What Makes a High-quality Report of Adverse Event: 
from MedDRA Coding Perspective

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MedDRA MSSO
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Overview

- Importance of good quality data
- How clinical data are coded
- MedDRA overview
- Company-specific conventions
- Benefits of good quality data
- How to improve data entry quality?
Importance of good quality data
What is Meant by Good Quality Data?

- Complete
- Accurate
- Diagnosis supported by appropriate investigations
- Causality assessment for adverse events
MedDRA \hspace{1cm} \text{Quality of Input} = \text{Quality of Output}
Quality of Serious Adverse Event (SAE) Reporting in Clinical Trials

• Study finds frequent errors in SAE reports to academic trial sponsors
  – Event verbatim inconsistent with report: 15%
  – Patient outcome not reported: 12.1%
  – Investigational product not identified: 11.2%
  – No causality assessment reported: 9.3%
  – Event seriousness unknown: 3.6%

• Study authors: Knowledge of MedDRA basics and coding practices key to data accuracy and completeness

Crepin S, Villeneuve C, Merle L. Quality of serious adverse events reporting to academic sponsors of clinical trials: far from optimal. Poster at 18th Annual Meeting of French Society of Pharmacology and Therapeutics; 2014 April 22-24, Poitiers, France.
How clinical data are coded
What is Coding?

- Verbatim
- Coding
- Standardized Terminology
表2. AURA研究期间报告的不良反应

<table>
<thead>
<tr>
<th>MedDRA SOC</th>
<th>MedDRA术语</th>
<th>CIOMS分类/总体频率 (所有CTCAE分)</th>
<th>3级或3级以上的CTCAE的频率</th>
</tr>
</thead>
<tbody>
<tr>
<td>呼吸、胸部及纵膈系统疾病</td>
<td>间质性肺病</td>
<td>常见 (3.2%)</td>
<td>1.3%</td>
</tr>
<tr>
<td>胃肠道疾病</td>
<td>腹泻</td>
<td>极常见 (44%)</td>
<td>1.0%</td>
</tr>
<tr>
<td></td>
<td>口腔炎</td>
<td>极常见 (15%)</td>
<td>0%</td>
</tr>
<tr>
<td>眼部疾病</td>
<td>角膜炎</td>
<td>少见 (0.9%)</td>
<td>0%</td>
</tr>
<tr>
<td>皮肤及皮下组织疾病</td>
<td>皮疹</td>
<td>极常见 (41%)</td>
<td>0.7%</td>
</tr>
<tr>
<td></td>
<td>皮肤干燥</td>
<td>极常见 (29%)</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>甲沟炎</td>
<td>极常见 (27%)</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>瘙痒</td>
<td>极常见 (15%)</td>
<td>0%</td>
</tr>
<tr>
<td>辅助检查</td>
<td>QTc间期延长</td>
<td>少见 (0.7%)</td>
<td>0%</td>
</tr>
<tr>
<td>(依据检验结果确定, 并按CTCAE级别的变化情况给出)</td>
<td>血小板计数下降</td>
<td>极常见 (54%)</td>
<td>2.1%</td>
</tr>
<tr>
<td></td>
<td>白细胞减少</td>
<td>极常见 (66%)</td>
<td>2.4%</td>
</tr>
<tr>
<td></td>
<td>中性粒细胞减少</td>
<td>极常见 (32%)</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

表中所列的数据均为Ⅲ期(AURA3)和Ⅱ期(AURAX和AURA 2)研究中累积获得的数据;仅对至少服用了1次本品的患者所发生的不良事件进行了总结。
Data to be Coded in a Case Report Form

Clinical Database

Screening
- I/E Criteria
- Demography
- Medical History
  - Baseline Characteristics

Therapy
- Study Drug Administration
- Concomitant Medication
- Concomitant Procedures
- Therapy Compliance

Efficacy
- Base on Protocol

Indication

Safety
- Adverse Events
- Lab Results
- Vital Signs
- Reason of Death
Coding in Clinical Trials

**Study Design**
- Protocol
- Case Report Form
- Technical Designer

**Study Conduct**
- Clinical Research Coordinator
- Clinical Research Associate
- Investigator
- Data Manager
- Coder
- SAE Reconciliation
- Pharmacovigilance

**MedDRA**
How many queries on AE form?

NUMBER OF QUERIES IN A CLINICAL STUDY

- Auto query: 53%
- Manual query: 47%
- AE: 9%
- Other Forms: 38%
How many coding queries for AE Term?

NUMBER OF QUERIES IN AN ADVERSE EVENT FORM

- Other Variables: 72%
- AETERM: 28%

Coding query: 5%
Non-coding query: 23%
MedDRA overview
What is MedDRA?

