Applying MedDRA® in Clinical Safety and Pharmacovigilance

Judy E. Harrison, MD
Medical Officer
MedDRA MSSO

Sonja Brajovic, MD
Medical Officer
Office of Surveillance and Epidemiology
CDER, FDA

Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to Drug Information Association, Inc. (“DIA”), its directors, officers, employees, volunteers, members, chapters, councils, Special Interest Area Communities or affiliates, or any organization with which the presenter is employed or affiliated.

These PowerPoint slides are the intellectual property of the individual presenter and are protected under the copyright laws of the United States of America and other countries. Used by permission. All rights reserved. Drug Information Association, DIA and DIA logo are registered trademarks or trademarks of Drug Information Association Inc. All other trademarks are the property of their respective owners.
Disclaimer

- The information within this presentation represents the views of the presenter, not necessarily those of the FDA

Learning Objectives

- Review the various strategies for retrieval and subsequent analysis of MedDRA-coded data in clinical safety and pharmacovigilance
- Discuss the issues relating to MedDRA versioning
Tutorial Overview

- Overview of MedDRA
- Coding and the "MedDRA Term Selection: Points to Consider" document
- Data quality issues
- MedDRA’s application in data retrieval and analysis: the “MedDRA Data Retrieval and Presentation: Points to Consider” document
- Standardised MedDRA Queries (SMQs)
- Customized searches
- MedDRA versioning

Overview of MedDRA
Why MedDRA?

ICH initiative (M1)

- An international multi-lingual terminology
- Standardized communication between industry and regulators
- Support of electronic submissions
- Application throughout regulatory process for medical products
- Classification for a wide range of clinical information
- Global ICH-endorsed “Points to Consider” documents
- Global version synchronization

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.
Applications of MedDRA in Clinical Safety and Pharmacovigilance

- Clinical trial databases (adverse events, medical & social history, investigations etc.)
- Investigator’s Brochures, Core Safety Information
- Safety summaries, Clinical Study Reports
- Individual Case Safety Reports
- Periodic Safety Update Reports
- Product Labeling

Regulatory Status

- US FDA
  - Used in FDA’s Adverse Event Reporting System (AERS)
- Japanese Ministry of Health, Labour and Welfare
  - Mandatory use for electronic reports
  - Used in Periodic Infection and Safety Reports
  - For medical devices with biological components, infections to be described with MedDRA terms
Regulatory Status (cont)

• European Union
  • Clinical trials
    ▪ SUSARs (Suspected Unexpected Serious Adverse Reactions) – use MedDRA LLTs (current or previous version)
    ▪ Volume 9A (all authorized medicinal products, including OTC)
      ▪ Individual Case Safety Reports (ICSRs) – use MedDRA LLTs (current or previous version)
      ▪ For adverse reactions in Periodic Safety Update Report
      ▪ Standardised MedDRA Queries (SMQs) recommended for signal detection

Regulatory Status (cont)

• European Union (cont)
  • Interface between EudraVigilance and EU Risk Management Plan
    ▪ To code indications, risks, interactions (potential and identified)
  • Summary of Product Characteristics guideline
    ▪ MedDRA to be used throughout; in particular for Contraindications, Special warnings and precautions for use, and Undesirable effects sections
Regulatory Status (cont)

- ICH M4E Guideline on Common Technical Document
  - Recommended in adverse event summary tables
- Canada
  - Guidance Document for Industry - Reporting Adverse Reactions to Marketed Health Products
    - Recommended as standard for adverse reaction reports
  - Guidance for Industry - Product Monograph (labeling)
    - Preferred terminology for adverse drug reactions

Scope of MedDRA

- NOT
  - Diseases
  - Diagnoses
  - Signs
  - Symptoms
  - Therapeutic indications
  - Investigation names & qualitative results
  - Medical & surgical procedures
  - Medical, social, family history
  - Medication errors
  - Product quality, device issues
  - Terms from other terminologies

- IN
  - Frequency qualifiers
  - Numerical values for results
  - Severity descriptors
  - Not an equipment, device, diagnostic product dictionary

- OUT
  - Not a drug dictionary

- Patient demographic terms
- Clinical trial study design terms
**MedDRA Structure**

System Organ Class (SOC) (26)

High Level Group Term (HLGT) (335)

High Level Term (HLT) (1,709)

Preferred Term (PT) (18,919)

Lowest Level Term (LLT) (68,661)

