

***Review of a performance study with in-vitro  
diagnostics or companion diagnostics -  
guidance document for MRECs***

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## Colophon and disclaimer

This guidance has been written thanks to the input of a working group in which the following persons participated:

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- The Health and Youth care Inspectorate (IGJ) was an observer at this working group.

The guidance has been sent for consultation to the accredited MRECs. The CCMO and NVMETC have adopted the guidance.

The contents of this guidance have been written with the greatest possible care. The focus is on the performance studies with in vitro diagnostics or companion diagnostics that need to be reviewed by an accredited medical research ethics committee (MREC) or the CCMO and on the new procedures for the submission, assessment and conduct of performance studies as a result of the In Vitro Diagnostics Regulation ([IVDR, EU no 2017/746](#)), applicable as of 26 May, 2022. The principles of medical ethical review, as laid down in the Dutch Act on Medical Research Involving Human Subjects (WMO), have not been changed and will not be addressed in this guidance. This guidance is written for the Netherlands. The procedures may be different in other member states of the European Union.

Topics relating to the scope of the IVDR and the interpretation of some articles in chapter VI of the IVDR were at the time of writing this guidance still under discussion in the European Commission working group on IVDR. The content of this guidance is not legally binding. The [official European documentation](#) is always leading.

This guidance should prove its usability in daily practice. It will be evaluated periodically and adapted based on best practice and new developments in the field of performance studies. This guidance will be a living document as experience with the assessment of performance studies is currently limited. Please send questions, remarks and suggestions to improve the document to the CCMO ([devices@ccmo.nl](mailto:devices@ccmo.nl)).

The Hague, 9 juni 2022

## List of abbreviations

ABR	General Assessment and Registration form (ABR form), the application form required for submission to the accredited review committee. In Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
AE	Adverse Event
BCB	The decree on Central Review of Medical Research Involving Human Subjects Act. In Dutch: Besluit centrale beoordeling Medisch-wetenschappelijk Onderzoek met Mensen
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CCMO-LB	National Clinical Trial Office of the CCMO (in Dutch: Landelijk Bureau, LB)
CDx	Companion diagnostic
CMR	Carcinogenic, mutagenic or toxic for reproduction
CPSP	Clinical Performance study plan
CS	Common Specifications
CTR	Clinical trial regulation; regulation (EU) 536/2014 of the European parliament and the council of 16 April 2014.
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EU	European Union
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation. In Dutch: Algemene Verordening Gegevensbescherming (AVG)
IB	Investigator's brochure
ICF	informed consent form
IFU	Instructions for Use
IGJ	Dutch Health and Youth Care Inspectorate. In Dutch: Inspectie Gezondheidszorg en Jeugd.
IMDD	Investigational Medical Device Dossier
ISO	International Organization for Standardization
IVD	In vitro diagnostic medical device
IVDs	In vitro diagnostic medical devices
IVDD	In vitro diagnostic medical devices Directive; Directive 98/79/EC

IVDR	In Vitro Diagnostic medical devices Regulation; regulation EU no 2017/746 of the European parliament and the council of 5 April 2017
MDR	Medical devices regulation (EU) 2017/745 of the European parliament and the council of 5 April 2017
MREC	(accredited) Medical research ethics committee (MREC); in Dutch: (erkende) medisch-ethische toetsingscommissie (METC)
MS	Member state
PEP	Performance evaluation plan
PMPF	Post-market performance follow-up
PSR	Performance Study Report
QMS	Quality Management System
SAE	Serious Adverse Event
SIN	Single Identification Number
SM	Substantial Modification
UDI	Unique Device Identifier
Wmh	Medical Devices Act. In Dutch: Wet op de medische hulpmiddelen
WMO	Medical Research Involving Human Subjects Act. In Dutch: Wet medisch-wetenschappelijk onderzoek met mensen
WzL	in Dutch: Wet zeggenschap Lichaamsmateriaal. 2022: in preparation

## Chapter 1 Introduction

As of May 26<sup>th</sup> 2022 the [European regulation \(EU\) 2017/746](#) on in vitro diagnostic medical devices (IVDR) applies in the European Union (EU). This regulation harmonises the rules in the EU for placing on the market and putting into service of an in vitro diagnostic medical device (IVD) and their accessories. It sets high standards of quality and safety for IVDs. Data generated in performance studies should be reliable and robust and the safety and rights of subjects participating in performance studies must be protected. The new rules for performance studies will ensure that the procedures and conditions for conducting and assessing performance studies are uniform throughout the EU. This is vital to ensure that EU member states, in authorising and supervising the conduct of a performance study, base themselves on the same rules.

With this harmonisation at EU level, the ultimate goal is to create an environment that is favourable for conducting performance studies, with the highest standards of quality and patient safety, for all EU member states. It will not only harmonise decisions, but also foster work-sharing and collaboration between member states and enhance the transparency regarding performance studies.

This guidance is intended for committee and staff members of accredited MRECs and the CCMO involved in the assessment of performance studies with an IVD or companion diagnostic (CDx) subjected to the rules of chapter VI of the IVDR. There are common parts that apply to all members and specific parts that will be primarily addressed by experts on IVDs/CDx. The common purpose is to provide information on the review procedure and to give guidance on what to review and to which extent. In general, topics applying to all types of clinical studies are not discussed in this guidance, except in cases where they need special attention in the context of the IVDR.

## Chapter 2 Most important points

An overview of the most important points applicable to performance studies is listed below. These points are either directly described in the IVDR or a result from the Dutch Act on Medical Devices (Wet op de medische hulpmiddelen, Wmh) and the Act on Medical research involving Human Subjects (Wet Medisch-wetenschappelijk Onderzoek met mensen, [WMO](#)). These and other points will be explained in more detail throughout the document.

### Points directly arising from the IVDR

- In the IVDR, there are several articles on categories of performance studies (Article 57, 58 or 70), each having specific requirements.
- The classification rules have been altered in comparison to the IVD Directive (IVDD). As a result many IVDs are now classified (Annex VIII IVDR).
- There is a major difference in IVDs that should have CE-marking. Where only a minor fraction of IVDs needed a notified body under the IVDD, this is now a major fraction under the IVDR.
- The requirements for supplying clinical evidence to demonstrate compliance to the IVDR are stricter in comparison to how they were under the IVDD, which may result in the need for more clinical data.
- Post-Market Performance Follow-up (PMPF) by the manufacturer is mandatory (IVDR, article 10, sub 3).
- A procedure to validate the application for Article 58 performance studies.
- The procedures for recording and reporting of adverse events occurring during performance studies have been changed.
- The timelines of initial application validation, their assessment and substantial modifications, notification of temporary halt, and (premature) end of the performance study may have changed. This depends on the article under which the performance study falls.
- There will be a period of voluntarily coordinated assessment of multinational performance studies by EU member states. This will start after Eudamed is functional (expected date for go live clinical investigation module is Q4 2023)

### Points specific for the Dutch procedures

- In WMO article 17a the CCMO has been given tasks with respect to performance study applications. These are performed by the CCMO National Clinical Trial Office (in Dutch: Landelijk Bureau; CCMO-LB) and includes among others validation of specific initial applications, a coordinating and supporting role for multinational applications and collection/distribution of fee. The latter task will be postponed. Until then, the MREC is responsible for collection fees for performance studies.
- A validation decision for Article 58 performance studies is issued by the CCMO-LB<sup>1</sup>.
- The accredited MREC needs to have an accredited 'WMO-member medical devices' if assessing performance studies.
- There are some changes in the application dossier (Annex XIV of the IVDR). New documents to be submitted are the performance evaluation plan and a signed statement by the manufacturer of the IVD (see section 5.3 of this guidance). For registration in forthcoming Eudamed, a submission form with details of the performance study is required. It is not

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<sup>1</sup> For studies that also fall under the scope of the CTR, the procedures from the CTR will be followed for the time being.



mandatory anymore to have an independent expert who can be consulted voluntarily by the subjects (WMO, Article 9). However, it is still possible to have an independent expert approved by the reviewing MREC.

- There are new conditions for conducting performance studies with pregnant and breastfeeding women (IVDR, article 62) and/or performance studies in an emergency situation (IVDR, article 64).

## Chapter 3 Definitions

This chapter describes the most important definitions in the IVDR. The list follows the order and definitions as in Article 2 of the IVDR. Appendix A of this guidance contains all definitions.

**In vitro diagnostic medical device:** means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:

- (a) concerning a physiological or pathological process or state;
- (b) concerning congenital physical or mental impairments;
- (c) concerning the predisposition to a medical condition or a disease;
- (d) to determine the safety and compatibility with potential recipients;
- (e) to predict treatment response or reactions;
- (f) to define or monitoring therapeutic measures.