Med = Medical

D = Dictionary for

R = Regulatory

A = Activities

《监管活动医学词典》
MedDRA is a clinically-validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry. The terminology is used through the entire regulatory process, from pre-marketing to post-marketing, and for data entry, retrieval, evaluation, and presentation.
Scope of MedDRA

Medical conditions
Indications
Investigations (tests, results)
Medical and surgical procedures
Medical, social, family history
Medication errors
Product quality issues
Device-related issues
Product use issues
Pharmacogenetic terms
Toxicologic issues
Standardized queries

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

First Level

- System Organ Class (SOC) (27)
  - High Level Group Term (HLGT) (337)
    - High Level Term (HLT) (1,737)
  - Preferred Term (PT) (23,708)
  - Lowest Level Term (LLT) (80,262)

Analysis Level

Coding Level

Grouping Terms

MedDRA Version 22.0
• 使用 MedDRA 结构来检索病例
Making the Most of MedDRA

- To take advantage of MedDRA’s richness and specificity, the source data should be
  - Clear
  - Concise
  - Complete
  - Accurate
- General principles apply to all clinical data
Problems With Coding Data

• Appropriate coding requires clear initial data
• What is clear to the investigator at the point of data entry may be unclear to the sponsor at the point of data coding
• Sponsor must only code reported verbatim term; not permitted to interpret or draw information from other sources
• Example: Ambiguous information
  – Congestion (nasal, liver, sinus, pulmonary?)
  – Cramp (muscle, menstrual, abdominal?)
  – Pain (pain where?)
Problems With Coding Data (cont)

- Example: Ambiguous abbreviations
  - MI (myocardial infarction or mitral incompetence?)
  - GU pain (gastric ulcer pain or genito-urinary pain?)
  - Decreased BS (breath sounds, bowel sounds or blood sugar?)

- Exercise caution with abbreviations that could be misinterpreted

- ECG, COPD, HIV are examples of standard abbreviations
Problems With Coding Data (cont)

• Example: Vague information
  – Patient felt “fuzzy”, “weird”, “experienced every adverse event”

**Try to use accepted medical terminology**

• Example: Non-specific information
  – “Left wrist edema” (coded as *Peripheral edema*)
  – More specific - “Injection site edema left wrist” (coded as *Injection site edema*)
• Death, hospitalization, and disability are outcomes and are not usually considered to be adverse events
• Provide details of the underlying event, if known
• Examples:
  – “Death due to myocardial infarction” (Coded as *Myocardial infarction* with death captured as the outcome)
  – “Hospitalization due to congestive heart failure” (Coded as *Congestive heart failure* with hospitalization captured as the outcome)
Problems With Coding Data (cont)

• Example: Ambiguous laboratory data
  – “Glucose of 40”
  – (Source of specimen - blood, urine, CSF? What units?)
  – Would have to code as Glucose abnormal if additional clarification is not obtained

• Example: Conflicting laboratory data
  – “Hyperkalemia with serum potassium of 1.6 mEq/L”
  – Would have to code as Serum potassium abnormal

If using numeric values, provide units and reference range. Be specific about specimen source and diagnostic result/clinical diagnosis.
• Example: Combination terms
  – Diarrhea, nausea, and vomiting

Try to avoid combination terms - these will have to be split into three individual terms:
  – Diarrhea
  – Nausea
  – Vomiting
• Where possible, report the most important medical event or specific diagnosis rather than individual signs and symptoms
• Can provide provisional diagnosis e.g. “possible”, “presumed”, “rule out”
• Accuracy is important in preventing dilution of safety signals or generating false signals

<table>
<thead>
<tr>
<th>SIGNS and SYMPTOMS</th>
<th>DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain, dyspnea, diaphoresis, ECG changes</td>
<td>Myocardial infarction</td>
</tr>
</tbody>
</table>
Generating Quality Data

• Clear
• Concise
• Complete
• Accurate
• Be specific if necessary - MedDRA can handle multiple specific medical concepts:
  – Headache - more than 50 types, including cluster, sinus, migraine, lumbar puncture headache
  – Organisms - down to species level e.g. Staphylococcus aureus
MSSO developed and maintains list of unqualified test name terms
- These terms (e.g., PT *Blood glucose*) should never be reported as AEs
- Intended for use in E2B test name field only

List can be used to check data quality
- Identifies inappropriate terms in data fields other than test name data element
- Intended as recommendation only
List Available for Download

