Applying MedDRA® in Clinical Safety and Pharmacovigilance

DIA Tutorial
10 January 2010

Judy E. Harrison, M.D.
Medical Officer, MedDRA MSSO

MedDRA® is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).

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
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 of Mandate

• US FDA
  ◆ Used in FDA’s adverse event database (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 of Mandate (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 of Mandate (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
    ▪ Use in Undesirable Effects section

Regulatory Status of Mandate (cont)

• ICH M4E Guideline on Common Technical Document
  ◦ Recommended in adverse event summary tables

• Canada
  ◦ Reporting Adverse Reactions to Marketed Health Products (draft guidance)
    ▪ Recommended as standard for adverse reaction reports
  ◦ Product Monograph (labeling)
    ▪ Preferred terminology for adverse drug reactions
**Scope of MedDRA**

- Diseases
- Diagnoses
- Signs
- Symptoms
- Therapeutic indications
- Investigation names & qualitative results
- Medical & surgical procedures
- Medical, social, family history
- Terms from: COSTART®
  - WHO-ART®
  - HARTS®
  - J-ART®

**MedDRA Structure**

- System Organ Class (SOC) (26)
- High Level Group Term (HLGT) (333)
- High Level Term (HLT) (1,699)
- Preferred Term (PT) (18,483)
- Lowest Level Term (LLT) (67,159)
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 (Non-current)
Dysrhythmias
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

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
A Multi-Axial Terminology (cont)

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
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

General Principles

- Quality of source data
- Level of term selection
- Use of “Current”/“Non-current” Lowest Level Terms (LLTs)
- Choice of term
- Do not subtract or add information
- Quality Assurance
Quality of Source Data

- Obtain clarification of data that are confusing, ambiguous, or unintelligible
- Can be optimized by careful design of data collection forms and proper training of relevant staff
- **REMEMBER:** No terminology (including MedDRA) will help in understanding data that is of poor quality; best to get good information at the beginning

Level of Term Selection

Use of “Current”/”Non-current” LLTs

- Lowest level term(s) that "most accurately reflects the reporter’s words" should be selected
  - Example: “Abscess on face” → select “Facial abscess,” not simply “Abscess”
- Select **current** LLTs only
  - Non-current terms for legacy conversion/ historical purposes
Choice of Term

- Avoid company-specific “work-arounds” for MedDRA deficiencies. If concept not adequately represented in MedDRA, submit Change Request to MSSO.
- If no exact match in MedDRA, use medical judgment to match to an existing term that adequately represents the concept.

Do Not Subtract or Add Information

- Select terms for every ADR/AE reported, regardless of perceived relationship to drug:
  - If diagnosis reported with characteristic signs and symptoms, acceptable to select term only for diagnosis.
- Do not make diagnosis if only signs/symptoms reported:
  - Example: “Abdominal pain” + “Increased serum amylase” + “Increased serum lipase” → inappropriate to select “Pancreatitis”.
Quality Assurance

• Human oversight of automated coding results
• Qualification of coder/review staff
• Errors in MedDRA should be addressed by submission of Change Requests to MSSO; no *ad hoc* structural alterations to MedDRA

Term Selection Points

• Diagnoses 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 vs. Infectious agent
• Pre-existing medical conditions
• Exposure during pregnancy and breast feeding
• Congenital terms
• Neoplasms
• Medical/surgical procedures
Term Selection Points (cont)

- Investigations
- Medication/administration errors and accidental exposures
- Transmission via medicinal product of infectious agent
- Overdose/Toxicity/Poisonings
- Device terms
- Drug interactions
- No adverse effect
- Unexpected therapeutic effect
- Modification of effect
- Social circumstances
- Medical and/or social history
- Indication for product use
- Off label use

---

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>Provisional diagnosis (only possible option)</td>
</tr>
<tr>
<td>• Diagnosis (only possible option)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Example: &quot;Myocardial infarction&quot; → select &quot;Myocardial infarction&quot;</td>
<td>Example: &quot;Possible myocardial infarction&quot; → 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>
</tr>
</thead>
<tbody>
<tr>
<td>DEFINITIVE DIAGNOSIS</td>
</tr>
<tr>
<td>Single diagnosis with signs/symptoms</td>
</tr>
<tr>
<td>•Preferred: Diagnosis only</td>
</tr>
<tr>
<td>Example: &quot;Anaphylactic reaction with rash, dyspnea, hypotension, and laryngospasm&quot; → select &quot;Anaphylactic reaction&quot;</td>
</tr>
</tbody>
</table>

