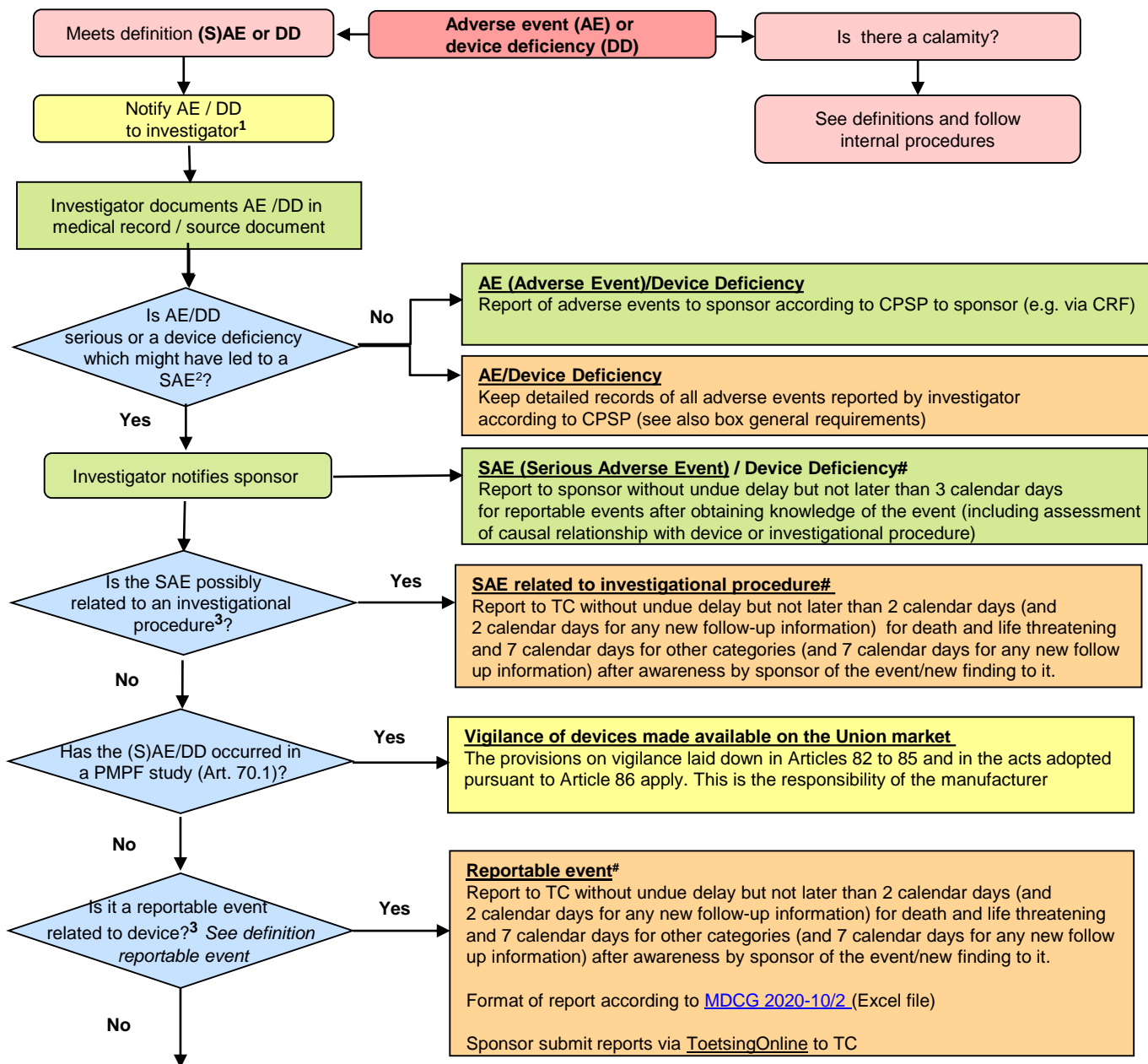


# Adverse Event Flow

## Performance study with in vitro diagnosticum, IVDR (art 58 and 70)



**(S)AE – upon request MS<sup>2</sup>**  
 The sponsor should keep detailed records of:  
 (a) any adverse event of a type identified in the CPSP as being critical to the evaluation of the results of that performance study;  
 (b) any serious adverse event;  
 (c) any device deficiency that might have led to a SAE 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-c  
 Upon request of MS, the sponsor should provide this safety Information (art 76, sub 2)

	<b>Responsibility investigator</b>
	<b>Responsibility sponsor</b>
	<b>Responsibility manufacturer</b>

## # Reporting timelines investigator and sponsor

### General

The reporting requirements are applicable for events related to the device for performance study, 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 performance study 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

- Format is given in MDCG 2020-10/2 (Excel file)

### Other obligations

- A sponsor may not downgrade the causality assessment done by the investigator
- If the sponsor has temporarily halted a performance study or has terminated a performance study early because of safety reasons, it shall inform all MS in which that performance study 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 (IVDR, art 76, sub 2).

### Sponsor is not manufacturer

- It is advised to inform manufacturer of the IVD.

### National/multinational clinical investigations

The safety reporting requirements are applicable for all performance studies 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 performance study is performed under the same performance study plan as the one applying to a performance study 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 performance study is authorized to be carried out about reportable events.

# Definitions and explanatory notes

## **Adverse Event (AE)** (IVDR, art 2.60)

- any untoward medical occurrence, inappropriate patient management decision, 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 performance study, whether or not related to the device for performance study.
- Device for performance study means a device intended by the manufacturer to be used in a performance study.

## **Serious Adverse Event (SAE)** (IVDR, art 2.61)

Any adverse event that led to any of the following:

- a patient management decision resulting in death or an imminent life-threatening situation for the individual being tested, or in the death of the individual's offspring,
- death,
- serious deterioration in the health of the individual being tested or the recipient of tested donations or materials, 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** (IVDR, art 2.62)

'Device deficiency' means any inadequacy in the identity, quality, durability, reliability, safety or performance of a device for performance study, including malfunction, use errors or inadequacy in information supplied by the manufacturer;.

## **Reportable events** (IVDR, art 76, sub 2)

A reportable event is:

- a. any serious adverse event that has a causal relationship with the device, the comparator or the study 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 causality 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** (IVDR, art 2.48)

Investigator means an individual responsible for the conduct of a performance study at a performance study site;.

## **Sponsor** (IVDR, art 2.57)

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 performance study

## **Reviewing Committee (TC) and competent authority (CA)**

For performance studies that are subject to IVDR article 58 or article 70, the CCMO or an accredited MREC is the reviewing committee. [See committee finder tool](#). The CCMO is also the competent authority for performance studies. 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 performance study 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 (IVDR, art. 76, sub 1):
  - a. any adverse event of a type identified in the performance study plan as being critical to the evaluation of the results of that performance study;
  - 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 76, sub 2 of IVDR describes the reportable events for the sponsor to be submitted to MS. These reportable events are applicable for article 58 and 70.2 performance studies.
  - o In article 76, sub 6, it is described that for article 70.1 PMPF studies 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 58 and 70 performance studies.

WMO text valid on 26 May 2021; wet van 26 februari 1998

IVDR EU no 2017/746, dd 5 April 2017, applicable on 26 May 2022

MDCG 2020-10/1, May 2020

MDCG 2020-10/2, May 2020

ISO14155, version 2020

# Abbreviations

AE	Adverse Event
CCMO	Centrale Commissie Mensgebonden Onderzoek
CPSP	Clinical Performance Study 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