Review of a performance study with *in-vitro* diagnostics or companion diagnostics

Guidance document for MRECs

Version 2

Update June 2026

Content

Colophon and disclaimer

The contents of this guidance have been written with the greatest possible care, in consultation with the accredited MRECs. The CCMO and NVMETC have adopted the guidance. 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 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 the first version of this guidance, just after the IVDR came into force, still under discussion in the European Commission working groups on IVDR. In the meantime, the same groups have provided many guidance documents aiming at an effective and harmonised implementation of the IVDR legislation. In addition, MRECs became more and more experienced in assessing performance studies. Therefore, the new version of the guidance (version 2.0) will provide more guidance and better insights for assessing performance studies. At the same time many questions are still open and under debate. 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. Please send questions, remarks and suggestions to improve the document to the CCMO (devices@ccmo.nl).

The Hague, June 2026

Version history

Version 1.0, 9 June 2022, has been written thanks to the input of a working group in which the following persons participated:

- Hanneke van Deutekom (Department of Genetics, UMCU),
- Ewoud Schuit (Julius Center for Health Sciences and Primary Care, UMCU)
- Yolanda de Rijke (Department. Clinical Chemistry, Erasmus MC),
- Monique Al (CCMO national clinical trial office),
- Anneriet Heemskerk (CCMO national clinical trial office).
- The Health and Youth care Inspectorate (IGJ) was an observer at this working group.

Version 2.0, June 2026, has been adapted by the CCMO and send to the NVMETC. Please note that version 2.0 was written before the revision of the IVDR was announced and available.

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
MDCG	Medical Device Coordination Group
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 26th 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. At the same time many articles of the IVDR are interpreted differently by Member States and are under debate.

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. Chapter 2 of this guidance starts with the most important points arising from the IVDR and WMO. Chapter 3 gives an overview of the most important definitions as stated in the IVDR. Chapter 4 starts with an explanation of the definition of an IVD followed by the scope of a performance study and when a performance study is required. Chapter 5 described the submission procedure of a dossier for a performance study and provides tools to assess the dossier. Chapter 6 gives an overview what can be expected after approval of the performance study and how a modification can be submitted.

There are common parts that apply to all members and specific parts of the dossier 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

- 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).
- There is a procedure to validate the application for Article 58 performance studies (by the CCMO). See chapter 5 of this guidance.
- The procedures for recording and reporting of adverse events occurring during performance studies have been changed. See chapter 5 of this guidance.
- 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 performances study falls. See chapter 5 of this guidance.
- 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 unknown). The coordinated assessment will already be tested in a pilot before the start of Eudamed. See chapter 5 of this guidance.
- The same legal requirements apply for commercial and non-commercial performance studies. This in contrast to the MDR where academic sponsors apply for a so-called article 82 clinical investigation, which is less strict than the article 62 clinical investigation for conformity assessment.

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 and the MREC remains responsible for collection fees for performance studies.
- A validation decision for Article 58 performance studies is issued by the CCMO-LB.

- The accredited MREC needs to have an accredited 'WMO-member medical devices' (with a profile IVDR) if assessing performance studies. The requirements are published in the Staatscourant.
- 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 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).
- The Netherlands offer sponsors a coordinated process for combined studies (IVDR and CTR). In this process, the combined study is assessed simultaneously under both regulations. Within this coordinated process, a specific set of requirements applies (see chapter 5.9).
- The WMO has been adapted to accomodate implementation of the IVDR (Het bepaalde in de artikelen 2, eerste en derde lid, 2a, 3, 3a, eerste tot en met derde lid, 4, 5, 6, tweede tot en met negende lid, 8, tweede lid, 9, 10, 10a, 11, 12, 13, 21 en 30 is niet van toepassing op wetenschappelijk onderzoek met medische hulpmiddelen en op wetenschappelijk onderzoek met geneesmiddelen.)

Medical Device Coordination Group (MDCG)

The European Medical Device Coordination Group (MDCG) is established to coordinate the tasks conferred on it in the MDR and IVDR. Under the MDCG are several working groups, see **Figure 1.** The CIEPSE working group provides assistance to the MDCG on issues relating to clinical investigation and evaluation of medical devices and relating to performance studies and performance evaluation of IVDs. Within the CIE-PSE working group delegates from the CCMO and IGJ are represented from The Netherlands.

All relevant MDCG guidance documents can be found on the MDCG website (**Guidance - MDCG endorsed documents and other guidance - Public Health**)

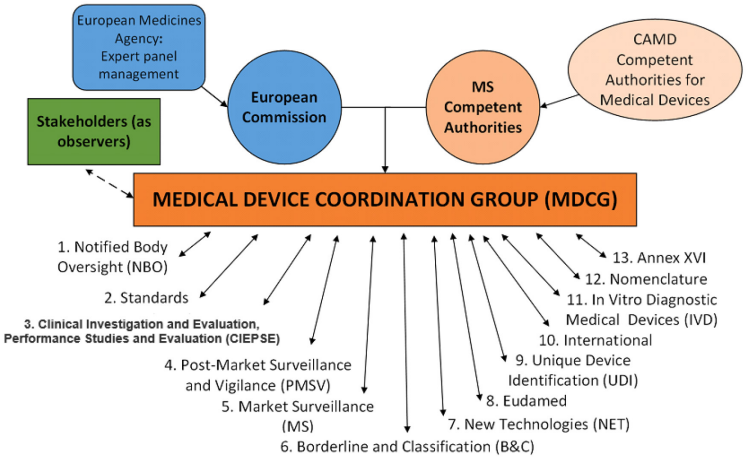


Figure 1. Overview of the MDCG working groups and their interaction with stakeholders.

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)

Competent authority: is a government or official body that has been legally empowered to perform specific tasks within a particular jurisdiction, such as enforcing regulations, issuing permits, or supervising markets

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 use (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 (verrichter): 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.

Notified body: is an independent third-party organization designated by a European Union member state to assess products, such as medical devices and personal protective equipment, for conformity with safety and legal requirements before they can be sold in the EU

Chapter 4 Scope of the IVDR in performance studies

This chapter describes the scope of the IVDR with respect to performance studies (chapter 6 of the IVDR). When assessing a clinical study that includes devices it is important to investigate whether a device could classify as an IVD and whether a performance study is required. Here we provide guidance on what is considered an IVD and a CDx. In addition, the definition and scope of performance studies is described. A CDx is an IVD, but is mentioned explicitly in this guidance due the the specific regulations in article 58.2 in the IVDR.

First the most relevant articles in the IVDR are shown in scope of a performance study. The definition and classification of an IVD and CDx is explained with an extra note on IVDR software. In addition, this chapter will go into depth in clinical trial assays, their legal status and the implication on whether the IVDR is applicable and potential MREC approval.

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 58.1 : additional requirements for certain performance studies
    - 58.1a: in which the surgically invasive sampling is carried out solely for the purpose of the performance study;
    - 58.1b: which is an interventional clinical performance study in which the test results may influence patient care decisions and/or be used to guide treatment, or;
    - 58.1c: in which the conduct of the study involves additional invasive procedures or other risks to the subjects of the studies/
- Article 58.2: performance studies involving companion diagnostics (CDx)
- 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?

The definition of an IVD (see article 2.2 and page 11 of this guidance) is broad and includes a wide range of products from reagents, assays, software (more information below) to equipment that are used *in vitro* for the examination of human specimens with the purpose to provide information on a range of

conditions. In general a device is an IVD if body material is examined with the device *in-vitro* (outside the body) with a medical purpose, such as diagnosis, prognosis, prediction or monitoring. Specimen receptacles (e.g. fingerprick) are also considered an IVD (see chapter 4.4 of this guidance).

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

Software: In article 2 of IVDR, software (defined as a set of instructions that processes data) has input data and creates output data, and 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 in-vitro based 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.

If the software classifies as medical device and is within scope of the IVDR the software can be defined as medical device software (MDSW). MDCG 2019-11 defines MDSW as follows: *Medical Device Software (MDSW) MDSW is software that is intended to be used, alone or in combination, for a purpose as specified in the definition of a "medical device" in the medical devices regulation or in vitro diagnostic medical devices regulation.*

The infographic "Is your software a Medical Device?" uses decision steps to assist in qualification of IVDR software (**Figure 2, page 15**) . in general, software is IVDR software when the vast majority of the input is received from IVD's. More information can be found in the guidance on qualification and classification of software (MDCG2019-11).

