



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Important Medical Event (IME) list

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An agency of the European Union





Disclaimer and Acknowledgements

The views expressed in this presentation are the views of the speaker and do not necessarily reflect the views or policies of the European Medicines Agency (EMA). Terminology used may not necessarily be consistent with MedDRA official terms.

The presentation is based on the work of Aniello Santoro and other colleagues at the EMA, EV EWG, MedDRA MSSO and other parties involved in the development and maintenance of IME list; but also on the feedback of IME list users.



Summary

1. IME list

- Background and development
- Improvements
- Maintenance mechanism and schedule

2. IME list survey results and actions

3. New IME list v14





Purpose and Use

- Used for day to day pharmacovigilance activities of stakeholders in the EU:
 - facilitates the classification of suspected adverse reactions
 - aggregated data analysis
 - case assessment
- Guidance purposes only
 - it is not a mandatory requirement for seriousness assessment and regulatory reporting
 - option to use it for other purposes



Background

- Development started in 2007 (EV-EWG)
- Initial list based on a MHRA MedDRA v 10.0 list
- Included terms that are medically important and “serious”, regardless of the presence of the *classical* seriousness criteria
- It is the longest and most used list by a regulator in the EU, to our knowledge



Development of the IME list – first version

- Included all terms in 3 SOC_s:
 - Congenital, familial and genetic disorders
 - Neoplasms benign, malignant and unspecified (including cysts and polyps)
 - Infections and infestations

- Excluded all terms in 2 SOC_s:
 - Social circumstances
 - Surgical and medical procedures



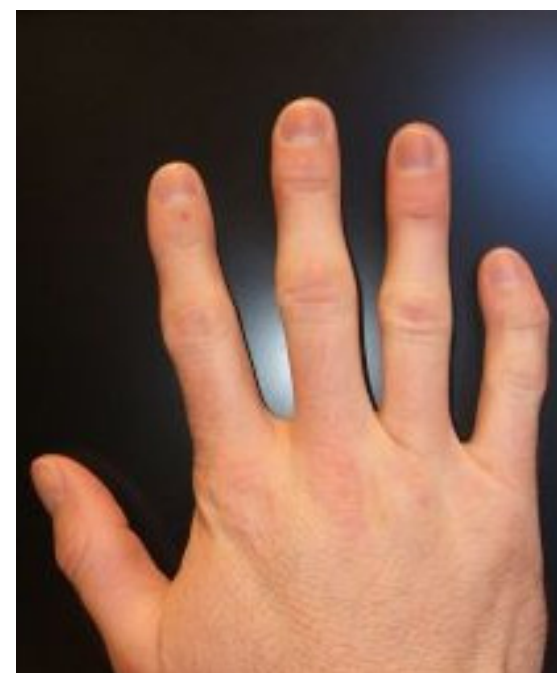
Development of the IME list – first version

- Remaining 21 SOCs assessed by volunteers with medical background. Included only a selection of terms:
 - Core Serious (CS) = terms that are “always” serious
 - Extended Serious (ES) = can be serious according to the circumstances (e.g. intensity, severity)
- Decisions made based on simple majority
 - If split decision, more conservative approach favoured



Challenges following initial development

- Maintenance of the list without inclusion/ exclusion criteria
 - Similar lists have inclusion/exclusion criteria. e.g. Gender-specific Adverse Events; Paediatric Adverse Events; SMQs
- ICH definition of IME is not straight forward to apply to the list
- List comprehensive but proved to be too wide. e.g., PT Clinodactyly was classified as a CS term





Challenges following initial development

- Terms in the excluded SOCs may be reported if no other AR/AE information is reported or if they add valuable clinical information
 - *Social circumstances* and *Surgical and medical procedures* SOCs terms not usually used to report AEs
- SOCs with all terms included in the IME list may contain trivial/non-serious conditions (e.g. *Nasopharyngitis*)





Improvements of IME list and maintenance

Improvements since version 12.1:

- ✓ Development of criteria based on the ICH definition of IME
 - Overall inclusion and exclusion criteria
 - SOC specific criteria, i.e. terms selected from every SOC
- ✓ Definitions for CS&ES terms:
 - CS definition fits the definition of IMEs (e.g. *stroke in evolution*)
 - ES definition is a broader concept. With additional clinical information, may be or evolve into an IME (e.g. Anaemia)
- ✓ New maintenance mechanism
- ✓ IME list survey and actions



New Maintenance Mechanism

Objective: to ensure that new IME list releases are in synchrony with releases of MedDRA

- Version X.0 available by end of March
- Comments from users received by 1st June
- Comments integrated in Version X.1, available by end of September
- Comments from users received by 1st Nov
-> next version: (X+1).0

CALENDAR 2011

MedDRAIMElist@ema.europa.eu

www.ema.europa.eu



IME list survey - Objectives

May-October 2010

- ✓ Describe users testing the IME list
- ✓ Describe testing and use environment
- ✓ Assess the usefulness of the list
- ✓ Collate suggestions for improvement
 - Address the comments and further improve the IME list



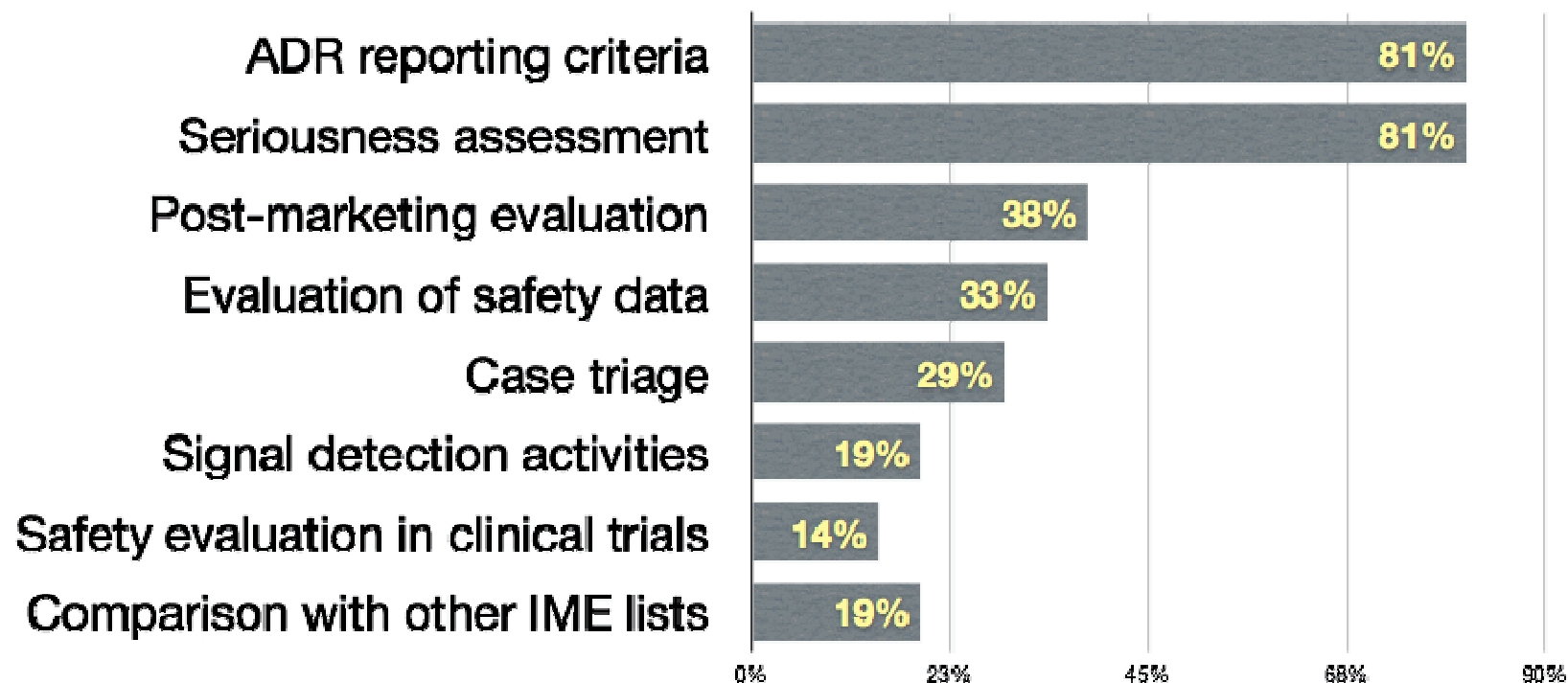
IME list survey results

Responders (n=35):