- Link on Support Documentation page on MedDRA website
- Spreadsheet of LLT/PT names and codes from SOC Investigations
  - >3,800 terms in v22.0
- Explanatory document
  - Purpose, uses, development of list
<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>17 ketosteroids urine</td>
<td>10000005</td>
<td>PT</td>
</tr>
<tr>
<td>3</td>
<td>17-hydroxycorticosteroid activity</td>
<td>10051618</td>
<td>LLT</td>
</tr>
<tr>
<td>4</td>
<td>2',5'-oligoadenylate synthetase test</td>
<td>10058945</td>
<td>PT</td>
</tr>
<tr>
<td>5</td>
<td>24 hour electrocardiogram</td>
<td>10073349</td>
<td>LLT</td>
</tr>
<tr>
<td>6</td>
<td>5-HIAA urine</td>
<td>10060014</td>
<td>LLT</td>
</tr>
<tr>
<td>7</td>
<td>5-hydroxyindolacetic acid</td>
<td>10050342</td>
<td>PT</td>
</tr>
<tr>
<td>8</td>
<td>5-hydroxyindolacetic acid in urine</td>
<td>10059972</td>
<td>PT</td>
</tr>
<tr>
<td>9</td>
<td>5'nucleotidase</td>
<td>10059898</td>
<td>PT</td>
</tr>
<tr>
<td>10</td>
<td>A/G ratio</td>
<td>10000037</td>
<td>LLT</td>
</tr>
<tr>
<td>11</td>
<td>Abdomen CT</td>
<td>10077423</td>
<td>LLT</td>
</tr>
<tr>
<td>12</td>
<td>Abdomen scan</td>
<td>10061936</td>
<td>PT</td>
</tr>
<tr>
<td>13</td>
<td>Abdominal CAT</td>
<td>10057791</td>
<td>LLT</td>
</tr>
<tr>
<td>14</td>
<td>Abdominal scan NOS</td>
<td>10000091</td>
<td>LLT</td>
</tr>
<tr>
<td>15</td>
<td>Abdominal wall biopsy</td>
<td>10000102</td>
<td>LLT</td>
</tr>
<tr>
<td>16</td>
<td>Abdominal X-ray</td>
<td>10061612</td>
<td>PT</td>
</tr>
<tr>
<td>17</td>
<td>Abdominal X-ray NOS</td>
<td>10050402</td>
<td>LLT</td>
</tr>
<tr>
<td>18</td>
<td>Absolute lymphocyte count</td>
<td>10073552</td>
<td>LLT</td>
</tr>
<tr>
<td>19</td>
<td>Absolute neutrophil count</td>
<td>10052033</td>
<td>LLT</td>
</tr>
</tbody>
</table>
Company-specific conventions
General Coding Guidelines - Example

• Coding will be carried out in adherence with MedDRA Term Selection: Points to Consider.

• General Points:
  – Misspelling
  – Translations
  – Abbreviations and Acronyms
  – Combination Terms
• Provides term selection advice for industry and regulatory purposes
• Objective is to promote accurate and consistent term selection to facilitate a common understanding of shared data
• Recommended to be used as basis for individual organization’s own coding conventions
Do not make diagnosis if only signs/symptoms reported

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT Selected</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain, increased serum amylase, and</td>
<td>Abdominal pain</td>
<td>It is inappropriate to assign an LLT for diagnosis of “pancreatitis”</td>
</tr>
<tr>
<td>increased serum lipase</td>
<td>Serum amylase increased</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lipase increased</td>
<td></td>
</tr>
</tbody>
</table>
Investigations

- Grouped investigation result terms

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT Selected</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased alkaline phosphatase, increased SGPT, increased SGOT and elevated LDH</td>
<td>Alkaline phosphatase increased SGPT increased SGOT increased LDH increased</td>
<td>Select four individual terms. A single term such as LLT Liver function tests abnormal should not be selected.</td>
</tr>
</tbody>
</table>
• Medical condition vs. investigation result

<table>
<thead>
<tr>
<th>Reported</th>
<th>LLT Selected</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycaemia</td>
<td>Hypoglycaemia</td>
<td>LLT Hypoglycaemia 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>
• Medical condition vs. investigation result

- Endocrine disorders
  - Glucose metabolism disorders (incl diabetes mellitus)
    - Hypoglycaemic conditions NEC
      - Hypoglycaemia
    - Hypoglycaemia

- Metabolism and nutrition disorders
  - Glucose metabolism disorders (incl diabetes mellitus)
    - Hypoglycaemic conditions NEC
      - Hypoglycaemia
    - Hypoglycaemia

- Investigations
  - Metabolic, nutritional and blood gas investigations
    - Carbohydrate tolerance analyses (incl diabetes)
      - Blood glucose decreased
        - Glucose decreased
Sponsor or Project Specific Conventions - Example

**Chest Pain**

- Code to Chest pain?
- Query to specify the type?
  - Cardiac chest pain
  - Non-cardiac chest pain
  - Musculoskeletal Chest Pain
- Depend on the panel / form?
  - Adverse event – query
  - Medical history – not query
Benefits of good quality data
Benefits of Quality Data

• Accurate and timely information on issues that affect conduct of clinical trial and affect patient safety

• Improved communication among sponsors, investigators, and regulatory agencies about medicinal products
  – Aids in safety signal detection and evaluation
  – Ensures accuracy of information about the product including investigators’ brochures and prescribing information
  – Benefits medical professionals
  – Benefits patients
Benefits of Quality Data (cont)

- Fewer queries for investigator and sponsor
Quality Data

IN

OUT
How to improve data entry quality?
How to avoid coding queries?
How to avoid coding queries?

- Data Completion Guidelines
- CRF Design
- CRC/Investigator Training
- CRA Coordination
- Communication with Coders
MSSO Contacts

- Website
  - www.meddra.org
- Email
  - mssohelp@meddra.org
- Frequently Asked Questions
  - www.meddra.org/faq