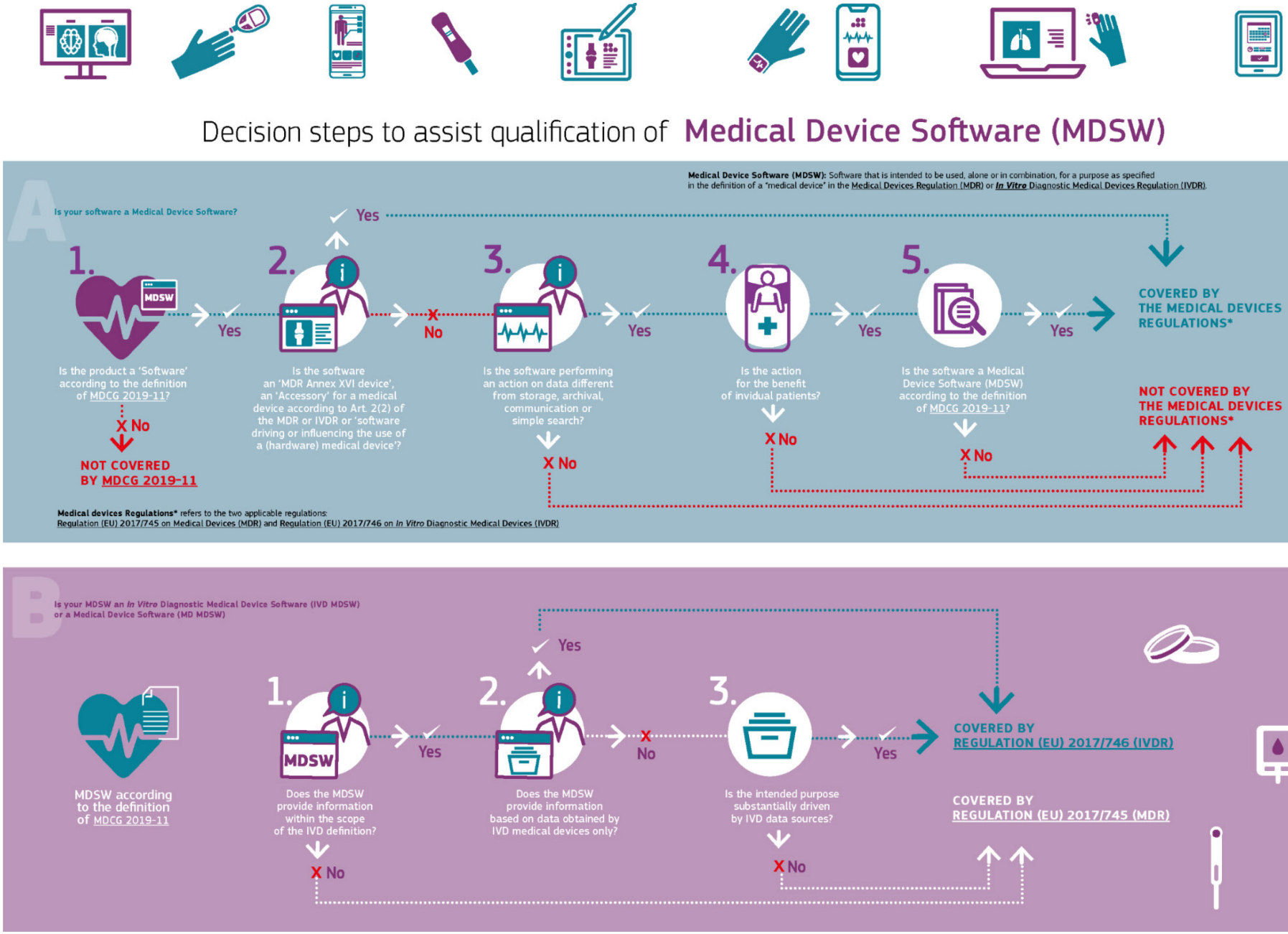


Figure 2: Infographic Medical device software (MDCG2019-11)

4.2.1 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. Please see **figure 3** for some examples per class.

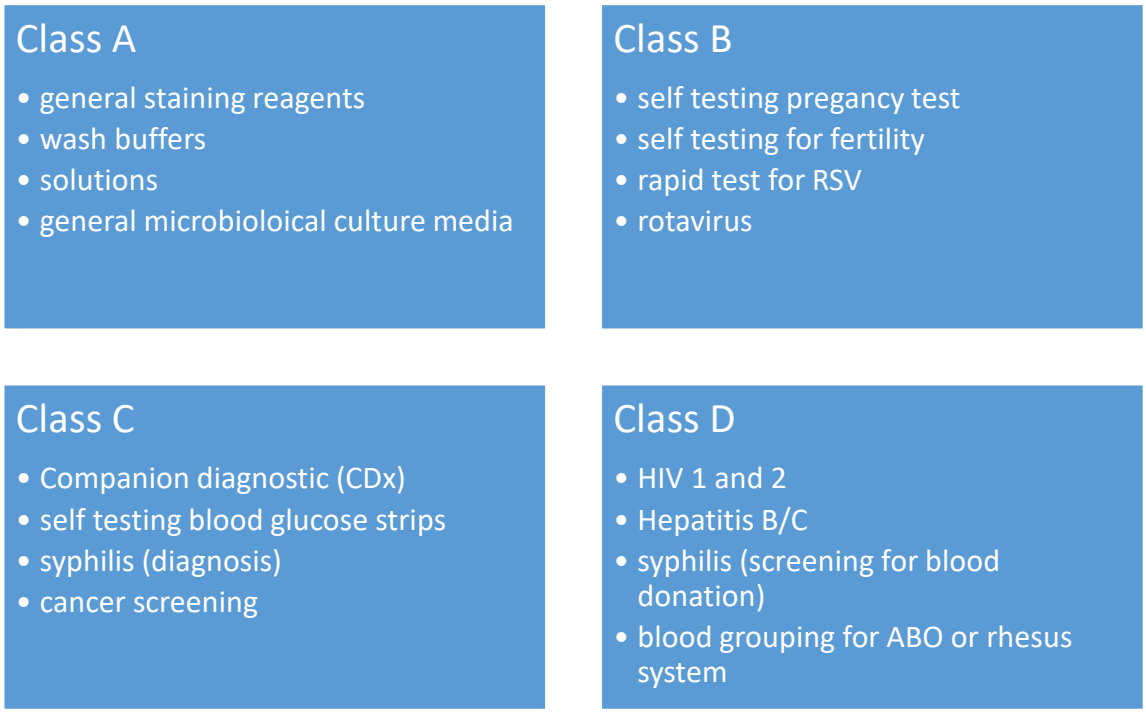


Figure 3: IVD Classification Examples. See for more detailed description MDCG guidance 2020-*6*

4.2.2 Clinical trial assays in general

[*adapted from MDCG guidance 2022-10*] In a clinical trial many assays, also known as clinical trial assays, are used at different stages in development. They may be used for, amongst others, inclusion/exclusion, primary/secondary endpoint, safety monitoring, exploratory endpoint or development as CDx. An assay (pharmacokinetic, pharmacodynamic, immuno-assay, anti-drug-antibody, biomarker etc) 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.

An example of a clinical trial flow is visualised below **(Figure 4)**, where the key processes for which assays might be utilised are highlighted. The processes in green are 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. PK assays that are specifically designed for the study should not be considered an IVD.

The processes in red 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.

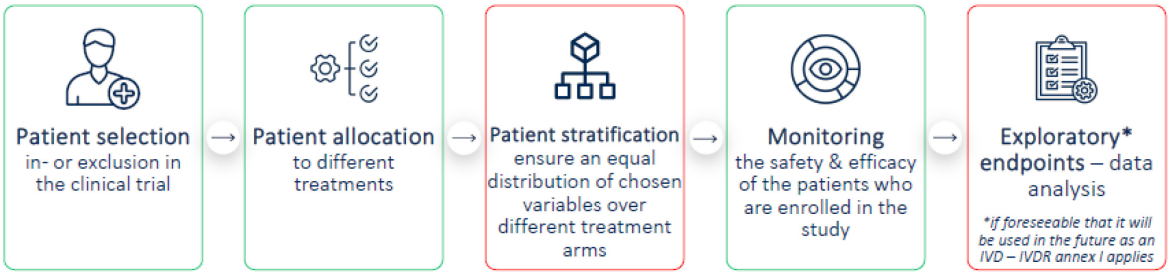


Figure 4. Simplified example of use of assays on human samples in a clinical trial. Assays marked in green are assays which will likely be considered IVDs as they are used for medical management decisions of trial subjects within the trial. The processes in red do not impact the medical management of the trial subjects and therefore would not have a medical purpose in the trial. Figure modified from MDCG guidance (2022-10).

4.2.3 Legal status of IVDs

If a device classifies as an IVD it should/must comply to the IVDR and either be legally on the market or comply with the requirements for a performance study. Different types of legal status can be categorized:

CE-certified IVD: these IVDs are CE-certified and used within the manufacturer's intended use.

Modified CE-certified IVD: when modifications are made to a CE IVD, the IVD is no longer CE certified. Small modifications might not alter the CE-IVD certification, these are described in MDCG 2022-06.

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. Therefore the drug label also indicates that an IVD must be used before administrating the drug. Of note, the drug label will state the IVD used during the performance study for CDx registration, but will also describe alternative assays that are suitable.

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 and should fulfil both regulations. The final label 'CDx' is only applied after consultation between a notified body and relevant medicinal authorities, and is initiated by the manufacturer of the CDx. 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*)

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. Please note that the term LDT, laboratory developed test, is not stated in the IVDR. LDT is defined in the CLIA regulation which is only applicable in the United States of America.

RUO assay: [*copied from MDCG 2025-5*] research use only products do not qualify as an IVD and cannot have a CE-IVD-mark nor fullfil the definition of an in-house product. These products may have a CE-mark not related to the IVDR. RUO products can not possess any link to a medical purpose, nor bear any reference to in vitro diagnostic medical procedures. Additionally, Article 2(45) of the IVDR states that a device intended to be used for research purposes, without any medical objective, shall not be deemed a device for performance study.

However, when a RUO product (e.g., reagent, reagent product, control material, kit, instrument, apparatus, piece of equipment, software system) is assigned a medical purpose in a way that it fulfils the definition of an IVD according to Article 2(2) of the IVDR, it becomes an IVD and can no longer be considered as a RUO product. It consequently becomes regulated under the IVDR. Where a sponsor (or another party) does assign such an in vitro diagnostic medical purpose to what was initially a RUO product, the sponsor (or the other party) needs to assume the role of a manufacturer under the IVDR and should also follow the relevant provisions of the IVDR.

There are several different ways in which RUO products can be used in connection to performance studies.

- RUO product used for research purposes (no IVD intended purpose) alongside a performance study of another product which is an IVD. The RUO product is outside the scope of the IVDR.
- RUO product is assigned an IVD intended purpose and is itself the object of the performance study – in this case the RUO product becomes an IVD and a device for performance study. The product is in scope of the IVDR and the requirements for devices for performance study apply to it.
- RUO product is assigned an IVD intended purpose but is not itself the object of the performance study. The product is in scope of the IVDR and relevant IVDR requirements apply to it (i.e. requirements for conformity assessment and CE-marking or Article 5(5)).

4.3 Performance studies

4.3.1 Performance study definition

When is a performance study required? A performance study is required when the IVD is not legally on the market. 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. By definition a performance study should thus investigate the **safety or performance** of an **IVD** with **defined endpoints** related to the IVDs **analytical** or **clinical** parameters (see below). Testing should be performed within the EU or on patient samples from the EU. An investigational IVD may have the following legal status within a performance study:

1. Under development, no legal status: use of the IVD is only allowed within a performance study. This can be an IVD under development by a commercial manufacturer or within a health institution.
2. CE-certified, outside intended use: use of the IVD is only allowed within a performance study.
3. In-house developed, outside intended use: use of the IVD is only allowed within a performance study.