Specimen receptacles shall also be deemed to be *in vitro* diagnostic medical devices; (IVDR article 2.2)

**Companion diagnostic:** means a device which is essential for the safe and effective use of a corresponding medicinal product to:

- (a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or
- (b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product; (IVDR article 2.7)

**CE marking or CE marking of conformity:** marking by which a manufacturer indicates that a device is in conformity with the applicable requirements set out in the IVDR and other applicable Union harmonisation legislation providing for its affixing. (IVDR article 2.35)

**Performance of a device:** means the ability of a device to achieve its intended purpose as claimed by the manufacturer. It consists of the analytical and, where applicable, the clinical performance supporting that intended purpose; (IVDR article 2.39)

**Analytical performance:** means the ability of a device to correctly detect or measure a particular analyte; (IVDR article 2.40)

**Clinical performance:** means the ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user; (IVDR article 2.41)

**Performance study:** means a study undertaken to establish or confirm the analytical or clinical performance of a device; (IVDR article 2.42)

**Interventional clinical performance study:** means a clinical performance study where the test results may influence patient management decisions and/or may be used to guide treatment; (IVDR article 2.46)

**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. (IVDR article 2.57) With this definition the investigator-initiated investigations are explicitly brought under the IVDR.

## Chapter 4 Scope of the IVDR in performance studies

This chapter describes the scope of the IVDR with respect to performance studies. It gives guidance on what is considered an IVD and a CDx. The definition and scope of performance studies is described.

### 4.1 Relevant articles in the IVDR for the scope of performance studies

This is a list of the most relevant articles concerning the scope of performance studies in the IVDR:

- Article 2: definitions
- Article 5.5: in-house devices
- Chapter VI: performance evaluation and performance studies (articles 56-75)
- Article 57: General requirements regarding performance studies
- Article 58: Additional requirements for certain performance studies
- Article 70: performance study with CE-marked medical devices
  - 70.1: post-market performance follow-up (PMPF) study with additional invasive or burdensome procedures.
  - 70.2: performance study with a CE-marked medical device used outside the scope of its intended purpose.
- Annex I: general safety and performance requirements
- Annex II: technical documentation
- Annex VIII: classification rules
- Annex XIII: Performance evaluation, performance studies and PMPF-studies
- Annex XIV: Interventional clinical performance studies and certain other performance studies

### 4.2 Is the product an IVD/CDx?

The definition of an IVD is broad and includes a wide range of products from reagents to equipment that are used in vitro for the examination of human specimens with the purpose to provide information on a range of conditions.

A product should be regarded as an IVD/CDx in one or more of the following situations:

- When the manufacturer of a product claims that the intended purpose of the product fulfils the definition of an IVD/CDx. This claim is substantiated by the description of the intended purpose of the IVD/CDx, which can be found in the user manual and/or the investigator's brochure.
- When the potential aim of the product under development has an intended purpose that fulfils the definition of an IVD/CDx. Although the product is in the development phase and may not fulfil its intended purpose yet, the product nevertheless already qualifies as an IVD/CDx.
- When a competent authority has defined the product as an IVD.

#### 4.2.1 Specific cases

Extra attention should be paid to a number of products:

## Assays

Section on assays copied from: Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR) ([https://ec.europa.eu/health/system/files/2022-05/mdcg\\_2022-10\\_en.pdf](https://ec.europa.eu/health/system/files/2022-05/mdcg_2022-10_en.pdf))

An assay is considered an IVD if the manufacturer assigns an intended purpose that fulfils the definition of an IVD according to IVDR Article 2. Where a clinical trial sponsor assigns a medical purpose to an assay in the context of the clinical trial in a way that the assay fulfils the definition of an IVD according to IVDR Article 2, the clinical trial sponsor may assume the role of a manufacturer under the IVDR (article 16.1). In this role, it is up to the clinical trial sponsor to determine the regulatory status of the assay based on the planned use in the clinical trial.

Assays can be used in a clinical trial to provide information for clinical trial related medical management decisions (typically to select patients for enrolment in the trial, assign patients to a treatment arm, etc.) and/or may be used to guide follow up measures during and beyond the clinical trial. This would, for example, not be the case, in settings where all trial participants are tested irrespective of treatment arm or medical management and the analysis of impact is conducted retrospectively and where medical management is not impacted by assay results.

Figure 1 visualises, as an example, the flow of a blinded clinical trial with two treatment arms, where the key processes for which assays might be utilised are highlighted. The processes in blue are considered to be used for medical management decisions of trial subjects. These include assays used for inclusion and exclusion of subjects, treatment allocation as well as monitoring the safety and efficacy of the treatment during the trial.

The processes in pink are likely not to impact the medical management of the trial subjects. These include stratification and endpoint analysis or other exploratory assays for which correlation with clinical parameters is investigated retrospectively without impact on patient treatment (medical purpose). In relation to endpoints, it is important to acknowledge that these assays may be considered IVDs in future clinical trials (e.g. used for allocation or monitoring). Where this development is predictable, the assay should be developed and validated in compliance with the applicable requirements of Annex I of the IVDR as an IVD from the beginning. Importantly, in most cases, the assay will also be utilised during the trial as part of the monitoring of the trial subjects, which implies need for compliance with IVDR requirements.

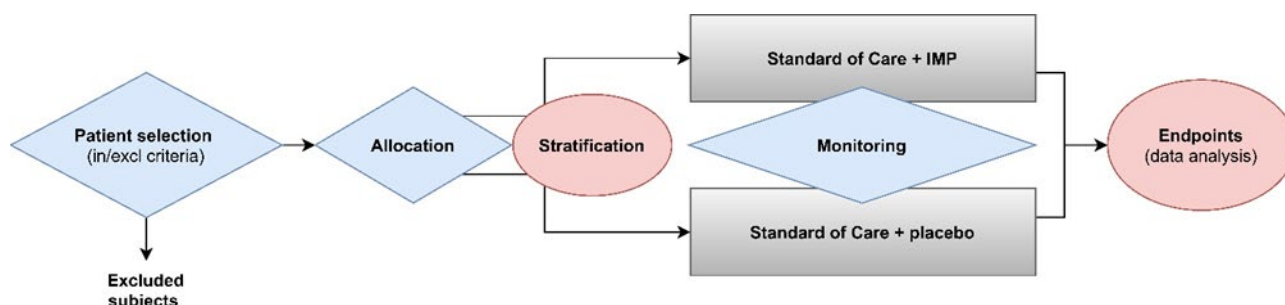


Fig. 1 Simplified examples of use of assays on human samples in a clinical trial. Assays marked in blue (diamonds) are considered to be assays which will likely be considered IVDs as they are used for medical management decisions of trial subjects within the trial. The processes in yellow pink (ellipses) are considered to likely not to impact the medical management of the trial subjects and therefore would not have a medical purpose in the trial.

**Companion diagnostic (CDx):** a CDx is a specific type of IVD that is used in direct relation with a medicinal product. The CDx identifies which patient is eligible for a specific medicinal product treatment or who is at risk for adverse reactions to this treatment. A CDx is part of personalized medicine. A study investigating a CDx and a medicinal product will fall under the scope of both the IVDR and CTR/CTD and should fulfil both regulations. See also Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR) ([https://ec.europa.eu/health/system/files/2022-05/mdcg\\_2022-10\\_en.pdf](https://ec.europa.eu/health/system/files/2022-05/mdcg_2022-10_en.pdf))

**Modified CE-marked IVD:** these IVDs are not CE-marked anymore due to the modifications or the use of accessories other than those supplied by the manufacturer. The use of these altered IVDs is only allowed in a performance study or when modified and applied within a single institution (in-house product).

**In-house product:** healthcare institutions have the possibility of manufacturing, modifying and using IVDs in-house and thereby address, on a non-industrial scale, the specific needs of target patient groups which cannot be met at the appropriate level of performance by an equivalent IVD available on the market. This also includes in-house developed software. Article 5.5 lists the specific requirements for such IVDs when used for patient care. When such IVDs are being assessed in a performance study, article 58 may apply

**Software:** In article 2 of IVDR, software is specifically mentioned in the formal definition of an in-vitro diagnostic medical device. Briefly, software is therefore considered IVDR software if it is intended to be used (alone or in combination) for the examination of specimens derived from the human body to provide information on for example physiological or pathological processes, predisposition of diseases and to predict treatment responses. The classification of IVDR software is similar to other in vitro diagnostic medical devices (see Annex VIII). See also the current version of MDCG guidance: MDCG 2019-11 [Guidance on Qualification and Classification of Software](#).