- Pharmaceutical companies: 62%
- Regulatory agencies: 14%
- Consultants: 8%
- CROs, IT providers or other: 2 each
- One non-profit organisation

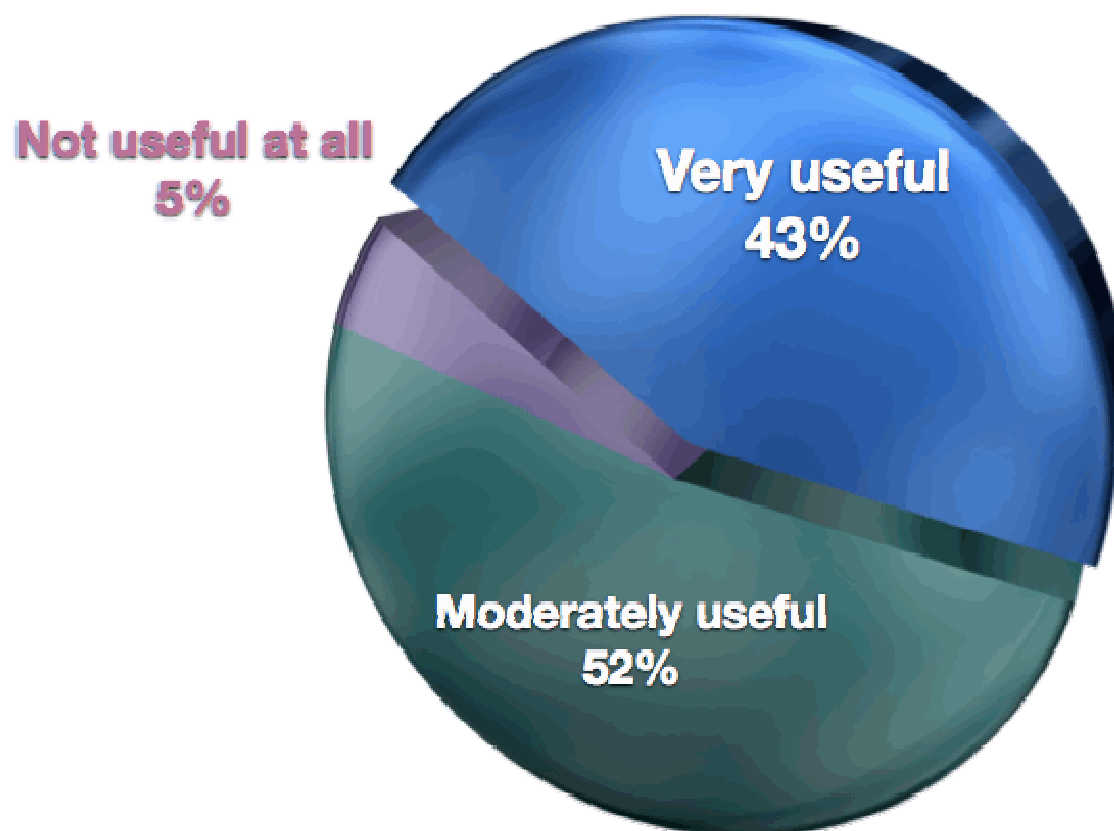


IME list usage (n=21)