In the following cases a performance study is not (always) required if an IVD is used that is:

1. CE-certified, within intended use: the use of the IVD is allowed, no application for performance study is required. WMO could still be applicable or 70.1 for post-marked performance study.
2. In-house developed, within intended use: the use of the IVD is allowed, no application for performance study is required. WMO could still be applicable.

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. As a general rule, analytical performance must always be demonstrated on the basis of analytical performance studies

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. Clinical performance studies must be performed unless due justification is provided for relying on other sources of clinical performance data.

MDCG 2022-2 provides guidance on general principles of clinical evidence for In Vitro Diagnostic medical devices (IVDs).

4.3.2 Performance studies: articles 57, 58.1, 70.1 and 70.2

All performance studies fall under IVDR chapter VI, but not all performance studies need to be reviewed by a review committee (MREC 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 4.3.4 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 (except for CDx). For performance studies that entail some risk for the subject IVDR article 58 is also applicable. For article 58 an MREC or CCMO approval is needed (**Figure 5**).

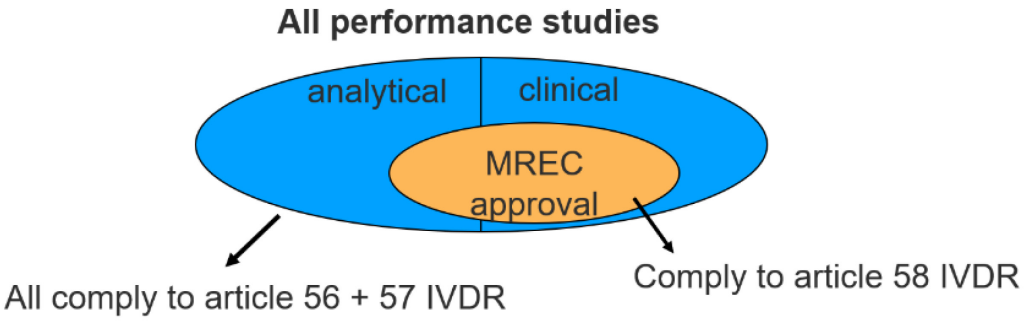


Figure 5. Overview of all performance studies and the applicable articles from the IVDR. Performance studies can be separated in analytical and clinical performance studies. In many cases analytical performance studies are performed with left-over samples and do not require MREC approval. Most clinical performance studies are approved by an MREC.

In **appendix F** 18 cases are presented showing the difference in IVDR legislation types, including an explanation why the IVDR is applicable or why not. In **Figure 6** on page 21 a flowchart is presented to guide in the decision which IVDR article is applicable and whether MREC approval is needed. Below the flowchart more detailed information is provided per article.

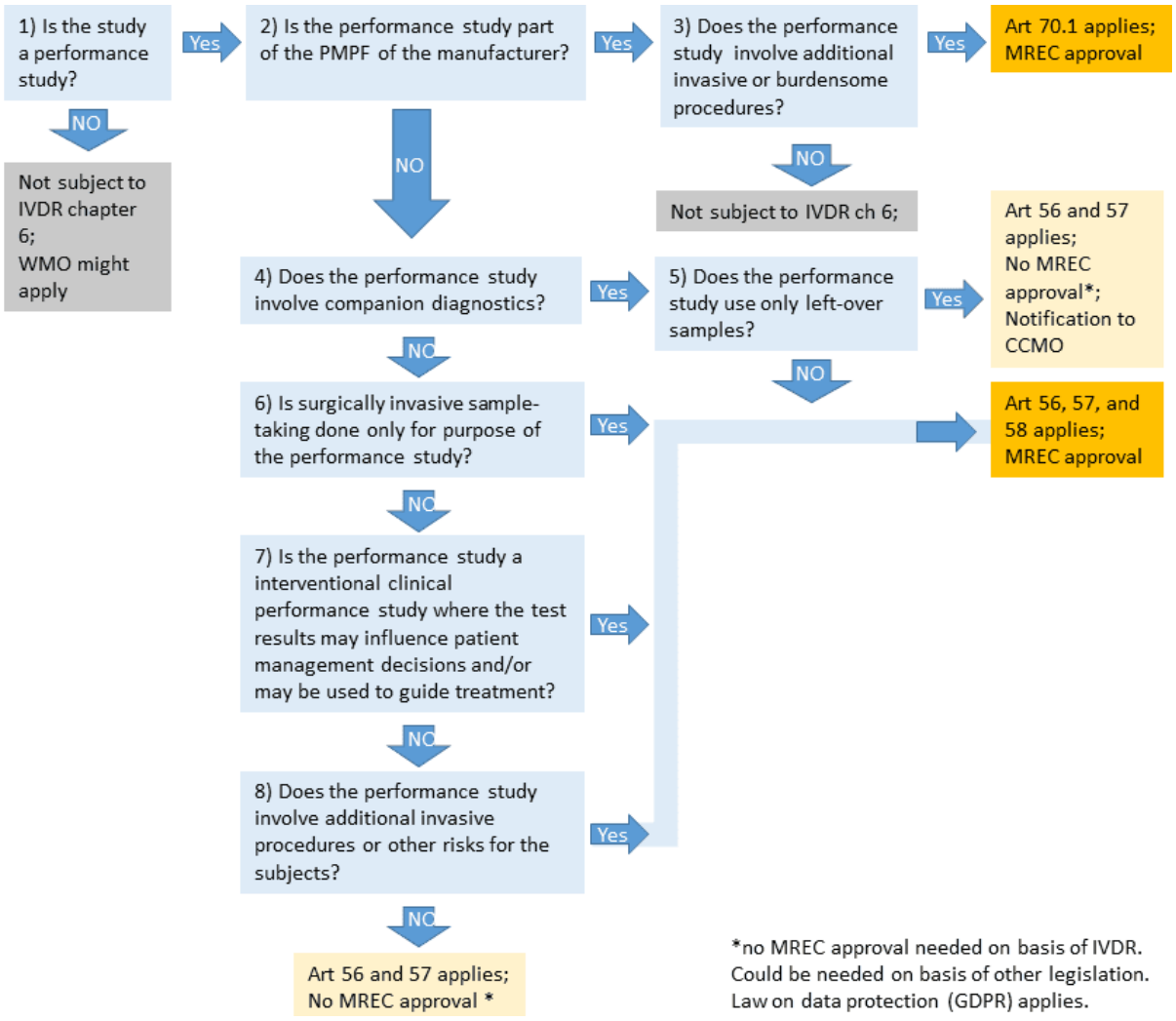


Figure 6. Flowchart to guide in the decision which IVDR article is applicable and whether MREC approval is needed. Numbers are explained below:

Questions 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. If this question is answered with yes MREC approval is needed.***
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. Please note that if the left-over samples will be used to guide treatment or medical management decisions article 58.1 is applicable and MREC approval 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.2 If this question is answered with yes MREC approval is needed.***
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 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. In addition, the manufacturer shall ensure that a device for performance study complies with the general safety and performance requirements set out in Annex I. These type of studies are not assessed by an MREC. Also no notification is needed. WMO might be applicable.

Example article 57 study

An extra venous blood sample is taken during routine care. This extra sample is used to perform an analytical performance of an IVD under development. No risk for participant and no clinical decision is made based on the data of the study.

Article 58: performance studies that fall under article 58 may include risk for the subject and need to be assessed by an MREC. The procedures are described in detail in this document. For these studies article 56 and 57 are also applicable. According to article 58 additional requirement are needed in the following cases:

- 58.1a: in which the surgically invasive sampling is carried out solely for the purpose of the performance study;
- 58.1b: which is an interventional clinical performance study in which the test results may influence patient care decisions and/or be used to guide treatment, or
- 58.1c: in which the conduct of the study involves additional invasive procedures or other risks to the subjects of the studies.

More information for each risk factor defined in article 58.1 is described below. This section is *copied from MDCG 2025-5:*

1. With reference to Article 58(1) point (a), what does “surgically invasive sample-taking” mean?
   Surgically invasive sample-taking is sample-taking with a surgically invasive device.

   A surgically invasive device is defined in the MDR as:
   a. an invasive device which penetrates inside the body through the surface of the body, including through the 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.
      Thus, surgically invasive sample-taking includes
      (a) sample-taking that penetrates inside the body through the surface of the body, including through the mucous membranes of body orifices; and
      (b) using a device which produces penetration other than through a body orifice for sample taking.

      Further, a body orifice means “any natural opening in the body, as well as the external surface of the eyeball, or any permanent artificial opening, such as a stoma”

   Examples of surgically invasive sampling:
   - blood sampling (arterial, venous or capillary),
   - puncture (body liquids, incl. cerebrospinal fluid or abscess),
   - collection of fresh tissue biopsy

2. With regards to Article 58(1) point (a) which addresses performance studies “in which surgically invasive sample-taking is done only for the purpose of the performance study”, what is meant by “only for the purpose of the performance study”?

   The following scenarios should be considered “only for the purpose of the performance study”:
   - The procedure of surgically invasive sample taking is done only for the purpose of the performance study, as a separate procedure;
   - A surgical procedure is performed, but an additional invasive sample is taken only for use in the performance study, e.g. a biopsy taken only for performance study purposes during surgery (additional sub-procedure is performed which is surgically invasive).

The following scenarios should <u>not</u> be considered "only for the purpose of the performance study":

- Surgically invasive sample taking is performed as part of routine care or per the protocol of a clinical trial and only part of the sample is needed for the routine or clinical trial purpose and another part of the sample is used for performance study purposes.
- Surgically invasive sample taking is performed as part of routine care or per the protocol of a clinical trial, but an additional volume of biological material is collected in a separate container for performance study purpose, without the need for an additional invasive procedure (e.g. an extra tube of blood collected via e.g. an indwelling catheter that has been inserted for other purposes than to obtain material for the performance study).