## 4.3 Performance studies

### 4.3.1 Performance study

A performance study is defined by the IVDR as a study undertaken to establish or confirm the analytical or clinical performance of a (potential) IVD. This IVD can either be under development, CE-marked or CE-marked but used outside the intended purpose.

Analytical performance means the ability of a device to correctly detect or measure a particular analyte. Components of analytical performance are: analytical sensitivity, analytical specificity, trueness (bias), precision (repeatability and reproducibility), accuracy (resulting from trueness and precision), limits of detection and quantitation, measuring range, linearity, cut-off, including determination of appropriate criteria for specimen collection and handling and control of known relevant endogenous and exogenous interference, cross reactions.

Clinical performance means the ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user. Components of clinical performance are: diagnostic sensitivity, diagnostic specificity, positive predictive value, negative predictive value, likelihood ratio, area under the receiver operating characteristic or c-statistic, expected values in normal and affected populations.

#### 4.3.1.1 PERFORMANCE STUDIES

All performance studies fall under IVDR chapter VI, but not all performance studies need to be reviewed by a review committee (aMREC or CCMO).

Most of the performance studies for IVDs use samples resulting from the remnants of specimens taken for purposes of standard of care (left-over or archived samples (see section 4.3.3 for detailed information)). In these studies, there is no risk for the subjects arising from either the information provided by the IVD or from the collection procedure of the specimen. These studies are subject to IVDR articles 56 and 57. For performance studies that entail some risk for the subject, IVDR article 58 is also applicable and an MREC or CCMO approval is needed.

Figure 1 shows a flow chart to guide in the decision which IVDR article is applicable and whether MREC approval is needed.

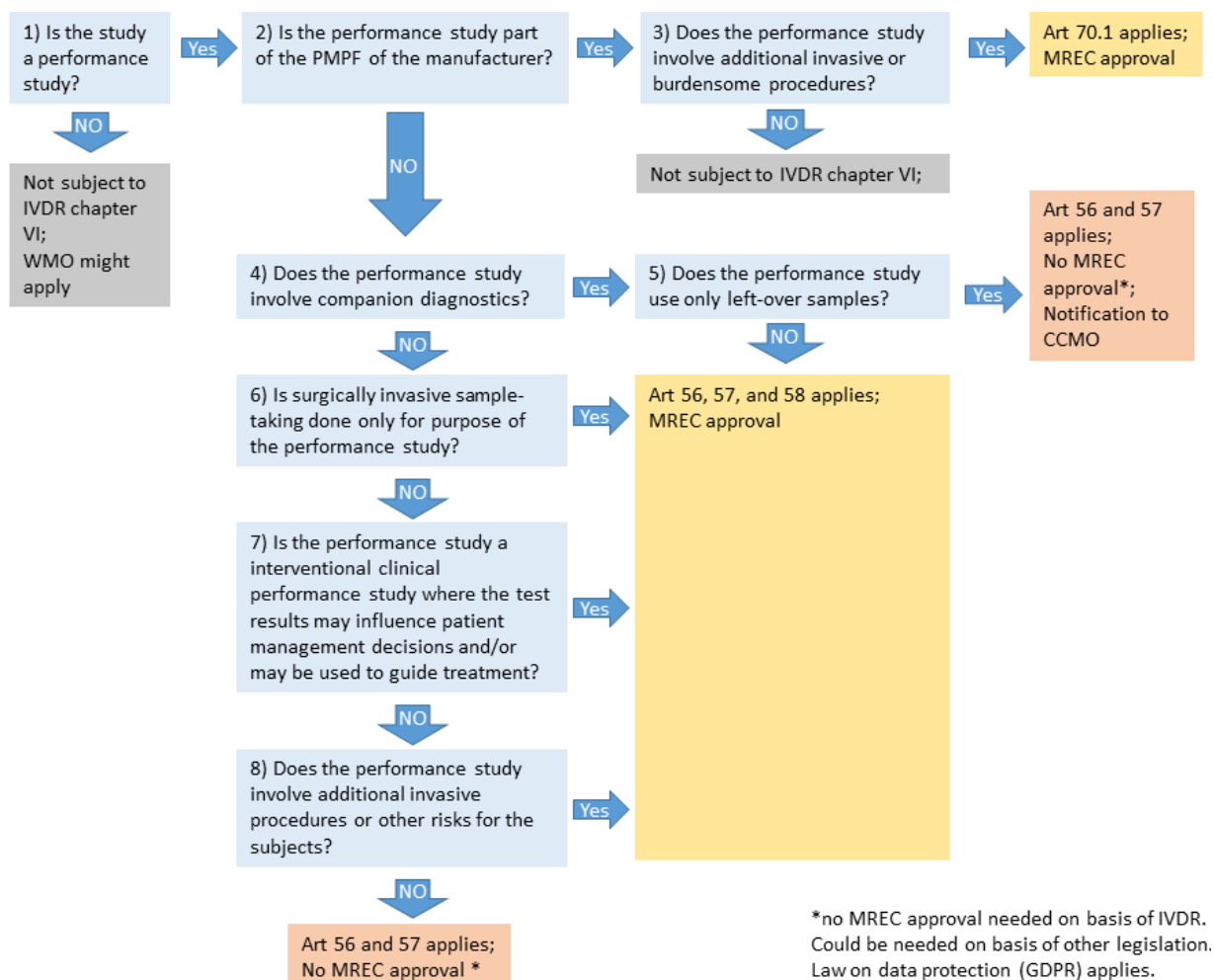


Figure 1 flowchart to determine which IVDR article is applicable and if MREC approval is needed for the performance study.

1. Is the study a performance study as defined in the IVDR? In other words; Will the study establish or confirm the analytical or clinical performance of an IVD? Will this study determine whether the IVD can correctly detect or measure a particular analyte (analytical performance)? Will this study determine whether the IVD yields results that are correlated

- with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended purpose (clinical performance)?*
2. *Post-market performance follow-up (PMPF) studies are performed with IVDs that do have a valid CE-mark and are used as part of the standard of care of the patients. PMPF studies will be commissioned by the manufacturer of an IVD and be part of the performance evaluation plan to generate additional evidence on the clinical performance of the IVD (Annex XIII of the IVDR).*
  3. *PMPF studies in which subjects are submitted to additional invasive or burdensome procedures compared to the standard of care are subject to article 70.1 of the IVDR. PMPF studies which are non-interventional, for instance clinical data are obtained by file research and no additional invasive or burdensome procedures compared to standard of care are applied, fall outside the scope of chapter VI of the IVDR and outside the scope of the WMO and are considered nWMO studies.*
  4. *Performance studies that involve companion diagnostics are subject to chapter VI of the IVDR. Companion diagnostics are IVDs which are essential for the safe and effective use of a corresponding medicinal product. Please note that in addition to the IVDR also the EU clinical trial regulation 536/2014 is applicable for the corresponding medicinal product.*
  5. *Left-over samples are archived samples or samples that would otherwise be discarded. When the performance study with a companion diagnostic only uses such left-over samples, there is no MREC or CCMO approval needed for this performance study based on article 58.2 of the IVDR. However, MREC approval based on other legislation (CTR) can be required. Based on the IVDR the study should comply with articles 56 and 57 and a notification to the competent authority (CCMO for the Netherlands) is needed.*
  6. *Surgically invasive sample taking for the sole purpose of the performance study means taking a sample by penetration inside the body through the surface of the body, including mucous membranes of body orifices. This includes venous and capillary blood draws.<sup>2</sup>*
  7. *When the results of the IVD might have an effect on the clinical care of a subject as described in the protocol, the performance study falls within the scope of article 58 of the IVDR and MREC or CCMO approval is needed.*
  8. *If the performance study involves additional invasive procedures, other than surgical as specified under 6, or other risks for the subject in addition to normal clinical practice, the performance study falls within the scope of article 58.1c of the IVDR and MREC approval is needed.*

*Performance studies that do not fall within scope of article 58 of the IVDR, do not need an MREC approval based on the IVDR. These performance studies should comply with certain IVDR articles (including 56 and 57), and should be conducted in accordance with the general data protection regulation 2016/679 (GDPR). Additionally, these studies can be subject to other legislation that requires an MREC approval.*

**Article 58:** performance studies that fall under article 58 may include risk for the subject and need to have a review by an MREC. The procedures are described in detail in this document. For these studies article 56 and 57 are also applicable.

#### Example article 58.2 study

The evaluation of the use of the companion diagnostic CDXA (used to determine whether a patient overexpresses EGFR) in the treatment of patients with tumors that overexpress the epidermal growth factor receptor (EGFR) with medicinal product XYZ.

<sup>2</sup> There is still debate whether venous and capillary blood draws should be included. For the time being, performance studies that would fall under the WMO also fall under IVDR.



