Use of MedDRA: Focus on the New Scope of Adverse Event Reporting

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Overview

- Existing terms in MedDRA for off label use, overdose, misuse, abuse, medication errors, and occupational exposure
- Current coding recommendations in MedDRA Term Selection: Points to Consider document (MTS:PTC) for MedDRA
  - Significant revision to PTC document to support these types of terms
• There are two PTC documents
  – Term Selection
  – Data Retrieval and Presentation

• Using MedDRA is a big step forward
• Using MedDRA the same way is a leap toward harmonization

Off Label Use – Terms in MedDRA (1)

• Currently in MedDRA

  - Off label use
  - Adult product administered to child
  - Child product given to infant
  - Drug use for unapproved indication
  - Drug use in unapproved population
  - Drug use via unapproved administration route
  - Intentional use for unlabeled indication
  - Intentional use for unlabelled indication
  - Off label use
• MedDRA Introductory Guide, Appendix B (Concept Descriptions) includes the following:

**Off Label Use**

Off label use is defined as a practice of prescribing pharmaceuticals outside the scope of the drug’s approved label, most often concerning the drug’s indication.

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**Off Label Use – EMA Definition**

• Off label use

This relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information

EMA. Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products
3.26.1 Off label use when reported as an indication

"Off label use" refers to use of a product for an indication for which it is not labeled.

If a medical condition is reported as an indication along with "off label use", the preferred option is to select terms for the medical condition and LLT Off label use or other appropriate LLTs linked to PT Off label use for the "indications" field. Alternatively, select a term for the medical condition/indication alone. Select LLT Off label use alone only if it is the only information available.

Example

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT Selected</th>
<th>Preferred Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension; this is off label use</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Off label use</td>
<td></td>
</tr>
</tbody>
</table>

✓
Off Label Use – MTS:PTC (3)

Example

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT Selected</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off label use</td>
<td>Off label use</td>
<td></td>
</tr>
<tr>
<td>Off label use in paediatric patients</td>
<td>Drug use in unapproved population</td>
<td>Refers to a population of patients</td>
</tr>
<tr>
<td>Drug X given to a 10 year old boy; the drug is not indicated for use below 18 years</td>
<td>Adult product administered to child</td>
<td>LLT: Adult product administered to child is linked to PT Off label use</td>
</tr>
</tbody>
</table>

Off Label Use – MTS:PTC (4)

3.26.2 Off label use when reported with an AR/AE

If an AR/AE occurs as a result of off label use, the preferred option is to select LLT Off label use, or other appropriate LLTs linked to PT Off label use, and a term for the medical condition for the “indications” field in addition to a term for the AR/AE. Alternatively, select a term for the medical condition for the “indications” field and a term for the AR/AE in the “AR/AE” field.
Off Label Use – MTS:PTC (5)

Example

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT Selected</th>
<th>Preferred Option</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient was administered a drug off label for pulmonary hypertension and suffered a stroke</td>
<td>Stroke Pulmonary hypertension</td>
<td>Record LLT Stroke in an AR/AE field.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stroke Off label use Pulmonary hypertension</td>
<td></td>
<td>Record LLT Pulmonary hypertension in an indications field.</td>
</tr>
</tbody>
</table>

Off Label Use – Proposed Changes

- Add revised definition of “off label use” to MTS:PTC and MedDRA Introductory Guide
- Remove all references to using specific “indications” and “AR/AE” data fields
### “Overdose” LLTs (MedDRA v15.0) [TOTAL = 27]