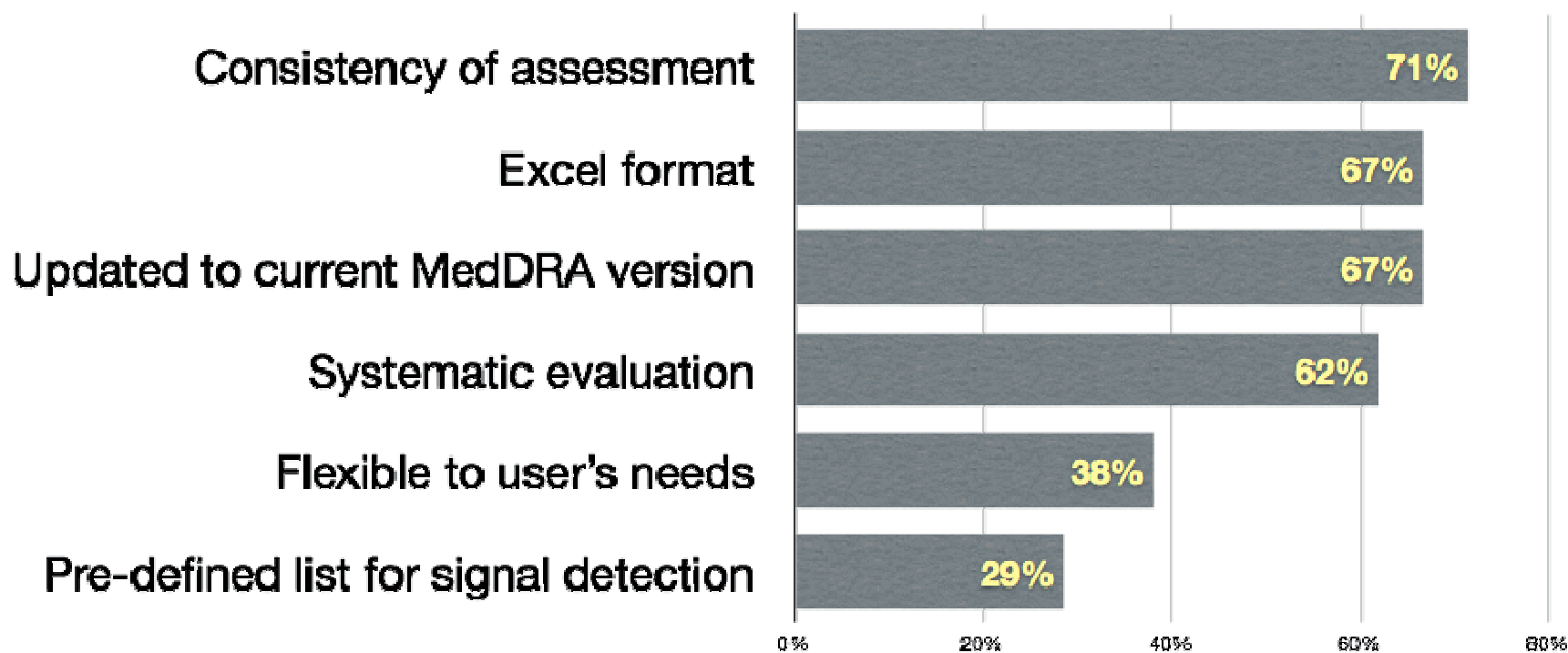


Is the IME list useful?