---

**MedDRA Term Level Definitions**

- **SOC** - Highest level of the terminology, and distinguished by anatomical or physiological system, etiology, or purpose
- **HLGT** - Subordinate to SOC, superordinate descriptor for one or more HLTs
- **HLT** - Subordinate to HLGT, superordinate descriptor for one or more PTs
- **PT** - Represents a single medical concept
- **LLT** - Lowest level of the terminology, related to a single PT as a synonym, lexical variant, or quasi-synonym (Note: All PTs have an identical LLT)
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
- 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

Examples of LLTs

SOC = Cardiac disorders

HLGT = Cardiac arrhythmias

HLT = Rate and rhythm disorders NEC

PT = Arrhythmia

LLT Arrhythmia NOS

LLT Arrhythmia

LLT Dysrhythmias

LLT (Non-current)

Other specified cardiac dysrhythmias
Non-Current Terms

- Non-current terms are flagged at the LLT level within MedDRA
- Not recommended for continued use
- Retained within the terminology to preserve historical data for retrieval and analysis
- Terms that are vague, ambiguous, outdated, truncated, or misspelled
- Terms derived from other terminologies that do not fit MedDRA rules

MedDRA Codes

- Each MedDRA term assigned an 8-digit numeric code
- The code is non-expressive
- Codes can fulfill a data field in various electronic submission types (e.g., E2B)
- Initially assigned alphabetically by term starting with 10000001
  - New terms are assigned sequentially
- Supplemental terms are assigned codes
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
• Purpose of Primary SOC
  ◦ Determines which SOC will represent a PT during cumulative data outputs
  ◦ Is used to support consistent data presentation for reporting to regulators

A Multi-Axial Terminology (cont)

• A PT can be associated with one or more SOCs
• One of the associations is primary; all others are secondary
• A PT will have one and only one path to any particular SOC
• MedDRA can express multi-axiality at the PT, HLT, or HLGT level
A Multi-Axial Terminology (cont)

SOC = Respiratory, thoracic and mediastinal disorders
HLGT = Respiratory tract infections
HLT = Viral upper respiratory tract infections
PT = Influenza

SOC = Infections and infestations
HLGT = Viral infectious disorders
HLT = Influenza viral infections

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
Rules for Primary SOC Allocation

- 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:

1st: *Congenital, familial and genetic disorders*

2nd: *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*

3rd: *Infections and infestations*
Browser Demonstration

SOC View and Search

Coding with MedDRA

Overview of “MedDRA Term Selection: Points to Consider” Document
“MedDRA Term Selection: Points to Consider”

• An ICH-endorsed guide for MedDRA users
• Developed to promote medically accurate and consistent use of MedDRA in exchange of data (ultimately, for “medically meaningful” retrieval and analysis)
• In some cases with more than one option for selecting terms, a “preferred option” is identified but this does not limit MedDRA users to using that option

MedDRA Term Selection PTC (cont)

• Developed by a working group of the ICH Steering Committee
  - Regulators and industry representatives
  - EU, Japan, USA
  - Canadian observer, MSSO, JMO

• Current version available on MedDRA MSSO Web site (http://www.meddrarmsso.com/subscriber_library_ptc.asp)
General Principles

- Quality of Source Data
- Quality Assurance
- Do Not Alter MedDRA
- Always Select a Lowest Level Term
- Select Only Current Lowest Level Terms
- When to Request a Term
- Use of Medical Judgment in Term Selection
- Selecting More than One Term
- Check the Hierarchy
- Select Terms for All Reported Information, Do Not Add Information

Term Selection Points

- Definitive and Provisional diagnoses with or without Signs and Symptoms
- Death and Other Patient Outcomes
- Suicide and Self-Harm
- Conflicting/Ambiguous/Vague information
- Combination Terms
- Age vs. Event Specificity
- Body Site vs. Event Specificity
- Location Specific vs. Microorganism Specific Infection
- Modification of Pre-existing Conditions
- Exposures During Pregnancy and Breast Feeding
- Congenital Terms
- Neoplasms
- Medical and Surgical Procedures
Term Selection Points (cont)

- Investigations
- Medication/Administration Errors and Accidental Exposures
- Transmission of Infectious Agent via Medicinal Product
- Overdose, Toxicity and Poisoning
- Device-related Terms
- Drug Interactions
- No Adverse Effect and “Normal” Terms
- Unexpected Therapeutic Effect
- Modification of Effect
- Social Circumstances
- Medical and Social History
- Indication for Product Use
- Off Label Use
- Product Quality Issues

