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Inclusion/exclusion criteria for the "Important Medical Events" list

Introduction

The EudraVigilance Expert Working Group (EV-EWG) has coordinated the development of an Important Medical Event Terms (IME) list. This IME list aims to facilitate the classification of suspected adverse reactions as well as aggregated data analysis and case assessment in the frame of the day-to-day pharmacovigilance activities of stakeholders in the European Union. The IME list is intended for guidance purposes only. Inclusion/exclusion criteria for the IME list were developed during review of the current list for maintenance related to MedDRA Version 12.1. They have been updated to the current version of MedDRA. The criteria – and the proposed additions and deletions to the upversioned list – were based on the official ICH definition of seriousness and of an "important medical event" as noted below:

A serious adverse event (experience) or reaction is
any untoward medical occurrence that at any dose:
* results in death,
* is life-threatening,
* requires inpatient hospitalisation or prolongation of existing hospitalisation,
* results in persistent or significant disability/incapacity, or
* is a congenital anomaly/birth defect. *It is recommended that reconsideration of this criterion be made relative to inclusion of terms on the IME list (see criterion 15). Not all congenital anomalies have clinical consequence and can be considered even normal variants. Furthermore, not all genetic conditions have a drug related aetiology.*

[NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.]

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the patient or may require

[1] This revision introduces a minor clarification on criterion 15.

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intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.
Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

NOTES:

- The overarching criterion for terms that should be included on the IME list is that the concept must fit the ICH definition of an IME. Use of the phrase "Relevant forms of" and other such qualifiers in this document are meant to convey that not *all* forms of a type of disorder will always fulfil the definition of an IME. Certain categories of events that could be considered medically important but are not likely to be relevant in the context of pharmacovigilance activities are excluded from the IME list. These include events due to trauma and exposures and poisonings to external agents.
- The phrase "vital organ" is interpreted in the context of these criteria as meaning a bodily organ that is essential for life.
- Surgical and medical procedures terms that imply an IME has occurred, e.g., PT *Liver transplant* have now been excluded from the IME list. In practice, these terms are typically co-reported with terms on the IME list representing the underlying condition that led to the procedure, and coding should be performed in accordance with the guidance in the MedDRA Term Selection: Points to Consider document. In cases where only a procedure term has been reported, follow-up should first be attempted to obtain information on the underlying condition. If clarification cannot be obtained, the procedure term can be reported as a standalone event and, in many cases, this will meet a seriousness criterion such as hospitalisation. Medical judgement should always be applied and, even though procedure terms are no longer included in the IME list, consideration should be given to reporting them as serious events, when appropriate. Procedure terms may convey the severity and seriousness of a condition. For instance, if a case reports anaemia that requires a blood transfusion, the anaemia should be considered a serious event, although anaemia and blood transfusion are not included in the IME list.

Criteria for MedDRA terms on the IME list:

1. Cardiovascular conditions leading to important organ alterations:

- Relevant forms of **embolism**
- Vascular **aneurysms**, **dissection** and rupture of important vessels and heart cavities and structures
- **Arteriosclerosis** in vital organs
- Relevant forms of **gangrene**
- **Ischaemic** conditions

- Relevant forms of **infarction**
- Relevant **necrotic** conditions, including those that may not be clearly of vascular origin (e.g., some skin conditions such as PT *Toxic epidermal necrolysis*)
- **Vascular occlusions** that threaten the function and viability of critical organs
- Arterial **thromboses** and other vascular thromboses where significant compromise of organ function or other significant consequences could result
- Relevant terms for **cardiac valve disorders**
- Relevant forms of **cardiomyopathy**
- Relevant terms for cardiac **arrhythmias** except trivial ones such as extrasystoles.

2. Haemorrhages and significant blood disorders including:

- Relevant haemorrhages, especially these related to an internal organ
- Haematomas in anatomic sites where there may be a severe clinical consequence (e.g., PT *Extradural haematoma*)
- Bone marrow depressions and cytopenias
- Acquired haemoglobinopathies, acquired haemophilias and other forms of non-hereditary clotting factor deficiencies and coagulation disorders, including nonspecific factor deficiencies and related findings
- Relevant forms of haemolysis.

3. Obstructions of gastrointestinal, respiratory, hepatobiliary, genitourinary tracts, and ductal systems of vital organs.

4. Perforations and ruptures of gastrointestinal, respiratory, hepatobiliary and genitourinary tracts.

5. Relevant types of ulcers

- Ulcers occurring at less significant anatomic sites such as PT *Mouth ulceration* **are excluded.**

6. Fistulas between organs or structures where significant compromise of organ function and other significant consequences (e.g., haemorrhage) could result (e.g., PT *Aorto-oesophageal fistula*).

7. Failure and severe insufficiency of life-sustaining organ systems (e.g., PT *Cardiac failure*, PT *Renal failure, PT Hepatic failure*).

8. Relevant conditions affecting consciousness, cognition, mood, sensorimotor functions and other important neurological or neuro-psychological function impairments, including:

- Coma
- Dementia
- Seizures
- Encephalopathy
- Neuropathies including peripheral neuropathies
- Depression and psychosis and their prominent symptoms (e.g., delusions)
- Autism.

9. Failure of special senses (e.g., PT *Deafness*, PT *Blindness*) and relevant forms of eye disorders such as retinopathies, glaucoma, keratitis, and cataracts.

