MedDRA was developed under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The activities of the MedDRA Maintenance and Support Services Organization (MSSO) are overseen by an ICH MedDRA Management Board, which is composed of the six ICH parties (EU, EFPIA, MHLW, JPMA, FDA, PhRMA), the Medicines and Healthcare products Regulatory Agency (MHRA) of the UK, Health Canada, and the WHO (as Observer).
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Overview

To provide an understanding of:

- Importance of good quality data
- How clinical data are coded
- MedDRA background
- Coding examples
- Benefits of good quality data
Data Quality in Clinical Development

- Highly regulated environment with strong emphasis on safety surveillance and data quality
- Applies to clinical trials and post-marketing arena
- Increasing harmonization of safety reporting regulations globally

What is Meant by Good Quality Data?

- Complete
- Accurate
- Diagnosis supported by appropriate investigations
- Causality assessment for adverse events
Coding of Clinical Trial Data

- Most data entered on Case Report Forms are “coded” in some form
- Facilitates storage, retrieval, analysis, and presentation of data
- Some coding is performed by investigators at point of data entry
  - For example, numeric codes for severity of adverse event: 1= mild, 2= moderate, etc.
- Other coding of text data is performed by the sponsor company after data collection
- Accuracy of initial coding determines accuracy of analysis
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.

MedDRA Background
What is MedDRA?

Med = Medical
D = Dictionary for
R = Regulatory
A = Activities

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.
Where MedDRA is Used

- Preclinical Testing
- Clinical Phase I
- Clinical Phase II
- Clinical Phase III
- Marketed Product Phase IV

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

Key Features of MedDRA

- Standardized terminology
- International scope – currently available in 11 languages including English, Spanish, French, Chinese, and Japanese
- Managed by Maintenance and Support Services Organization (MSSO) and updated bi-annually with input from users
Key Features of MedDRA (cont)

- Structure facilitates data entry, analysis, reporting, and electronic communication
- Large terminology with > 77,000 terms at lowest level - allows greater specificity
- Approx. 22,000 Preferred Terms, each representing a unique medical concept
- Used to classify a wide range of information associated with the use of biopharmaceuticals and other medical products (e.g., medical devices and vaccines).

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

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

• US FDA
  – Used in several databases including FAERS (drugs and biologics), VAERS (vaccines), and CAERS (foods, dietary supplements, cosmetics)
  – Recommended terminology for adverse event reporting in several Proposed Rules and Guidances
  – Effective June 2015, electronic submission required for postmarketing safety reports for drugs, biologics, and vaccines (relies upon ICH standards)

• Japanese Ministry of Health, Labour and Welfare
  – Mandatory use in electronic reporting

Regulatory Status (cont)

• European Union
  – EudraVigilance database
    • Clinical trial SUSARs (Suspected Unexpected Serious Adverse Reactions)
    • Post-authorization Individual Case Safety Reports (ICSRs)
    • Requires current version of MedDRA or the one previous to it
  – Good pharmacovigilance practices (GVP) specifically mention MedDRA
  – Pharmacovigilance legislation covers suspected adverse reactions from:
    • Use inside and outside terms of marketing authorization
    • Overdose, misuse, abuse, and medication errors
    • Occupational exposures
Regulatory Status (cont)

• European Union (cont)
  – Used in interface between EudraVigilance and EU Risk Management Plan
  – Used throughout Summary of Product Characteristics (labeling)
• ICH M4E Guideline on Common Technical Document
  – Recommended in adverse event summary tables
• Canada
  – Used in Canada Vigilance database
  – Recommended/preferred terminology for adverse reaction reporting and Product Monograph (labeling)
  – Electronic reporting via Gateway requires current version of MedDRA

MedDRA Maintenance

• MedDRA is a user-responsive terminology
• Users may submit change requests (CRs) to the MSSO for consideration
  – Each organization: up to 100 CRs per month
  – For simple changes (PT and LLT levels), notification of final disposition within 7-10 working days
  – Complex changes above PT level received all year round. Posted for users’ comments mid-year.
• Twice yearly official updates
  – 1 March X.0 release (Complex and simple changes)
  – 1 September X.1 release (Simple changes only)
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*)
Problems With Coding Data (cont)

- 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.
Problems With Coding Data (cont)

• 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

Reporting a Specific Diagnosis

• 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>
Safety Signals

- Accuracy in diagnosis is important for detection and evaluation of safety signals
- Events of importance in drug safety surveillance include:
  - QTc prolongation
  - Hepatotoxicity
  - Stevens Johnson syndrome
  - Convulsions
  - Rhabdomyolysis

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
Quality Assurance

• Human oversight of automated coding results
  – Example: “Allergic to CAT scan” autoencoded as: *Allergic to cats*
• 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

Unqualified Test Name Term List

• MSSO developed an unqualified test name term list
  – Example: PT *Blood glucose*
  – These terms should never be reported as AEs
  – Intended for use in E2B test name field only
• Standardised, complete list of test name terms is a useful tool for checking data quality
  – Identify inappropriate use of terms in data fields other than test name data element
  – Intended as recommendation only
  – Maintained by MSSO with each MedDRA release
List Available for Download

- Link on Support Documentation page on MedDRA website
- Spreadsheet of LLT/PT names and codes from SOC Investigations
  - >3,600 terms in v19.1
- Explanatory document
  - Purpose, uses, development of list
- Also available in Japanese on JMO website
Important 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

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Important Coding Errors (cont)

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

Acknowledgement: Dr. Toni Piazza-Hepp, Office of Surveillance and Epidemiology, CDER, FDA
Miscellaneous Verbatims: Coding Challenges

- Went to hell
- Recurrent fatal stroke
- Hears New Age music when the furnace turns on
- LK RTCTL UNSP XTRNDL
- Charcoal-like, gritty granules in his underwear
- Can’t control patient during menses
- His nodule is sticking out
- Normally normal after drinking coffee
- Died of cancer of the placebo
- Superior members fornication
- Barely visible posterior
- Seeing people in room, seeing chickens at window
- Seeing stars and chicken farting
- Patient recently began new job where he works around chicken wings and barbecue sauce

Company-Specific Conventions

- Insert slides as required to cover company’s specific data collection and recording conventions
- Could include instructions on how to complete data fields for adverse events, medical history etc. on paper or electronic CRFs
- Could include general principles of how to record text-based information as well as specific instructions for particular therapeutic areas
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

MSSO Contacts

- Website
  - [www.meddra.org](http://www.meddra.org)

- Email
  - [mssohelp@meddra.org](mailto:mssohelp@meddra.org)

- Frequently Asked Questions
  - [www.meddra.org/faq](http://www.meddra.org/faq)