Diagnoses and Provisional Diagnoses

<table>
<thead>
<tr>
<th>SINGLE DIAGNOSIS</th>
<th>DEFINITIVE DIAGNOSIS</th>
<th>PROVISIONAL DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single diagnosis without signs and symptoms</td>
<td>Single provisional diagnosis without signs and symptoms</td>
<td></td>
</tr>
<tr>
<td>Diagnosis (only possible option)</td>
<td>Provisional diagnosis (only possible option)</td>
<td></td>
</tr>
<tr>
<td>Example: &quot;Myocardial infarction&quot;</td>
<td>Example: &quot;Possible myocardial infarction&quot;</td>
<td></td>
</tr>
<tr>
<td>select &quot;Myocardial infarction&quot;</td>
<td>select &quot;Myocardial infarction&quot; (select term as if definitive diagnosis)</td>
<td></td>
</tr>
</tbody>
</table>

Similar principles apply for multiple diagnoses
Diagnoses and Provisional Diagnoses (cont)

<table>
<thead>
<tr>
<th>SINGLE DIAGNOSIS</th>
<th>DEFINITIVE DIAGNOSIS</th>
<th>PROVISIONAL DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single diagnosis with signs/symptoms</td>
<td>Single provisional diagnosis with signs/symptoms</td>
<td></td>
</tr>
<tr>
<td>• Preferred: Diagnosis only</td>
<td>• Preferred: Provisional diagnosis and signs/symptoms</td>
<td></td>
</tr>
<tr>
<td>Example: &quot;Anaphylactic reaction with rash, dyspnea, hypotension, and laryngospasm&quot; → select &quot;Anaphylactic reaction&quot;</td>
<td>Example: &quot;Possible myocardial infarction with chest pain, dyspnea, diaphoresis&quot; → select &quot;Myocardial infarction&quot;, &quot;Chest pain&quot;, &quot;Dyspnea&quot;, and &quot;Diaphoresis&quot;</td>
<td></td>
</tr>
</tbody>
</table>

Similar principles apply for multiple diagnoses

Diagnoses and Provisional Diagnoses (cont)

<table>
<thead>
<tr>
<th>SINGLE DIAGNOSIS</th>
<th>DEFINITIVE DIAGNOSIS</th>
<th>PROVISIONAL DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single diagnosis with signs/symptoms</td>
<td>Single provisional diagnosis with signs/symptoms</td>
<td></td>
</tr>
<tr>
<td>• Alternate: Diagnosis and signs/symptoms</td>
<td>• Alternate: Signs/symptoms only (as provisional diagnosis may change)</td>
<td></td>
</tr>
<tr>
<td>Example: &quot;Anaphylactic reaction with rash, dyspnea, hypotension, and laryngospasm&quot; → select &quot;Anaphylactic reaction&quot;, &quot;Rash&quot;, &quot;Dyspnea&quot;, &quot;Hypotension&quot;, and &quot;Laryngospasm&quot;</td>
<td>Example: &quot;Possible myocardial infarction with chest pain, dyspnea, diaphoresis&quot; → select &quot;Chest pain&quot;, &quot;Dyspnea&quot;, and &quot;Diaphoresis&quot;</td>
<td></td>
</tr>
</tbody>
</table>

Similar principles apply for multiple diagnoses
# Investigation vs. Medical Condition

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT Selected</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>Hypoglycemia</td>
<td>LLT Hypoglycemia links to SOC Metabolism and nutrition disorders</td>
</tr>
<tr>
<td>Decreased glucose</td>
<td>Glucose decreased</td>
<td>LLT Glucose decreased links to SOC Investigations</td>
</tr>
</tbody>
</table>

# Medication Errors and Product Quality Issues

- Important to capture; may have clinical consequences

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT(s) Selected</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient was administered wrong drug and experienced hypotension</td>
<td>Wrong drug administered Hypotension</td>
<td>Medication error with clinical consequences</td>
</tr>
<tr>
<td>Sterile lumbar puncture kit received in broken packaging (sterility compromised)</td>
<td>Product sterile packaging disrupted</td>
<td>Product quality issue without clinical consequences</td>
</tr>
</tbody>
</table>
Data Quality Issues

EU Report Quality and MedDRA

- Volume 9A EU *Pharmacovigilance guidelines for medicinal products for human use*:
  - PSUR non-compliance includes poor quality reports due to “absence of use of standardised medical terminology (e.g. MedDRA)”, among other criteria
FDA Evaluates Manufacturer-submitted MedDRA Coding

• FDA depends on many different companies to submit accurate and complete MedDRA coded reports
   Reliance on coded data to perform analyses and generate important safety signals
• Inaccurate and/or incomplete coding: delayed, misdirected or missed safety concerns
• AERS Data entry contractor has a coding staff, performs Quality Assurance of Mfr coding