**Article 56/57:** performance studies that do not fall under article 58 or 70.1 do not need an MREC approval based on the IVDR. These performance studies are outside the scope of this document. The responsibility of such performance study lies with the manufacturer. The general rules for the collection and use of tissue samples should be obeyed.

**Article 70.1:** a Post-Market Performance Follow-up (PMPF) study is a performance study of a CE-marked device used within the scope of its intended purpose, and where the investigation would involve submitting subjects to procedures additional to those performed under the normal conditions of use of the device and those additional procedures are invasive or burdensome.

An invasive procedure is considered to be a medical procedure invading (entering) the body, usually by cutting or puncturing the skin or by introducing instruments into the body.

An additional procedure is a procedure which is not foreseen by the manufacturer in the instructions for use of the medical device or not foreseen in the standard of care. An additional procedure can be interpreted as burdensome for the subject if this procedure involves a risk of causing physical or mental strain (or harm) exceeding the limits of normal daily life for the research participants. This may include non-invasive procedures, collecting biological samples, filling out questionnaires, recording diary entries, et cetera depending on the circumstances. Whether a procedure is burdensome may vary according to age, health status and vulnerability of the subject and to the duration, previous experience, repetition or accumulation of the procedure compared to the standard of care.

#### 4.3.2 Performance studies involving companion diagnostics

Performance studies with a companion diagnostic are specifically mentioned in the IVDR and need to be reviewed by an MREC. An exception is when the performance study uses only left-over samples; such study should however be notified to the competent authority (via [devices@ccmo.nl](mailto:devices@ccmo.nl)).

There is no common EU procedure for a single combined trial that will serve both as a performance study for the IVD and a clinical trial for the medicinal product. For the Netherlands, the MREC will assess the trial both on the basis of the CTR and of the IVDR. The timelines between both regulations are different. Until Eudamed is functional or when otherwise necessary, such a single combined trial will follow the procedures and timelines of the CTR. Submission is therefore through CTIS. A single combined trial submitted under the CTD will follow the procedures and timelines of the IVDR. Submission is through [devices@ccmo.nl](mailto:devices@ccmo.nl) and procedures as described in this guidance will be followed.

#### 4.3.3 Performance studies (only) using left-over/archived samples

In the IVDR only the term left-over samples is used and this term is not defined. ISO-20916 defines left-over and archived samples and for both types of samples the same regulation applies. Therefore, throughout this guidance the term left-over samples is used to stick with the IVDR naming and with the understanding that this term includes both left-over samples and archived samples as defined by the ISO-20916.

ISO-20916 definition: left-over samples are unadulterated remnants of human derived specimens collected as part of routine clinical practice and after all standard analysis has been performed. Those samples would be otherwise discarded as there is no remaining clinical need for them.

ISO-20916 definition: archived samples are samples that were collected in the past and are obtained from repositories (e.g. tissue banks, commercial vendor collections).

Performance studies only using left-over/archived samples are currently not required to be reviewed by an MREC based on the IVDR. Those studies should however comply with IVDR articles 56 and 57 and



other legislation, including General Data Protection Regulation (GDPR). A review by an MREC might be needed in the future when the “Wet zeggenschap Lichaamsmateriaal (WzL)” becomes applicable.

#### 4.3.4 Other studies using IVDs

Other studies using IVDs are studies in which the performance of the IVD is not being investigated (therefore not falling under the definition of a performance study and therefore chapter VI of the IVDR is not applicable) but in which IVDs are used in the study for other purposes, for instance for screening or as an outcome measurement. The IVDR states that IVDs can be put on the market or may be put into service only if they comply with the IVDR when duly supplied and properly installed, maintained and used in accordance with their intended purpose (Article 5.1, IVDR). An exception is made for investigational IVDs meaning IVDs assessed in a performance study (chapter VI, IVDR) or in-house developed IVDs that are exempted from most of the provisions of the IVDR provided that they adhere to the conditions laid out in Article 5(5). The consequence of these provisions is that in studies with IVDs (other than a performance study) only CE marked IVDs or in-house IVDs can be used.

For these other studies with IVDs, the WMO, CTR or other legislation might apply. In all circumstances, the performance of the IVD must be guaranteed before using it with subjects or patients. When the study is assessed by an MREC or the CCMO, the product information should be of such quality that the review committee can do their assessment.

## 4.4 Classification of IVDs

The classification of an IVD depends on several factors including the intended purpose and the inherent risk. The classification is described in Annex VIII of the IVDR and a total of 7 rules apply. There are four classes of IVDs: class A (lowest risk), B, C and D (highest risk). For more guidance see [MDCG guidance 2020-16](#).

### Class A

- general staining reagents
- wash buffers
- solutions
- general microbiological culture media

### Class B

- self testing pregnancy test
- self testing for fertility
- rapid test for RSV
- rotavirus

### Class C

- Companion diagnostic (CDx)
- self testing blood glucose strips
- syphilis (diagnosis)
- cancer screening

### Class D

- HIV 1 and 2
- Hepatitis B/C
- syphilis (screening for blood donation)
- blood grouping for ABO or rhesus system

Figure 2: IVD Classification Examples. See for more detailed description MDCG guidance 2020-6

## 4.5 Transitional provisions

### 4.5.1 Eudamed

The delivery of a fully functional Eudamed is delayed until 2023 or 2024. Although this has consequences for the exchange of information, the IVDR will nevertheless become applicable on May 26<sup>th</sup> 2022. Until Eudamed is fully functional ToetsingOnline will be used.

The sponsor has the obligation to upload the following information in Eudamed:

Obligation	Transitional provision
Initial application	ToetsingOnline (registration via ABR form)
Substantial modifications	ToetsingOnline (only if ABR form is modified)
A single identification number (SIN)	If not already available, the CCMO-LB will request this number
Notification of Article 70.1 performance study	ToetsingOnline (registration via ABR form)
Recording and reporting of reportable adverse events	ToetsingOnline (upload MDCG 2020-10/2 Excel)
A performance study report and a lay summary	ToetsingOnline (upload pdf document)

### 4.5.2 Authorised performance studies

Performance studies which have been authorised by an MREC in the Netherlands prior to May 26<sup>th</sup> 2022 may continue to be conducted following the rules and regulations before May 26<sup>th</sup> 2022.

Performance studies for which an authorisation was not necessary and that have started to be conducted, in the Netherlands before May 26<sup>th</sup> 2022 may also continue to be conducted. As of May 26<sup>th</sup> 2022, however, the reporting of serious adverse events and device deficiencies must be carried out in accordance with the IVDR.

### 4.5.3 Performance studies under review

There is no transitional period specified for performance studies which are submitted to the MREC prior to May 26<sup>th</sup> 2022 and for which no decision has been reached before May 26<sup>th</sup> 2022. Studies which have been submitted prior to May 26<sup>th</sup> 2022 must be reviewed and conducted in accordance with the IVDR. In case this situation occurs, the MREC can contact the CCMO via [devices@ccmo.nl](mailto:devices@ccmo.nl) to define a procedure around validation.

## Chapter 5 Initial application

This chapter describes the procedures and assessment of the initial application. It gives information on the procedures and timelines for the different categories of performance studies. The regulatory grounds for the assessment by the review committee are provided. Part of these procedures are laid down in the IVDR others follow from national law.

### 5.1 Which committee?

Currently, all MRECs may review all performance studies.

### 5.2 Pathways and timelines

The different performance study categories result in different pathways for validation, assessment, and substantial modifications, and can have different maximum timelines. Some of the timelines are determined by the IVDR, when not defined the timelines of WMO studies have been adhered to.

What	Article	Timeline
<b>Validation</b>	58	Maximum 55 calendar days including response time sponsor
	70.1	No separate validation, but part of the assessment
<b>Assessment</b>	58	Maximum 45 (+20 in case of consulting expert) calendar days + clock stop for response sponsor
	70.1	Maximum 2x56 calendar days + clock stop for response sponsor
<b>Substantial modifications</b>	58/70.1	Maximum 38 calendar days (+ 7 days for consulting expert) + clock stop for response sponsor

#### 5.2.1 Article 58 performance study

Ultimately, the article 58 performance studies will be submitted through Eudamed. Until this is functional, the national web portal ToetsingOnline will be used.

Applications for performance studies under article 58 are validated by the CCMO-LB. The CCMO-LB checks if the performance study falls within the scope of the IVDR and that the application dossier is complete. The same validation procedure applies as for the MDR, see [guidance document MDR](#).

Starting from the validation date, the review committee has a maximum 45 calendar days to assess the application and reach a decision. This period can be extended by 20 days for consulting with experts. Additional information from the sponsor can be requested by the review committee. The review time is suspended from the date of the request until the additional information is received.