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accidental overdose</td>
<td>Drug toxicity due to accidental dosage</td>
<td>Overdose</td>
</tr>
<tr>
<td>Accidental overdose (nontherapeutic agent or chemical)</td>
<td>Drug toxicity due to intentional overdose</td>
<td>Overdose accidental</td>
</tr>
<tr>
<td>Accidental overdose (therapeutic agent)</td>
<td>Intentional overdose</td>
<td>Overdose deliberate self-inflicted</td>
</tr>
<tr>
<td>Acute overdose</td>
<td>Medically prescribed overdose</td>
<td>Overdose effect</td>
</tr>
<tr>
<td>Chronic overdose</td>
<td>Multiple drug overdose</td>
<td>Overdose intentional</td>
</tr>
<tr>
<td>Deliberate overdose</td>
<td>Multiple drug overdose accidental</td>
<td>Overdose NOS</td>
</tr>
<tr>
<td>Drug overdose</td>
<td>Multiple drug overdose intentional</td>
<td>Prescribed overdose</td>
</tr>
<tr>
<td>Drug overdose accidental</td>
<td>Multiple drug overdose prescribed</td>
<td>Radiation overdose</td>
</tr>
<tr>
<td>Drug overdose deliberate self-inflicted</td>
<td>Non-accidental overdose</td>
<td>Suicide attempt other than overdose</td>
</tr>
</tbody>
</table>

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### MedDRA Introductory Guide (v15.1), Appendix B (Concept Descriptions)

**Overdose**

More than medically recommended dose (in quantity and/or concentration) is administered. An excessive dose.
Overdose – EMA Definition

• Overdose
  This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorised product information. Clinical judgement should always be applied.

EMA. Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products.
3.17.2 Overdose reported *without* clinical consequences

If an overdose report specifically states that there were no clinical consequences, select I I T Overdose and the additional I I T No adverse effect can be selected (See Section 3.20).

Example

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT Selected</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient received an overdose of medicine without any adverse consequences</td>
<td>Overdose&lt;br&gt;No adverse effect</td>
<td>LLT No adverse effect can also be selected</td>
</tr>
</tbody>
</table>
Misuse – Terms in MedDRA

- Concept has been challenging to define
  - Is all misuse “intentional”?
- No wording in current MTS:PTC addressing “misuse”

Misuse – EMA Definition

- Misuse
  This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information.

EMA. Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products.
Misuse – Proposed Changes

• Add a new sub-section to MTS:PTC – Misuse, abuse and addiction
• Add definitions of these concepts to MTS:PTC and MedDRA Introductory Guide
• Provide examples of term selection

Abuse – Terms in MedDRA (1)

<table>
<thead>
<tr>
<th>Abusive behavior</th>
<th>Analgesic abuse</th>
<th>Cannabis abuse, episodic use</th>
<th>Diuretic abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abusive behaviour</td>
<td>Antabuse effect</td>
<td>Cannabis abuse, in remission</td>
<td>Drug abuse</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>Antabuse implant</td>
<td>Cannabis abuse, unspecified use</td>
<td>Drug abuse in remission</td>
</tr>
<tr>
<td>Alcohol abuse chronic</td>
<td>Antidepressant type abuse</td>
<td>Chemical abuser</td>
<td>Drug abuse NOS</td>
</tr>
<tr>
<td>Alcohol abuse, continuous drinking behavior</td>
<td>Antidepressant type abuse, continuous use</td>
<td>Child abuse</td>
<td>Drug abuser</td>
</tr>
<tr>
<td>Alcohol abuse, continuous drinking behavior</td>
<td>Antidepressant type abuse, episodic use</td>
<td>Child abuser</td>
<td>Drug abuser NOS</td>
</tr>
<tr>
<td>Alcohol abuse, episodic drinking behavior</td>
<td>Antidepressant type abuse, in remission</td>
<td>Child sexual abuse</td>
<td>Elder abuse</td>
</tr>
<tr>
<td>Alcohol abuse, episodic drinking behavior</td>
<td>Antidepressant type abuse, unspecified use</td>
<td>Cocaine abuse</td>
<td>Elder abuser</td>
</tr>
<tr>
<td>Alcohol abuse, in remission</td>
<td>Barbiturate abuse</td>
<td>Cocaine abuse, continuous use</td>
<td>Enema abuse</td>
</tr>
<tr>
<td>Alcohol abuse, unspecified drinking behavior</td>
<td>Caffeine abuse</td>
<td>Cocaine abuse, episodic use</td>
<td>Ex-drug abuser</td>
</tr>
<tr>
<td>Alcohol abuse, unspecified drinking behavior</td>
<td>Cannabis abuse</td>
<td>Cocaine abuse, in remission</td>
<td>Hallucinogen abuse</td>
</tr>
<tr>
<td>Amphetamine abuse</td>
<td>Cannabis abuse, continuous use</td>
<td>Cocaine abuse, unspecified use</td>
<td>Hallucinogen abuse, continuous use</td>
</tr>
</tbody>
</table>
Abuse – Terms in MedDRA (2)