Strength





Weakness

Not adapted to specific situations

48%

Too extensive

48%

Not regularly maintained

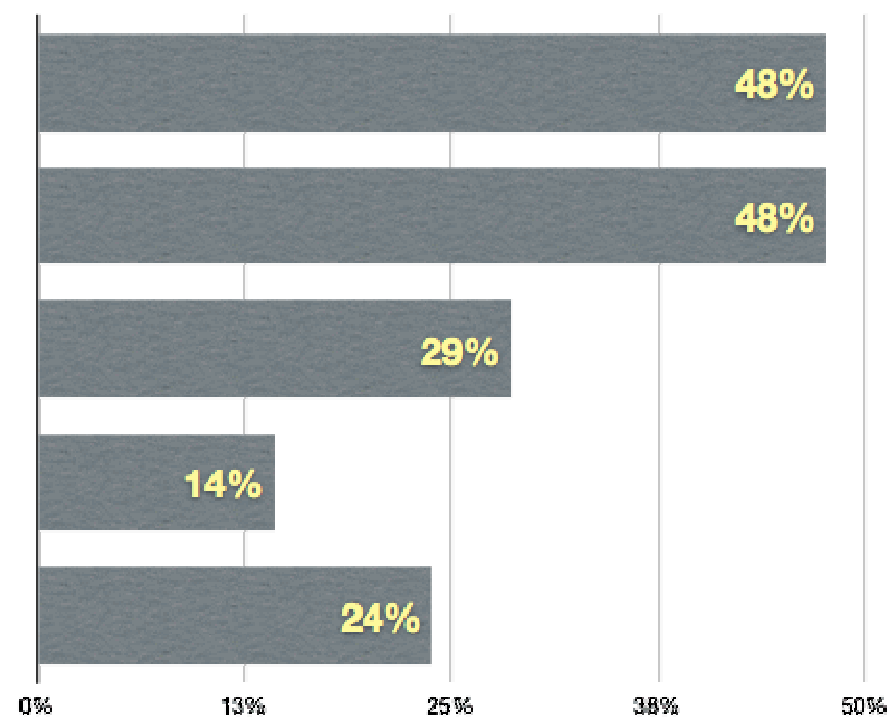
29%

Definitions too broad for CTs

14%

Other

24%





Suggestions for improvement & implementation

1. Size of the list: “downsize it!”

- ✓ We need specific suggestions!

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- ✓ All suggestions are reviewed!

2. Rationale for term inclusion/designation

- ✓ Developed inclusion/exclusion criteria
- ✓ Developed definitions of ES/CS



Suggestions for improvement & implementation

3. Lack of regular maintenance

- ✓ Maintenance mechanism developed as of version 14.0

4. Rigidity: “Why all PTs under SOC *Infections and Infestations* are included?”

- ✓ Inclusion and exclusion criteria for all SOC

5. Possible discrepancy between ICSR seriousness assessment and inclusion of term in IME

- ✓ IME for guidance, not replacement of medical judgment



Suggestions for improvement & implementation

6. IME list should include only PTs
 - ✓ Now includes only PTs, the few LLTs removed
7. MedDRA hierarchy should be added (HLTs, HLGTS)
 - ✓ Will be discussed with EV-EWG
8. Proposed change in designation or addition/deletion of terms
 - ✓ Will be discussed with EV-EWG
 - ✓ Only terms already in MedDRA can be added to the IME list!
9. Proposal to have the list additionally in word/PDF/ASCII
 - ✓ Will be discussed with EV-EWG. User can export and modify the data.

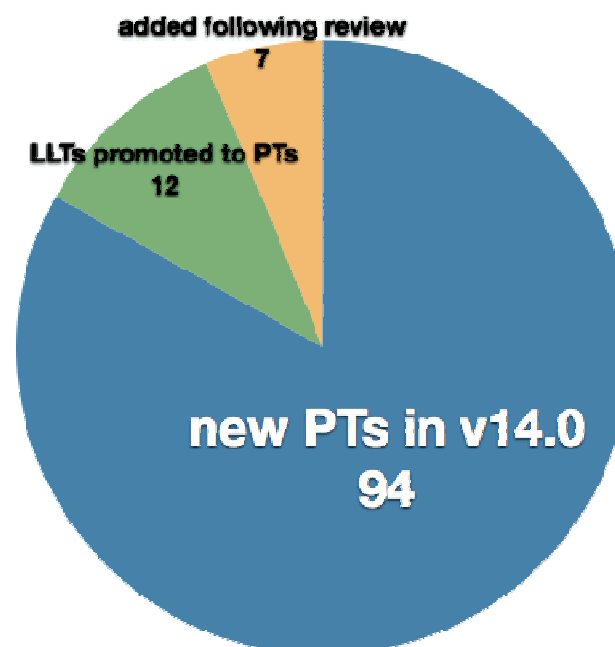


New IME list version 14.0

10246 PTs: 70% CS, 30% ES

113 PTs added:

- **61** terms changed designation
 - **55** ES → CS
 - **6** CS → ES
- **3** terms changed primary SOC
- **2** terms renamed





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Coding of Indication Using MedDRA and Qualifiers

MedDRA User Group Meeting – Geneva, 2011

Presented by: Emil Cochino
Patient Health Protection

An agency of the European Union





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The data presented reflects only the intermediate results of the project.