#### 5.2.2 Article 70.1 performance study (PMPF)

The article 70.1 performance studies (PMPF) are registered in the national web portal ToetsingOnline. The sponsor submits the research dossier directly to the selected MREC.

For PMFP studies, the MREC is responsible for the validation of the application. The MREC checks whether the application is complete and whether they are qualified to assess the PMPF study. If the MREC considers the study is an article 58 performance study, the sponsor is requested to submit the application dossier to the CCMO for validation. If the application is not complete, the MREC will request the sponsor to complete the dossier. The review time is suspended from the date of the request until the additional information is received.

For these studies the maximum timeline of 56 calendar days applies for the assessment (including the time used for validation). This period can be extended once with another 56 calendar days. Additional information from the sponsor can be requested by the review committee. The review time is suspended from the date of the request until the additional information is received.

When Eudamed is ready, the sponsor needs to notify the member states concerned through Eudamed 30 calendar days prior to the start of the performance study. Until Eudamed is ready, the need to notify in the Netherlands is already fulfilled by the initial application via ToetsingOnline.

### 5.3 Standard research file – application dossier

There are some changes to the application dossier for performance studies that fall under the scope of the IVDR or documents that are specific to IVDs. These are mentioned below. An overview of all the documentation is given in appendix D. This is based on the requirements for the application dossier for article 58 as described in Annex XIV of the IVDR. Cross-reference between documents is allowed.

**Cover letter:** A template cover letter is available on the CCMO website.

**Application form:** Eudamed application form and ABR-form via ToetsingOnline.

**Clinical Performance study plan (CPSP):** This CPSP is the protocol in which the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of a single performance study are described. The CPSP contains the requirements as mentioned in Annex XIII, part A, 2.3.2 of the IVDR.

**Performance evaluation plan (PEP):** The PEP shall specify the characteristics and the performance of the device and the process and criteria applied to generate the necessary clinical evidence up to the date of application and beyond. It should be clear where the clinical performance study that is applied for at the MREC falls within the PEP. The exact details are described in Annex XIII, part A, 1.1 of the IVDR.

**Investigator's brochure (IB):** The IB contains the information on the IVD that is relevant for the performance study and available at the time of application. IVDR Annex XIV, chapter I, section 2 explicitly describes which information is required.

**Technical documentation:** IVDR annex II contains detailed requirements for the technical documentation that a manufacturer must prepare to prove that the IVD complies with the requirements of the IVDR. In order to allow for a uniform submission of documentation for IVDs in performance studies, an equivalent to the investigational medical device dossier (IMDD) for medical devices will be developed.

**Signed statement:** A signed statement by the natural or legal person responsible for the manufacture of the IVD that the IVD in question conforms to the general safety and performance requirements apart from the aspects covered by the performance study and that, with regard to those aspects, every

precaution has been taken to protect the health and safety of the subject. This statement is mandatory for article 58 performance studies.

Specifically for IVDs used in a clinical trial: Where the clinical trial sponsor is also the manufacturer of the IVD or assumes the role as manufacturer of the IVD according to Article 16 IVDR, the clinical trial sponsor must draw up their own statement as above. In case the study falls under IVDR Art 58 (1) or (2), it must be designed, authorised, conducted, recorded and reported in accordance with IVDR Art. 58-77 and Annex XIV.

For **article 70.1 performance studies** the applicable documents are: cover letter, ABR-form, Eudamed application form, CPSP, and PEP. In addition, the EU declaration of conformity and the instructions for use should be provided.

## 5.4 Assessment by MREC/CCMO

This section primarily focuses on the assessment of the performance of the IVD. On basis of the WMO, articles 1 sub 1n and 16 sub 2a, a review committee assessing performance studies has to have an accredited WMO-member with expertise on medical devices. However, the expertise needed for the assessment of the performance study is different from that for clinical investigation with medical devices. It requires knowledge on for instance (bio)chemistry or genetics.

The review committee should consider whether advice from an external expert is needed. The existing procedures as described in the MRECs rules or procedures for external advice can be followed.

In the meantime, a network of IVD experts will be set up as an extension of the existing network of medical device expert network. The qualifications and working procedures for this IVD expertise network are under discussion.

### 5.4.1 MREC/CCMO as part of the European regulatory system

The implementation of Chapter VI of the IVDR on performance studies in the Netherlands is similar to that of the MDR and the Clinical Trial Regulation (EU no 536/2014). This means continuation of the current review system and with the appointment of the CCMO as the competent authority for performance studies on IVDs. MRECs, accredited by the CCMO, and the CCMO (for specific types of performance studies) form the opinion on the approval of the performance studies on medical, scientific, ethical and methodological grounds. It is important to realise that this system with decentralised integrated assessment is unique in Europe. In other European member states, assessment of the medical and scientific grounds is carried out by centralised competent authorities. These competent authorities on IVDs perform vigilance on the entire chain of market approval and performance of IVDs on the market. Therefore, lessons learned from incidents can, in such centralised authorities, be weighed against the risks of innovative devices to be assessed in new performance studies.

For accredited MRECs it is therefore important to realise that they may need to include information on experience with previous versions of the IVD or lessons learned elsewhere on comparable IVDs.

Moreover, it is important that the review committee reviews performance studies, as part of a performance evaluation plan, within the context of future market approval, rather than solely the question if it is acceptable for patients to participate in this one single performance study. This means evidence from previous performance studies, e.g., analytical performance studies, should be taken into account in the assessment of the new clinical performance study. In addition, it means that the context of the performance studies should be considered (e.g., market approval) and that review committees consider if the IVD and performance study are in line with applicable (harmonised) guidance standards and/or common specifications.

### 5.4.2 Regulatory grounds for review

The performance study category determines which regulatory framework applies. The European IVDR takes precedence over the Dutch WMO. This can entail that performance studies that previously were not subject to the WMO, are now subject to the IVDR. In the table a short overview is shown which regulatory grounds are applicable.

In general, the planning and conduct of performance studies should be in line with well-established international guidances in this field, such as the international standard ISO 20916 on Clinical performance studies using specimens from human subjects- good study practice. In addition, the rules should be in line with the most recent version of the [World Medical Association Declaration of Helsinki](#) on Ethical Principles for Medical Research Involving Human Subjects.

Category study	Regulatory grounds
<b>Performance studies</b>	IVDR
IVDR article 58	<ul style="list-style-type: none"> <li>Articles 57-77</li> <li>Annex XIII and XIV</li> <li>Common specifications or harmonized standards</li> </ul>
<b>Post-market performance follow-up (PMPF) study</b>	IVDR
IVDR article 70.1	<ul style="list-style-type: none"> <li>Article 58, sub 5b-l, p (includes articles 59-64)</li> <li>Article 71, 72, 73</li> <li>Article 76, sub 5</li> <li>relevant provisions of Annexes XIII and XIV</li> </ul>

### 5.4.3 Vulnerable populations and subjects

Incapacitated subjects, minors (in the Netherlands: <16 years), pregnant women and breastfeeding women require specific protection measures. These additional measures are laid down in articles 60-64 of the IVDR. These conditions are valid for all performance studies. The estimation of whether there is direct benefit for the participant is based on the scientific hypothesis made at the inception of the performance study. This will be assessed by the review committee and weighed against the risks and burdens involved.

#### 5.4.3.1. INCAPACITATED SUBJECTS AND MINORS (ARTICLE 60 AND 61, IVDR)

With respect to the benefit of the performance study, the IVDR states that there are scientific grounds for expecting that participation in the performance study will produce:

- (i) a direct benefit to the incapacitated subject or minor subject outweighing the risks and burdens involved; or
- (ii) some benefit for the population represented by the incapacitated subject or minor concerned when the performance study will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition;

#### 5.4.3.2 PREGNANT OR BREASTFEEDING WOMEN (ARTICLE 62, IVDR)

The IVDR mentions additional conditions for performance studies with pregnant and breastfeeding women. For these performance studies there must be the potential to produce a direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth. If there is no direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth, a performance study can be conducted only if:

- (i) a performance study of comparable effectiveness cannot be carried out on women who are not pregnant or breastfeeding;
- (ii) the performance study contributes to the attainment of results capable of benefiting pregnant or breastfeeding women or other women in relation to reproduction or other embryos, fetuses or children; and
- (iii) the performance study poses a minimal risk to, and imposes a minimal burden on, the pregnant or breastfeeding woman concerned, her embryo, foetus or child after birth;

Performance studies with pregnant or breastfeeding women are assigned to the CCMO for review on the basis of the “besluit centrale beoordeling (BCB)”.

#### 5.4.3.3 PERFORMANCE STUDIES, ADDITIONAL NATIONAL MEASURES (ARTICLE 63, IVDR)

IVDR article 63 is about national legislation for maintaining additional measures regarding persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision, cannot take part in performance studies, or persons in residential care institutions. The Netherlands has not implemented IVDR article 63.