  Note, however, that even in these cases, depending on e.g. the extent of extra sample collection or use of the IVD output for treatment decisions, the study may be considered to be interventional or involve "other risks for the subjects of the studies" and that an application for the performance study may still be needed per Article 58(1) (b) or (c).

3. With reference to Article 58(1) point (b), what is an interventional clinical performance study?

   '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.

   In interventional studies extra caution shall be taken, as there might be a risk of indirect harm to the study subject due to potentially, false negative or false positive results from the device for performance study, leading to inappropriate patient management decisions.

4. With reference to Article 58(1) point (c) and Article 70(1), what does the term "invasive procedures" mean?

   Invasive procedures include (but are not limited to) penetration inside the body through the surface of the body, including through mucous membranes of body orifices, or penetration of a body cavity via a body orifice. Note that it is necessary to consider also invasive procedures that are not related to the sample collection, e.g. gastroscopy, i.e. other than those covered by Article 58(1) point (a).

   Note that for PMPF studies mentioned in Article 70(1), the concept of additional burdensome procedures also needs to be considered.

Example article 58 study

An non-CE certified IVD is used to investigate antibiotic resistance. A nose swab is taken from study participants. The results from this IVD are used to determine whether the study participants will receive a specific antibiotic regimen.

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 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.

Article 70.2: performance studies that fall under article 70.2 may include risk for the subject and need to have a review by an MREC. This article is applicable to IVDs with a CE-mark, but used outside the intended use. In this case article 58 may be applicable, in addition to articles 56 and 57.

> Example article 70.2 study
>
> The evaluation of the use of an CE-certified IVD, with an intended use to quantify the levels of protein X in lung tumors. In the current study the aim is to investigate if the IVD is also suitable to quantify the levels of protein X in skin tumors.

4.3.3 Performance studies involving companion diagnostics: article 58.2

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 (article 58.2); such study should however be notified to the competent authority (via devices@ccmo.nl). Please note that when the data generated from the left-over sample are used to guide treatments or patient management within the study article 58.1b is applicable and MREC approval is needed.

Examples:

- When the purpose of the performance study is to establish or confirm analytical or clinical performance of a not yet CE marked device with an intended purpose as companion diagnostic.
- In situations where a CE marked device is used outside its intended purpose and an aim of the performance study is to extend the device's intended purpose as companion diagnostic device

> Example article 58.2 study
>
> The evaluation of the use of the companion diagnostic CDx A (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.

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

(copied from MDCG 2025-5) 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. Of note, if left-over samples are used but the results are used within the study to guide treatment article 58 is applicable.

4.3.5 Combined studies

Performance studies may also be submitted combined with a clinical trial under the CTR or a clinical investigation under the MDR. More information can be found in chapter 5.9.

4.3.6 Performance studies for IVDs manufactured and used only within health institutions

According to Article 5(5) of the IVDR, the requirements of the IVDR do not apply to devices manufactured and used only within health institutions established in the Union, provided that they comply with the applicable provisions laid out in that Article. One of these provisions is compliance with the relevant general safety and performance requirements (GSPR) set out in Annex I of the IVDR.

Data that needs to be collected for GSPR demonstration has to be collected before an IVD qualifies as an in-house device. As a consequence, the provisions on performance studies may be of relevance for such data collection.

Two possible scenarios for performance studies related to this context can be envisaged (This section is copied from MDCG 2025-5):

- If the performance study is intended to establish or confirm the performance of a new device, or of a device outside of its intended purpose, the device cannot be considered to fulfil all the relevant GSPR, in particular those related to clinical and/or analytical performance. These devices do not fall under the exemption of Article 5(5). Thus Article 57 applies for such performance studies, and if any of the criteria in Article 58(1) or 58(2) are relevant for the performance study in -question, the provisions in article 58 apply. Note that when article 58 is not applicable (e.g. when left-over samples are used), the performance study is not subject to application or notification requirements per the IVDR, i.e. it can be managed within the health institution with adequate data protection measures as specified in article 57.
- If the performance study is conducted to further assess, within the scope of its intended purpose, an existing device that already complies with Article 5(5), it can be concluded that the device already fulfils the relevant GSPR. Then, provided all the other requirements of Article 5(5) are also fulfilled, Article 5(5) applies. Articles 57 and 58 do not apply.

Further, national requirements may apply to performance studies with IVDs in scope of Article 5(5).

4.3.7 Scientific study versus performance study

(*copied from MDCG 2025-5)* Performance study requirements apply to a study of an IVD where a study seeks to establish or confirm the analytical or clinical performance of a device. Early stage, design studies which seek to establish product specifications before verification of the design, where neither the analytical nor clinical performance is being investigated, are not to be considered performance studies. In this stage the assay also does not classify as IVD, there is no medical purpose. Studies for validation of the design are considered as performance studies where they seek to establish or confirm analytical or clinical performance. If the analytical or clinical performance is not being investigated the study is considered a scientific study and the IVDR is not applicable. Of note, other legislation may still be applicable. *See **Figure 7** for more information.*

Example of a scientific study:

A study to investigate if a biomarker can be detected in a specific patient population. An ELISA is developed. The primary endpoint of the study is to evaluate whether the assay is able to detect the biomarker in this population. This is not a performance study.

The results of the study show that the ELISA is valid and show promising signal-to-noise ratio's. The sponsor assigns a medical purpose to the device and wants to investigate the sensitivity and specificity. This study should be classified as performance study.

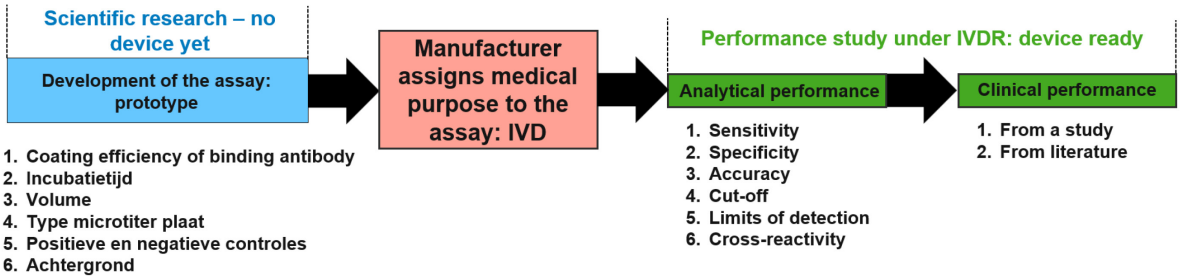


Figure 7. Differences between a scientific research study and a performance study.

4.3.8 Laboratory activities using IVDs regulated under ISO15189

Medical Laboratories, in hospitals and general practitioner organizations, in the Netherlands are ISO-15189 accredited. In general, this includes Clinical Chemistry, Medical Microbiology, Medical Immunology, Pathology, Genetics and Pharmacy, all of these accredited laboratories provide patient diagnoses and/or treatment plans based on a solid Quality Management System. The requirements for this QMS have a overlap with Annex I of the IVDR.

The ISO15189 norm sets requirements for how the quality of laboratory analyses is defined. This includes, amongst others, validating whether an IVD meets the manufacturer's specifications, establishing reference values, clinical decision limits, and quality assurance. These activities generally use left-over material, extra material collected during standard care, or material specifically collected for this purpose.

Activities carried out for the purpose of complying with the ISO15189 do not fall under the definition of medical-scientific research. Therefore, this type of activities is not subject to the Dutch Medical Research Involving Human Subjects Act (WMO), even if the results of the quality analyses are published in (inter)national scientific journals. Chapter 6 of the IVDR is also not applicable as it does not concern the development of a new IVD. Nevertheless, additional requirements may be imposed by the Executive Board of an organization.

This is only applicable for IVDs that are CE-IVD marked or marked as in-house developed IVD (and compatible with article 5.5 of the IVDR). For IVDs under development (no legal status) the chapter 6 of the IVDR is applicable.

4.3.9 Specimen collected in EU but analysed outside EU

(*copied from MDCG 2025-5)* A study in which specimen is collected in an EU member state for a performance study but sent outside the EU for analysis, must fulfil the requirements in Article 57(1) of the IVDR. The performance study in itself may have additional requirements to meet, dependent upon study design and objective of the performance study, Article 58(1), Article 58(2) and Article 70 may also be applicable. In all member states where the specimen collection takes place a performance study submission is required.

4.3.10 Multiple devices per performance study

(*copied from MDCG 2025-5)* It is possible to assess more than one device for performance study within the same performance study plan. In that case, all the devices for performance study should be included in the application form by duplicating and completing the section of the form related to device information. Further, the device related documentation to accompany the application per chapter I, Annex XIV to the IVDR (such as investigator's brochure per section 2 and statement per section 4.1) needs to cover all the devices for performance study. If it is not possible/feasible to include all the different devices for performance study in one performance study plan, they should be split over different performance studies.

4.5 Transitional provisions

4.5.1 Eudamed

The delivery of a fully functional Eudamed is delayed until (probably) 2030. Until Eudamed is fully functional Research Portal will be used. The CCMO will create an Eudamed number for studies falling under article 58/70.2 and 70.1.

The sponsor has the obligation to upload the following information in Eudamed (**Table 1**).

Table 1. Obligations of sponsor in Eudamed including transitional provisions.

Obligation	**Transitional provision**
Initial application	Research Portal (registration via ABR form)
Substantial modifications	Research Portal (only if ABR form is modified)
Eudamed PS number	If not already available, the CCMO-LB will request this number
Notification of Article 70.1 performance study	Research Portal (registration via ABR form)
Recording and reporting of reportable adverse events	Research Portal (upload MDCG 2020-10/2 Excel)
A performance study report and a lay summary	Research Portal (upload pdf document)
Notification of Article 58.2 left-over samples	Email to devices@ccmo.nl

4.5.2 Transitional period article 5(5) point d

Article 5(5) point d states that a health institution that uses in-house IVDs have to justify that the target patient group's specific needs cannot be met, or cannot be met at the appropriate level of performance, by an equivalent CE-marked device available on the market. The condition set out in Article 5(5), point (d), of the IVDR will apply from 31 December 2030, according to the Q&A provided by the EU commission.

