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MedDRA: Safety Data Analysis and SMQs

Presented by Joy Zhu
Medical Officer, MedDRA MSSO
19 September 2019
## 2.2.2 The Events Observation Class

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>Variable Label</th>
<th>Type</th>
<th>Role</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>--TERM</td>
<td>Reported Term</td>
<td>Char</td>
<td>Topic</td>
<td>Topic variable for an event observation, which is the verbatim or pre-specified name of the event.</td>
</tr>
<tr>
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<td>Synonym Qualifier of --TERM</td>
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Agenda

1. MedDRA overview
2. MedDRA Data Retrieval and Presentation: Points to Consider document
3. SMQ background and definition
4. SMQ data characteristics
5. SMQ applications
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 ICH parties, the Medicines and Healthcare products Regulatory Agency (MHRA) of the UK, Health Canada, and the WHO (as Observer).
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MedDRA Overview
What is MedDRA?

Med = Medical
D = Dictionary for
R = Regulatory
A = Activities

《监管活动医学词典》
MedDRA Definition

MedDRA is a clinically-validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry. The terminology is used through the entire regulatory process, from pre-marketing to post-marketing, and for data entry, retrieval, evaluation, and presentation.
MedDRA is in 125 countries
MedDRA Users Profile (cont)

- 5,800 Subscribing organizations by March 2019

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ICH Working Office, NMPA

Regulatory Status in China

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
   Product use 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

IN

OUT
Data to be Coded by MedDRA

Clinical Database

Screening
- I/E Criteria
- Demography
- Medical History
- Baseline Characteristics

Therapy
- Study Drug Administration
- Concomitant Medication
- Concomitant Procedures
- Therapy Compliance

Efficacy
- Base on Protocol

Safety
- Indication
- Adverse Events
- Lab Results
- Vital Signs
- Reason of Death

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MedDRA Structure

First Level
- System Organ Class (SOC) (27)
  - High Level Group Term (HLGT) (337)
  - High Level Term (HLT) (1,737)

Analysis Level
- Preferred Term (PT) (23,708)

Coding Level
- Lowest Level Term (LLT) (80,262)

Grouping Terms

MedDRA Version 22.0
### 2.2.2 The Events Observation Class

<table>
<thead>
<tr>
<th>Variable Name</th>
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</table>
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
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
Codes and Languages

Cefaleia
Portuguese

Kopfschmerz
German

Hoofdpijn
Dutch

Headache
English

Céphalée
French

Bolest hlavy
Czech

Fejfájás
Hungarian

Cefalea
Italian

頭痛
Japanese

Cefalea
Spanish

Головная боль
Russian

Electronic Submission
MedDRA and Coded Cases

- Retrieve cases with MedDRA hierarchy
MedDRA Data Retrieval and Presentation: Points to Consider
## PtC Documents

<table>
<thead>
<tr>
<th>PtC Category</th>
<th>PtC Document</th>
<th>Purpose</th>
<th>Languages</th>
<th>Release Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term Selection</td>
<td>MedDRA Term Selection: Points to Consider</td>
<td>Promote accurate and consistent coding with MedDRA</td>
<td>English and Japanese</td>
<td>Updated with each MedDRA release</td>
</tr>
<tr>
<td></td>
<td>MedDRA Term Selection: Points to Consider Condensed Version</td>
<td>Shorter version focusing on general coding principles to promote accurate and consistent use of MedDRA worldwide</td>
<td>All MedDRA languages (except English and Japanese)</td>
<td>Update as needed</td>
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<tr>
<td>Data Retrieval and Presentation</td>
<td>MedDRA Data Retrieval and Presentation: Points to Consider</td>
<td>Demonstrate how data retrieval options impact the accuracy and consistency of data output</td>
<td>English and Japanese</td>
<td>Updated with each MedDRA release</td>
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<tr>
<td></td>
<td>MedDRA Data Retrieval and Presentation: Points to Consider Condensed Version</td>
<td>Shorter version focusing on general retrieval and analysis principles to promote accurate and consistent use of MedDRA worldwide</td>
<td>All MedDRA languages (except English and Japanese)</td>
<td>Update as needed</td>
</tr>
<tr>
<td>General</td>
<td>MedDRA Points to Consider Companion Document</td>
<td>More detailed information, examples, and guidance on specific topics of regulatory importance. Intended as a &quot;living&quot; document with frequent updates based on users’ needs. First edition covers data quality and medication errors.</td>
<td>English and Japanese</td>
<td>Updated as needed</td>
</tr>
</tbody>
</table>
MedDRA Data Retrieval and Presentation: Points to Consider (DRP:PTC)

