ASEAN workshop on MedDRA; Industry perspective
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Disclaimer:

The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.
Topics to be covered (1)

- Introduction
  - Why is clinical coding required?
  - When is a clinical coding dictionary used?
  - Clinical coding in a large company
  - Regulatory authority/Industry interface
    - European example: Eudravigilance and EVWEB

Topics to be covered (2)

- Implementation (industry)
  - Planning
  - Implementation issues
    - Examples in 2 companies
    - Database, MedDRA browser
  - Data conversion issues
    - Pilot, Revision of standard operating procedures, Training
    - What, when and how to convert
Topics to be covered (3)

- Current production use
  - Synonym list
  - Versioning
  - Clinical trials
  - Pharmacovigilance (PVG)
  - Other company specific applications
  - Advantages of MedDRA

Introduction –
*why is clinical coding required?*

- Uncontrolled verbatim from reporters describes the same adverse event in many ways.
- Coding classifies data for subsequent cumulative analysis

- Example: Headache may be reported as:
  - Tenderness above temple
  - Dull aches back of head
  - Feels like someone hit back of head
Introduction –
when is a clinical coding dictionary used?

A clinical coding dictionary is generally used from the first clinical trial in man and then throughout the life cycle of the product.

Clinical coding in a large company

Users include:
- Clinical data management (dictionary analysts & statisticians)
- Clinical trial teams
- Pharmacovigilance
- Regulatory
- Prescribing information
- Supported by:
  - Central coding dictionary team
  - Information Technology (IT)

Information stored in:
- Coding dictionary team’s database (routine maintenance, version updates)
- Clinical trial database
- Safety (reporting) database
- Regulatory submissions
- Product labels
- etc
Regulatory /industry interface –
European example

- EudraVigilance is a central data-processing network and management system in the European Union (EU) to promote the protection of public health
  - Interlinks the European Medicines Agency (EMEA) and all National Competent Authorities (NCAs) in the EU and European Economic Area (EEA)
  - Implemented in 2001 with access to all NCAs
    - The final goal is access to healthcare professionals, public and industry
  - Processes an average of 45,000 ICSRs on a monthly basis
  - Provides electronic reporting facilities to companies and sponsors of clinical trials

EudraVigilance Network

Central EU PhV System
ICH E2B and MedDRA Standards
EVWEB - Eudravigilance web application

- EVWEB is for Small and Medium Size Enterprises (SMEs) and non-commercial sponsors, which do not have a fully ICH E2B (R2) compliant pharmacovigilance system and/or ESTRI gateway in place.
- It is a tool for SMEs to report electronically
  - Registration and training required
  - No fee for using MedDRA within EVWEB

Implementation - planning

- Deadlines: set by regulatory agencies* implementing MedDRA for electronic safety reporting
  *initially European and Japan
- Interdisciplinary project team, including
  - Regulatory affairs
  - Pharmacovigilance
  - Data management/Dictionary administrators
  - Clinical research
  - Information Technology (IT)
- Realistic timelines: Make allowance for the unexpected
Implementation issues (1)
(examples in companies X and Y)

In company X
- 1998 MedDRA v1.9 testing for AERs (FDA database)
- 2H 1999 In house terminology* to MedDRA mapping started
  - IT support, Dictionary analysts, Medical quality control
  - Developed audit trail, MedDRA autoencoder
- Intended completion of pharmacovigilance (safety) database data mapping in 1Q 2001

* more specific than MedDRA

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Implementation issues (2)
(examples in companies X and Y)

In company Y
- Simultaneous planning to migrate to MedDRA
- Mapping modified WHO-ART* to MedDRA
  *less specific than MedDRA

On merger of companies X and Y
  - Dictionary teams compared notes and found that philosophies were different.
  - STOP both processes, AGREE philosophy and START mapping again
  - Delayed implementation in merged company by a year

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Implementation issues (3)
(Database, MedDRA browser)

- Older safety databases may not be MedDRA compatible
  - E2B field for MedDRA terms initially specified 100 characters
- Early conversions to MedDRA*
  - Few if any commercial browsers available then
  - Some companies developed in-house browser for in-house safety database
- Many commercially available databases now have MedDRA browsing capabilities

*2001/2002

Data conversion issues (1)