Chapter 5 Primary submission performance study

This chapter describes the procedures and assessment of the initial application of a performance study. 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 laws. Finally, tools are provides how to assess a performance study file.

5.1 Which committee?

Currently, all MRECs may review all performance studies (all classifications) on the condition that the committee has appointed an expert on medical devices with the profile IVDR. These experts must be appointed by the CCMO.

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. Please see the **Table 2** below for an overview (also see **Appendix C**):

Table 2. Overview of timelines for validation and assessment of the different performance study categories*.

Submission phase	Article (IVDR)	Timelines (days)
Validation	58	Submission via Research portal. Maximum 55 calendar days including response time sponsor
	70.1	Submission via Research portal. No separate validation, but part of the assessment
Assessment	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
Substantial modifications	58	Submission via Research portal within one week. Maximum 38 calendar days (+ 7 days for consulting expert) + clock stop for response sponsor
Non-substantial modification	58	Submission via Research portal.
Only notification	58.2	Notification to devices@ccmo.nl for studies with companion diagnostics with left-over samples. CCMO will react within one week.

*Please note that currently in NCP these timelines are not applied.

5.2.1 Article 58 performance study

Ultimately, the article 58 (and 70.2) performance studies will be submitted through Eudamed (not available yet). Until this is functional, the national web portal Research Portal 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 check for completeness only concerns the presence of all documents; it is not a substantive assessment. During the validation the CCMO will create an Eudamed (CIV) number. The maximum validation time is 55 days, including response of the sponsor.

A validation checklist has been created (**appendix B**). In **appendix C** the exact validation timelines are presented.

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 an expert. 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.

Manufacturers are required to demonstrate the safety, performance, and clinical benefit of their IVD based on clinical data. To this end, manufacturers must specify the clinically relevant outcome parameters (“endpoints”) with which they consider this evidence to be provided. During the validation it is important to confirm whether the protocol of performance study of the IVD contains well defined endpoints. The primary endpoints must be related to at least one analytical or clinical performance parameter as defined in the IVDR. Secondary endpoints may not always be related to an analytical or clinical performance parameter. For candidate CDx the primary endpoint is usually related to the investigational medicinal product.

5.2.2 Article 58.2 performance study CDx with left-over samples

For performance studies with companion diagnostics a specific provision has been included in the IVDR (IVDR article 58(2)). This means that these performance studies must be reviewed by an accredited review committee. An exception applies if only leftover samples are used without any medical consequence for the study participants within the study; in that case a notification to the CCMO at devices@ccmo.nl is sufficient. The notification must contain the following documents:

1. Cover letter;
2. Authorisation of EU person if sponsor is not established in the EU;
3. Information on the source of the left-over samples;
4. Eudamed form;
5. Protocol (clinical performance study plan);
6. Confirmation that the performance study using left-over samples will be conducted in accordance with applicable data protection legislation.

The CCMO checks whether the application is complete and whether the study falls within the scope of article 58.2. In case the data from the left-over samples will be used in the clinical study for patient selection or patient management article 58.1 is applicable.

5.2.3 Article 70.1 performance study (PMPF)

The article 70.1 performance studies (PMPF) are registered in the national web portal Research Portal. The sponsor submits the research dossier directly to the selected MREC. Nevertheless, the CCMO will create an Eudamed PS number.

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 (a new submission must be created in Research portal). 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 only 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 Research Portal.

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, compared to a standard research file under the WMO. These are mentioned below. An overview of all the documentation is given in **appendix B** This is based on the requirements for the application dossier for article 58.1/70.2 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. Sponsors are able to provide consent in the cover letter for using the national process for combined studies.

Application form: Eudamed application form and ABR-form via Research Portal.

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. The CPSP must be signed by the sponsor and main researcher involved.

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. This document is not obligatory, but can be requested by the competent authority.

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, the investigational medical device dossier for IVD (IMDD_IVD) is available.

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, with an IVDR profile. 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, IVD development or genetics. The official requirements has been published in the Staatscourant. A network of IVD experts is available for questions and 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 (local) accredited MRECs, in The Netherlands, 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 (**Table 3**). 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 and state-of-the-art in this field, such as the international standard ISO 14155:2020 (Good Clinical Practise), ISO 15189 (quality and competence in medical laboratories) and ISO13485 (quality management system, QMS). 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.

Table 3. Regulatory grounds for performance studies.

Category study	Regulatory grounds
Performance studies IVDR article 58	IVDR ● Articles 57-77 ○ Scope of art. 58 correct? ○ Scientific and ethical justification? (art. 58(3), 58(5)(b)) ○ Risks acceptable? (art. 58(5)(e) jo. Annex XIII/Annex I) ○ Participant protected? (art. 58(5)(d),(h),(i),(k) jo. art. 60–64) ○ Informed consent? (art. 58(5)(f),(g) jo. art. 59) ○ Sponsor acceptable? (art. 58(4)–(5)(c)) ○ IVD acceptable? (art. 57(1), 58(5)(l), Annex I) ○ Dossier complete? (art. 57(2), Annex XIII, Annex XIV) ● Annex XIII and XIV: full documentation ● Common specifications or harmonized standards ○ ISO14155 – GCP ○ GCLP ○ ICH M10 - bioanalytical method validation ○ ISO15189 – Medical laboratory ○ ISO13485 – quality management system
Post-market performance follow-up (PMPF) study IVDR article 70.1	IVDR ● Article 58, sub 5b-l, p (includes articles 59-64) ● Article 71, 72, 73 ● Article 76, sub 5 ● relevant provisions of Annexes XIII and XIV

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, foetuses 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 performance study dossier

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 has been 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 has been 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 of multinational documents

The multinational documents (such as Eudamed form, protocol, IB, technical documentation, CEP) will in the future be assessed in a multination coordinated assessment.

To support the assessment of the multinational documents of a performance study a template has been designed by the European CIE-PSE Working Group (see **teams Kennisbank, not a public document**). The template consists of two parts. First, an administrative part, Chapter 1, with questions about the study details, the sponsor, the investigational IVD, and aspects of the performance study plan. Answers to these questions can be found in the Eudamed application form (the numbers in parentheses refer to the Eudamed form) and the performance study plan. This part is intended to summarize the performance study plan as provided by the sponsor.

The second part, Chapter 2, is the actual assessment of the performance study concerning the international documents (similar to part 1 in the CTR). The template is not a checklist of all requirements stated in the IVDR. Instead, the template highlights the key assessment aspects to enable a harmonized judgment on whether the performance study is designed in such a way that any potential residual risks to subjects or third parties, after risk minimization, are justified when weighed against the expected clinical benefits. Sections 2.2 and 2.3.2 conclude with a general question on whether there are other aspects in Annex XIII and Annex XIV, respectively, that require assessment. Each question refers to the relevant IVDR articles or includes a reference to an MDCG guideline.

The template consists of questions addressed to the IVDR expert, but also questions for a methodologist, legal expert, and ethicist. Additionally, the secretariat of the MREC may play a role in completing and managing the template (this is different per MREC). The following division of roles could be applied.

Table 4. Questions in the template assessment form*.

Committee member	Relevant questions
Secretariat	Chapter 1 Section 2.1 Section 2.2: 9 Section 2.3.1
IVD Expert	Section 2.2: 1- 8 Section 2.3.2 Section 2.3.3: 1-7 Section 2.4: 9
Legal Expert	Section 2.2: 6-8, 10 and 11 Section 2.4: 10
Methodologist	Section 2.2: 1 Section 2.3.2: 7
Ethical expert	Section 2.2:1, 7, 8
Physician	Section 2.2: 1 Section 2.3.2: 6
All members	Section 2.2: 12 Section 2.3.3: 8 Chapter 3 Chapter 4

***Based on Performance Study_Assessment Report Template__version 200825**

Additionally, in the Netherlands we composed an overview of the important review questions which are listed in the table at page 38. The questions are categorized in different domains: participants, IVD, primary endpoints, participant flow, analysis, risks and ethical justification. These domains reflect the legal ground for the assessment of a performance study. The questions can be used to form a constructive opinion whether the performance study is acceptable.

Domain	Participants	Investigational IVD (IVD)	Primary endpoints	Participant flow	Analysis	Ethical justification	Risks
Description	Describe the method for recruiting of participants for the study	Describe the IVD (method and intended use)	Describe the primary outcomes of the study	Describe any participants lost to follow-up or excluded from the analysis	Describe the statistical methods	Describe the ethical considerations	Describe the risks for the participant
Signaling questions (yes, no, unclear)	Was a consecutive or random sample of participants enrolled? Did the study avoid inappropriate selection criteria? Is the inclusion justified in case vulnerable subjects minors, incapacitated subjects, pregnant or breastfeeding women are included? Is the informed consent properly described?	Is the scientific validity of the IVD described? Is the analytical validity of the IVD described? Is the clinical validity of the IVD described? If a threshold was used, was it prespecified? Was the IVD used for all participants? Is the comparator justified? Is the type of specimen justified for the IVD?	Was the method used to measure the outcome valid and reliable? Was the method for measuring the outcome the same for all participants? Is the overall study design adequately justified in relation to the objectives? Is the rationale for the choice and characteristics of any control groups or comparator methods sound?	Describe the time horizon from the IVD measurement to the outcome Did all participants receive the IVD? Was treatment avoided/introduced after the IVD was measured? Was the time horizon sufficient to capture the outcome? Was information on the outcome available for all participants? Are criteria for early termination described?	Were all enrolled participants included in the analysis? If data were missing, were appropriate methods used? Are blinding methods (if applicable) described and justified Is the sample size determination statistically valid, clearly explained, and adequate to meet the objectives? Are power calculations presented and appropriate? Is the planned statistical methodology for analyzing the data appropriate for the study design, endpoints, and objectives?	Are the procedures concerning incidental findings described? If an interventional study design is used, is the rationale clearly explained Does the performance study plan contain a statement of compliance with the recognized ethical principles?	Is the collection of specimens specifically for the study justified, particularly concerning any additional risks posed to subjects? Is the design and manufacturing of the device according to an appropriate QMS? Have all applicable GSPRs been identified and is the selection appropriately justified? Is the chance of false-positives or negatives described? Are the procedures for reporting SAEs well described?
Risk of bias or erroneous outcome (high, low, unclear)	Could the selection of participants have introduced bias?	Could the use or interpretation of the outcome of the IVD introduced bias?	Could the method to measure the outcome have introduced bias?	Could the study flow have introduced bias?	Could the analysis have introduced bias?	n.a.	Are the procedures implemented by the sponsor to control or mitigate the risks acceptable?
Concerns about applicability (high, low, unclear)	Are there concerns that the participants are not suitable to answer the primary endpoint?	Are there concerns that the IVD, its conduct, interpretation, or threshold is not sufficient or suitable to answer the primary endpoint?	Are there concerns that the primary outcomes do not match the hypothesis of the study?	Are there concerns that the study time horizon is not adequate to answer the primary endpoint?	Are there concerns that the statistical analysis is not adequate to answer the primary endpoint?	Are there concerns that the procedures are unethically?	n.a.