FDA-Defined Coding Errors

• Missed Concepts
   All medical concepts described after the product is taken should be coded
   Example: “The patient took drug X and developed alopecia, increased LFTs and pancreatitis”. Manufacturer only codes alopecia and increased LFTs (missed concept of pancreatitis)
   Example: “The patient took drug X and developed interstitial nephritis which later deteriorated into renal failure”. Manufacturer only codes interstitial nephritis (missed renal failure concept)
FDA-Defined Coding Errors (cont)

• “Soft Coding”
  - Selecting a term which is both less specific and less severe than another MedDRA term is “soft coding”
  - Example: “Liver failure” coded as hepatotoxicity or increased LFTs
  - Example: “Aplastic anemia” coded as unspecified anemia
  - Example: “Rash subsequently diagnosed as Stevens Johnson syndrome” coded as rash

FDA Recommendations

• Organizations should utilize MedDRA specificity and avoid soft coding errors
  - Critical for later retrieval / signal generation
• FDA encourages organizations to follow the ICH-endorsed MedDRA Term Selection: Points to Consider document
  - Organizations should establish their own coding guidelines based on, and not conflicting with, the ICH MTS:PTC document
  - FDA Coding Principles for Postmarketing Adverse Event Reports document is harmonized with the ICH MTS:PTC document
New Drug Safety Review

Adverse event (AE) and coding review

- Major sections of a safety submission review
  - Deaths
  - Serious adverse events (SAEs)
  - AEs related to dropouts/discontinuations
  - Common adverse events

*Note: FDA recommends submitting data in a single terminology and integrated safety summary (ISS) in the same version of that terminology.*

Verbatim – LLT/PT Coding

Verification of medical accuracy, consistency

Potential coding issues:

- Lumping dissimilar terms
  - Specific AEs all coded under an “umbrella” term
  - May obscure a safety signal under the lumped term
- Splitting similar terms
  - Splitting results in lower incidence
  - May minimize or mask a safety signal
- Miscoding
Miscoding

- General term selected instead of specific
  - “Infection, expired due to salmonella sepsis” - miscoded to PT Infection

- Complex verbatim and miscoding
  - “Fall due to dizziness” - miscoded to only PT Dizziness
  - “Acute renal failure due to cardiac arrest” - miscoded to only PT Cardiac arrest

Overview of “MedDRA Data Retrieval and Presentation: Points to Consider” Document
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

- General Principles
  - Quality of Source Data
  - Documentation of Data Retrieval and Presentation Practices
  - Do Not Alter MedDRA
  - Organization-Specific Data Characteristics
  - Characteristics of MedDRA that Impact Data Retrieval and Analysis
  - MedDRA Versioning
- General Queries and Retrieval
- Standardised MedDRA Queries
- Customized Searches
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)
  - Quality assurance procedures
  - MedDRA version used for search
  - Search strategy methods
  - Version update processes
  - Processes for customized MedDRA queries

Do Not Alter MedDRA

- MedDRA is a **standardized** terminology
- No *ad hoc* structural alterations, including changing primary SOC allocation
- Submit a change request to the MSSO for any incorrectly placed terms
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 – 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
Data Retrieval Example

Data Retrieval: MedDRA Specificity

- A toxicity can manifest with multiple signs, each coded with a different Preferred Term
- Example:
  - These PTs may represent the same toxicity:
    - Vision blurred
    - Visual impairment
    - Accommodation disorder
    - Visual acuity reduced
    - Diplopia
    - Presbyopia
Data Retrieval: MedDRA Levels

Perform analyses on all levels of MedDRA hierarchy

- **PT**
  - Vision blurred 2/200 (1.0%)
  - Visual impairment 2/200 (1.0%)
  - Diplopia 1/200 (0.5%)
  - Visual acuity reduc. 1/200 (0.5%)
  - Accomm disorder 1/200 (0.5%)
  - Presbyopia 1/200 (0.5%)

- **HLGT**
  - Vision disorders 8/200 (4%)

All of these PTs are grouped in HLGT Vision Disorders. An AE analysis of HLGT Vision Disorders shows a higher percentage of events and appears higher up in a table sorted according to frequency.

