Important Medical Events: Current Status and Maintenance Principles

Patricia Mozzicato, MD
MedDRA MSSO

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Topics Covered

• Background of IME list
  – What is the IME List?
  – Purpose of IME List
• IME List survey results
• Considerations in maintaining MedDRA-based term lists
  – Inclusion/exclusion criteria
  – Version updates
  – Recent developments
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**

- **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**
  - Not a drug dictionary
  - Not an equipment, device, diagnostic product dictionary
  - Frequency qualifiers
  - Numerical values for results
  - Severity descriptors
  - Patient demographic terms
  - Clinical trial study design terms
Background of IME List

What Is the IME List?

- List of MedDRA Preferred Terms (PTs)
- Development coordinated by the Eudravigilance Expert Working Group (EV-EWG)
- Updated with each release of MedDRA
- User input is collected and assessed for version updates
Purpose of IME List

- Reference: “Eudravigilance Important Medical Event Terms (IME) List (30 July 2009)
  - EMEA/457378/2008
- 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

Initial Development of IME 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
• 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)
• All stakeholders who requested the IME list were invited to participate
• Survey created by EV-EWG
• Run from May – October 2010
  – 35 responders
• Objective was 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
• (Data on the following slides were kindly provided by EMA)
IME List Survey – Usefulness

- Not useful at all: 5%
- Very useful: 43%
- Moderately useful: 52%

IME List Survey – Strengths

- Consistency of assessment: 71%
- Excel format: 67%
- Updated to current MedDRA version: 67%
- Systematic evaluation: 62%
- Flexible to user’s needs: 36%
- Pre-defined list for signal detection: 29%
IME List Survey – Weaknesses

Not adapted to specific situations: 48%
Too extensive: 48%
Not regularly maintained: 29%
Definitions too broad for CTs: 14%
Other: 24%

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

Maintenance of IME List (2)

• 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 (1)

• 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)

Examples: Inclusion/Exclusion Criteria (2)

• 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

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**Development of CS/ES Criteria**

• 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

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**Maintenance of IME List (1)**

• 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
**Maintenance of IME List (2)**

- Apply inclusion/exclusion criteria to **new** PTs
- Check for other PT changes (demotion to LLT, change of primary SOC)
- Address input from stakeholders
- EV-EWG reviews updated lists and criteria with each new version

**IME List Challenges**

- Size of list (Version 14.1)
  - PTs in MedDRA = 19,294
  - PTs on IME List = 10,372 (54% of all MedDRA PTs)
  - "Core Serious" PTs = 7547 (39% of all MedDRA PTs; 73% of PTs on IME list)
  - "Extended Serious" PTs = 2825
- Application of “Extended Serious” criterion
- Consistency (e.g., some diabetes terms CS, others ES)
“Extended Serious” Terms (1)

• Current definition:

Such PTs do not precisely fit the definition and are sometimes rather broad (e.g., terms for “disorders” of vital organs). Although the term in isolation may not represent a clear cut IME, it could be envisioned that — with additional clinical information and medical circumstances (medical history, age of patient, etc.) available to the recipient of the report — the event may be or evolve into an IME.

• Challenging to apply this criterion to MedDRA terms (devoid of the needed context)

“Extended Serious” Terms (2)

• Almost any event – with additional information known by recipient – could be ES. For example:
  − A headache could be sudden, disabling and severe enough for hospital visit
  − Implant site inflammation could result in disability if unable to use limb

• What is the value of ES terms?
• EMA and EV-EWG agreed that ES terms will be dropped from IME list
• Consistency issues will be addressed at a future date

Thank You