MedDRA Important Medical Events (IME) in the EU

Patricia Mozzicato, MD
MedDRA MSSO
Topics Covered

• MedDRA refresher
• Background of IME list
• Considerations in maintaining MedDRA-based term lists
  – Inclusion/exclusion criteria
  – Version updates
  – Examples from draft IME list
• IME list survey
MedDRA Refresher
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.
Regulatory Status of MedDRA in EU

- Clinical trials
  - SUSARs (Suspected Unexpected Serious Adverse Reactions)
- Volume 9A
  - Individual Case Safety Reports (ICSRs)
  - Adverse reactions in PSUR
  - Standardised MedDRA Queries (SMQs) recommended for signal detection
- Interface between EudraVigilance and EU Risk Management Plan – indications, risks, interactions
- Summary of Product Characteristics guideline
Scope of MedDRA

IN
- Diseases
- Diagnoses
- Signs
- Symptoms
- Therapeutic indications
- Investigation names & qualitative results
- Medical & surgical procedures
- Medical, social, family history
- Medication errors
- Product quality, device issues
- Terms from other terminologies

OUT
- Frequency qualifiers
- Numerical values for results
- Severity descriptors
- Not an equipment, device, diagnostic product dictionary

Not a drug dictionary

Patient demographic terms

Clinical trial study design terms
MedDRA’s Structure

- SOC = Cardiac disorders
- HLG = Cardiac arrhythmias
- HLT = Rate and rhythm disorders NEC
- PT = Arrhythmia

LLT:
- Arrhythmia NOS
- Arrhythmia
- Cardiac arrhythmia NOS

LLT:
- Dysrhythmias
Multi-Axiality

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
• For multi-axial terms, one SOC is **primary**
• Primary SOC rules for:
  – SOC *Congenital, familial and genetic disorders*
  – SOC *Infections and infestations*
  – SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*

• Three SOCs are not multi-axial:
  – SOC *Investigations*
  – SOC *Social circumstances*
  – SOC *Surgical and medical procedures*
MedDRA and the MSSO

• International support and development of terminology
• Foster use of MedDRA through communications and educational offerings
• “Custodians”, not owners, of the terminology
• JMO (partner organization for Japanese-language MedDRA)
• Governed by a Management Board (industry, regulators, multi-national, other interested parties)
Background of IME List
Purpose of IME List

• Facilitate:
  – Classification of suspected adverse reactions
  – Aggregate data analysis
  – Case assessment for pharmacovigilance activities

• Intended for guidance purposes only
  – Not mandatory requirement for regulatory reporting
  – Option to use it for other purposes
• Development by EV-EWG started in May 2007
• Identified MedDRA Preferred Terms (PTs) that are medically important regardless of presence of other regulatory seriousness criteria
• Based on an MHRA list
• **All terms** in three SOCs initially INCLUDED:
  – SOC *Congenital, familial and genetic disorders*
  – SOC *Infections and infestations*
  – SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*

• **All terms** in two SOCs initially EXCLUDED:
  – SOC *Social circumstances*
  – SOC *Surgical and medical procedures*

• Remaining terms in 21 SOCs were assessed by volunteers with medical background
Inclusion of PTs on IME List

• Divided terms for inclusion into:
  – “Core serious” (CS) – always serious
  – “Extended serious” (ES) – serious in some circumstances only

• Teams of 4 – 6 volunteers reviewed the terms:
  – If majority agreed, term added
  – If “tie”, the more conservative assessment was taken (e.g., if 3 for CS and 3 for ES, term became CS)
Maintaining MedDRA-based Term Lists
• Term lists maintained by MedDRA MSSO
  – Gender-Specific Adverse Events
  – Pediatric Adverse events
  – Standardised MedDRA Queries (SMQs)
Considerations for Maintaining Term Lists

• Understand **purpose** of list
  – What is the intended use of the list?
  – Are there other ways the list may be used?
• Understand **scope** of list
  – What are the inclusion/exclusion criteria?
• List received for review in MedDRA v12.0; approx. 9000 PTs
• To update list to MedDRA v12.1, first inclusion/exclusion criteria needed to be developed
• Draft incl/excl criteria:
  – Overall
  – SOC-specific
• Inclusion/exclusion criteria based on ICH definition of an IME

“…may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.”
Examples: Inclusion/Exclusion Criteria

• Overall
  – Included
    • Generally, all infarct/infarction terms (e.g., PT Renal infarct)
    • Terms for failure or insufficiency of life-sustaining organ systems (PT Hepatic failure)
  – Excluded
    • “Pain” and “discomfort” terms (PT Pain of skin)
• **SOC Cardiac disorders:**
  
  – Included
    - All terms for cardiac valve disorders (e.g., PT *Aortic valve stenosis*)
    - All terms for endocardial disorders (PT *Endocardial fibrosis*)
  
  – Excluded
    - Terms for trivial arrhythmias that do not lead to more significant consequences (PT *Extrasystoles*)
• Core serious
  – Precisely fits definition of an IME
    • Example: PT *Stroke in evolution*

• Extended serious
  – Does not precisely fit definition
  – Sometimes rather broad concept
  – *With additional clinical information*, may be or evolve into an IME
    • Example: PT *Anaemia*
• Original scope of IME list changed
  – **Selected** (not all) PTs from these SOCs are included:
    • SOC Congenital, familial and genetic disorders
    • SOC Infections and infestations
    • SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps)
  – **Selected** PTs from these SOCs are included (had originally been excluded):
    • SOC Social circumstances
    • SOC Surgical and medical procedures
• Apply incl/excl criteria to **new** v12.1 PTs
• Review existing terms on list against new criteria
• Review terms *not* on list against new criteria
• Check for other PT changes (demotion to LLT, change of primary SOC)
• EV-EWG and PhVWP have both reviewed revised term list and proposed inclusion/exclusion criteria
• List will be updated with each new MedDRA version
• Experts will review updated lists and criteria with each new version
Current Activities

• EV-EWG created a survey for those who downloaded IME list
• Survey will be available online until 26 October 2010 (EudraVigilance Web site, under “News” - http://eudravigilance.emea.europa.eu/human/index.asp)
• Takes about 15-20 mins to complete
• Data will be treated in a confidential way: summary will be shared with MSSO, MedDRA Management Board and other interested parties
Goals of Survey

• To assess:
  – Type of users who tested the IME list
  – How IME list has been tested
  – How useful IME list has been
  – How to improve IME list in the future
Thank you