Summary

1. Project description

- Scope
- Objective
- Activities

2. Coding

3. Results

4. Next steps



What is an indication?

Physician -> eligible **patients**:

- "on label"
- off label: compassionate use, clinical trial, public health interest, price

Disease: "treatment of metastatic breast cancer"

Intended effect: "reduction of intraocular pressure";
"prevention of atherothrombotic events"



What is an indication?

Regulators:

- MedDRA term: EPARs website, EU-RMP, RMP annex I (electronic summary), EudraVigilance, ICSRs, Signal Detection,...
- SmPC chapter 4.1: a complex description of the patient, disease and treatment characteristics, nominating the patients eligible to receive the medicinal product



Indications in CAPs SmPCs (4.1)

actual disease +

- + Clear description of the patient, disease and treatment characteristics = qualifiers + attributes
- + Additional data:
 - + pharmaceutical form,
 - + posology,
 - + warnings and contraindications (partially codable)
 - + clinical evidence from development program, missing information
 - + PD/PK data
 - + all other data important to the Rapporteurs/CHMP (risk minimisation measure/ summary of SmPC)



Project description: Scope

- ✓ To assess the appropriateness of MedDRA terminology in coding centrally authorized medicinal products indications and identify additional improvements and qualifiers needed to develop an approach for the potential coding of indications of medicinal products.



Objectives

- ✓ To assess the percentage of sampled medicinal products indications that can be fully coded by MedDRA terms using the current MedDRA version.
- ✓ To propose improvements of the MedDRA terminology and assess the percentage of sampled indications that can be fully coded using MedDRA terms.
- ✓ To define a set of qualifiers to be used in addition to MedDRA terminology to facilitate the coding of indications.



Activities

- ✓ Synopsys
- ✓ Preparatory phase (small sample)
- ✓ Test phase, all CAPs coded (544)
- ✓ Propose MedDRA terms to add to v14
- ✓ Finalise list of qualifiers (input in the ISO IDMP DIS ballot)
 - Mapping of indications + qualifiers + attributes for every individual indication for all CAPs (current activity)
 - CAPs' indications data analysis in EVPM module



Coding

Time consuming process, requires excellent medical and MedDRA terminology knowledge (support from MedDRA MSSO)

SmPC INDICATION

Codable/relevant data	Non-codable data
-----------------------	------------------

disease	disease circumstances	discarded/ free form
---------	-----------------------	----------------------

disease	qualifiers	attributes	discarded/ free form
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MedDRA terms (existing and proposed)	new categorical description (expanding)	disease/treatment terms associated with specific qualifiers	SmPC searchable free text (redundant, backup)
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categorical data	free form data
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Qualifiers

In grammar, a **modifier** (or **qualifier**) is an optional element in phrase structure or clause structure; the removal of the modifier typically doesn't affect the grammaticality of the construction. Modifiers can be a word, a phrase or an entire clause. Semantically, modifiers describe and provide more accurate definitional meaning for another element.

Wikipedia (Cambridge Grammar of the English Language)



List of Qualifiers (1)

Patient related:

- Age Group (Neonates, Infants, Children, Adults, Elderly, Premature Newborns, Adolescents, Paediatric, Of Fertile Age, Specific Age Group)
- Gender
- Nutritional Status (Underweight, Normal weight, Overweight, Obese)
- Relation to natural events (Premenopausal, Postmenopausal, Prepubertal Children, Pubertal Children, Pregnant)



List of Qualifiers (2)

Disease related:

- Risk (Low, Moderate, High)
- Type (Stable, Active, Progressive, Relapsed, Advanced, Metastatic, Residual)
- Co-morbidities
- Specific Characteristic (Stage, Immune to, Non-immune to, Target organ damage, Pandemic)