- **Company X**
  - In house terminology more specific than MedDRA
  - Controlled (near verbatim) synonym list mapped to MedDRA LLT
- **Company Y**
  - Modified WHO-ART was less specific than MedDRA
  - No controlled synonyms. Coded terms mapped to MedDRA LLT
  - Later data clean up: remapped verbatim to MedDRA LLT for specified projects
- **Merged company**
  - Common coding philosophy and medical quality checking
Data conversion issues (2)

Historical terminology may be

- More specific/granular terminology → MedDRA
  - Historical: Nervousness (PT), Restlessness (PT)
  - MedDRA: Nervousness (PT), Restlessness (PT)

or

- Less specific/granular terminology → MedDRA
  - Historical: Nervousness (PT), Restlessness (synonym)
  - MedDRA: Nervousness (PT), Restlessness (PT)

Data conversion issues (3)

- May require a pilot (trial period) with one product
- Revise standard operating procedures
  - Communicate with licence partners, clinical research organisations (CROs)
- Training
  - Within company
  - Study investigators, CROs, etc
Data conversion issues (4)
what, when and how to convert

Safety (reporting) database

- Many companies converted safety database before clinical trial database
  - Safety database often contains all spontaneous (post marketing) data as well as clinical trial Serious Adverse Events (SAEs)
  - Clinical SAEs in MedDRA and non serious adverse events (AEs) in old terminology require data reconciliation/explanations:
    - E.g. clinical study report may include term mapping in appendix

Impact of converting safety database on Postmarketing data –

- Periodic Safety Update Reports (PSUR):
  - Event terms have different body systems (e.g. “Cardiovascular” split into “Cardiac” and “Vascular”)
  - Change in granularity results in different number of reports for some AEs
  - Explain impact of change in first PSUR using MedDRA

- Safety monitoring:
  - Review new signals for potential labelling changes
Data conversion issues (6)
what, when and how to convert (cont’d)

Clinical trial database
- Start new studies in MedDRA
- Convert ongoing studies to MedDRA as soon as possible
- Integrated data analysis necessary for submissions
  - Convert old studies that are to be included in integrated safety summary
  - Unless old terminology was very specific/granular, advisable to start from reporter verbatim.
  - Conversion using codes from non specific terminology results in loss of detail.

Current production use
Synonym list

- Used by some companies
  - May be across all products
  - May be product specific
- Not part of MedDRA structure
- Stores previously encountered verbatim link to LLT
- Aids consistency of coding

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Synonym list

- LLT *Headache*
- Synonyms include:
  - Burning pain to back of head
  - Aching sensation on head
  - Throbbing over eyebrow
  - Pulsating pain in entire head
  - Felt like someone hit back of head
  - Tenderness above temple
  - Dull aches back of head
Versioning – general principles

- MedDRA versions update 6 monthly
- Synchronise updating for electronic regulatory reporting
  - upversion on first Monday two months after new version release
- Versioning process is company specific: *Examples*
  - Relink company synonyms to new LLTs as appropriate. Entire company (clinical and safety databases) upversions at once as relinks are taken off common IT platform overnight
  - Recode data by product or by active study.
- MSSO had a “Blue ribbon panel” on ways to upversion

Summary will be in the ICH Points to Consider documents (late 2010)

Versioning – clinical trials (1)

Six suggestions on MSSO web page*

- Industry prefers freedom of choice.
- Clearly state in the study report/marketing application what has been done.
- Clearly explain any impact of MedDRA version on potential safety signal in the Integrated Safety Summary.

Versioning – clinical trials (2)

Options 1-3:
- Freeze at start of project, report with same version
- Freeze at start of project, report with latest version
- Freeze at initiation of each trial within project and report with latest version

Versioning – clinical trials (3)

Options 4-6:
- Hold all coding till end of each trial; recode all studies at end of project.
- Freeze at start of trial & optionally recode with the latest version at conclusion of trial using criteria defined in project plan
- Do not freeze; recode data for all trials in project on an ongoing basis with the latest version.
Clinical trials

Clinical trials – data entry

Processes vary by organisation; these are generic examples:

- Reporter verbatim for AEs/SAEs obtained from case report forms (CRFs)
- Synonym list (if available) makes autoencoding of reporter verbatim more efficient and consistent
- Autoencoder failures are manually coded
- Quality controls may include:
  - One dictionary analyst codes, another checks/approves
  - Clinical trial team sees all coded terms and reporter verbatim (unique term report*) during study monitoring

