# Important Medical Events: Current Status and Maintenance Principles

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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 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.

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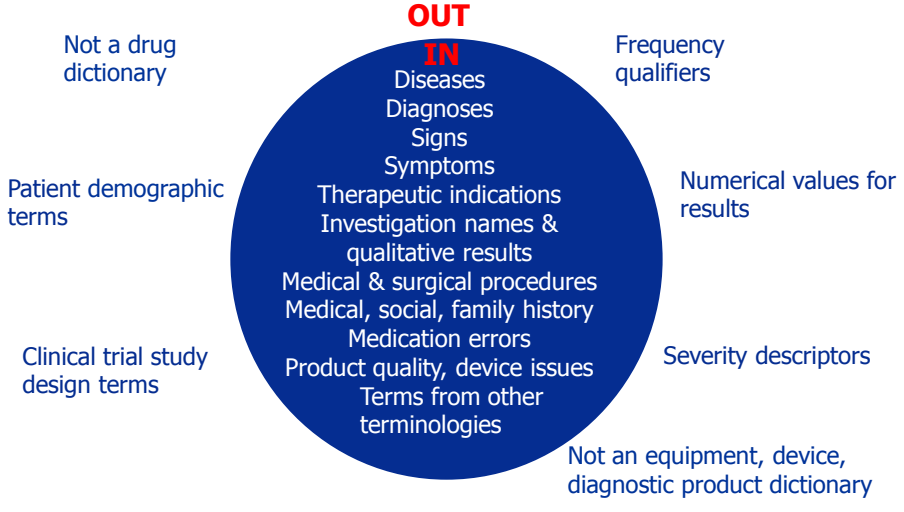
## Scope of MedDRA

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# 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
  - http://eudravigilance.ema.europa.eu/human/docs/Explanatory_note_IME_list.pdf
- 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

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## 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

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## Inclusion of PTs on Initial 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)

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# IME List Survey Results

## IME List Survey

- 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*)**

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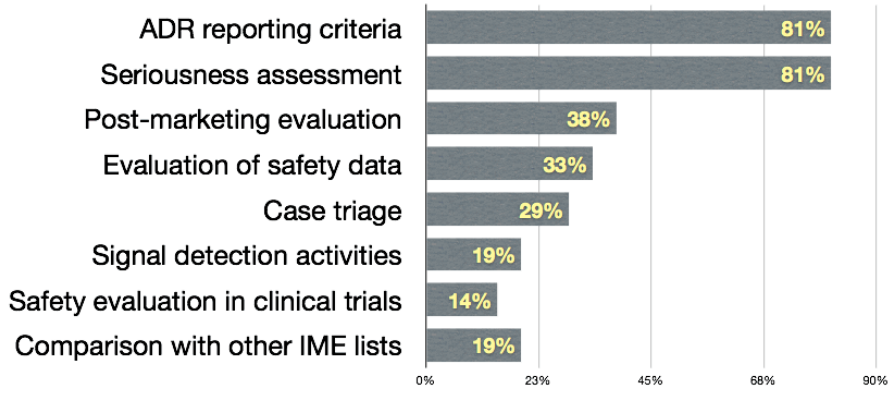
## IME List Survey – Uses of List

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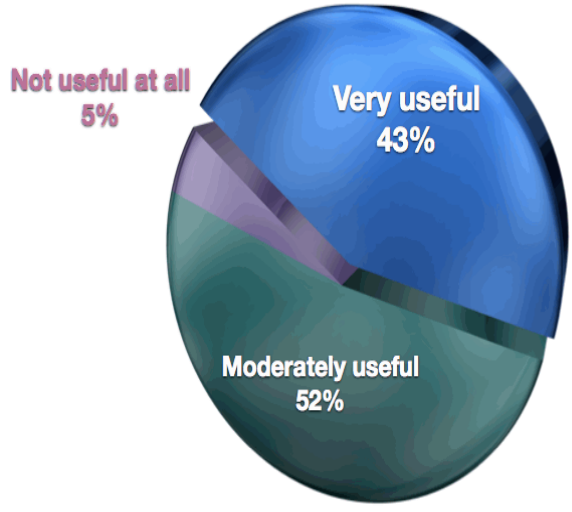
## IME List Survey – Usefulness

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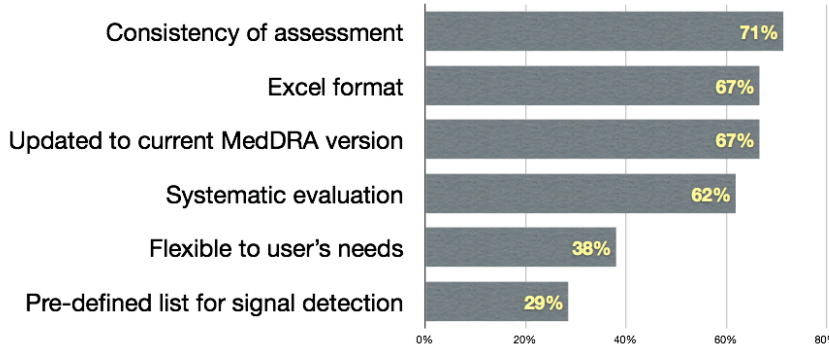
## IME List Survey – Strengths

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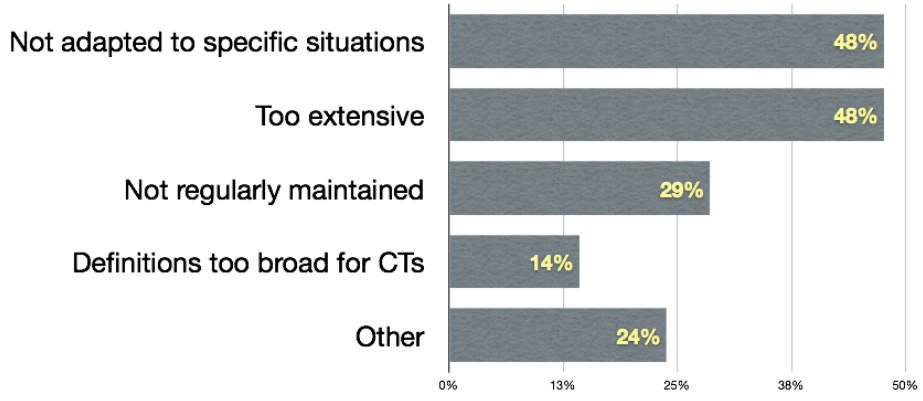
## IME List Survey – Weaknesses

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# Maintaining MedDRA-based Term Lists

## MSSO and MedDRA Term Lists

Term lists maintained by MedDRA MSSO

- Gender-Specific Adverse Events
- Pediatric Adverse events
- Standardised MedDRA Queries (SMQs)

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## 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?

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## Maintenance of IME List (1)

- 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

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## 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."*

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## 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*)

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## 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*)

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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*

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## 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

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## 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)

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## "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)

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## "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?

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## Recent Developments

- EMA and EV-EWG agreed that ES terms will be dropped from IME list
- Consistency issues will be addressed at a future date

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# Thank You

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