Meeting evolving pharmacovigilance needs
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Introduction

• Introduction: A standardised international medical terminology used throughout the clinical development cycle
• Recent developments in MedDRA for coding and analysis of *medication errors, overdoses*, and *off label use*
• Forthcoming changes: The 27th System Organ Class.
MedDRA Structure

System Organ Class (SOC) (26)

High Level Group Term (HLGT) (335)

High Level Term (HLT) (1,721)

Preferred Term (PT) (21,345)

Lowest Level Term (LLT) (74,229)
MedDRA

Levels in MedDRA

Synonyms, lexical variants, sub-elements

SOC = Cardiac disorders

HLGT = Cardiac arrhythmias

HLT = Rate and rhythm disorders NEC

PT = Arrhythmia

LLT = Arrhythmia NOS

LLT (Non-current)
Other specified cardiac dysrhythmias

Dysrhythmias

Not all LLTs

Not all LLTs shown
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

**HLT** = Viral upper respiratory tract infections
Where MedDRA is Used

Regulatory Authority and Industry Databases
Individual Case Safety Reports and Safety Summaries

Clinical Study Reports
Investigators’ Brochures
Core Company Safety Information
Marketing Applications
Publications
Prescribing Information
Advertising
Complex Changes
MedDRA Version 18.0
Medication errors are defined as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer.

Medication error with clinical consequences

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT 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></td>
</tr>
<tr>
<td>Insulin was given using the wrong syringe resulting in the administration of an overdose. The patient developed hypoglycaemia.</td>
<td>Wrong device used Accidental overdose Hypoglycaemia</td>
<td>If an overdose is reported in the context of a medication error, the more specific term LLT Accidental overdose can be selected</td>
</tr>
</tbody>
</table>
Medication Errors (cont)

• Medication error **without** clinical consequences

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT Selected</th>
<th>Preferred Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication was given intravenously instead of intramuscularly without sequelae</td>
<td>Intramuscular formulation administered by other route</td>
<td>✔</td>
</tr>
<tr>
<td></td>
<td>Intramuscular formulation administered by other route</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No adverse effect</td>
<td></td>
</tr>
</tbody>
</table>
Medication Errors (cont)

- Important to record potential occurrence of medication error
- Unlikely to be reported as an adverse event but may need to be recorded in periodic safety reports

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT Selected</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacist notices that the names of two drugs are similar and is concerned that this may result in a medication error</td>
<td>Drug name confusion</td>
<td>Note: this example is a potential medication error and LLT Drug name confusion provides additional information about the nature of the potential medication error</td>
</tr>
<tr>
<td></td>
<td>Circumstance or information capable of leading to medication error</td>
<td></td>
</tr>
</tbody>
</table>

Note: this example is a potential medication error and LLT Drug name confusion provides additional information about the nature of the potential medication error.
Definitions of misuse may not always include the concept of therapeutic use; misuse may be similar to the concept of abuse in some regions.
Updates to Product Use Concepts in v18.0

- MSSO and ICH M1 Points to Consider Working Group collaborated on improved organization of product use concepts
- New HLGT *Product use issues* in SOC *Injury, poisoning and procedural complications*
  - Overdoses, underdoses, misuse, off label use now grouped in one SOC with HLGT *Medication errors*
  - Facilitates coding and retrieval
- New HLTs
  - HLT *Product use issues NEC* (misuse, intentional use and non-specific use concepts)
  - HLT *Overdoses NEC* (replaces HLT *Overdoses*)
  - HLT *Underdoses NEC*
  - HLT *Off label uses*
MTS: PTC Section 3.16 Misuse, Abuse and Addiction

- Select the most specific term available and always check the MedDRA hierarchy above the selected term to be sure it is appropriate for the reported information. In some cases, it may be appropriate to select more than one MedDRA LLT to represent the reported information.
HLGT *Product use issues*

- Improved organization of product use concepts in MedDRA Version 18.0
- New HLGT *Product use issues*
- Medication errors, overdoses, underdoses, misuse, and off label use now in one SOC
- Facilitates coding and retrieval
5 years gap: From v8.0 to v18.0

Surgical and medical procedures
The 27th System Organ Class
Questions for BRP 8

- 29 April 2014, Gaithersburg, Maryland, USA
- BRP to discuss and provide recommendations to Management Board on:
  - What should be the scope of MedDRA as a medical and regulatory terminology?
  - What are the general criteria when considering new topic areas for expansion?
  - Where should new topics be placed in MedDRA?
Potential Topic Areas for Expansion

• New types of terms falling into “gray area” as defined by current scope
• Examples
  – Manufacturing product quality terms
  – Additional device related terms
  – Drug utilization terms
  – Labeling qualifiers
Harmonization of quality issue reporting and patient safety reporting is a benefit.

