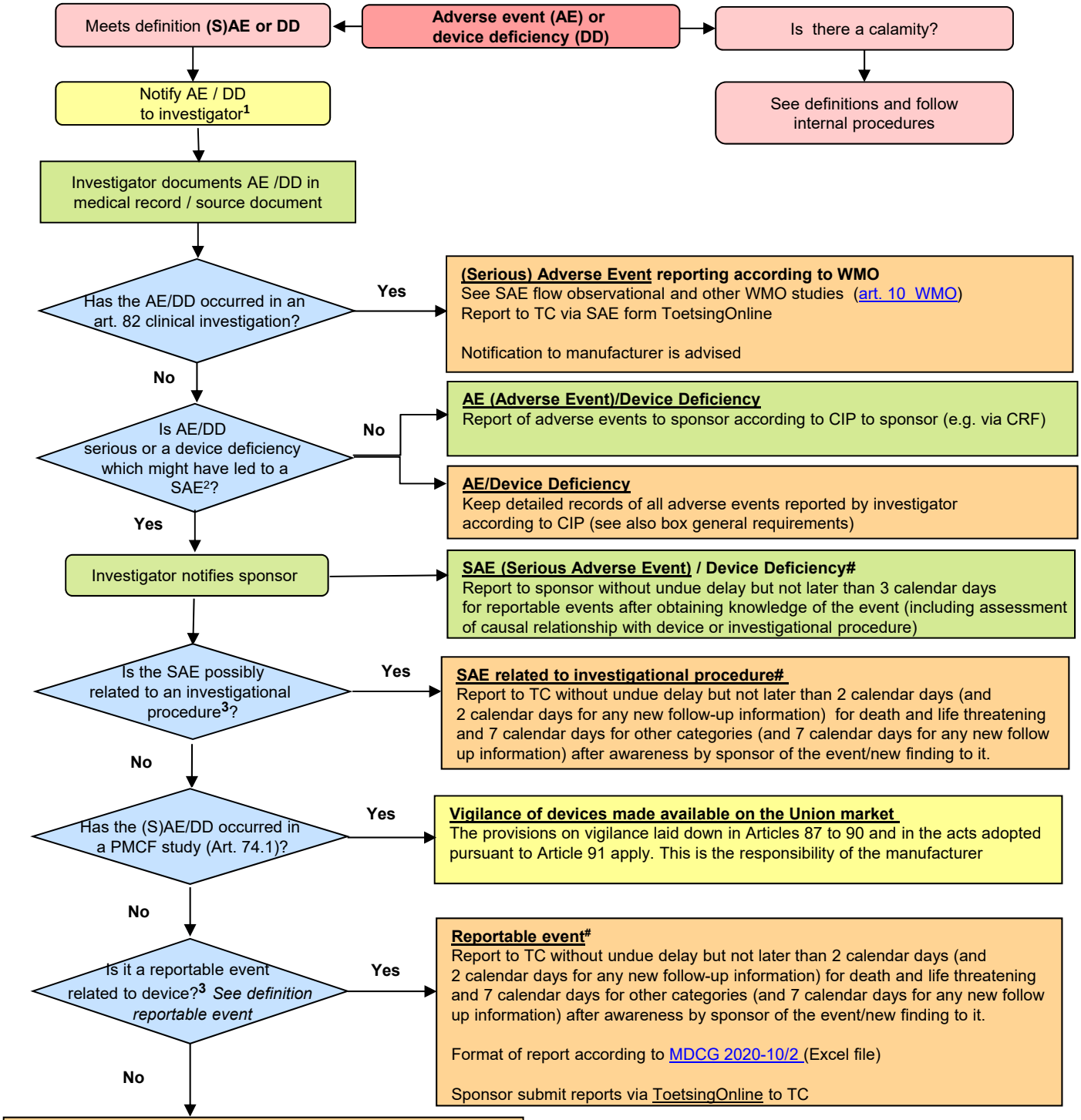
Adverse Event Flow

Clinical investigations with medical devices, MDR (art 62, 74 and 82)



CCMO, version 2, 24 april 2021

 # Reporting timelines investigator and sponsor

General
The reporting requirements are applicable for events related to investigational device, the comparator device and investigational procedures

Timeline investigator
Reportable events
► First initial report < 3 calendar days after awareness investigational site study personnel, unless a different procedure and reporting timeline has been agreed between sponsor and MREC/CCMO (for instance in oncology trials in which SAE frequency is expected to be high due to progression of disease). The SAE procedure should be laid down in the clinical investigational plan (protocol).