10. Infections that fulfil the definition of an IME, such as encephalitis, infective endocarditis, pneumonias, and hepatitis

- Relevant forms of bacteraemia, fungaemia, sepsis/septicaemia, and toxaemia conditions
- Abscesses and cellulitis of clinical significance or affecting vital organs

- Terms that represent modes of infection transmission (e.g., PT *Indirect infection transmission*) **are excluded**, as these are not events but a disease mechanism. However, PT *Transmission of an infectious agent via product* and PT *Suspected transmission of an infectious agent via product* are exceptions to this criterion and **are included** because these are important concepts requiring expedited reporting.

11. Inflammatory processes which fulfil the definition of an IME, such as aseptic encephalitis, non-infective pericarditis, and polyarthritis

- Unqualified (e.g., PT *Cystitis*, PT *Rhinitis*) and nonspecific inflammations (e.g., PT *Connective tissue inflammation* of **non-vital organs** and tissues, **are excluded**.

12. Immune disorders which fulfil the definition of an IME, such as immunodeficiency syndromes, autoimmune disorders, anaphylaxis and severe forms of angioedema and urticaria.

13. Malignant and occupying processes:

- All malignant neoplasms, including metastatic conditions
- All histological dysplasias and premalignant conditions with a high likelihood of progression to malignancy (e.g., PT *Myeloproliferative neoplasm*)
- Benign tumours of clinical significance due to space-occupying effects, or causing increased intracranial pressure, focal deficits, seizures, etc.; also, cardiac myxomas, etc

- Cysts and polyps (unless qualified as malignant), benign and unspecified neoplasms and neoplasms in remission (e.g., PT *Acute leukaemia in remission*), **are excluded**.

14. Injures fulfilling IME criteria, including:

- Terms for several types of fractures except trivial ones (e.g., PT *Greenstick fracture*)
- Most nerve injury terms, particularly of specific nerves

- Nonspecific "complication" terms (e.g., PT *Vascular access complication*) **are excluded**, unless they imply that a vital organ or structure is threatened.
- Terms referring to trauma or clearly implying a traumatic aetiology **are generally excluded.** However, trauma terms related to pregnancy, e.g., PT *Birth trauma* are included as well as trauma terms referring to bleeding because of the relevance in patients taking anticoagulants, e.g., PT *Traumatic intracranial haemorrhage*.

15. Because the ICH definition of seriousness includes "congenital anomaly or birth defect", many terms in SOC *Congenital, familial and genetic disorders* are included. Terms that describe genetic diseases/syndromes that qualify as an IME are included

- However trivial conditions and normal variants **are excluded** (e.g., PT Birth mark, PT Accessory spleen, PT Persistent left superior vena cava). Gene carrier states (e.g., PT Cystic fibrosis carrier) in which the affected patient is disease free **are also excluded**.
- Isolated genetic mutations (e.g., PT BRCA1 gene mutation) and other genetic conditions that can have spontaneous or de-novo occurrences (non-familial inheritance) and which do not have significant clinical manifestations **are excluded**.
- Congenital conditions for which the aetiology is not known, and which have significant clinical manifestations **are included**.
- Genetic conditions with a clear inheritance pattern **are excluded**:
    - Chromosomal abnormalities, e.g., Trisomy 21, Turner's syndrome
    - Mitochondrial diseases, e.g., MELAS syndrome, Kearns-Sayre syndrome.
    - Other, e.g. haemophilia, thalassaemia, Huntington's disease

16. Miscellaneous

- Investigation concepts that represent **measured parameters** that do not need additional contextual information to fulfil the criteria for an IME
    - Most **cerebrospinal fluid (CSF) test terms** (with qualifiers) due to the clinical significance of any abnormality of the CSF
    - However, isolated findings of an increased or decreased measured parameter (e.g., PT *Blood magnesium increased*) and unqualified test terms (e.g., PT *Angioscopy*) **are excluded**
- **Social circumstances** (mainly lifestyle issues) that could potentially be reported as AEs/ADRs and that would fit into the definition of an IME (e.g., PT *Substance abuser*)

- Surgical and medical procedures terms that imply that an IME has occurred **are excluded**

- Most **abortion** terms and placental and umbilical cord conditions, which imply a threat to the health or viability of the foetus

- "Elective abortion" terms **are excluded**

- **Infertility terms**
- Terms for **pregnancy with contraceptive**, which imply a lack of efficacy of the contraceptive
- **Device-related terms** causing a direct injury or complication to a patient that fulfils the definition of an IME (e.g., PT *Device related sepsis*)
- **Occupational exposure terms** that fulfil the criteria for an IME
- **Alcohol abuse and alcohol poisoning terms** are included because of the association with drug abuse and dependence
- Terms that in large pharmacovigilance databases have been frequently associated with high rate of fatality

- Nonspecific "disorders" and "anomalies", and other categorisations referring broadly to an organ system (e.g. PT *Skin disorder*) **are excluded**
- Exposures and poisonings to external agents, e.g., PT Gas poisoning**, are excluded,**

- "Lesion" terms **are excluded**, unless the finding automatically implies an IME, such as for PT *Precancerous mucosal lesion* and certain nervous system lesions
- "Mass" terms **are excluded** because they are nonspecific

- Signs and symptoms (such as pain and discomfort) **are excluded** as they generally do not fulfil the definition of an IME

- Medication error, accidental exposures, and product quality concepts are generally **excluded.** Administration site and other "site" concepts are generally **excluded** except for the following: site ischaemia, site joint infection, site necrosis, site thrombosis and other site conditions that have the potential to spread systematically and result in immediate clinical consequences with the loss or compromise of arteriovenous fistula/arteriovenous graft function (e.g. PT *Arteriovenous fistula site infection,* PT *Arteriovenous graft site abscess* and PT *Arteriovenous graft site infection*).