These terms should be separated from the rest of MedDRA (a 27th SOC is the favored option).

Terms need to be unambiguous to avoid confusion in coding (including auto-encoding) and in retrieval.

Terms should focus on product defects and process issues, less on human factors.
Device Related Terms – Scope Considerations

<table>
<thead>
<tr>
<th>Term Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Existing MedDRA Term</td>
</tr>
<tr>
<td>PT Wrong device used</td>
</tr>
</tbody>
</table>

- **Coordinate with other** stakeholders on device-related projects to harmonize multiple device reporting requirements and **terminologies**
- Terms need to be **unambiguous**
- Consider human **use factor terms** to identify root causes and systems/process errors, **not individual human errors**
Drug Utilization Terms
– Scope Considerations

<table>
<thead>
<tr>
<th>Term Example</th>
<th>Out of Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Existing MedDRA Term</td>
<td>Potential MedDRA Term (Gray area)</td>
</tr>
<tr>
<td>PT Refusal of treatment by patient</td>
<td>Drug withdrawn from market</td>
</tr>
</tbody>
</table>

✓ These terms relate to reasons why patients stop, start, or change medications

• *Identify use cases to learn* how these terms are used (likely to be more applicable for pharmacoeconomic analyses rather than ICSRs and patient safety reporting)
• The addition of these terms is a *low priority*
### Labeling Qualifiers – Scope Considerations

<table>
<thead>
<tr>
<th>Existing MedDRA Term</th>
<th>Potential MedDRA Term (Gray area)</th>
<th>Out of Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT Convulsion prophylaxis</td>
<td>Failed first-line treatment</td>
<td>15-17 years</td>
</tr>
</tbody>
</table>

- **Identify use cases to learn** how these terms are used
  - ✓ (reference EMA and MSSO’s review of the use of MedDRA in coding indications in labeling for centrally authorized products)
- **Low priority**
- If added, the circumstances for using these qualifiers should be clearly defined
- Labeling qualifiers should be in a maintained **list outside of MedDRA’s current structure**
MedDRA Management Board endorsed creation of an additional (27th) SOC

To accommodate non-clinical/non-patient concepts covering issues related to medical products
  – Important because they may affect patient safety

Will include product quality issues

Complex change proposals to be posted July 2015

Planned implementation date March 2016 (MedDRA Version 19.0)
• Updates, presentations, information
• Communication Document
  – Purpose, timing, potential impact of new SOC
27th SOC Features

• Same structure and characteristics of other SOCs
  – Five level hierarchy (SOC, HLGT, HLT, PT, LLT)
  – 100 character limit for terms
  – 8 digit MedDRA codes
  – Multi-axial links to aid in retrieval and preserve links to patient safety
    • PT Transmission of an infectious agent via product (primary link to SOC Infections and infestations)
• Terms must be *unambiguous* at all levels
  – Clear concept descriptions where necessary
• No general need to distinguish between issues occurring during manufacturing vs. post-distribution phase
• Important distinction between concepts
  – Quality system issue/deviation - may or may not lead to:
  – Product quality issue – may or may not lead to:
  – Adverse event
Miscoding Vs. Non apparent Medication Error cases

- **Accidental poisoning**
  - In a regulator database, 50% relevant ME cases without ME code (missing PTs: *Accidental exposure to product by child*, *Accidental overdose*, *Incorrect dose*)

- **Failure of child resistant mechanism for pharmaceutical product**
  - Cases co-coded with PT *Accidental exposure to product by child*

- **Product label on wrong product**
  - In a regulator database, 90% of cases with this PT are true product quality issues, but ~10% are miscodings of a medication error
• **Device infusion issue**
  – There are some cases missing the code for the stated ME

• **Product label issue**
  – PT used for a variety of scenarios, including other specific product quality issues and also for label-confusion medication error
References