* Example utilizes MedDRA version 13.1

---

Frequency by MedDRA Levels

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>HLT</th>
<th>HLGT</th>
<th>SOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision blurred</td>
<td>1%</td>
<td>Vision disorders NEC 2.5%</td>
<td>Vision disorders 4.0%</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>1%</td>
<td></td>
<td>Eye disorders 4.0%</td>
</tr>
<tr>
<td>Diplopia</td>
<td>0.5%</td>
<td>Partial vision loss 0.5%</td>
<td></td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>0.5%</td>
<td>Refractive and accommodative disorders 1.0%</td>
<td></td>
</tr>
<tr>
<td>Accommodation disorder</td>
<td>0.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presbyopia</td>
<td>0.5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All of these PTs are grouped under HLGT Vision Disorders. An AE analysis of HLT Visual Disorders NEC shows a higher percentage of events and appears higher up in a table sorted according to frequency.
## Adverse Event Profile with a Rate of ≥2%*

<table>
<thead>
<tr>
<th>Preferred Term (PT)</th>
<th>Study Drug n (%)</th>
<th>Control n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>32 (16%)</td>
<td>29 (14.5%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>31 (15.5%)</td>
<td>25 (12.5%)</td>
</tr>
<tr>
<td>Headaches</td>
<td>20 (10%)</td>
<td>22 (11%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18 (9.0%)</td>
<td>18 (9.0%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (3.5%)</td>
<td>9 (4.5%)</td>
</tr>
<tr>
<td>Vulvovaginal candidiasis</td>
<td>6 (3%)</td>
<td>5 (2.5%)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>4 (2%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

* Includes all adverse events with a rate of ≥2%

## Adverse Events with a Rate of <2%

<table>
<thead>
<tr>
<th>Preferred Term (PT)</th>
<th>Study Drug n (%)</th>
<th>Control n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>3 (1.5%)</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2 (1%)</td>
<td>3 (1.5%)</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>2 (1%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>2 (1%)</td>
<td>3 (1.5%)</td>
</tr>
<tr>
<td>Skin exfoliation</td>
<td>2 (1%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>2 (1%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Glossitis</td>
<td>1 (0.5%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Accommodation disorder</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>1 (0.5%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Diplopia</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Mucocutaneous rash</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Presbyopia</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>
Adverse Event Profile*

<table>
<thead>
<tr>
<th>High Level Group Term (HLGT)</th>
<th>Study Drug n (%)</th>
<th>Control n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal signs and symptoms</td>
<td>49 (24.5%)</td>
<td>40 (20%)</td>
</tr>
<tr>
<td>Gastrointestinal motility and defaecation conditions</td>
<td>32 (16%)</td>
<td>29 (14.5%)</td>
</tr>
<tr>
<td>Headaches</td>
<td>20 (10%)</td>
<td>22 (11%)</td>
</tr>
<tr>
<td><strong>Vision disorders</strong></td>
<td>8 (4%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>General system disorders NEC</td>
<td>7 (3.5%)</td>
<td>9 (4.5%)</td>
</tr>
<tr>
<td><strong>Epidermal and dermal conditions</strong></td>
<td>6 (3.0%)</td>
<td>3 (1.5%)</td>
</tr>
<tr>
<td>Fungal infectious disorders</td>
<td>6 (3%)</td>
<td>5 (2.5%)</td>
</tr>
</tbody>
</table>

* Includes all adverse events with a rate of ≥2%

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)
- Main presentation is by Primary SOC; secondary SOCs used for alternate views
### Primary SOC Analysis – SOC Infections and infestations

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA 13.1)</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 13.1)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Respiratory, thoracic and mediastinal disorders</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>SOC Infections and infestations</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Viral infection</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Patients may have more than one event reported
Secondary SOC Analysis – SOC Infections and infestations (cont)

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA 13.1)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT Urinary tract infection</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>SOC Ear and labyrinth disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT Ear infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>SOC Gastrointestinal disorders</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
- Terms used for queries should be in same version as data being queried
### MedDRA Versioning - Effect of Primary SOC Change

<table>
<thead>
<tr>
<th>SOC Description</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MedDRA Version 13.0</strong></td>
<td></td>
</tr>
<tr>
<td>SOC Gastrointestinal disorders</td>
<td>20</td>
</tr>
<tr>
<td>PT Intra-abdominal haemorrhage</td>
<td></td>
</tr>
<tr>
<td><strong>MedDRA Version 13.1</strong></td>
<td></td>
</tr>
<tr>
<td>SOC Cardiovascular disorders</td>
<td>0</td>
</tr>
<tr>
<td>PT Intra-abdominal haemorrhage</td>
<td>20</td>
</tr>
</tbody>
</table>

### Developing Queries Using MedDRA
General Principles

- Define the medical condition
- Develop inclusion/exclusion criteria
- Know your data, e.g., how specific coding conventions impact retrieval strategy
- Good browser is key component
  - Flexible search capabilities
  - Ability to view secondary SOC assignments