5.4.4.5 Assessment of national documents

Currently, there is no template available to assess national documents of a performance study (similar to part 2 in CTR), such as the IVO, VGO, CVs investigator, WMO insurance, liability insurance, compliance with national data protection, financial and other arrangements. The following questions could be used to assess the national documents:

Table 5. Template assessment national documents (copied and adjusted from CTR template).

Subject information and informed consent form	a. Is the Dutch model ICF used or is deviation justified? b. Do all subject information sheets meet all of the requirements specified below and comply with the requirements in? (1) adequately describe the nature, objectives, benefits, implications, risks, and inconveniences, of the performance study, including description of the IVD. (2) adequately describe the subject's rights and guarantees regarding his or her protection, in particular his or her right to refuse to participate and the right to withdraw from the clinical trial at any time without any resulting detriment and without having to provide any justification. (3) adequately explain that withdrawal of the informed consent will not affect the results of activities already carried out and the use of data obtained, based on informed consent, before its withdrawal. (4) adequately describe the conditions under which the clinical trial is to be conducted, including the expected duration of the subject's participation in the clinical trial. (5) adequately describe, if applicable, a. the follow-up measures if the participation of the subject in the clinical trial is discontinued b. contraceptive measures (6) is comprehensive, concise, clear, relevant, and understandable to a layperson taking into account the study population (7) provide information about the damage compensation according to national law of concerned member state, if applicable. (8) provide the NL-number (research portal) (9) provide information about the availability of the clinical trial results, i.e. that the summary of the results of the clinical trial and a summary presented in terms understandable to a layperson will be made available in OMON (10) provide the contact details of an entity for further information (11) provide adequate information about planned personal data collection and processing (12) provide adequate information about planned collection, storage and future use of biological samples (13) in the case of a trial with minors, adequately pay attention to language and the information needs of the involved age groups (14) in the case of a trial with incapacitated subjects, adequately pay attention to the information needs of these subjects (15) Provide information on the chance and consequences of false-positives/negatives. c. Additional requirements in case of a trial in an emergency situation (16) in case no prior informed consent has been obtained from subject or legal designated representative), adequately explain that if the subject or, where applicable, his or her legally designated representative does not give consent, he or she has the right to object to the use of data obtained from the clinical trial d. Do all Informed Consent Forms meet all of the requirements as specified in the Dutch model ICF?
Proof of insurance	a. Is the arrangement for damage compensation in accordance with **national law**? b. Is the duration of the insurance sufficient to cover the performance study? If not, specify: ☐ WMO insurance certificate trial participants inadequate ☐ Proof of coverage liability sponsor inadequate ☐ Proof of coverage liability investigator inadequate
Suitability facilities	Is the list of the planned clinical trial sites completed with the required documents per trial site (CV and Doi investigator plus Signed Site Suitability Declaration, part A or research declaration)?

Financial and other arrangements	a. Is there no undue influence, including that of a financial nature, exerted on subjects to participate in the clinical trial? b. In trials with incapacitated subjects, minors, pregnant or breastfeeding subjects: Are no incentives or financial inducements given to the subjects or their legally designated representatives, except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial? c. Are arrangements for financial transactions and compensation paid to the investigator/site for participating in the clinical trial acceptable? d. Do the conditions on "publication and authorship" comply with the standard clauses of the Dutch model clinical trial agreement and the principles of the latest version of Declaration of Helsinki? e. Do the conditions on "term and termination" comply with the standard clauses of the Dutch model clinical trial agreement?
Compliance with national requirements on data protection	a. Have all of the requirements specified below been met? (1) the processing of special category of personal data is justified (2) the procedure to encode data and for access code list and data is appropriate (3) the duration of storage (personal) data is acceptable (4) if data will be transferred to a country outside the EEA with a reduced level of data protection, and no equal level of privacy protection can be guaranteed, the subjects are informed and there is a placeholder to consent on data transfer to this country outside the EEA. (5) if applicable, the procedure for future use (personal) data is appropriate
Suitability investigator	a. Does the investigators of the trial site meet all the requirements specified below? (1) There is an informative current CV (2) There is sufficient previous experience with clinical trials (3) There is sufficient previous experience with patient care (4) The DoI does not indicate a conflict of interest with respect to the clinical trial
Compliance with use of biological samples	a. Have all of the requirements specified below been met? (1) the procedure for collection human biological samples is appropriate (2) the procedure to encode the samples and for access code list and samples is appropriate (3) the duration of storage biological samples is acceptable (4) if human biological samples will be transferred to a country outside the EEA with a reduced level of data protection, and no equal level of privacy protection can be guaranteed, the subjects are informed and there is a placeholder to consent on sample transfer to this country outside the EEA. (5) if applicable, the procedure for future use of human biological samples is appropriate

5.4.4.6 Assessment of other assays in the clinical study

In clinical trials many assays are used to collect data. Some of these assays qualify as IVD and should comply with the IVDR (legally on the market or part of performance study) and some of the assays do not qualify as IVD, ref interface Q&A.. These IVDs or assays do not have to be assessed separately. Nevertheless, IVDs or other assays may play a role in the assessing whether the protocol is suitable to collect data to answers the primary endpoints.

5.4.4.7 Assessment of IVD software

Performance studies that investigate IVD software must also comply to the international harmonized standard IEC 62304 and requires specific documentation next to the standard research file. The provided Annex I by the manufacturer should have IEC62304 mentioned at point 16.2 If this standard is not present, the following processes should be properly documented; Software development life cycle, risk management, including information security, verification and validation.

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 sponsor 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 (if relevant) 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. If the investigator requires more time at least the pro-forma appeal must be submitted within 6 weeks. Within a reasonable time the grounds for the appeal must be submitted.

5.7 Coordinated multinational assessment

A multinational coordinated assessment procedure is described in the IVDR. Currently it is unknown when this procedure will be officially start as the requirements of Eudamed are not in place yet.

In 2025 the European Commission has decided to start with a voluntary pilot procedure, so called pilot coordinated assessment. Because the Eudamed module for clinical investigation/performance study is not available yet CIRCABC/Microsoft Teams is used to share documents between member states. Lessons will be learned from this pilot to further implement the multinational assessment.

5.8 IVDR and Artificial Intelligence

MDCG 2025-6 provides a first set of answers to the most frequently asked questions related to the joint application of the Artificial Intelligence Act (AIA) and IVDR for manufacturers. The IVDR requirements address risks related to medical device software, however, they do not explicitly address risks specific to AI systems. The AIA complements the MDR/IVDR by introducing requirements to address hazards and risks for health, safety and fundamental rights specific to AI systems. In line with the New Legislative Framework approach, this means a simultaneous and complementary application of the MDR/IVDR and the AIA for medical devices that contains one or more high-risk AI system. It is currently unclear which committee in the Netherlands will review an application under the AIA.

5.9 Combined studies: CTR/IVDR/MDR

In combined studies two different product types (medicinal product, medical device and/or in-vitro diagnostic) are being investigated. As a result, the study must be assessed on the basis of multiple EU-regulations, as shown in the table below:

Table 6. Combined studies.

Possible combined studies	EU regulation
Medicinal product and medical device	CTR and MDR
Medicinal product and in vitro diagnostic	CTR and IVDR
Medicinal device and in vitro diagnostic	IVDR and MDR

Within combined studies, the part of the study that falls under the CTR, IVDR and/or MDR must be assessed by an authorized review committee. Combined studies often lead to many questions from sponsors and review committees. The majority of the combined studies are CTR/IVDR combinations. Of the performance studies submitted in The Netherlands around 90-95% are combined with a CTR trial. Usually the investigational IVD is used as inclusion/exclusion criteria for the CTR trial. The primary endpoint of the performance study is therefore usually related to the investigational medical product.

To ease the submission of the review process of combined studies the CCMO, in collaboration with the MRECs, developed a coordinated process for combined studies. In this process, the combined study is assessed simultaneously under both regulations. Within this coordinated process, a specific set of requirements applies, as described on the CCMO website. Please note that within the coordinated process both studies remain legally independent, meaning that all relevant EU-regulations apply.

The coordinated process aims to harmonize the submission procedure of a CTR clinical trial with the submission procedure of an IVD performance study or an MDR clinical investigation. When the validation and assessment phase of the studies are performed in the Netherlands, they are coordinated by CCMO (see **Figure 8**). The assessment under both regulations is carried out by the same authorized review committee and the decision always follows on day 76 according to the CTIS deadline. This coordinated process allows for a more rapid assessment, preventing a delay in the start of the combined study.