  - Quality system and five manufacturing systems

- ICH Quality Guidelines including Q10 Pharmaceutical Quality System
  - Harmonization with ICH standards is goal
• Must describe contents/purpose but not restrict addition of other non-clinical/non-patient topics in future

• Some suggestions to start
  – Product issues
  – Medical product issues
  – Product related issues
  – Medical product related issues
  – Product and quality system issues
  – Product and production system issues
MedDRA Files

MedDRA files distributed with each release
• Detail of SOC file displayed

<table>
<thead>
<tr>
<th>Code</th>
<th>Name</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>10005329</td>
<td>Blood and lymphatic system disorders</td>
<td>Blood</td>
</tr>
<tr>
<td>10007541</td>
<td>Cardiac disorders</td>
<td>Card</td>
</tr>
<tr>
<td>10010331</td>
<td>Congenital, familial and genetic disorders</td>
<td>Cong</td>
</tr>
<tr>
<td>10013993</td>
<td>Ear and labyrinth disorders</td>
<td>Ear</td>
</tr>
<tr>
<td>10014688</td>
<td>Endocrine disorders</td>
<td>Endo</td>
</tr>
<tr>
<td>10015919</td>
<td>Eye disorders</td>
<td>Eye</td>
</tr>
<tr>
<td>10017947</td>
<td>Gastrointestinal disorders</td>
<td>Gastr</td>
</tr>
<tr>
<td>10018065</td>
<td>General disorders and administration site conditions</td>
<td>Genrl</td>
</tr>
<tr>
<td>10019805</td>
<td>Hepatobiliary disorders</td>
<td>Hepat</td>
</tr>
<tr>
<td>10021428</td>
<td>Immune system disorders</td>
<td>Immun</td>
</tr>
<tr>
<td>10021881</td>
<td>Infections and infestations</td>
<td>Infec</td>
</tr>
<tr>
<td>10022117</td>
<td>Injury, poisoning and procedural complications</td>
<td>Inj&amp;P</td>
</tr>
<tr>
<td>10022891</td>
<td>Investigations</td>
<td>Inv</td>
</tr>
<tr>
<td>10027433</td>
<td>Metabolism and nutrition disorders</td>
<td>Metab</td>
</tr>
<tr>
<td>10028395</td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musc</td>
</tr>
<tr>
<td>10029104</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Neopl</td>
</tr>
<tr>
<td>10029205</td>
<td>Nervous system disorders</td>
<td>Nerv</td>
</tr>
<tr>
<td>10036585</td>
<td>Pregnancy, puerperium and perinatal conditions</td>
<td>Preg</td>
</tr>
<tr>
<td>10037175</td>
<td>Psychiatric disorders</td>
<td>Psych</td>
</tr>
<tr>
<td>10038359</td>
<td>Renal and urinary disorders</td>
<td>Renal</td>
</tr>
<tr>
<td>10038604</td>
<td>Reproductive system and breast disorders</td>
<td>Repro</td>
</tr>
<tr>
<td>10038738</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Resp</td>
</tr>
<tr>
<td>10040785</td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Skin</td>
</tr>
<tr>
<td>10041244</td>
<td>Social circumstances</td>
<td>SocCi</td>
</tr>
<tr>
<td>10042613</td>
<td>Surgical and medical procedures</td>
<td>Surg</td>
</tr>
<tr>
<td>10047065</td>
<td>Vascular disorders</td>
<td>Vasc</td>
</tr>
</tbody>
</table>

New # | New SOC Name | Abbrev
------|--------------|-------

Two Levels of IT Systems

Commercial systems

- Clinical, Safety, and Electronic Data Capture
- Validated by developer and end user organization
- MedDRA loading based on contents of MedDRA files

Locally developed

- No major impact on AE data summaries or subsequent conclusions
- If no terms are reported, SOC is not displayed, e.g., SOC Social circumstances
- Minimal impact on organizations not involved in product quality
MSSO Tools

- No impact on Desktop Browser, Web-Based Browser, MVAT, WebCR
- Mock files successfully loaded and tested
Impact on Documentation and Processes

- MSSO documents, e.g., Introductory Guide
- SOPs, procedures documentation
- In-house coding and retrieval guidelines
- Points to Consider documents
- Regulatory data standards, guidances, and rules
Thank You

Questions?