*Unique term report included in study data file
Clinical trials - data output

- Study data review/analysis
  - Traditional review of tables or may use electronic tool in addition
    - PTs shown by incidence
    - PTs arranged by primary SOC
    - some companies use secondary SOC output also
    - by SMQ (when appropriate)
    - by statistical analyses (for signal detection)
  - Safety review team* may request different analyses
  - Company specific applications
    - e.g. Case Awareness Tool (alerts for SAEs of interest)

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Clinical trials — Single study, most common AEs

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo (n=54)</th>
<th>Study drug (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>10 (19%)</td>
<td>11 (20%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (6%)</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (4%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (4%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5 (9%)</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>2 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>0</td>
<td>2 (4%)*</td>
</tr>
</tbody>
</table>

*Verbatim Text: Allergy symptoms
Clinical trials – Single study, AEs by primary SOC

Aggregated clinical data – signal scores
Clinical trials - expedited SAE reporting

- Electronic reporting is possible if database is compatible with regulator’s.
- MedDRA used for
  - AE field, drug indications, medical history, investigations (if any), cause of death (as appropriate)

See backup slides for details of MedDRA coding for Individual Case Safety Reports [ICH E2B (R2)]

- Physical appearance of report may be similar to CIOMS I reports for spontaneous data.

ICH
CIOMS 1 – expedited report (page 1)

INTERNATIONAL EVENT REPORT

EVENT INFORMATION

SUBJECT ID: [Redacted]
Country: [Redacted]
Date of Birth: [Redacted]

The subject, a 40-year-old female, was enrolled in an open-label study for the treatment of depression. The subject received 400 mg of a medication from 14 July 2003 to 15 March 2004.

The subject’s past medical history included hypertension and diabetes mellitus, medical conditions at the time of the event. Concurrent medications included lithium carbonate, insulin, gabapentin, and lamotrigine.

On 21 July 2003, seven days after the start of treatment, the subject developed bipolar depression, which was exacerbated by stress. The subject was hospitalized from 21 July 2003 to 18 August 2003. On an unspecified date in 2009, she had a minor event with her hospitalization due to depression, and symptoms.

The investigator considered the event to be related to the study medication, and the report was received on 14 August 2013. Investigator conclusion was unknown at the time of reporting.

CIOMS 1 – expedited report (page 2)

1. & 2. DESCRIBE EVENT(S)

the time of reporting:

MEDICAL HISTORY: [Redacted]

CIOMS 1 – expedited report
Clinical trials - other uses of MedDRA

- Annual Safety Reports (ASRs) for Clinical Trials (EU)
- Common Technical Document (CTD) and e-CTD
  - common format for new drug and biologic product applications to regulatory authorities with coding of adverse events in the clinical section (ICH regions)

Pharmacovigilance
Pharmacovigilance - spontaneous reports

- Data coding* assisted by:
  - Tools: autoencoder and synonym list
  - Physician on duty
  *Company working practice in line with ICH Points to Consider guidelines

- MedDRA for some E2B fields (similar to Clinical SAEs)

- Electronic reporting to regulatory authorities
  (e.g. EU, Japan, FDA)

- Electronic reporting from regulatory agency to industry (e.g. MHRA)

Pharmacovigilance - Signal detection

Processes vary by company

- One company has an electronic tool similar to that used for clinical trial signal detection
  - Compares signal score in company database vs score on FDA Adverse Event Reporting (AERs) database
  - Others may use the WHO Uppsala database

- Variety of signal detection techniques: AEs may be sorted by
  - Any level of MedDRA hierarchy
  - Primary SOC, Secondary SOC
  - Signal score
  - Standardised MedDRA Queries (SMQs), Ad hoc queries
Pharmacovigilance – Search strategies

- Signal detection may lead to search of database and full review.
  - E.g. false signals may result from MedDRA version changes
- SMQs often applied as first search strategy
  - (preferred by ICH regulators)
- Scan cumulative summary of all PTs for product
  - to ensure complete search
- Apply search strategy; medically review output
- If issue is drug related, consider prescribing information update or other risk management strategy

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Risk management plans (EU)

- EU risk management plans request *Terms* and *Codes* for items perceived as risk for that marketed product
  - May be any level of MedDRA hierarchy
  - May include SMQs
- The list is generated by the Marketing Application Holder and agreed by the regulator
- Common understanding makes risk monitoring more efficient

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Prescribing information

- If MedDRA used, applications include drug indication and undesirable effects.
- European Summary of Product Characteristics:
  - Use any hierarchical level (often PT), arranged by SOC
  - Use Internationally agreed SOC order

