Standardised MedDRA Queries (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 ICH parties, 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 the MedDRA Data Retrieval and Presentation: Points to Consider document
- Discuss and demonstrate the use of MedDRA for developing queries
- Discuss features of SMQs including:
  - Background and data characteristics
  - Analysis of a data set using SMQs
  - SMQ applications
  - SMQ browser view demonstration
Course Overview (cont)

• Discuss the creation of customized searches
• Conclude with question and answer session
• Appendix - MedDRA’s scope, structure, and characteristics

MedDRA Data Retrieval and Presentation: Points to Consider
ICH M1 Points to Consider Working Group (PtC WG)

- Regulators and industry from EU, US, and Japan
- Health Canada, Canada
- MFDS, Republic of Korea
- ANVISA, Brazil
- NMPA, China
- MSSO
- JMO
- WHO (Observer)

November 2017, Geneva, Switzerland

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### PtC Documents

<table>
<thead>
<tr>
<th>PtC Category</th>
<th>PtC Document</th>
<th>Purpose</th>
<th>Languages</th>
<th>Release Cycle</th>
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<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, Japanese, and other selected languages</td>
<td>Updated annually with the March release of MedDRA (starting with MedDRA Version 23.0)</td>
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<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>
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<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>
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<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 “living” document with frequent updates based on users’ needs. First edition covers data quality and medication errors. New section on product quality is being drafted.</td>
<td>English and Japanese</td>
<td>Updated as needed</td>
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**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
MedDRA Data Retrieval and Presentation: PTC (cont)

• Developed by a working group of the ICH Management Committee
• Updated annually in step with the March release of MedDRA (starting with MedDRA Version 23.0)
• Available on MedDRA and JMO websites
  – English, Japanese, and other selected languages
  – 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://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)
MedDRA Version Analysis Tool (MVAT) (cont)

• User interface and report output available in all MedDRA languages
• Ability to run reports on supplemental changes
• Option to run reports on secondary SOC changes

Developing Queries Using MedDRA
What is a Query?

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
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

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)

- 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 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 23.0, a total of 106 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 Data Characteristics

- MedDRA term inclusion
- Broad/narrow
- Algorithms
- Hierarchy
- SMQ status/term status within an SMQ
- Term versioning in an SMQ

MedDRA Term Inclusion

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

Narrow Terms

Broad Terms

Broad Search

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 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 - Clinical presentation in type II 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 varatbles 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/ 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 23.0:
  - PT *Hormone receptor positive breast cancer* in SMQ *Breast malignant tumours*
- Using version 22.1 SMQs which do not contain these PTs would fail to identify cases coded to these terms in a database using MedDRA Version 23.0
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)

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/
- Mobile MedDRA Browser (MMB)
  - https://mmb.meddra.org

Features
- Each 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 (MDB and WBB only)
MDB and WBB Special Features

- Preview upcoming (supplemental) changes in next release*
- View primary **and** secondary link information
- Upload terms to run against SMQs
- Advanced search options (e.g., NOT, OR)

*Supplemental view not available on MDB

Standardised MedDRA Query (SMQ) Analysis

- In my dataset, which cases are “hits” for SMQs (potential cases of interest)?

<table>
<thead>
<tr>
<th>Row</th>
<th>Term</th>
<th>Code</th>
<th>Case ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Amylase abnormal</td>
<td>10072327</td>
<td>1</td>
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<tr>
<td>2</td>
<td>Abdominal distension</td>
<td>10020960</td>
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<td>3</td>
<td>Acute kidney injury</td>
<td>10089339</td>
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<td>4</td>
<td>Blood creatinine increased</td>
<td>10055483</td>
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<td>5</td>
<td>Status asthmaticus</td>
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<td>6</td>
<td>Gout</td>
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<tr>
<td>7</td>
<td>Joint effusion</td>
<td>10003216</td>
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<tr>
<td>8</td>
<td>Major depression</td>
<td>10107940</td>
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<tr>
<td>9</td>
<td>Suicidal ideation</td>
<td>10042958</td>
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<tr>
<td>10</td>
<td>Cataract operation</td>
<td>10083707</td>
<td>6</td>
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<tr>
<td>11</td>
<td>Abdominal pain</td>
<td>10002861</td>
<td>7</td>
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<tr>
<td>12</td>
<td>Dactylitis</td>
<td>10012735</td>
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<td>13</td>
<td>Pedal edema</td>
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<td>Paroxysmal atrial flutter</td>
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<td>15</td>
<td>Pancreatitis acute</td>
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<td>16</td>
<td>Dementia Alzheimer's type</td>
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<td>17</td>
<td>Hypertension</td>
<td>10020772</td>
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<td>18</td>
<td>Anaphylactic shock</td>
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<td>19</td>
<td>Bronchospasm</td>
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<td>Swelling face</td>
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<td>Hypoesthesia</td>
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<td>Urticaria</td>
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<td>Acute renal failure</td>
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<td>26</td>
<td>Double stranded DNA antibody positive</td>
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<td>Disease progression</td>
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<td>31</td>
<td>Exercise tolerance decreased</td>
<td>10013130</td>
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</table>
SMQ Analysis (cont)