Timelines sponsor
All reportable events which indicate imminent risk of death, serious injury, or serious illness and that require prompt remedial action for other patients/subjects, users or other persons;
► First initial report **< 2 calendar days** after awareness sponsor
► New findings to initial report **< 2 calendar days** after awareness sponsor of new finding
Other reportable events;
► First initial report **< 7 calendar days** after awareness sponsor
► New findings to initial report **< 7 calendar days** after awareness sponsor of new finding

Upload in national webportal ToetsingOnline untill Eudamed is available
- Clinical investigations art 62 and 74: Format is given in MDCG 2020-10/2 (Excel file)
- Other clinical investigations : SAE form ToetsingOnline

Other obligations
- A sponsor may not downgrade the causality assessment done by the investigator
- If the sponsor has temporarily halted a clinical investigation or has terminated a clinical investigation early because of safety reasons, it shall inform all MS in which that clinical investigation is being conducted within 24 hours. The notification will also provide a justification.
- The sponsor has the obligation to submit safety information other than the reportable events if the MS has requested for it (MDR, art 80, sub 2).

Sponsor is not manufacturer
- It is advised to inform manufacturer of the medical device.

National/multinational clinical investigations
The safety reporting requirements are applicable for all clinical investigations authorised to be carried out national (Netherlands only) and multinational (Netherlands plus one or more MS(s) of the EEA plus Switzerland and Turkey and/or a third country). If an event occurred in a third country in which a clinical investigation is performed under the same clinical investigation plan as the one applying to a clinical investigation covered by this Regulation the same reporting requirements apply (art 80, sub 3).

In a multinational investigation, the sponsor of the clinical investigation must inform all MSs of the EEA plus Turkey and Switzerland in which the clinical investigation is authorized to be carried out about reportable events.

Definitions and explanatory notes

Adverse Event (AE) (MDR, art 2.57)
- Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.
- Investigational device means also comparator medical device or procedures related to the use of a medical device.

Serious Adverse Event (SAE) (MDR, art 2.58)
Any adverse event that led to any of the following:
- death,
- serious deterioration in the health of the subject, that resulted in any of the following:
  i. life-threatening illness or injury,
  ii. permanent impairment of a body structure or a body function,
  iii. hospitalisation or prolongation of patient hospitalisation,
  iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
  v. chronic disease,
- foetal distress, foetal death or a congenital physical or mental impairment or birth defect

Device deficiency (MDR, art 2.59)
Device deficiency' means any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

Reportable events (MDR, art 80, sub 2)
A reportable event is:
a. any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;
b. any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
c. any new findings in relation to any event referred to in points (a) and (b).

All causility assessments should be done according to section 9 of MDCG 2020-10/1. Only causality level 1 (not related) is excluded from reporting.

Calamity (Wet kwaliteit, klachten en geschillen zorg (Wkkgz), art 11, lid 1 sub a)
A calamity is (in Dutch):
- een niet-beoogde of onverwachte gebeurtenis die betrekking heeft op de kwaliteit van de zorg en die tot de dood van of een ernstig schadelijk gevolg voor een cliënt heeft geleid.

A calamity must be reported to Dutch Health and Youth Inspectorate (IGJ) within 3 working days (https://www.igj.nl/onderwerpen/calamiteiten/melding-doen-van-een-calamiteit)

Investigator (MDR, art 2.54)
Investigator means an individual responsible for the conduct of a clinical investigation at a clinical investigation site.

Sponsor (MDR, art 2.49)
Sponsor means any individual, company, institution or organisation which takes responsibility for the initiation, for the management and setting up of the financing of the clinical investigation.

Reviewing Committee (TC) and competent authority (CA)
For clinical investigations with medical devices, the CCMO or an accredited MREC is the reviewing committee. See committee finder tool. The CCMO is also the competent authority for clinical investigations. Tasks are described in WMO, article 17a.

Footnotes and references

1. A notification to the investigator of an adverse event which took place with a subject participating in a clinical investigation to the investigator can be done by the subject, but also for example by a research nurse, partner of subject etcetera or can also be noticed by investigator himself.
2. The sponsor shall fully record all of the following (MDR, art. 80, sub 1):
   a. any adverse event of a type identified in the clinical investigation plan as being critical to the evaluation of the results of that clinical investigation;
   b. any serious adverse event;
   c. any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
   d. any new findings in relation to any event referred to in points (a) to (c).
3. Article 80, sub 2 of MDR describes the reportable events for the sponsor to be submitted to MS. These reportable events are applicable for article 62 and 74.2 clinical investigations.

- In article 80, sub 6, it is described that for article 74.1 PMCF investigations the sponsor has to report to MS any SAE for which a causal relationship has been established with the preceding investigational procedure (see also section 5.1 of MDCG 2020-10/2). Therefore, in the flowchart SAE related to investigational procedure is a separate step and applicable for art 62 and 74 clinical investigations.

WMO text valid on 26 May 2021; wet van 26 februari 1998
MDR EU no 2017/745, dd 5 April 2017, applicable on 26 May 2021
MDCG 2020-10/1, May 2020
MDCG 2020-10/2, May 2020
ISO14155, version 2020

Abbreviations

AE	Adverse Event
CCMO	Centrale Commissie Mensgebonden Onderzoek
CIP	Clinical Investigation Plan
CRF	Case Report Form
MREC	Medical Research Ethics Committee
MS	Member State
SAE	Serious Adverse Event
TC	Reviewing committee (CCMO or MREC)
ToL	ToetsingOnline (CCMO)
WMO	Wet Medisch-wetenschappelijk Onderzoek met mensen