List of Qualifiers (3) - Treatment related

- Diagnostic Use
- Experiences Status (Naive, Experienced)
- Line Indication (First, Second, Third Line)
- Other Therapies (Contraindicated, Not Clinically Appropriate, Not Available, Not Tolerated, Inadequate Response, Failure, Refractory)
- In Combination With (other therapies)
- Number of Co-therapies
- Relationship with Other (concomitant) Therapies (Adjunctive, Substitution, Supportive)
- Indication for other treatment/procedure
- Objective (Prophylaxis, Palliative, Curative, Active/ Passive/ Primary/ Booster Immunisation)
- Strategy (Induction, Consolidation, Maintenance)



Attributes

Attributes can be:

- indications, co-morbidities (fully codable)
- medicinal products, substances, procedures
- infectious agents, causal factors
- age intervals (non-standardized)
- any other relevant information in the SmPC indication that can help the signal detection process using EV database



Example Indication (SmPC)

Clopidogrel is indicated in **adults** for the **prevention of atherothrombotic events** in:

- Patients suffering from **myocardial infarction** (from a few days until less than 35 days), **ischaemic stroke** (from 7 days until less than 6 months) or **established peripheral arterial disease**.
- Patients suffering from **acute coronary syndrome**:
 - **Non ST segment elevation acute coronary syndrome** (unstable angina or non Q wave myocardial infarction), including patients undergoing a **stent placement following percutaneous coronary intervention**, **in combination with acetylsalicylic acid (ASA)**.
 - **ST segment elevation acute myocardial infarction**, **in combination with ASA** in medically treated patients **eligible for thrombolytic therapy**.

For further information please refer to section 5.1.



Extracted indications

Extracted text	Corresponding MedDRA 13 PT or LLT
prevention of atherothrombotic events	Thrombosis prophylaxis *
myocardial infarction	Myocardial infarction
ischaemic stroke	Ischaemic stroke
peripheral arterial disease	Peripheral arterial disease
acute coronary syndrome	Acute coronary syndrome
Non ST segment elevation acute coronary syndrome	Acute coronary syndrome *
unstable angina	Unstable angina
non Q wave myocardial infarction	Non-Q wave MI
stent placement following percutaneous coronary intervention	Coronary arterial stent insertion
stent placement following percutaneous coronary intervention	Percutaneous coronary intervention
ST segment elevation acute myocardial infarction	ST segment elevation myocardial infarction
thrombolytic therapy	Thrombolysis



Extracted qualifiers

- Patient/age/major group/adults
- Treatment/in combination with (other therapies)
- Treatment/indication for other treatment/procedure

P114

T05A

T08A



Extracted attributes

- acetylsalicylic acid (ASA)
- thrombolytic therapy



Coded indications

10043634/P114

10028596/P114

10061256/P114

10067825/P114

10051592/P114/T05A/"acetylsalicylic acid"

10046251/P114/T05A/"acetylsalicylic acid"

10029506/P114/T05A/"acetylsalicylic acid"

10052086/P114/T05A/"acetylsalicylic acid"

10064345/P114/T05A/"acetylsalicylic acid"

10064345/P114/T08A/"thrombolytic therapy"



Project results

1. Can MedDRA terminology be used for coding of indications based on centrally authorised medicinal products ?

YES

- Most of extracted indications have a corresponding MedDRA v13 PT or LLT (96%)
- 55 PTs and LLTs already proposed for addition to MedDRA v14
- 100% of extracted indications codable in v14
- Qualifiers are an important attribute to add further granularity required to describe indications



Next steps

1. Map agreed indications, qualifiers and attributes to all CAPs (ongoing)
2. Assess integration in EudraVigilance
3. Perform analysis of indication distribution in EVPM module ICSRs
4. Improve signal detection process



Anticipated benefits for the coding of indications

Ability to answer questions such as:

- How many and what types of reports were received for drugs indicated in a certain disease?
- What are the drugs indicated as second line treatment for a certain condition? How many reports were received for these drugs?
- What is the reporting ratio for a drug vs. all other drugs indicated in the same indication/same SOC/ same age groups/ only in metastatic cancer/ only in co-administration with methotrexate? i.e. targeted proportional reporting ratios (PRRs)