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Metabolism and nutrition disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
</tr>
</tbody>
</table>

Pharmacovigilance - other uses of MedDRA

- Periodic Safety Update Reports (PSURs) in ICH regions
  - Contains MedDRA coded data for time period
  - Summary tabulations (PT) of adverse reactions by SOC
  - Line listings of cases by SOC
  - Graphical display (if appropriate)
Graphical display
blue consumer reporting: red health care professional

Other company specific applications

- Case awareness tool
- Automated listedness
- Automated seriousness
Case Awareness Tool –
Clinical and Post marketing

- Bespoke safety database permits selection of PTs of interest
  - Designated Medical Events (common for all products)
  - Selected PTs for each compound/protocol.
- Will automatically retrieve cases with selected terms (clinical SAEs & spontaneous reports)
- Assigned safety reviewer checks retrieved cases regularly
- Case alert may trigger full search and review
Pharmacovigilance – Automated listedness

- Listedness* may be assessed inconsistently in a large organisation.
  - Example: If headache is labelled, would migraine be listed?

- For consistency, some companies maintain a set of MedDRA terms that are considered listed for each undesirable effect in the core label.

*Expectedness of undesirable effect(s) in core safety label

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Pharmacovigilance – Automated serious list

- EU, FDA and ICH SAE definitions include medically important events / those needing medical intervention to prevent a regulatory serious outcome

- For consistency, company may maintain a list of MedDRA terms that the database will recognise as always serious (for spontaneous, post marketing and literature cases)

- EMEA has an equivalent list (Important Medical Events) in pilot.
  
Advantages of MedDRA

- Regulators and industry using the same terminology
- Electronic transmission of expeditable regulatory reports
- Enables data mining/signal detection using large databases (e.g. FDA AERs, WHO databases)
- Easier review of safety data for co-licensing opportunities
- Terminology maintained by external body (MSSO)
  - License fees (where charged) are relatively low
  - MedDRA language translations assist local operating companies with data transcription

Other data sources

- Signal detection
  - CIOMS VIII on Application of Signal Detection in Pharmacovigilance - to be published
  
  http://www.cioms.ch/index.html

- ICH guidelines
  
Acknowledgements

- Sabine Brosch, EMEA
  - European regulatory slides
  - Backup slides
    - Acronyms
    - MedDRA e-reporting

Questions?
Acronyms (1)

- AE: Adverse Event
- AERS: Adverse Event Reporting System database (US FDA)
- CIOMS: Council for International Organizations of Medical Sciences
- CRF: Case Report Form
- CTD: Common Technical Document

Acronyms (2)

- E2B: Data Elements for Transmission of Individual Case Safety Reports
- EC: European Commission
- EEA: European Economic Area
- EMEA: European Medicines Agency
- ESTRI: Electronic Standards for the Transfer of Regulatory Information and data (ICH M2)
- EVWEB: EudraVigilance Web Application
- EU: European Union
- FDA US: Food and Drug Administration United States
Acronyms (3)
- ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
- ICSR: Individual Case Safety Reports
- IFPMA: International Federation of Pharmaceutical Manufacturers & Associations
- MHRA: Medicines and Healthcare products Regulatory Agency
- MedDRA: Medical Dictionary for Regulatory Activities
- MSSO: MedDRA Support Service Organisation
- NCA: National Competent Authority

Acronyms (4)
- PSUR: Periodic Safety Update Report
- PT: Preferred Term
- SAE: Serious Adverse Event
- SMEs: Small and Medium Sized Enterprises
- SMQs: Standardised MedDRA Queries
- SOC: System Organ Class
- WHO: World Health Organisation
- WHO-ART: World Health Organisation Adverse Reaction Terminology
MedDRA: e-reporting

MedDRA coding in Individual Case Safety Reports (ICH E2B(R2)):
- Past Medical History
- Past Drug Therapy Indication and Drug Reaction
- Reported Cause of Death
- Autopsy-Determined Cause of Death
- Parent Past Medical History
- Parent Past Drug Therapy Indication
- Parent Drug Reaction to Past Drug Therapy

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MedDRA: e-reporting (2)

MedDRA coding in Individual Case Safety Reports (ICH E2B(R2)):
- Reaction MedDRA Lowest Level Term (LLT)
- Reaction MedDRA Preferred Term (PT)
- Test/Procedure Name
- Drug Indication
- Drug Reaction Recurrence
- Drug Reaction Assessment
- Sender’s Diagnosis

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