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallucinogen abuse, episodic use</td>
<td>Nondependent abuse of drugs</td>
</tr>
<tr>
<td>Hallucinogen abuse, in remission</td>
<td>Nondependent abuse of drugs of amphetamine type</td>
</tr>
<tr>
<td>Hallucinogen abuse, unspecified use</td>
<td>Nondependent abuse of drugs of cocaine type</td>
</tr>
<tr>
<td>Infection in patient who abuses drugs</td>
<td>Nondependent abuse of drugs of morphine type</td>
</tr>
<tr>
<td>Intravenous drug abusers</td>
<td>Nondependent abuse of drugs, antidepressants</td>
</tr>
<tr>
<td>Laxative abuse</td>
<td>Nondependent abuse of hallucinogens</td>
</tr>
<tr>
<td>Narcotic abuse</td>
<td>Nondependent abuse of tobacco</td>
</tr>
<tr>
<td>Neonatal complications of substance abuse</td>
<td>Non-dependent tobacco abuse</td>
</tr>
<tr>
<td>Neonatal complications of substance abuse</td>
<td>Opioid abuse</td>
</tr>
<tr>
<td>NOS</td>
<td>Spousal abuse</td>
</tr>
<tr>
<td>Nicotine abuse</td>
<td>Opioid abuse, continuous use</td>
</tr>
<tr>
<td>Nondependent abuse of alcohol</td>
<td>Opioid abuse, episodic use</td>
</tr>
<tr>
<td>Nondependent abuse of cannabis</td>
<td>Opioid abuse, in remission</td>
</tr>
<tr>
<td>Tobacco abuse</td>
<td></td>
</tr>
<tr>
<td>Physical abuse</td>
<td></td>
</tr>
<tr>
<td>Tranquilizer abuse</td>
<td></td>
</tr>
<tr>
<td>Polydrug abuse</td>
<td></td>
</tr>
<tr>
<td>Verbal abuse</td>
<td></td>
</tr>
<tr>
<td>Psychological abuse</td>
<td></td>
</tr>
<tr>
<td>Verbally abused</td>
<td></td>
</tr>
</tbody>
</table>

Abuse – Terms in MedDRA (3)

- No wording in current MTS:PTC specifically addressing “abuse”
- MedDRA Introductory Guide (v15.1)

**SOC Psychiatric disorders, “Basis for Classification”**

Conditions associated with substance abuse (e.g., LLT Enema abuse, LLT Laxative abuse under PT Drug abuse, and PT Alcoholism) are included in SOC Psychiatric disorders in HLT Substance-related disorders.

According to DSM-IV, the official psychiatric term for addiction is “substance dependence.” Therefore, the word “addiction,” in general, only appears at the LLT level in MedDRA.

For new “abuse” terms in MedDRA, the text string is devised to distinguish terms in SOC Social circumstances from those in SOC Psychiatric disorders. “Abuse” terms are linked to SOC Psychiatric disorders and kept independent of “dependence” counterparts PTs. Terms that refer to a person, such as PT Drug abuser, are in SOC Social circumstances.
Abuse – EMA Definition

• Abuse
  This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects

EMA. Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products.

Abuse – Proposed Changes

• Add a new sub-section to MTS:PTC – Misuse, abuse and addiction
• Add definitions of these concepts to MTS:PTC and MedDRA Introductory Guide
• Provide examples of term selection
Expansion of Medication Error Terms

- Prior to MedDRA Version 8.0, only one term existed - PT Medication error
- Medication error section expanded in v8.0
  - Added HLGT Medication errors in SOC Injury, poisoning and procedural complications
  - HLT Maladministrations
  - HLT Medication errors due to accidental exposures
  - HLT Medication monitoring errors
  - HLT Overdoses
  - HLT Medication errors NEC

Medication Error Definition (1)

- MedDRA Introductory Guide (v15.1), Appendix B (Concept Descriptions)

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 control of the health care professional, patient or consumer. Such events may be related to professional practice, health care products, procedures and systems, including prescribing, order communication, product labeling, packaging and nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use.