#### 5.4.3.4 PERFORMANCE STUDIES IN EMERGENCY SITUATIONS (ARTICLE 64, IVDR)

New additional measures are described in article 64 for performance studies in an emergency situation. The conditions to be fulfilled to include subjects in the performance study without prior informed consent by the subject or his/her legal representative are being addressed in the [CCMO memorandum deferred consent](#).

### 5.4.4 Assessment of the IVD(s)

#### 5.4.4.1 REQUIRED EXPERTISE

The review committee must assess whether the necessary expertise is available. If not, additional experts have to be sought externally to make a technical assessment of the IVD. The review committee must determine if the overall benefit-risk ratio is sufficient to support a positive judgement. Additional information from the sponsor can always be requested when the provided technical documentation is insufficient to make a judgement by the review committee.

#### 5.4.4.2 IMDD/TECHNICAL DOCUMENTATION

The technical information is described in the IB and in Annex II of the IVDR. In the Netherlands, an IMDD will be developed that covers the technical documentation. Within the IMDD, reference to other documentation such as the IB is allowed. The IMDD specifies all items that must be covered (if relevant) for an application to a review committee in the Netherlands. The IMDD will be written for non-CE marked IVDs within the scope of the IVDR, which are intended for a performance study. When a CE-marked IVD is assessed outside the scope of its intended purpose an IMDD also applies for those parts that are relevant to the new purpose.



An expert should assess whether the relevant parts of the IMDD have been filled out. The various subjects of the IMDD may be divided amongst the members or external experts in order to be able to assess all aspects of the IMDD.

#### 5.4.4.3 LOCAL INTRODUCTION OF THE IVD

The review committee reviews the statement suitability clinical trial site. The plan for training (or the absence of a need for it) is mentioned in the IB.

It is the investigators responsibility to follow the institute's introduction procedure for new medical devices.

#### 5.4.4.4 ASSESSMENT IVD AT COMMITTEE MEETING

During the assessment, the review committee shall give full consideration to risks related to technical specifications and applications of the IVD, including questions such as:

- What are the noticeable (residual) risks as mentioned and identified from relevant items?
- What is still unknown about the IVD?
- What clinical evidence is available, and is this appropriate to the risk of the performance study or are further studies needed before the current study can be performed?
- What were the risks and most relevant adverse events with previous versions of the IVD or existing comparable devices?
- Are raised expectations in the ICF in relation to the IVD correct? Are all risks sufficiently described in the ICF? Is the degree of uncertainty on the efficacy and risks sufficiently clear?
- Does the phasing of the research and the speed of patient inclusion match the risk of the (innovative) IVD?
- Is the performance study set up according to the applicable common specifications or harmonized standards?
- Are the measures planned for the safe installation, putting into service and maintenance of the IVD adequate?
- Is the supplied documentation proportional with regard to:
  - the phase of the development (first pilot or final step before CE marking) in relation to 'maturity' of the IVD
  - potential added value in relation to the risk (and can this added value only be demonstrated with this particular risk on the subjects?)

Overall, the benefit-risk ratio should be appropriate to support a positive opinion of the review committee.

## 5.5 Archiving

The documentation of the performance study (IVDR annex XIII and XIV) shall be kept by the sponsor for a period of at least 10 years after the end of the performance study or, in the event that the IVD is subsequently placed on the market, at least 10 years after the last IVD has been placed on the market.

The review committee will archive the documentation in line with the Dutch Archive law.



## 5.6 Decision

The review committee will inform the CCMO-LB on their decision via the national web portal within 7 days after the decision date. In case of a negative decision for article 58 performance studies, the CCMO-LB will inform all Member States and the European Commission about this decision and the grounds for that decision (article 72.3 IVDR).

### 5.6.1 Administrative appeal/objection

If an investigator, sponsor or other concerned party does not agree with a negative decision made by the review committee they may, under certain conditions, start an administrative appeal procedure/submit an objection to the CCMO. This must be carried out within 6 weeks after the day on which the decision was reached.

## 5.7 Coordinated multinational assessment

A voluntary coordinated assessment is possible until May 2029 and mandatory after May 2029. The European Commission has decided that the start of the voluntary procedure is postponed until the moment that the clinical investigation/performance study module of Eudamed is fully functional. This will not be before end 2023. See further [MDCG guidance 2021-6](#) (Q&A clinical investigations).

## Chapter 6 Notifications and assessment during and after the performance study

### 6.1 During the performance study

#### 6.1.1 AE/SAE

The safety reporting requirements are different for the two types of performance study identified in the IVDR:

- Article 58 performance studies have to comply with IVDR article 76 and [MDCG 2020-10/1&2](#);
- Article 70.1 performance studies (PMPF investigations) have to comply with the provisions of vigilance laid down in IVDR articles 82-85 (responsibility of manufacturer), with the exception of SAEs related to an investigational procedure (article 76, sub 5 and 6);

A flowchart of the (S)AE procedure is given in appendix E.

Since Eudamed will not be ready on May 26<sup>th</sup>, 2022, the sponsor has to upload the safety information via ToetsingOnline. The review committee will receive a message that safety information ([MDCG 2020-10/2 Excel](#)) has been uploaded and can start the review.

Performance studies that have been assessed by an MREC under the WMO and not under the IVDR have to comply with the provisions from the WMO.

#### 6.1.2 Substantial modifications

Substantial modifications are any modifications to a performance study that are likely to have a substantial impact on the safety, health or rights of the subjects or on the robustness or reliability of the clinical data generated by the study. This applies to all types of performance studies. Substantial modifications can result from for example modifications in the CPSP but also to modifications of the IVD.

Any application of a substantial modification must be accompanied by a cover letter describing the modifications, an update of the application form (Eudamed and/or ABR, if applicable), the modified or new documents and the documents with track changes.

The timeline to review the substantial changes is 38 calendar days plus a clock-stop after notification of the substantial modification. This period can be extended by 7 days for consulting experts.

#### 6.1.3 Corrective measures

Where the review committee has grounds for considering that any of the requirements for performance studies are not met, the review committee may take a corrective measure:

- revoke authorisation;
- suspend or terminate the performance study;
- require the sponsor to modify any aspect of the performance study.

Before revoking or suspending authorisation or request for substantial modification, the review committee requests the sponsor to submit their view within 7 calendar days, except when immediate

action is required. In case of a corrective measure the review committee notifies the CCMO-LB of this decision, including a justification. The CCMO-LB will inform all other Member States and the Commission.

#### 6.1.4 Temporary halt/early termination

The review committee and the CCMO-LB are informed by the sponsor:

- within 15 calendar days, if the performance study has been temporarily halted or terminated early in the Netherlands and a justification is provided.
- within 24 hours, if the performance study has been temporarily halted or terminated early on safety grounds. The sponsor shall notify all member states in which that performance study is being conducted.

A restart of a performance study after a temporary halt of the performance study due to safety reasons, is in the Netherlands considered a substantial modification. See paragraph 6.1.2.

## 6.2 End of performance study

### 6.2.1 Notification

The end of a performance study is considered to be the last visit of the last subject unless another point in time for such an end is set out in the CPSP. The review committee is informed by the sponsor within 15 days of the end of the performance study in the Netherlands and, in case of a multinational performance study, the end of the performance study in all EU member states.

### 6.2.2 Results of the performance study

A performance study report and lay summary is submitted to the review committee irrespective of the outcome of the performance study (article 73, IVDR):

- within one year of the end of the performance study (or later if this is justified for scientific reasons and specified in CPSP);
- within 3 months of the early termination or temporary halt<sup>3</sup>.

The report and lay summary becomes publicly available:

- immediately after submission in cases of early termination or temporary halt;
- when the IVD is registered (Article 26) and before it is placed on the market;
- at the latest one year after submission of the report and summary if it is not registered before that time.

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<sup>3</sup> In the event that the performance study is restarted within three months of the temporary halt, the sponsor does not have to submit a performance study report until the performance study has been completed (See [MDCG 2021-6](#)).

# Appendix

## Appendix A Definitions

**Accessory for an in vitro diagnostic medical device:** means an article which, whilst not being itself an in vitro diagnostic medical device, is intended by its manufacturer to be used together with one or several particular in vitro diagnostic medical device(s) to specifically enable the in vitro diagnostic medical device(s) to be used in accordance with its/their intended purpose(s) or to specifically and directly assist the medical functionality of the in vitro diagnostic medical device(s) in terms of its/their intended purpose(s).