Query Strategy Tips

- ALWAYS search the “non-multi-axial” SOCs
- Consider searching the “support” SOCs
- Use “Top-down” and “Bottom-up” searches
- Use multi-axial links
- Use grouping terms; exclude non-relevant PTs
- Avoid using LLTs in queries
  - Exception: for infections, specific species information is found at the LLT level
Query Development Exercise

Cardiac Arrhythmias

Data Retrieval Example:

Identify all Hepatobiliary Adverse Events in a Dataset
Example

Hepatobiliary 1° SOC
- PT Jaundice hepatocellular
- PT Hyperbilirubinemia
- PT Jaundice cholestatic
- PT Liver disorder
- PT Hepatomegaly
- PT Hepatitis acute
- PT Cytolytic hepatitis
- PT Acute hepatic failure

Hepatobiliary 2° SOC
- PT Kernicterus
- PT Ocular icterus
- PT Yellow skin
- PT Jaundice acholuric
- PT Asterixis
- PT Coma hepatic
- PT Hepatic encephalopathy
- PT Radiation hepatitis

Primary SOC
- Nervous system disorder
- Eye disorders
- Skin and subcut tissue
- Blood and lymphatic
- Nervous system disorder
- Nervous system disorder
- Injury, poisoning...

A Search Looking at only Primary Hepatobiliary SOC Will Miss ALL OF THESE AE's (and more)

Example (con’t)

Combine 1° and 2° PTs to SOC Hepatobiliary

Hepatobiliary 1° SOC
- PT Jaundice hepatocellular
- PT Hyperbilirubinemia
- PT Jaundice cholestatic
- PT Liver disorder
- PT Hepatomegaly
- PT Hepatitis acute
- PT Cytolytic hepatitis
- PT Acute hepatic failure

Hepatobiliary 2° SOC
- PT Kernicterus
- PT Ocular icterus
- PT Yellow skin
- PT Jaundice acholuric
- PT Asterixis
- PT Coma hepatic
- PT Hepatic encephalopathy
- PT Radiation hepatitis
Are we done?

Combine 1° and 2 ° PTs to SOC

Hepatobiliary

Hepatobiliary 1° SOC
- PT Jaundice hepatocellular
- PT Hyperbilirubinemia
- PT Jaundice cholestatic
- PT Liver disorder
- PT Hepatomegaly
- PT Hepatitis acute
- PT Cytolytic hepatitis
- PT Acute hepatic failure

Hepatobiliary 2 ° SOC
- PT Kernicterus
- PT Ocular icterus
- PT Yellow skin
- PT Jaundice acholuric
- PT Asterixis
- PT Coma hepatic
- PT Hepatic encephalopathy
- PT Radiation hepatitis

SOC Investigations
- PT Alanine aminotransferase increased
- PT Aspartate aminotransferase increased
- PT Blood bilirubin increased
- PT Alkaline phosphatase increased
- PT Liver scan abnormal

SOC Surgical and medical procedures
- PT Liver transplant

And there is more...

Uniaxial – no secondary associations

SOC Investigations
- PT Alanine aminotransferase increased
- PT Aspartate aminotransferase increased
- PT Blood bilirubin increased
- PT Alkaline phosphatase increased
- PT Liver scan abnormal
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
SMQ Benefits and Limitations

• Benefits
  ◦ Application across multiple therapeutic areas
  ◦ Reusable programming
  ◦ 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

SMQ Development Summary

• Pre-release: tested on databases available to CIOMS Working Group members; typically, at least one company and one regulator database
• Production Phase: continue to be fine-tuned by MedDRA subscribers through the MSSO maintenance process
SMQs in Production - Examples

• As of Version 13.1, a total of 84 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. Intracardiac conduction may be impaired, and anemia may be present due to the release of intracellular anions. Peripheral arterial vasoconstriction and central vasoconstriction can be present. Central nervous system function is depressed with headache, lethargy, stupor, and, in some cases, even coma. Characterized by an increase in plasma l-lactate. Acidosis is evident if blood lactate exceeds 5 mmol/L. Clinical presentation in type B lactic acidosis: Symptomatic hyperventilation or hypoxia, shock or coma, vomiting, diarrhea, 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 reactions to terms of an older terminology or other coding practices).