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

• Always include signs/symptoms not associated with diagnosis
  ◦ Example: “Myocardial infarction” is reported with “chest pain, dyspnea, diaphoresis, ECG changes and jaundice” → appropriate to select at least “Myocardial infarction” and “Jaundice”

Investigations

• Medical condition vs. laboratory result
  ◦ “Hypoglycemia” → “Hypoglycemia” can be selected
  ◦ “Decreased glucose” → “Glucose decreased” can be selected

• Unambiguous laboratory result
  ◦ Value reported is clearly out of reference range. Example: “Glucose 40 mg/dL” → “Glucose low” can be selected

• Ambiguous laboratory result
  ◦ “Glucose was 40” (note: no units) → “Glucose abnormal” can be selected
Investigations (cont)

• If diagnosis/condition and diagnostic (test) result provided, appropriate to code only diagnosis/condition
  ▪ Example: “Elevated potassium, K 7.0 mmol/L, and hyperkalemia” → “Hyperkalemia” can be selected
• Do not combine separate tests results into one single term
  ▪ Example: “Increased alkaline phosphatase, increased SGPT, increased SGOT and increased LDH” → “Alkaline phosphatase increased,” “SGPT increased,” “SGOT increased,” and “LDH increased” can be selected

Transmission via Medicinal Product of Infectious Agent

• If reported, appropriate to select term for transmission (suspected or confirmed). If specified, also appropriate to select term for infectious agent.
  ▪ Example: “Suspected transmission of Hepatitis C via a blood product” → “Suspected transmission of an infectious agent via a medicinal product” and “Hepatitis C” can be selected
Data Quality Issues

Pharmacovigilance Data Quality

• Volume 9A on PSURs: non-compliance may include poor quality reports
  - “Absence of use of standardised medical terminology (e.g. MedDRA)”
  - Poor documentation/ insufficient information for adverse reactions
  - New safety signals not or poorly assessed
  - Misuse not highlighted
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)

Acknowledgement: Dr. Toni Piazza-Hepp, Office of Surveillance and Epidemiology, CDER

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: “Stevens Johnson syndrome” coded as rash

Acknowledgement: Dr. Toni Piazza-Hepp, Office of Surveillance and Epidemiology, CDER
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

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

Quality of Source Data

- High quality data output is dependent on maintaining quality of original information reported by using consistent and appropriate term selection (Refer to “MedDRA Term Selection: Points to Consider” document)
- Method of conversion of data into MedDRA might impact retrieval and presentation - legacy data conversion using verbatims or coded terms
Legacy Data Conversion – Comparing Verbatim to Coded Term Approach

<table>
<thead>
<tr>
<th>Verbatim</th>
<th>MedDRA PT (based on verbatim)</th>
<th>Orig coded term (COSTART)</th>
<th>MedDRA PT (based on orig COSTART term)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R) knee effusion</td>
<td>Joint effusion</td>
<td>ARTHROSIS</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>Common cold</td>
<td>Nasopharyngitis</td>
<td>INFECTION</td>
<td>Infection</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td>Periorbital oedema</td>
<td>FACE EDEMA</td>
<td>Face oedema</td>
</tr>
<tr>
<td>Seasonal allergies</td>
<td>Seasonal allergy</td>
<td>ALLERGIC REACTION</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Skin injury</td>
<td>Skin injury</td>
<td>SKIN DISORDER</td>
<td>Skin disorder</td>
</tr>
</tbody>
</table>

Documentation of Data Retrieval and Presentation Practices

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

- Database structure
- Data storage
- Data migration
- Coding practices over time
- Limitations/restrictions (inability to view secondary SOCs)
- Term selection principles
  - More than one term selected increases counts
  - Diagnosis term only selected reduces counts

Impact of MedDRA’s Characteristics – Grouping Terms

- HLGTs and HLTs provide clinically relevant groupings
  - HLGT *Cardiac arrhythmias*
    - HLT *Cardiac conduction disorders*
    - HLT *Rate and rhythm disorders NEC*
    - HLT *Supraventricular arrhythmias*
    - HLT *Ventricular arrhythmias and cardiac arrest*
Data Retrieval PTC
Impact of MedDRA’s Characteristics – Grouping Terms

• 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

Which level? – SOC Investigations

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA 12.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Investigations</td>
<td>13 (29.5%)</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>PT Aspartate aminotransferase increased</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>PT Alanine aminotransferase increased</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>PT Gamma-glutamyltransferase increased</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>PT Blood creatine phosphokinase increased</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>PT Blood alkaline phosphatase increased</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Blood glucose increased</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PT Blood lactate dehydrogenase increased</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Lipase increased</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT White blood cell count decreased</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Blood amylase increased</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Faecal fat increased</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Patients may have more than one event reported
### Which level? – SOC Investigations (cont)

