Standardised MedDRA Queries (SMQs)

MedDRA was developed under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The activities of the MedDRA Maintenance and Support Services Organization (MSSO) are overseen by an ICH MedDRA Management Board, 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

- Review MedDRA’s scope, structure, and characteristics
- Review the MedDRA Data Retrieval and Presentation: Points to Consider document
- Review use of MedDRA for developing queries
- Discuss features of Standardised MedDRA Queries (SMQs) including:
  - Background
  - Data characteristics
  - Using SMQs
  - Browser demonstration
- Discuss the creation and use of customized searches
- Conclude with a question and answer session
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.
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
- Pharmacogenetic terms
- Toxicologic issues
- Standardized queries

Not a drug dictionary

Patient demographic terms

Clinical trial study design terms

MedDRA Structure

System Organ Class (SOC) (27)

High Level Group Term (HLGT) (335)

High Level Term (HLT) (1,732)

Preferred Term (PT) (21,920)

Lowest Level Term (LLT) (75,818)
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
MSSO’s MedDRA Browsers

- MedDRA Desktop and Web-Based Browsers
  - View/search MedDRA and SMQs
  - Support for all MedDRA languages

- MedDRA Web-Based Browser (WBB) launched on 1 December 2014
  - [https://tools.meddra.org/wbb/](https://tools.meddra.org/wbb/)
  - MedDRA ID and password needed

- Updated MedDRA Desktop Browser (MDB) launched on 8 October 2015
  - New search features to match WBB
  - Language specific interface
  - Ability to export search results and Research Bin to local file system

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: Points to Consider (cont)

- 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
  - Word ("clean" and "redlined"), PDF, HTML formats
  - “Redlined” document identifies changes made from previous to current release of 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

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 Version Analysis Tool (MVAT)

- Web-based (https://mssotools.com/mvat)
- Free to all users
- Allows for comparison of any two versions
- 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

Developing Queries Using MedDRA
What is a Query?

Clinical Trial Database
Safety Database

Query

Case
LLT1
LLT2
LLT3

"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 SOC s (Other...)**
- **Signs & symptoms**
- **Operations** (Surgical and medical procedures)
- **Tests** (Investigations)
- **Social circumstances**

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

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 19.0, a total of 101 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 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 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
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

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**SMQ Lactic acidosis**

**Definition**

Lactic acidosis is a form of high anion gap metabolic acidosis. Intrinsic cardiac contractility may be depressed, but isotropic function can be normal because of catecholamine release. Peripheral arterial vasoconstriction and central vasoconstriction can 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: a. Symptoms: hyperventilation or dyspnea, stupor or coma, vomiting, diuresis, 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 varbitans to terms of an older terminology or other coding conventions).

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**Narrow vs. Broad Example**

<table>
<thead>
<tr>
<th>Narrow Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood lactic acid increased</td>
</tr>
<tr>
<td>Hyperlactacidaemia</td>
</tr>
<tr>
<td>Lactic acidosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Broad Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid base balance abnormal</td>
</tr>
<tr>
<td>Acidosis</td>
</tr>
<tr>
<td>Anion gap abnormal</td>
</tr>
<tr>
<td>Anion gap increased</td>
</tr>
<tr>
<td>Blood bicarbonate abnormal</td>
</tr>
<tr>
<td>Blood bicarbonate decreased</td>
</tr>
<tr>
<td>Blood gases abnormal</td>
</tr>
<tr>
<td>Blood lactic acid abnormal</td>
</tr>
<tr>
<td>Blood pH abnormal</td>
</tr>
<tr>
<td>Blood pH decreased</td>
</tr>
<tr>
<td>Coma acidotic</td>
</tr>
<tr>
<td>Kussmaul respiration</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>PO2 abnormal</td>
</tr>
<tr>
<td>PO2 decreased</td>
</tr>
<tr>
<td>Urine lactic acid increased</td>
</tr>
</tbody>
</table>
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
    • 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/ Urticaria, 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
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
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)

Clinical Trial Database
Safety Database

Case
LLT 1
LLT 2
LLT 3

"Hit"

SMQ
PT
LLT
LLT
LLT
LLT

Using an SMQ (Acute renal failure)
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 – Reviewing Prescribing Information

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

- 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)

<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>3.632</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>

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)

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

<table>
<thead>
<tr>
<th>Active Substances</th>
<th>SOCs</th>
<th>HILTs</th>
<th>ILTs</th>
<th>SMQ Broad</th>
<th>SMQ Narrow</th>
<th>PTs</th>
<th>Int. Doc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug A</td>
<td>Skin</td>
<td>Angioedema And Urticaria</td>
<td>Angioedema</td>
<td>Angioedema</td>
<td>Angioedema</td>
<td>Angioedema</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

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 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
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

Summary

In this course, we:
- Reviewed MedDRA’s scope, structure, and characteristics
- Reviewed the MedDRA Data Retrieval and Presentation: Points to Consider document
- Reviewed use of MedDRA for developing queries
- Discussed Standardised MedDRA Queries (SMQs)
- Discussed the creation and use of customized searches
MSSO Contacts

- Website
  - [www.meddra.org](http://www.meddra.org)
- Email
  - mssohelp@meddra.org
- Frequently Asked Questions
  - [www.meddra.org/faq](http://www.meddra.org/faq)

Question and Answer Session