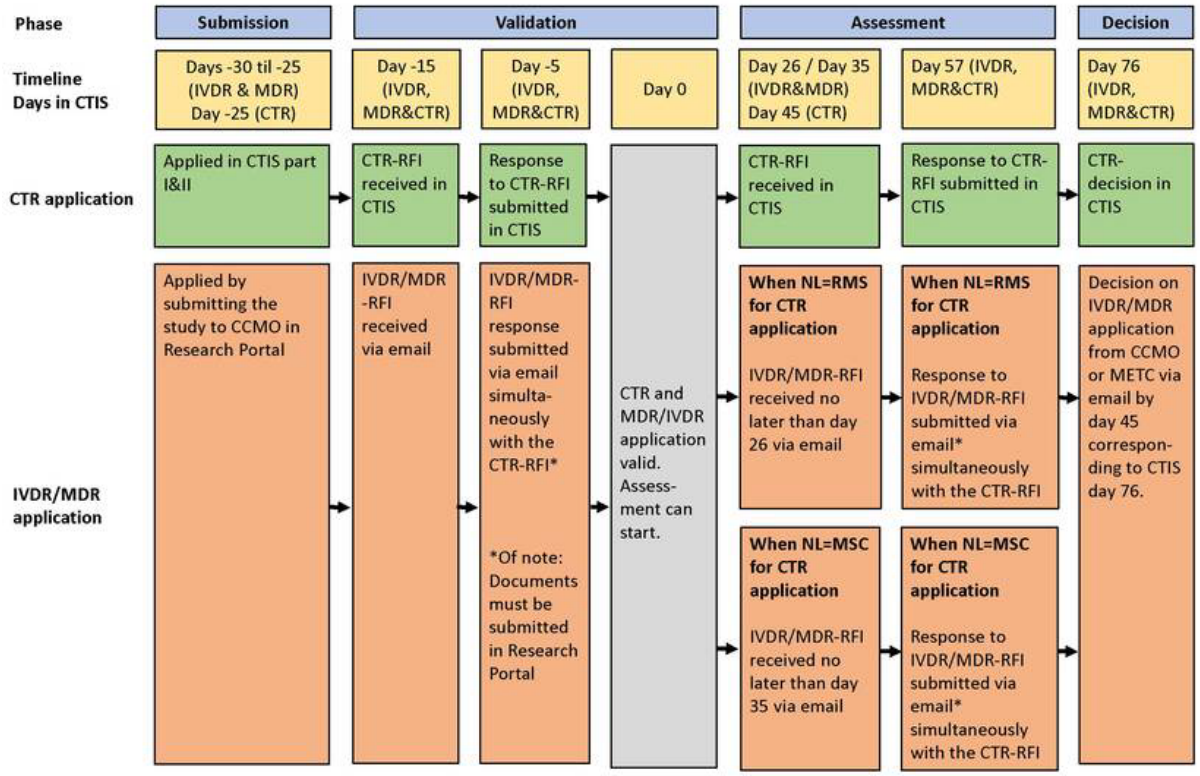


Figure 8. Flowchart parallel submission combined studies. All requirements and conditions can be found at the CCMO website Combined studies (CTR/IVDR/MDR) | Investigators | The Central Committee on Research Involving Human Subjects.

5.9.1 Assessment of combined studies

In combined studies the assessment of both studies must occur simultenously. The assessment of the use of the IVD must be viewed in light of the combined clinical trial. In addition, the protocols, VGO, insurance documents, contracts and ICFs are usually very similar or are even a identical document in both study files. As a result the request for information for both studies must be well coordinated and alligned.

In case identical documents are used it important that:

- The same version of the documents must be submitted for both files;
- The title of the CTR research file and the IVDR/MDR research file must be in the document;
- It must be indicated in the cover letter of both research files which documents are the same.

Special attention should be given the ICFs for combined trials. In most cases, one ICF will be desirable. If the studies are integrated in such a way (e.g. in studies with a companion diagnostic) that it can be seen as a single study, it is desirable to present one SIS to the research participant. Informed consent can then be given to both studies with one signature. Of note, it must be very clear to the research participant that consent is given for both studies. This can be done, for example, by having the research participant tick a box for both studies.

In other cases, two ICFs will be desirable. This is the case when only a small percentage of research participants from the IVD performance study are suitable for participation in the CTR clinical trial. In this case, informed consent must also be given separately.

5.9.2 COMBINE project

There is no common EU procedure for a single combined clinical trial that will serve both as a performance study for the IVD and a clinical trial for the medicinal product. The EU commission has started the COMBINE project in 2023 with the aim to address the bottlenecks for sponsors and assessors in combined studies. During the pilot that started in July 2025, it is possible to submit a single application for a combined study in CTIS. More information can be found here.

Chapter 6 Notifications and assessment during and after the performance study

A list of notifications the sponsor is required to send to the review committee is listed in **Appendix D** and some are explained in detail below.

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;
    - Domestic SAEs occurring within the study must be reported
    - Foreign SAE occurring within the study must be reported
    - SAE from other studies using the same device must not be reported
    - Line-listing is not required under the IVDR
- 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 is not ready yet, the sponsor has to upload the safety information via the Research Portal. 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. Of note, the definition of an SAE under the WMO is different compared to the definition in the IVDR. In addition, clinical studies that has been assessed under the CTD and include IVDs without CE-marking must comply with the safety reporting requirements in accordance with the IVDR.

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 (except for performance studies with left-over samples). 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 substantial modification must be uploaded in the Research Portal within one week after the document has been changed.

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 Substantial modifications combined studies

An amendment for a combined study can apply to only the performance study or also to the corresponding CTR/IVDR combined study. If the amendment results in a change to a shared document, the amendment must be submitted for both studies. The sponsor decides whether it is a substantial

amendment for both studies or only a notification for one or both studies. It is up to the review committee to determine whether this decision is correct. If the amendment is substantial for both studies, we advise to submit the amendment at the same time. If the amendment is substantial for only one study, we advise to submit the substantial amendment first. After approval the sponsor can submit the notification to the other study.

Amendments for combined studies are submitted separately. This means that an amendment under the CTR is submitted in CTIS and amendments under the IVDR in the Research Portal.

6.1.4 Non-substantial modifications

Article 71 of the IVDR does not describe how sponsors or authorities should deal with non-substantial modifications. Once EUDAMED is available, sponsors are expected to keep the information in the database up to date in accordance with Article 66(2) of the IVDR. For now non-substantial modifications must be submitted in the Research Portal. The review committee can assess whether the modification is non-substantial.

6.1.5 Progress report

In general, the sponsor is required to inform the review committee (MREC or CCMO) which assessed the IVD performance study on the progress of the study annually. A progress report contains at least:

- The number of subjects included (including those who left the study prematurely),
- An assessment of the extent to which research objectives are being met,
- Adverse events and other reports which may be important in assessing the progress of the study.

6.1.6 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.

6.1.7 Temporary halt/early termination

The review committee and the CCMO-LB are informed by the sponsor (via Research Portal):

- 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 (via the Research Portal) 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 (via the Research Portal) 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[1].

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.

[1] 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).

Appendices

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;

Analytical performance study: Analytical performance studies establish or confirm the ability of an IVD to detect or measure a particular analyte. This includes but is not limited to the determination of parameters such as 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, as well as cross-reactions. Data generated by analytical performance studies are necessary to demonstrate compliance with the relevant general safety and performance requirements in Annex I of the IVDR with respect to analytical performance.

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.

Clinical performance study: Clinical performance studies establish or confirm the ability of an IVD 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. This includes but is not

limited to the determination of parameters such as diagnostic sensitivity, diagnostic specificity, positive predictive value, negative predictive value, likelihood ratio, expected values in normal and affected populations.

The purpose of clinical performance studies is to establish or confirm aspects of an IVD performance which cannot be determined by analytical performance studies, literature and/or previous experience gained by routine diagnostic testing. This information is used to demonstrate compliance with the relevant general safety and performance requirements in Annex I of the IVDR with respect to clinical performance. When clinical performance studies are conducted, the data obtained shall be used in the performance evaluation process and be part of the clinical evidence for the device.

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 (CDx): 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;

Complementary diagnostic: means a device that identifies patients who are particularly likely to benefit from a specific drug, but it is not required for the patient to receive that drug (unlike a companion diagnostic). These devices use biomarkers to predict a drug's effectiveness or to help make informed benefit-risk decisions, providing valuable information for personalized medicine without being a mandatory prerequisite for the therapy.

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 the CIPS module will not be available soon.

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-IVD): The IMDD-IVD will provide the technical documentation on the IVD. The use of this document is best practice in the Netherlands for IVD performance studies with IVDs without a CE mark or a CE-marked IVD 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: This term should be understood as unadulterated remnants of human derived specimens37 collected as part of routine clinical practice, for research purposes or other purposes not connected to the clinical performance study in question and after all standard or intended analyses have

been performed. Such specimens/samples would be otherwise discarded as there is no remaining clinical need for the individual from which it was collected.

Left-over samples can include specimen or sample that are collected in the past and obtained from repositories (e.g. tissue banks, commercial vendor collections).

If there is a clinical need for samples such as when being used for an interventional performance study, they cannot be considered left-over samples.

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.

Research Portal 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 58.1/70.1 (PMCF)/70.2*

Class investigational medical device(s)** (appendix VIII)

☐ 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

Are files redacted? (METC should have access to all documents and must be readable)

☐ Yes, because …..……

☐ No, because ……

Is the METC authorized to assess the clinical study?

☐ Yes, because …..……

☐ No, because ……

Dossier complete?

☐ Yes

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

Is this a combined study?

☐ Yes, be aware for shared documents.