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA 12.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Investigations</td>
<td>13 (29.5%)</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>PT Blood pressure increased</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Blood urea increased</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Occult blood positive</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Liver function test abnormal</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Monocyte count decreased</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Protein urine present</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Patients may have more than one event reported

---

### Which level? – SOC Investigations (cont)

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA 12.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Investigations</td>
<td>13 (29.5%)</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>HLT Liver function analyses</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>HLT Tissue enzyme analyses NEC</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>HLT Digestive enzymes</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>HLT White blood cell analyses</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>HLT Skeletal and cardiac muscle analyses</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>HLT Carbohydrate tolerance analyses (incl diabetes)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HLT Faecal analyses NEC</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HLT Vascular tests NEC (incl blood pressure)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>HLT Renal function analyses</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>HLT Urinalysis NEC</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Patients may have more than one event reported
Granularity

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

Multi-Axiality

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

<table>
<thead>
<tr>
<th>Reported event (% subjects)</th>
<th>Other terminology</th>
<th>MedDRA Version 12.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coded term (% subjects)</td>
<td>Body System/SOC (% subjects)</td>
</tr>
<tr>
<td>Hyperglycemia (4.1)</td>
<td>Hyperglycemia (10.5)</td>
<td>Metabolism and nutritional disorders (10.5)</td>
</tr>
<tr>
<td>Increased blood sugar (2.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose increased (2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose was high (1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increasing glucoses (0.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Multi-Axiality (cont)

- Main presentation is by Primary SOC
- Secondary SOCs used for alternate views and presentation of data
### Primary SOC Analysis – SOC Infections and infestations

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA 12.0)</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 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 12.0)</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>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Localised 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 12.0)</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 (cont) -
Effect of Primary SOC Change

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

<table>
<thead>
<tr>
<th>MedDRA Version 12.0</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC General disorders and administration site conditions</td>
<td>0</td>
</tr>
<tr>
<td>SOC Vascular disorders</td>
<td>20</td>
</tr>
<tr>
<td>PT Peripheral coldness</td>
<td>67</td>
</tr>
</tbody>
</table>

General Queries and Retrieval

• General Principles
  • Data retrieval performed for multiple purposes; analysis of clinical trial data, pharmacovigilance, etc.
  • Various strategies, methods, and tools
  • Update previously used searches
  • Identify safety issues prior to retrieval
  • Consider data analysis plan
  • Group related events
  • Document strategy
  • Evaluate search results against original question
General Queries and Retrieval (cont)

• Types of searches
  - Overview of safety profile in summary reports
  - Comparison of frequency of ADR/AE (spontaneous reports or incidence for studies)
  - Analysis of a specific safety concern
  - Identification of patient subpopulations at risk
    - Searching medical history information
    - Pediatric and gender-specific data (see MSSO and JMO Web sites for adverse event term lists)

Overall Presentation of Safety Profiles

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

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

Primary SOC Graphical Display Example
Focused Search: Secondary SOC Assignments

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

Secondary SOC Graphical Display Example
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
Example – Cardiac Arrhythmias

- Obvious starting point – HLGT Cardiac arrhythmias (“Top-down” search)
- Also use “Arrhythmia” terms as starting point of “Bottom-up” search
- What about non-multi-axial SOCs?

Example – Cardiac Arrhythmias (cont)

- SOC Investigations
  - PTs subordinate to HLT ECG investigations and HLT Heart rate and pulse investigations should be reviewed
    - Example: PT Heart rate irregular
Example –
Cardiac Arrhythmias (cont)

- SOC *Surgical and medical procedures*
  Important to review:
  - PTs subordinate to HLT *Cardiac device therapeutic procedures*:
    - Example: PT *Implantable defibrillator insertion*
  - PTs subordinate to HLT *Cardiac therapeutic procedures NEC*:
    - Example: PT *Cardioversion*

*Note: Pacemaker and other cardiac therapeutic procedure terms were not included in SMQ *Cardiac arrhythmias*.