**Adverse event:** means 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;

**Analytical performance:** means the ability of a device to correctly detect or measure a particular analyte;

**Archived samples** (definition ISO-20916): samples that were collected in the past and are obtained from repositories (e.g. tissue banks, commercial vendor collections).

**Calibrator:** means a measurement reference material used in the calibration of a device.

**CE marking or CE marking of conformity:** marking by which a manufacturer indicates that a device is in conformity with the applicable requirements set out in the IVDR and other applicable Union harmonisation legislation providing for its affixing.

**Clinical benefit:** means the positive impact of a device related to its function, such as that of screening, monitoring, diagnosis or aid to diagnosis of patients, or a positive impact on patient management or public health.

**Clinical evidence:** means clinical data and performance evaluation results, pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer.

**Clinical performance:** means the ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user.

**Common specifications (CS):** means a set of technical and/or clinical requirements, other than a standard, that provides a means of complying with the legal obligations applicable to a device, process or system.

**Companion diagnostic:** means a device which is essential for the safe and effective use of a corresponding medicinal product to:

- (a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or
- (b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product;

**Conformity assessment:** means the process demonstrating whether the requirements of this Regulation relating to a device have been fulfilled.

**Control material:** means a substance, material or article intended by its manufacturer to be used to verify the performance characteristics of a device.

**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;

**Diagnostic sensitivity:** means the ability of a device to identify the presence of a target marker associated with a particular disease or condition.

**Diagnostic specificity:** means the ability of a device to recognise the absence of a target marker associated with a particular disease or condition.

**Eudamed:** European database on medical devices. The development of this database is delayed and will not be available before 2023.

**Harmonised standard:** means a European standard as defined in point (1c) of Article 2 of Regulation (EU) No 1025/2012;

**Label:** means the written, printed or graphic information appearing either on the device itself, or on the packaging of each unit or on the packaging of multiple devices;

**Manufacturer:** means a natural or legal person who manufactures or fully refurbishes a device or has a device designed, manufactured or fully refurbished, and markets that device under its name or trademark;

**Informed consent:** means a subject's free and voluntary expression of his or her willingness to participate in a particular performance study, after having been informed of all aspects of the performance study that are relevant to the subject's decision to participate or, in the case of minors and of incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in the performance study;

**Instructions for use:** means the information provided by the manufacturer to inform the user of a device's intended purpose and proper use and of any precautions to be taken;

**Intended purpose:** means the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements and as specified by the manufacturer in the clinical evaluation;

**Interventional clinical performance study:** means a clinical performance study where the test results may influence patient management decisions and/or may be used to guide treatment.

**Invasive procedure:** is considered to be a medical procedure invading (entering) the body, usually by cutting or puncturing the skin or by introducing instruments into the body.

**Investigational medical device dossier (IMDD):** The IMDD will provide the technical documentation on the IVD. A model IMDD for IVDs is under development. The use of this document is best practice in the Netherlands for clinical investigations with a medical device without a CE mark or a CE-marked medical device outside the scope of the intended purpose.

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

**Investigator's brochure (IB):** The IB contains the information on the device for performance study that is relevant for the investigation and available at the time of application. IVDR Annex XIV chapter I section 2 explicitly describes which information is required.

**in vitro diagnostic medical device:** means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:

- (a) concerning a physiological or pathological process or state;
- (b) concerning congenital physical or mental impairments;
- (c) concerning the predisposition to a medical condition or a disease;
- (d) to determine the safety and compatibility with potential recipients;
- (e) to predict treatment response or reactions;
- (f) to define or monitoring therapeutic measures.

Specimen receptacles shall also be deemed to be *in vitro* diagnostic medical devices;

**Kit:** means a set of components that are packaged together and intended to be used to perform a specific in vitro diagnostic examination, or a part thereof.

**Left-over sample:** In the IVDR only the term left-over samples is used and this term is not defined. ISO-20916 defines left-over and archived samples and for both types of samples the same regulation applies. Therefore, throughout this guidance the term left-over samples is used to stick with the IVDR naming and with the understanding that this term includes both left-over samples and archived samples as defined by the ISO-20916.

**Left-over sample** (definition from ISO 20916): unadulterated remnants of human derived specimens collected as part of routine clinical practice and after all standard analysis has been performed.

Note 1 to entry: Such specimens/samples would be otherwise discarded as there is no remaining clinical need for them.

Note 2 to entry: This can include specimens collected for research or other purposes not connected to the clinical performance study in question.

**Likelihood ratio:** means the likelihood of a given result arising in an individual with the target clinical condition or physiological state compared to the likelihood of the same result arising in an individual without that clinical condition or physiological state.

**Performance evaluation:** means an assessment and analysis of data to establish or verify the scientific validity, the analytical and, where applicable, the clinical performance of a device.

**Performance of a device:** means the ability of a device to achieve its intended purpose as claimed by the manufacturer. It consists of the analytical and, where applicable, the clinical performance supporting that intended purpose;

**Performance study:** means a study undertaken to establish or confirm the analytical or clinical performance of a device.

**Performance study plan:** means a document that describes the rationale, objectives, design methodology, monitoring, statistical considerations, organisation and conduct of a performance study;

**PMPF investigation:** a specific type of performance study to further assess, within the scope of its intended purpose, an IVD which already bears the CE marking, and where the performance study would involve submitting subjects to procedures additional to those performed under the normal conditions of use of the IVD and those additional procedures are invasive or burdensome.

**PMPF study:** a Post Market Performance Follow-up study to collect or evaluate performance data of an IVD which bears the CE marking and is placed on the market or put into service within its intended purpose with the aim of confirming the performance throughout the expected lifetime of the IVD. These studies shall be addressed in the manufacturer's post-market surveillance plan.

**Predictive value:** means the probability that a person with a positive device test result has a given condition under investigation, or that a person with a negative device test result does not have a given condition.

**Scientific validity of an analyte:** means the association of an analyte with a clinical condition or a physiological state.

**Serious adverse event:** means any adverse event that led to any of the following:

- (a) 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,
- (b) death,
- (b) 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,
- (c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect;

**Single identification number:** unique Union-wide single identification number for the performance study, which shall be used for all relevant communication in relation to that performance study.

**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. With this definition the investigator initiated performance studies are explicitly brought under the IVDR.

**Subject:** means an individual who participates in a performance study.

**Surgically invasive device:** means: (a) an invasive device which penetrates inside the body through the surface of the body, including through mucous membranes of body orifices with the aid or in the context of a surgical operation; and (b) a device which produces penetration other than through a body orifice. (MDR Annex VIII, Chapter 1, 2.2)

**Unique Device Identifier ('UDI'):** means a series of numeric or alphanumeric characters that is created through internationally accepted device identification and coding standards and that allows unambiguous identification of specific devices on the market;

**User:** means any healthcare professional or lay person who uses a device;

## Appendix B Checklist validation research dossier for performance studies with IVD under IVDR.

**Date of receipt:** Klik of tik om een datum in te voeren.

**ToetsingOnline number:** NL

**Eudamed number** (if available):

**Is the performance study within the scope of the IVDR?**

☐ Yes, because ....

☐ No, because .....

**Type of performance study:** Article 58/70.1 (PMCF)/70.2\*

**Class investigational medical device(s)\*\*:**

☐ class D

☐ class C

☐ class B

☐ class A

\* strike out what's not applicable

\*\* if there is more than one investigational device please cross box of the device with the highest class



## Documents initial application

				Received		
Section		Document	Comment	Yes	No	NA
A	A1	Cover letter		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	A2	Letter of authorisation if applicant is not the sponsor		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
B	B1	ABR form		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	B1a	Eudamed form		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
C	C1	Performance study Plan		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	C2	Substantial modifications of PSP	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
D	D1	Investigator's Brochure	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	D1	Other relevant safety information (not included in IB or PSP)	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	D2	Technical documentation;	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	D2	Product information IVD: EU declaration of conformity and the instructions for use	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	D3	Example of labelling attached to CE marked IVD (includes packaging labels and instruction for use)	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

				Received		
Section		Document	Comment	Yes	No	NA
	D4	A signed statement by the natural or legal person responsible for the manufacture of the device for performance study that the device in question conforms to the general safety and performance requirements laid down in Annex I apart from the aspects covered by the clinical performance study and that, with regard to those aspects, every precaution has been taken to protect the health and safety of the subject.	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
E	E1/E2	Subject information sheet(s) and informed consent form(s)		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	E3	Recruitment material	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	E4	Other information materials (newsletters, general brochures about trial specific procedures, etc)	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
F	F1	Questionnaires	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	F2	Patient diary	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	F3	Patient card	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
G	G1	Insurance certificate WMO research		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	G2	Proof of coverage liability of sponsor or investigator		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
H	H1	CV independent expert(s)	Not mandatory	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	H2	CV coordinating investigator (multicentre research)	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I	I1	List of participating centres (or refer to section C9 ABR-form)		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	I2	Research declaration form (for each participating centre)		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	I3	CV principal investigator (for each participating centre)		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

