MedDRA®: Safety Data Analysis and SMQs

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MedDRA Data Retrieval and Presentation: Points to Consider

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

- Quality of source data
- Documentation of data retrieval and presentation practices
- Organization-specific data characteristics
- Characteristics of MedDRA that impact data retrieval and Presentation
- MedDRA versioning
- General queries and retrieval
- Standardised MedDRA Queries
- Customized 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

- Organization-specific guidelines
  - Consistent with Points to Consider documents
  - Coding conventions
  - Data retrieval and output strategies (including SMQs)
  - Versioning update process
  - QA procedures
- Review by individuals with medical background and MedDRA training
- MedDRA is standardized and SOC assignments are pre-determined; no *ad hoc* structural alterations

Organization-Specific Data Characteristics

- Database structure
- Data storage
- Data migration
- 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

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

Impact of MedDRA’s Characteristics (cont)
– 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
Granularity

<table>
<thead>
<tr>
<th>Other Terminology Preferred Terms</th>
<th># of Subj</th>
<th>MedDRA Version 12.0 Preferred Terms</th>
<th># of Subj</th>
</tr>
</thead>
<tbody>
<tr>
<td>INFECTION</td>
<td>12</td>
<td>Upper respiratory tract infection</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nasopharyngitis</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Localised infection</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Lower respiratory tract infection</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonspecific reaction</td>
<td>1</td>
</tr>
</tbody>
</table>

Multi-Axiality

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

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

MedDRA Versioning (cont) - Effect of Primary SOC Change

<table>
<thead>
<tr>
<th>MedDRA Version 11.1</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC General disorders and administration site conditions</td>
<td>20</td>
</tr>
<tr>
<td>PT Peripheral coldness</td>
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</tbody>
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<td>SOC General disorders and administration site conditions</td>
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<td>20</td>
</tr>
<tr>
<td>PT Peripheral coldness</td>
<td></td>
</tr>
</tbody>
</table>
Overall Presentation of Safety Profiles

- Highlight overall distribution of ADRs/AEs
- Identify areas for in-depth analysis (focused searches)
- Approaches: full listing of terms to sophisticated statistical methods
- Standard approach: present by SOC and PTs
- This approach not always optimal due to unique characteristics of MedDRA

Overview by Primary SOC

- Use Internationally Agreed Order of SOCs when applicable (see PTC or MedDRA Introductory Guide)
- Consider use of HLTs and HLGTs for large data sets
- Line listings, tables, graphs
- Benefits - Broad overview, PTs displayed only once
- Limitations - Incomplete groupings, lengthy output
Focused Search: Secondary SOC Assignments

• Query the SOC, HLGT, or HLT to include both primary and secondary SOC assignments in display

• If database does not allow automated output by secondary SOC, then query should be performed using available processes (e.g., programming a list of all individual PTs in primary and secondary SOC locations).
  – Benefits - more comprehensive view of medically related events
  – Limitations - display by primary and secondary SOC could lead to double counting

Standardised MedDRA Queries (SMQs)
Definition of SMQ

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

SMQs in Production - Examples

• As of Version 12.0, a total of 74 in production (Other SMQs in development)
  • Adverse pregnancy outcome/reproductive toxicity (incl neonatal disorders)
  • Agranulocytosis
  • Anaphylactic reaction
  • Cerebrovascular disorders
  • Convulsions
  • Depression and suicide/self-injury
  • Hepatic disorders
  • Ischaemic heart disease
  • Lack of efficacy/effect
  • Peripheral neuropathy
  • Pseudomembranous colitis
  • Rhabdomyolysis/myopathy
  • Severe cutaneous adverse reactions
  • Systemic lupus erythematosus
Narrow and Broad Searches

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

Narrow vs. Broad Example

Lactic acidosis (SMQ)

Definition
Lactic acidosis is a form of high anion gap metabolic acidosis. Intrinsic cardiac contractility may be depressed, but exercise function can be normal because of catecholamine release. Peripheral arterial vasoconstriction and central venous obstruction can be present. Central nervous system function is depressed, with headache, lethargy, stupor, and, in severe cases, even coma. Observe asthenia may occur. Characterized by an increase in plasma l-lactate. Acidosis is usually significant unless lactate exceeds 2 mmol/L. Clinical presentation in type B lactic acidosis: Symptoms: hyperventilation or hyperventilation, stupor or coma, vomiting, diaphoresis, 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 set 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 older terminology or other coding conventions.
Algorithmic SMQs

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

Algorithmic SMQ Example

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

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

<table>
<thead>
<tr>
<th>Category B – Upper airway/Respiratory</th>
<th>Category C – Angioedema/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
  - Erythropenia
  - Leukopenia
  - Thrombocytopenia
  - Cytopenia and haematopoietic disorders affecting more than one type of blood cell

SMQ Applications

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

- Postmarketing
  - Selected SMQs to retrieve cases for suspected or known safety issue
  - Signal detection (multiple SMQs employed)
  - Single case alerts
  - Periodic reporting (aggregate cases for safety and other issues, e.g., lack of efficacy)
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

Customized Searches – Ad Hoc Queries

• Need medical knowledge
• Need knowledge of structure and characteristics of MedDRA and of your data
• Refer to 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
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