Example –
Cardiac Arrhythmias (cont)

- Because arrhythmias may produce various signs and symptoms, you may wish to review PTs subordinate to the following HLTs:
  - HLT *Disturbances in consciousness NEC*
  - HLT *Neurological signs and symptoms NEC*
  - HLT *Cardiac disorders NEC*
  - HLT *Cardiac signs and symptoms NEC*
  - HLT *Dyspnoeas*
Example – Cardiac Arrhythmias (cont)

• Lastly...
  ✷ PTs subordinate to HLT *Death and sudden death* (under SOC *General disorders and administration site conditions*) should be reviewed
    ▪ Example: PT *Cardiac death*

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 12.0, a total of 74 in production (Other SMQs in development)

- Adverse pregnancy outcome/reproductive toxicity (incl neonatal disorders)
- Agranulocytosis
- Anaphylactic reaction
- Cerebrovascular disorders
- Convulsions
- Depression and suicide/self-injury
- Hepatic disorders
- Ischaemic heart disease
- Lack of efficacy/effect
- Peripheral neuropathy
- Pseudomembranous colitis
- Rhabdomyolysis/myopathy
- Severe cutaneous adverse reactions
- Systemic lupus erythematosus
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
- 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 lactic acid metabolic acidosis. Lactic acid tolerance may be decreased, but metabolic function can be normal because of carbohydrate release. Peripherally arterial vasodilatation and central vasoconstriction can be present. Central nervous system function is depressed with headache, lethargy, stupor, and in some cases, even coma. Close adherence may occur. Characterized by an increase in plasma l-lactate. Acidosis is seldom significant unless blood lactate exceeds 5 mmol/L. Clinical presentation in type B lactic acidosis: symptoms: hyperventilation or hyperventilation, stupor 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 our regulatory database, the term “acids” identified cases, but this may be a phenomena of the database characteristics (coding of reactions 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
    - First use syndrome
    - Kounis syndrome
    - Shock
    - Type I hypersensitivity

(Narrow search terms = Category A)

Algorithmic SMQ Example (cont)

<table>
<thead>
<tr>
<th>Category B – Upper airway/Respiratory</th>
<th>Category C – Angioedema/Urticaria, etc.</th>
<th>Category D – Cardiovascular/Hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory failure</td>
<td>Allergic oedema</td>
<td>Blood pressure decreased</td>
</tr>
<tr>
<td>Asthma</td>
<td>Angioedema</td>
<td>Blood pressure diastolic decreased</td>
</tr>
<tr>
<td>Bronchial oedema</td>
<td>Erythema</td>
<td>Blood pressure systolic decreased</td>
</tr>
</tbody>
</table>

- Case = A (Narrow terms)
- Or Term from Category B and term from Category C
- Or Term from either Category B or Category C plus Term from Category D
Hierarchical SMQs

- Some SMQs may develop as set of queries related to one another in a hierarchical relationship
- Not related to MedDRA standard hierarchy
- One or more subordinate SMQs combined to create a superordinate, more inclusive SMQ

Hierarchical SMQ Example
Text Data Included in SMQ

- 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

- SMQs can be viewed from the IT perspective as stored queries
  - List of terms related to a medical condition
- Most organizations code at the LLT level of MedDRA
- SMQ ASCII files include PTs and LLTs assigned to each SMQ

How to “run” SMQs (cont)
SAS Program Code

- Asthma/bronchospasm (SMQ): Example of code for narrow search

```sas
proc sql;
connect to oracle (user=edu001 orapw=edu001 path="@dev_edu1");
title 'Asthma/bronchospasm (SMQ) Cases – Narrow Search';
title2 'since 1-Jan-2006';
select case_number as Case_ID,
       meddra_pt as MedDRA_PT,
       report_verbatim,
       date_created
from drug_safety_table
where (date_created >= '01-JAN-2006') and
     (meddra_pt in (select meddra_pt_name
                    from SMQ_content
                    where SMQ_name = 'Asthma/bronchospasm (SMQ)'
                    and scope = 'narrow'))
order by case_number;
quit;
```

For broad search, omit scope.

---

SAS Program Code (cont)

The SAS System

Asthma/bronchospasm (SMQ) Cases – Narrow Search
(since 1-Jan-2006)