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 have been developed as a 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
Other Data Included in SMQ Files

- 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 utilization of SMQs
  - Details of individual SMQs
  - Notes for implementation and/or expectation of results
- Production SMQ Spreadsheet
  - SMQs and included terms (.xls)
- “What’s New” document summarizes SMQ changes
- Original CIOMS Working Group documentation
How to “run” SMQs

SMQ Versioning

• Example of PT added to an SMQ in MedDRA Version 13.1:
  - PT *Traumatic renal injury* in SMQ *Accidents and injuries*

• Using the version 13.0 SMQ which does not contain this PT would fail to identify cases coded to this term in a database using MedDRA Version 13.1
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)

FDA Postmarketing Data Retrieval Using MedDRA
AERS Case Search Strategy

- Crucial: quality of submitted reports, quality of MedDRA coding
- Search: how inclusive or exclusive should it be?
  - Combination of MedDRA PT, HLT, HLGT, and SOC levels
  - Designated Medical Events (DMEs)
  - MedDRA OSE* reaction groups
  - SMQs
  - Customized retrieval strategy

*Office of Surveillance and Epidemiology

---

Designated Medical Events* (sample)

- Acute pancreatitis
- Acute respiratory failure
- Agranulocytosis
- Anaphylaxis / anaphylactoid reactions
- Aplastic anemia
- Blindness
- Bone marrow depression
- Deafness
- Disseminated intravascular coagulation
- Hemolytic anemia
- Liver failure/necrosis/ transplant
- Pancytopenia
- Seizure
- Stevens-Johnson Syndrome
- Sudden death
- Torsades de Pointes
- Toxic epidermal necrolysis
- Thrombotic thrombocytopenic purpura
- Ventricular fibrillation

* FDA internal working tool; DMEs have no regulatory significance
## DMEs and MedDRA PTs (sample)

<table>
<thead>
<tr>
<th>DME</th>
<th>PT terms (MedDRA v13.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pancreatitis</td>
<td>Pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Pancreatic necrosis</td>
</tr>
<tr>
<td>Haemolysis</td>
<td>Haemolysis, Intravascular haemolysis, Haemoglobinaemia, Haemoglobinuria, Haptoglobin decreased</td>
</tr>
<tr>
<td>Product infectious disease transmission</td>
<td>Transmission of an infectious agent via a medicinal product, Transfusion-transmitted infectious disease, Product contamination microbial</td>
</tr>
</tbody>
</table>

## OSE Reaction Groups

- Developed in 2001
  - No SMQs available at that time
- Purpose: FDA internal consistency in retrieving MedDRA AE data for analysis of safety issues / pre-defined searched strategies
- Built with MedDRA grouping terms (HLTs and HLGTs), plus specific PTs from other sections
- Many topics overlap with current SMQs
Standardised MedDRA Queries

- Used in clinical and postmarketing setting, by regulatory agencies and pharmaceutical companies
- SMQs: global consistency in retrieving MedDRA AE data for analysis of specific medical concepts over time and multiple organizations

AERS Search Screen
AERS – SMQ Search Selection

AERS Search Result on Selected SMQ and Suspect Product
Available Standard Reports

Available Standard Reports

- Standard Grouping 1 Report (1.5, 7, 8, 9)
- Standard Grouping 2 Report (1.5, 7, 8, 10)
- Standard Grouping 3 Report (1.5, 7, 8, 10)
- Targeted Grouping 4 Report (1.5)
  - Cases by MedDRA® and AE Group
  - Cases with Positive Dechallenge and Rechallenge
  - Cases by Year and Quarter
  - Cases by AE Name
  - Cases by Report Source
  - Cases by Suspect and Concomitant Products
  - Cases by Country and Region
  - All Preferred Terms in Cases
  - Cases by Primary Site and PT
  - USE LIST OF CASES
  - USE LIST OF CASES WITH DECLASSIFICATION

103

MedDRA and Signal Detection

Influence of the MedDRA® hierarchy on pharmacovigilance data mining results


* ProSensa Corporation, 225 Market St, Suite 502, Harrisburg, PA 17102, USA
b Pfizer Corporation, New York University School of Medicine, New York, NY, USA
c New York Medical College, Valhalla, NY, USA
d Brunel University, West London, UK
e Goldsmith Pharmacovigilance and Systems, New York, NY, USA
f Merck Research Laboratories, West Point, PA, USA
g Columbia University, New York, NY, USA


104
MedDRA and Signal Detection (cont)

• Methodology
  ◦ Data mining using three algorithms for signals of disproportionate reporting (SDRs) for 26 drugs in FDA’s AERS database
  ◦ Adverse events identified by PTs, HLTs, or SMQs

• Conclusions
  ◦ HLTs and SMQs can improve % of unlabeled supported SDRs in data mining
  ◦ Improvement holds for all algorithms tested
  ◦ Trade-off: HLTs, SMQs medically less-specific vs. PTs
  ◦ Need to examine component PTs of each HLT or SMQ that results in an SDR

Customized Searches
“Modified MedDRA Query Based on an SMQ”

- Do not modify SMQ unless there is a compelling reason – makes it non-standard
- 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
Browser Demonstration
SMQ View

MedDRA Versioning
Versioning BRP

- Blue Ribbon Panel (BRP)
  - Goal: develop recommendations on an issue
  - Panel members represent ICH regions
  - Observers play important role
  - MSSO presents recommendations to Board for approval

- Topics of this BRP
  - Extent of MedDRA versioning
  - Frequency of MedDRA releases

- Hosted by Schering-Plough, Kenilworth, NJ.
  13 May 2009.