				Received		
Section		Document	Comment	Yes	No	NA
	I4	Other information per participating centre	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
K	K1	Copy of (summary of) <u>scientific/technical opinion/review</u> by other body with respect to performance study or investigational device submitted (expert panel, competent authority, notified body etc)	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	K2	Copy <u>assessment</u> from other Member States (competent authority and/or ethics committee)	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	K3	Clinical trial agreement between sponsor and institution/investigator (for each participating centre)	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	K4	Relevant publications with respect to performance study submitted	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	K5	Data Safety Monitoring Board (DSMB) – composition and charter	If applicable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

			Received		
Section	Document	Comment	Yes	No	NA
K8	<p>Description of the arrangements to comply with the applicable rules on the protection and confidentiality of personal data (GDPR) if not addressed in Performance study Plan (section C1), in particular:</p> <ul style="list-style-type: none"> <li>organisational and technical arrangements that will be implemented to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data processed;</li> <li>a description of measures that will be implemented to ensure confidentiality of records and personal data of subjects; and</li> <li>a description of measures that will be implemented in case of a data security breach in order to mitigate the possible adverse effects.</li> </ul>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
K7	Performance evaluation plan (details or reference)	Mandatory for Article 58, 70.1 and 70.2 performance studies	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**Dossier complete?**

- ☐ Yes
- ☐ No, request sponsor to complete application and start assessment postponed
- ☐ No, request sponsor to complete application and start assessment

**Name validator:**.....

**Validation date:** Klik of tik om een datum in te voeren.

## Appendix C Timelines

Timeline – Single Member State		
Step	Timeline for the step	Maximum timelines
Application of sponsor	0  <b>D0</b>	D0
MS provides the outcome of validation (extension delay possible)	Within 10 days (+5)  <b>D10</b>	D15
If the application dossier is considered not complete, the sponsor provides additional information	Within 10 days (+20)  <b>D20...</b>	D45
If applicable, MS reviews additional information and provides its final outcome on validation	Within 5 days (+5)	D55
MS provides its outcome of (first) assessment (request for information [RFI] or decision)	Within 45 days (+ 20)	D120
Sponsor provides the responses* in case of RFI  <small>* a clock-stop, i.e. the time available for assessment by the MS, shall be suspended from the date of the request for information, until such time as the additional information has been received.</small>	Within a timeline communicated by MS (this time period is not defined in IVDR)	D120+X
MS provides its decision after assessment response sponsor on RFI	Within 45 days (+20) minus time of first assessment	D120+X

## Appendix D Notifications sponsor to review committee

Italic notifications are national requirements (NL) as they are not defined in IVDR.

SAE notifications, see flow chart in appendix E.

Notification	Definition	Timeline
Withdrawal application		Prior to decision review committee
<i>Date start performance study</i>	<i>Date on which the first subject signs the informed consent form</i>	<i>&lt; 2 years after authorisation performance study</i>
Date end performance study in NL	The last visit of the last subject, or at a later point in time as defined in the CIP	≤ 15 days of this date
Date end performance study in all MS concerned (MSc)		≤ 15 days of this date
<i>Date end performance study in all MSc and in all 3<sup>rd</sup> countries</i>		<i>≤ 15 days of this date</i>
Temporary halt or early termination performance study on other grounds than safety (including justification)		≤ 15 days of this date
Temporary halt or early termination performance study on safety grounds (including justification)		< 24 hours of this date
<i>Resume performance study after temporary halt for other reasons than safety (resume performance study after temporary halt for safety reasons requires approval from review committee)</i>		<i>≤ 15 days after restart</i>
Performance study report accompanied by summary that is easily understandable to the intended user *.	Performance study report: see section 2.3.3 of part A of Annex XIII  COM guideline regarding the content and structure of the summary of the performance study report (to be developed).	< 3 months of date early termination or temporarily halt**  < 1 year of end performance study ***

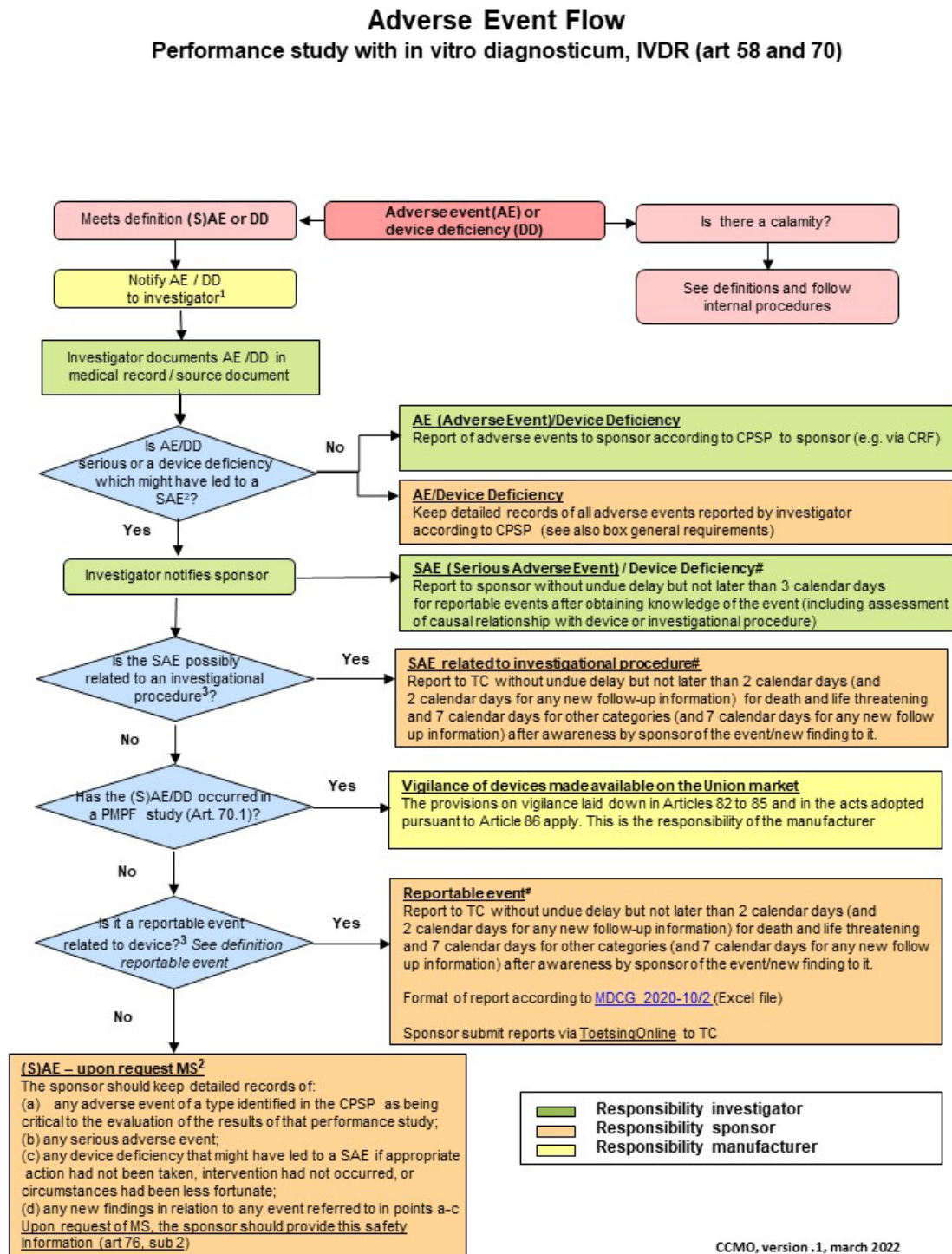
*\* Performance study report and/or summary shall become publicly accessible (IVDR Article 73.7) or CCMO-register (WMO, in case of no objection sponsor)*

*\*\* Performance study report after temporary halt only if performance study has not restarted within 3 months*

*\*\*\* Where, for scientific reasons, it is not possible to submit the performance study report within one year of the end of the investigation, it shall be submitted as soon as it is available. In such case, the performance study plan shall specify when the results of the performance study are going to be available, together with a justification.*

## Appendix E Reporting SAE or Device Deficiency

The flowchart for reporting SAEs is depicted below. (TC=review committee), see also CCMO website for flow chart with explanatory notes





## # 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 until 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:
  - life-threatening illness or injury,
  - permanent impairment of a body structure or a body function,
  - hospitalisation or prolongation of patient hospitalisation,
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
  - 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:

- 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;
- 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;
- 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