National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP)
Medication Error Definition (2)

- A preventable event
  - Intentional action is NOT an “error”
- Includes intercepted and not intercepted errors, because
  - Patient harm is NOT required
  - Inappropriate use of the medication is NOT required
- Applies to all stages of medication handling and process

Concept Descriptions

- Appendix B in MedDRA Introductory Guide
- To assist in understanding and appropriate use of medication error and product quality issue terms in regulatory reporting
- Medication error descriptions developed by FDA and MSSO
Medication Error Concept Description Example

• **Documented hypersensitivity to administered drug:** This medication error refers to the situation when a patient is administered a drug that is documented in the patient's medical file to cause a hypersensitivity reaction in the patient. Example: Despite the fact that the patient's medical record indicated "sulfa allergy," the physician prescribed a sulfa antibiotic. Subsequently, the patient took the antibiotic and experienced hives.

Medication Errors – Terms in MedDRA

• **163 LLTs under HLGT**
  - **Medication errors**
    - Examples
      - **LLT Intramuscular formulation administered by other route**
      - **LLT Wrong drug dispensed**
    - **Note:** Includes "overdose" terms
3.15 – Medication/Administration Errors and Accidental Exposures
Reports of medication errors may or may not include information about clinical consequences.

Appendix B of the ModDRA Introductory Guide contains descriptions of the interpretation and use of certain medication error terms (e.g., “Dispensing error”).

3.15.1 Medication error reported with clinical consequences
3.15.2 Medication error reported without clinical consequences
3.15.3 Accidental exposures
3.15.4 Medication errors in the context of labeled interactions
3.15.5 Do not infer a medication error

• There can be overlap between product quality issues and medication errors
• An example of both a product quality issue and a medication error is provided

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT Selected</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>The mother administered insufficient amount of prescribed antibiotic because the lines on the dropper were hard to read</td>
<td>Product dropper calibration unreadable Insufficient dosage</td>
<td>Product quality issue and medication error</td>
</tr>
</tbody>
</table>
Medication Errors – Proposed Changes

• Add definition of medication error to MTS:PTC

Occupational Exposure – Terms in MedDRA

“Occupational Exposure”
Terms [TOTAL = 11]
(MedDRA v15.0)

- Occupational exposure to air contaminants
- Occupational exposure to air contaminants NOS
- Occupational exposure to drug
- Occupational exposure to dust
- Occupational exposure to extreme temperature
- Occupational exposure to noise
- Occupational exposure to radiation
- Occupational exposure to toxic agent
- Occupational exposure to toxic agents NOS
- Occupational exposure to toxic agricultural agents
- Occupational exposure to vibration
• Occupational exposure
  This refers to the exposure to a medicinal product as a result of one’s professional or non-professional occupation

EMA. Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products.

• Not specifically referenced, but covered under “accidental exposures”

### 3.15.3 Accidental exposures
The same principles apply to accidental exposures.

**Example**

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT Selected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurse splashed injectable drug in her own eye resulting in excessive tearing</td>
<td>Inadvertent exposure to drug Excess tears</td>
</tr>
<tr>
<td>Child accidentally took grandmother’s pills and experienced projectile vomiting</td>
<td>Accidental drug intake by child Vomiting projectile</td>
</tr>
<tr>
<td>Father applying topical steroid to his arms accidentally exposed his child to the drug by carrying her</td>
<td>Exposure via skin contact</td>
</tr>
</tbody>
</table>
Occupational Exposure – Proposed Changes

• Add a new sub-section to MTS:PTC – Accidental exposures and occupational exposures
• Add definition of “occupational exposure” to MTS:PTC and MedDRA Introductory Guide
• Provide examples of term selection

Summary

• There is regulatory interest in “special situations”
  – Off label use
  – Overdose
  – Misuse
  – Abuse
  – Medication errors
  – Occupational exposure
• MedDRA covers most such concepts and can expand as needed through Change Requests
• MTS:PTC also addresses some of these; more may come in the future
Thank You