BRP Panel Members

- Barry Hammond (GlaxoSmithKline)
- JoAnn Medbery (Johnson & Johnson)
- Tom Paternoster (European Medicines Agency)
- Toni Piazza-Hepp (US Food and Drug Administration)
- Yasuo Sakurai (Japanese Maintenance Organization)
Recommendations – Extent of Versioning

1. Content to be added as appendix to “MedDRA Term Selection: Points to Consider” (MTS: PTC). PTC WG should further develop content, align it with existing versioning language.

2. Add recommendation that organizations document upversioning strategy.

Recommendations – Extent of Versioning (cont)

3. Emphasis on *communication* of version extent; not to be interpreted as regulatory requirement.

4. Include impact, positive and negative, of each method of version updates (e.g., recoding non-current LLTs).
Recommendations – Feasibility of Annual Release

1. Remain biannual for now; revisit in 2011
2. How to assist small, new subscribers:
   a. To implement a new version without recoding is acceptable
   b. Develop tool to assess impact of new version and facilitate upversioning task (MSSO)
   c. Additional training on version update processes (MSSO)
3. Add to MTS:PTC MSSO’s recommendation for implementation date/time (00:00 GMT on 1st Monday of 2nd month after release)

Recommendations – Feasibility of Annual Release (cont)

4. MSSO to collate the versioning requirements of ICH regulatory authorities and post on MSSO website
5. Regulatory authorities should consider future use of supplemental terms

All recommendations endorsed by Management Board
Implementation of Recommendations

  - Section 4.1. Versioning
    - 4.1.1 Versioning methodologies
    - 4.1.2 Timing of version implementation

- Development of MedDRA Version Analysis Tool

### Versioning Methodologies

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
<th>Resource Intensity</th>
<th>Data Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Begin to use new version for coding new data; no recoding of existing data</td>
<td>Least</td>
<td>Least</td>
</tr>
<tr>
<td>2</td>
<td>Identify verbatim terms linked to non-current LLTs and recode existing data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Identify verbatim terms linked to non-current LLTs and recode existing data and Recode verbatim terms to new LLTs that are direct or lexical matches</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Identify verbatim terms linked to non-current LLTs and recode existing data and Recode verbatim terms to new LLTs that are direct or lexical matches and Recode verbatim terms to new LLTs that are more accurate concepts</td>
<td>Most</td>
<td>Most</td>
</tr>
</tbody>
</table>
Timing of Version Implementation

A new release version of MedDRA should become the reporting version on the first Monday of the second month after it is released. To synchronize this event over the three ICH regions, the MSSO recommends midnight GMT, Sunday to Monday, for the switchover. For example:

- 1 March – MedDRA X.0 released
- First Monday of May – MedDRA X.0 becomes the reporting version
- 1 September – MedDRA X.1 released
- First Monday of November – MedDRA X.1 becomes the reporting version

AERS and MedDRA Upversioning

- Scheduled upversioning of all AERS data
  - PT comparison between the 2 versions
  - Identification of PTs in the old version which are no longer in the new version
  - Mapping these PTs to an existing PT in the new version
  - Replacing these PT codes in AE reports early am first Monday of November/May

- Upversioning of the MSSO MedDRA browser, FDA Coding principles, OSE groups, etc
- Information distribution to staff, training sessions
Tutorial Summary

LEARNING OBJECTIVE: Review the various strategies for retrieval and subsequent analysis of MedDRA-coded data in clinical safety and pharmacovigilance

• In this tutorial we have:
  • Learned about the ‘MedDRA Data Retrieval and Presentation: Points to Consider’ document and reviewed various options for data retrieval for industry and regulatory purposes
  • Reviewed data quality issues
  • Learned about Standardised MedDRA Queries
  • Discussed customized searches
Tutorial Summary (cont)

LEARNING OBJECTIVE: Discuss the issues relating to MedDRA versioning

- In this tutorial we have:
  - Considered how MedDRA versioning affects data analysis
  - Discussed the implementation of the BRP recommendations
    - Versioning methodologies
    - Timing of version implementation
    - Development of a versioning tool