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

Standardised MedDRA Query (SMQ) Analysis

- Run broad search on all SMQs

<table>
<thead>
<tr>
<th>SMQ ID</th>
<th>Term</th>
<th>Code</th>
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</tr>
<tr>
<td>2</td>
<td>Abdominal distension</td>
<td>10005090</td>
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</tr>
<tr>
<td>3</td>
<td>Acute kidney injury</td>
<td>10066331</td>
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</tr>
<tr>
<td>4</td>
<td>Blood creatinine</td>
<td>10054883</td>
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<tr>
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<td>Status asthmatic</td>
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<td>6</td>
<td>Gout</td>
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<td>7</td>
<td>Joint effusion</td>
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<td>Suicidal attempt</td>
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<td>Catheter operation</td>
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<td>13</td>
<td>Palpitations</td>
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<td>14</td>
<td>Atrial fibrillation</td>
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<td>Dementia Alzheimer’s</td>
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<tr>
<td>31</td>
<td>Exercise tolerance decreased</td>
<td>10051301</td>
<td>16</td>
</tr>
</tbody>
</table>
• Results of broad search on all SMQs
  – Includes narrow search
  – Includes hierarchical SMQs
  – Algorithmic SMQ analysis not shown

<table>
<thead>
<tr>
<th>SMQ Analysis</th>
<th>[BRM analysis exercise v13.3.edx]</th>
<th>2/7/2020 1:33:02 PM</th>
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<tr>
<td>SMQ Analysis</td>
<td>[BRM analysis exercise v13.3.edx]</td>
<td>2/7/2020 1:33:02 PM</td>
</tr>
</tbody>
</table>

| SMQ Analysis | [BRM analysis exercise v13.3.edx] | 2/7/2020 1:33:02 PM |
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)
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, HLG, 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)

<table>
<thead>
<tr>
<th>SMQ (Narrow Search)</th>
<th>RI</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)
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
  – 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 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
- Email
  - mssohelp@meddra.org
- Frequently Asked Questions
  - www.meddra.org/faq
- MedDRA Browsers
  - https://www.meddra.org/meddra-desktop-browsers (Desktop Browser)
  - https://tools.meddra.org/wbb/ (Web-Based Browser)
  - https://mmb.meddra.org (Mobile Browser)

MSSO Contacts (cont)

- Self-Service Application
  - https://www.meddra.org/meddra-self-service-application
- Training Schedule
  - https://www.meddra.org/training/schedule
- Change Request Submission
  - https://www.meddra.org/how-to-use/change-requests
- MedDRA Support Documentation
  - https://www.meddra.org/how-to-use/support-documentation
Question and Answer Session

Appendix – MedDRA’s Scope, Structure, and Characteristics
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.

Scope of MedDRA

- Not a drug dictionary
- Patient demographic terms
- Clinical trial study design terms
- Frequency qualifiers
- Numerical values for results
- Severity descriptors
- Not an equipment, device, diagnostic product dictionary
MedDRA Structure

System Organ Class (SOC) (27)
High Level Group Term (HLGT) (337)
High Level Term (HLT) (1,737)
Preferred Term (PT) (24,289)
Lowest Level Term (LLT) (81,812)

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
A Multi-Axial Terminology (cont)

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