FDA
Use of SMQs at FDA (cont)

Acknowledgement: Dr. Chuck Cooper, Office of Translational Sciences, CDER, FDA

Use of SMQs at FDA – Reviewing Prescribing Information

- **Proposed Prescribing Information:**
- **Warnings & Precautions:**
  - Dizziness/Somnolence
  - Withdrawal of Antiepileptic Drugs
  - Suicidal Behavior and Ideation (class labeling)

<table>
<thead>
<tr>
<th>SMQ (Narrow Search)</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Hostility/aggression</td>
<td>4.4</td>
</tr>
<tr>
<td>(2) Vestibular disorders</td>
<td>4.258</td>
</tr>
<tr>
<td>(1) Hearing and vestibular disorders</td>
<td>4.088</td>
</tr>
<tr>
<td>(1) Hyponatraemia/SIADH</td>
<td>3.832</td>
</tr>
<tr>
<td>(2) Hearing impairment</td>
<td>3.832</td>
</tr>
<tr>
<td>(1) Dyslipidaemia *</td>
<td>2.555</td>
</tr>
<tr>
<td>(1) Biliary disorders</td>
<td>2.135</td>
</tr>
<tr>
<td>(2) Functional, inflammatory and gallstone related biliary disorders</td>
<td>2.135</td>
</tr>
</tbody>
</table>

- **Final Prescribing Information**
- **Boxed Warning:**
  - Serious Psychiatric and Behavioral Reactions

- **Warnings & Precautions:**
  - Falls
  - Dizziness & somnolence
  - Withdrawal of Antiepileptic Drugs
  - Suicidal Behavior and Ideation (class labeling)

Acknowledgement: Dr. Christopher Breder, Office of New Drugs, CDER, FDA
EMA: Signal Detection Analysis

- 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 Angioedema - PT vs. SMQ

<table>
<thead>
<tr>
<th>Active Substance</th>
<th>SOCs</th>
<th>HLGTs</th>
<th>HLTs</th>
<th>SMQ Broad</th>
<th>SMQ Narrow</th>
<th>PTs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SMQ Angioedema (Narrow search)

<table>
<thead>
<tr>
<th>PT</th>
<th>N. ICSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioedema</td>
<td>9</td>
</tr>
<tr>
<td>Eye swelling</td>
<td>1</td>
</tr>
<tr>
<td>Face oedema</td>
<td>1</td>
</tr>
<tr>
<td>Laryngeal oedema</td>
<td>1</td>
</tr>
<tr>
<td>Oedema mouth</td>
<td>1</td>
</tr>
<tr>
<td>Pharyngeal oedema</td>
<td>4</td>
</tr>
<tr>
<td>Swelling face</td>
<td>10</td>
</tr>
<tr>
<td>Swollen tongue</td>
<td>6</td>
</tr>
<tr>
<td>Urticaria</td>
<td>4</td>
</tr>
</tbody>
</table>

Acknowledgement: Dr. Aniello Santoro, EMA
Signal of Lactic Acidosis - PT vs. SMQ

**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*.

**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>Hyperlactacidemia</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>

Acknowledgement: Dr. Aniello Santoro, EMA
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
  – For possible safety signal of dementia, user added PT Disturbance in attention to existing SMQ Dementia

• Excluding PTs
  – Antipsychotic (with known association with hypotension and fainting) being evaluated for QT prolongation
  – User excluded PT Syncope from SMQ Torsade de pointes/QT prolongation to prevent “noise” in retrieval
Modified MedDRA Queries Based on SMQs – Examples (cont)

• Changing scope of SMQ term
  – Product being investigated for hyperglycaemia and diabetes mellitus; specific (narrow) search result is required
  – Include PT *Increased insulin requirement* (normally a broad search term) with the narrow search terms in *Hyperglycaemia/new onset diabetes mellitus* (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 abnormal</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>Sudden death</td>
<td>97</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>140</td>
</tr>
<tr>
<td>Torsade de pointes</td>
<td>36</td>
</tr>
<tr>
<td>Ventricular anhyrhythmia</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>

EMA: Use of a Modified MedDRA Query Based on an SMQ

• 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

When an SMQ is modified, it should be called a “Modified MedDRA query based on a 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

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
  - A contraceptive
- Remember to document changes!
Modified SMQs

- Adding PTs
- Excluding PTs
- Changing scope of SMQ term (narrow to broad or vice versa)
- SMQ *Lack of efficacy/effect* often modified based on particular product

Course Summary

- In this course, we:
  - Reviewed MedDRA’s scope, structure, and characteristics
  - Reviewed key sections of the MedDRA Data Retrieval and Presentation: Points to Consider document
  - Reviewed key points for developing queries using MedDRA
  - Worked on MedDRA query exercises
Course Summary (cont)

• In this course, we:
  – Reviewed SMQ background and definition
  – Reviewed the development status of SMQs
  – Discussed SMQ data characteristics
  – Discussed SMQ testing, production maintenance, and versioning
  – Reviewed SMQ applications
  – Discussed customized searches

MSSO Contacts

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