• 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
General Queries and Retrieval

- Document search strategy
- Highlight overall distribution of ADRs/AEs
- Identify areas for in-depth analysis (focused searches)
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><strong>HLGT Mental impairment disorders</strong></td>
<td></td>
</tr>
<tr>
<td>HLT Mental impairment (excl dementia and memory loss)</td>
<td></td>
</tr>
<tr>
<td>PT Disturbance in attention</td>
<td>1</td>
</tr>
<tr>
<td><strong>HLGT Movement disorders (incl Parkinsonism)</strong></td>
<td></td>
</tr>
<tr>
<td>HLT Dyskinesias and movement disorders NEC</td>
<td></td>
</tr>
<tr>
<td>PT Psychomotor hyperactivity</td>
<td>2</td>
</tr>
<tr>
<td>HLT Tremor (excl congenital)</td>
<td></td>
</tr>
<tr>
<td>PT Tremor</td>
<td>3</td>
</tr>
<tr>
<td><strong>HLGT Neurological disorders NEC</strong></td>
<td></td>
</tr>
<tr>
<td>HLT Disturbances in consciousness NEC</td>
<td></td>
</tr>
<tr>
<td>PT Somnolence</td>
<td>1</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>
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 in Production - Examples

- As of Version 22.0, a total of 104 level 1 SMQs in production

- Agranulocytosis
- Anaphylactic reaction
- Central nervous system vascular 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 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
What is an SMQ?

Clinical Trial Database
Safety Database

Case
LLT 1
LLT 2
LLT 3

"Hit"

SMQ
PT
LLT
LLT
LLT 1
PT
LLT
LLT
LLT
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 - 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 lactate - Acidosis is seldom significant unless blood lactate exceeds 5 mmol/L - Clinical presentation in type B lactic acidosis: o Symptoms: hyperventilation or dyspnea, stupor or coma, vomiting, drowsiness, and abdominal pain o 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).
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
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
LLT1
LLT2
LLT3

SMQ
PT
LLT
LLT
PT
LLT
LLT
LLT

"Hit"
In my dataset, which cases are “hits” for SMQs (potential cases of interest)?
SMQ Analysis (cont)

- SMQ Analysis feature
- Apply SMQs to user’s MedDRA-coded data
  - Narrow/broad
  - Hierarchical
  - Algorithmic (separate search option to apply algorithm)
• Run broad search on all SMQs
SMQ Analysis (cont)

- Results of broad search on all SMQs
  - Includes narrow search
  - Includes hierarchical SMQs
  - Algorithmic SMQ analysis not shown

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<th>SMQ Analysis (SMQ analysis exercise v2.0.4.xls)</th>
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</table>

- Table with SMQs and related information
  - SMQ ID
  - SMQ Term
  - SMQ Code
  - SMQ Method
  - Scope (Narrow, Broad)
  - Category
  - Weight Status
  - Case ID
  - SMQ Hierarchy

![SMQ Analysis Table]

- Example SMQs:
  1. Abdominal distension
  2. Acute kidney injury
  3. Anaphylactic shock

- Algorithmic SMQ analysis not shown
**SMQ Analysis (cont)**

- Results of algorithmic SMQ analysis

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
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<td>LLT/PT Code</td>
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<td>Scope</td>
<td>Category</td>
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<td>Case ID</td>
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SMQ Applications

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

• Post-marketing
  – Selected SMQs to retrieve cases for suspected or known safety issue
  – Signal detection (multiple SMQs employed)
  – Single case alerts
  – Periodic reporting (aggregate cases for safety and other issues, e.g., lack of efficacy)
• 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)
**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>
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<tr>
<th>SMQ (Narrow Search)</th>
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Acknowledgement: Dr. Christopher Breder, Office of New Drugs, CDER, FDA
MSSO Contacts

- Website
  - www.meddra.org

- Free training (Face-to-Face training; Webinars)
  - https://www.meddra.org/training/schedule

- Email
  - mssohelp@meddra.org
Thank You!