<table>
<thead>
<tr>
<th>Case_ID</th>
<th>MedDRA_PT</th>
<th>REPORT_VERBATIM</th>
<th>DATE_CREATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asthma</td>
<td>Asthma attack</td>
<td>01-JAN-2006</td>
</tr>
<tr>
<td>2</td>
<td>Asthma</td>
<td>Severe asthma</td>
<td>05-APR-2006</td>
</tr>
<tr>
<td>3</td>
<td>Asthma exercise induced</td>
<td>Asthma when exercising</td>
<td>01-JUL-2006</td>
</tr>
<tr>
<td>4</td>
<td>Bronchospasm</td>
<td>Spasm, bronchial</td>
<td>31-MAR-2005</td>
</tr>
<tr>
<td>5</td>
<td>Bronchospasm</td>
<td>Bronchoconstriction</td>
<td>23-MAY-2005</td>
</tr>
<tr>
<td>6</td>
<td>Bronchial hyperreactivity</td>
<td>Airways hyperreactive</td>
<td>30-AUG-2006</td>
</tr>
<tr>
<td>7</td>
<td>Bronchial hyperreactivity</td>
<td>Reactive airways disease</td>
<td>17-FEB-2006</td>
</tr>
</tbody>
</table>
SMQ Versioning

• It is recommended that organizations utilize 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)

• Examples of PTs added to SMQs in MedDRA Version 12.0:
  ♦ PT *Basal ganglia infarction* in SMQ *Ischaemic cerebrovascular conditions*
  ♦ PT *Frontotemporal dementia* in SMQ *Dementia*
• Using version 11.1 SMQs which do not contain these PTs would fail to identify cases coded to these terms in a database using MedDRA Version 12.0
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)

Case study at EMEA

Signal detection using SMQ

*Hyperglycaemia/new onset diabetes mellitus*

Based on work by:
Victoria Newbould
Nick Halsey
Stefano Cappe
Panos Tsintis
Magnus Lerch
and Patricia Mozzicato

Acknowledgement: Jim Slattery, EMEA. Slides used with permission.
EMEA Signal Detection Activities (made simple)

- All newly arrived reports are reviewed
- Disproportionality measure – Proportional Reporting Ratio (PRR) – is calculated
- If the lower confidence bound exceeds one and the total number of cases is 3 or more further investigation may be started

Question

- Although not designed primarily for detection of drug safety issues, is it likely that the SMQs will have advantages over other levels of MedDRA in early signalling of new safety problems?
Design of Study

- SMQ *Hyperglycaemia/new onset diabetes mellitus*
- An antipsychotic with known association
- Calculate PRR as function of time
- Compare with PRR from single PTs, HLT, and HLGT

Signal Detection from various Adverse Event Groups

![Graph showing signal detection over weeks from first report in SMQ](image)

Note: Points marked with a black dot have counts of 3 or more cases
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
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)

Extent of MedDRA Versioning

- Proposed implementation levels

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</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 medically better matches</td>
</tr>
<tr>
<td>B</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>
</tr>
<tr>
<td>C</td>
<td>Identify verbatim terms linked to non-current LLTs and recode existing data</td>
</tr>
<tr>
<td>D</td>
<td>Begin to use new version for coding new data; no recoding of existing data</td>
</tr>
</tbody>
</table>
Frequency of MedDRA Releases

- Can MedDRA be released once a year instead of two times a year?

Recommendations – Extent of Versioning

1. Content to be added as appendix to “MedDRA Term Selection: Points to Consider” (TS: 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 TS: 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

Tutorial Summary
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:
  • Learnt 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
  • Learnt 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 BRP recommendations
    ▪ Extent of versioning
    ▪ Feasibility of an annual release
MSSO Contacts

• Mail
  MedDRA MSSO
  3975 Virginia Mallory Drive
  Chantilly, VA, USA 20151

• Telephone
  ✦ Toll-free Worldwide 877.258.8280 (AT&T)

• Fax
  ✦ 703.272.5635

• Products and Services
  ✦ Toll-free Worldwide 877.258.8280 (AT&T)

MSSO Contacts (cont)

• To Subscribe by
  ✦ E-mail
    ▪ mssosubscribe@ngc.com
  ✦ Web site
    ▪ www.meddrasso.com click on “Subscribe to MedDRA”

• Help desk
  ✦ Phone
    ▪ International AT&T Toll Free: 877.258.8280
    ▪ Direct Dial (USA): 703.272.5849
  ✦ E-mail
    ▪ mssohelp@ngc.com
Acknowledgements

- MedDRA® is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
- COSTART Thesaurus Fifth Edition Copyright® 1995 US Food and Drug Administration (FDA)
- Hoechst Adverse Reaction Terminology System (HARTS)© 1992 Aventis Pharma
- Japanese Adverse Reaction Terminology (J-ART), is a product of the Japanese Ministry of Health, Labour and Welfare (MHLW)
- WHO Adverse Reaction Terminology (WHO-ART), Copyright© World Health Organization Collaborating Centre for International Drug Monitoring