☐ No

Documents initial application checklist

				Received		
Section		**Document**	**Comment**	**Yes**	**No**	**NA**
A	A1	Cover letter	Mandatory	☐	☐	☐
	A2a	Letter of authorisation if applicant is not the sponsor	If applicable	☐	☐	☐
	A2b	Letter of authorisation if applicant is from outside the EU	If applicable	☐	☐	☐
B	B1	ABR form	Automatically generated in Research Portal	☐	☐	☐
	B8	Eudamed form	Mandatory	☐	☐	☐
C	C1	Performance study Plan	Mandatory	☐	☐	☐
	C2	Substantial modifications of PSP	If applicable	☐	☐	☐
D	D1	Investigator's Brochure	Mandatory	☐	☐	☐
	D1	Other relevant safety information (not included in IB or PSP)	If applicable	☐	☐	☐
	D2	Technical documentation/IMDD;	If applicable / IMDD not mandatory	☐	☐	☐
	D2	Product information IVD: EU declaration of conformity and/or the instructions for use	Mandatory	☐	☐	☐

Section		Document	Comment	Received		
				Yes	No	NA
	D3	Example of labelling attached to CE marked IVD (includes packaging labels and instruction for use)	If applicable	☐	☐	☐
	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.	Mandatory	☐	☐	☐
E	E1/E2	Subject information sheet(s) and informed consent form(s)	Mandatory, model CCMO not mandatory	☐	☐	☐
	E3	Recruitment material	If applicable	☐	☐	☐
	E4	Other information materials (newsletters, general brochures about trial specific procedures, etc)	If applicable	☐	☐	☐
F	F1	Questionnaires	If applicable	☐	☐	☐
	F2	Patient diary	If applicable	☐	☐	☐
	F3	Patient card	If applicable	☐	☐	☐
G	G1	Insurance certificate WMO research	Mandatory	☐	☐	☐
	G2	Proof of coverage liability of sponsor or investigator	Mandatory	☐	☐	☐
H	H1	CV independent expert(s)	Not mandatory	☐	☐	☐
	H2	CV coordinating investigator (multicentre research)	If applicable, not older than 2 years.	☐	☐	☐
I	I2	Research declaration form (for each participating centre)	Mandatory	☐	☐	☐
	I3	CV principal investigator (for each participating centre)	Mandatory, not older than 2 years.	☐	☐	☐

Section		Document	Comment	Received		
				Yes	No	NA
	I4	Other information per participating centre	If applicable	☐	☐	☐
K	K1	Copy of (summary of) scientific/technical opinion/review by other body with respect to performance study or investigational device submitted (expert panel, competent authority, notified body etc)	If applicable	☐	☐	☐
	K2	Copy assessment from other Member States (competent authority and/or ethics committee)	If applicable	☐	☐	☐
	K3	Clinical trial agreement between sponsor and institution/investigator (for each participating centre)	If applicable. If not present information about publication of the data and end of study must be part of the file.	☐	☐	☐
	K4	Relevant publications with respect to performance study submitted	If applicable	☐	☐	☐
	K5	Data Safety Monitoring Board (DSMB) – composition and charter	If applicable	☐	☐	☐

Section		Document	Comment	Received		
				Yes	No	NA
	K8	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: ● organisational and technical arrangements that will be implemented to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data processed; ● a description of measures that will be implemented to ensure confidentiality of records and personal data of subjects; and ● a description of measures that will be implemented in case of a data security breach in order to mitigate the possible adverse effects.	Mandatory	☐	☐	☐
	K7	Performance evaluation plan (details or reference)	Mandatory	☐	☐	☐

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	D0
MS provides the outcome of validation (extension delay possible)	Within 10 days (+5)	D15
If the application dossier is considered not complete, the sponsor provides additional information	Within 10 days (+20)	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 for consultation expert)	D120
Sponsor provides the responses* in case of RFI *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.	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.
All notifications are submitted in the Research Portal.

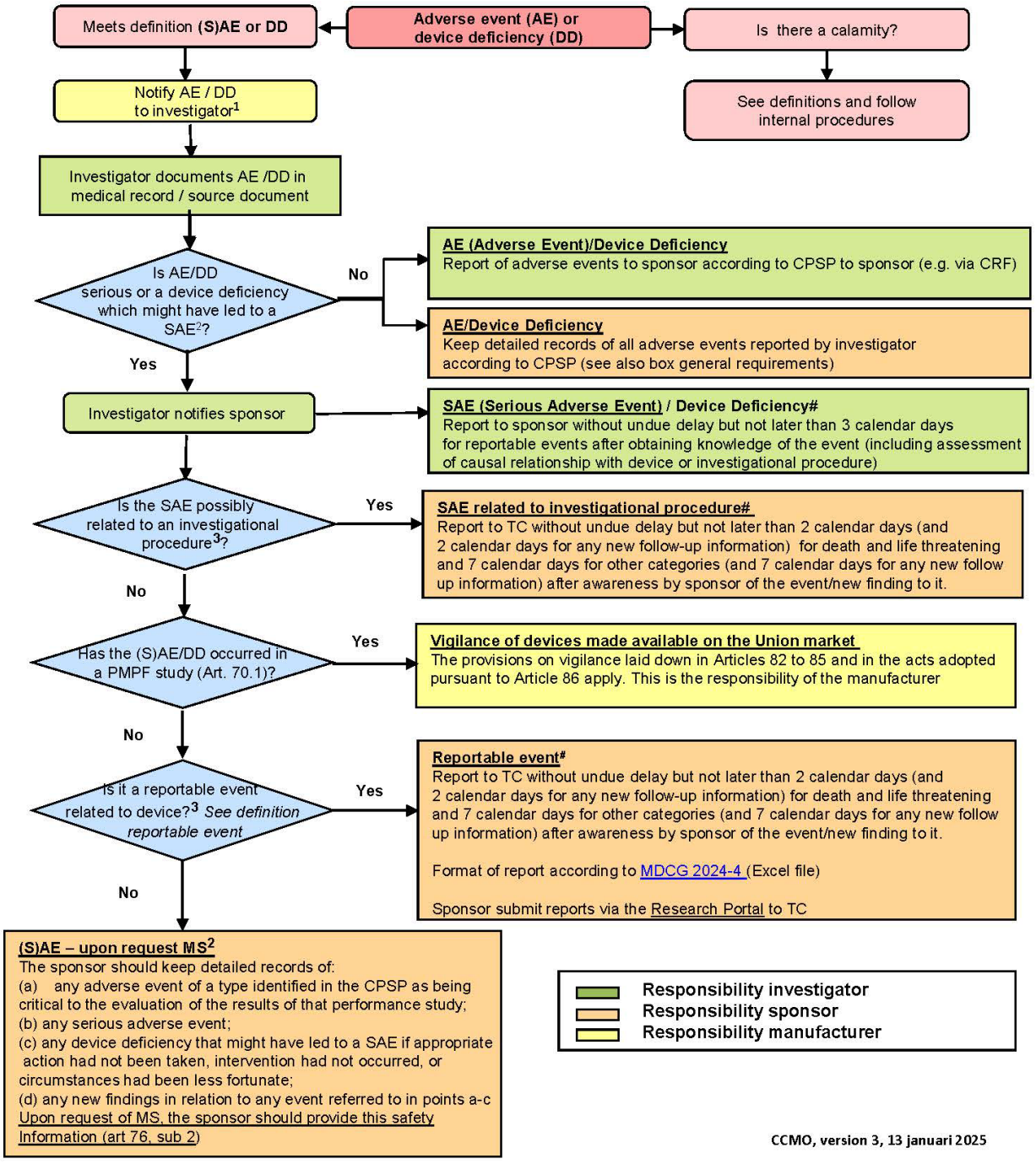
Notification	Definition	Timeline
Withdrawal application		Prior to decision review committee
Date start performance study	Date on which the first subject signs the informed consent form	< 2 years after authorisation performance study
Date end performance study in NL	The last visit of the last subject, or at a later point in time as defined in the CIP	≤ 15 days of this date
SAE notifications	Safety reporting	See appendix E
Date end performance study in all MS concerned (MSc)		≤ 15 days of this date
Date end performance study in all MSc and in all 3rd countries		*≤ 15 days of this date*
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
Annual progress report		Annually
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)		*≤ 15 days after restart*
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	< 3 months of date early termination or temporarily halt** < 1 year of end performance study ***

	summary of the performance study report (to be developed).	

** 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 the Research Portal until Eudamed is available
- Format is given in MDCG 2024-4 (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 of materials, that resulted in any of the following::
  i. life-threatening illness or injury,
  ii. permanent impairment of a body structure or a body function,
  iii. hospitalisation or prolongation of patient hospitalisation,
  iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
  v. chronic disease,
- foetal distress, foetal death or a congenital physical or mental impairment or birth defect

Device deficiency (IVDR, art 2.62)
Device deficiency' means any inadequacy in the identity, quality, durability, reliability, safety or performance of a device for performance study, including malfunction, use errors or inadequacy in information supplied by the manufacturer;.

Reportable events (IVDR, art 76, sub 2)
A reportable event is:
a. any serious adverse event that has a causal relationship with the device, the comparator or the study procedure or where such causal relationship is reasonably possible;
b. any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
c. any new findings in relation to any event referred to in points (a) and (b).

All causility assessments should be done according to section 10 of MDCG 2024-4. 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. 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 studyto 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.
   - In article 76, sub 6, it is described that for article 70.1 PMPF studies the sponsor has to report to MS any SAE for which a causal relationship has been established with the preceding investigational procedure (see also section 5.1 of MDCG 2020-10/2). Therefore, in the flowchart SAE related to investigational procedure is a separate step and applicable for art 58 and 70 performance studies.

WMO text valid on 26 May 2021; wet van 26 februari 1998
IVDR EU no 2017/746, dd 5 April 2017, applicable on 26 May 2022
MDCG 2020-10/1, May 2020
MDCG 2020-10/2, May 2020
ISO14155, version 2020

Abbreviations

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

Appendix F Casuïstiek (Dutch)

Opgesteld door het Medisch Technologie Team van de CCMO
Versie 10 februari 2025

In onderstaande casussen wordt uitgegaan van een IVD zonder wettelijke status. Dat wil zeggen:
- **een IVD zonder CE-markering;**
- **een IVD met CE-markering maar gebruik buiten de intended use;**
- **een in-house IVD in ontwikkeling die nog niet voldoet aan artikel 5.5 van de IVDR**

Als het IVD wel een wettelijke status (CE-gecertificeerd of in-huis status volgens 5.5) heeft en wordt gebruikt binnen de intended use dan is geen prestatiestudie nodig, tenzij het specifiek een post-market performance studie betreft. Let op dat in onderstaande voorbeelden niet wordt ingegaan of de studie mogelijk WMO plichtig is.

Casus 1
Binnen een klinische studie wordt een IVD gebruikt voor het meten van reuma factor. Het doel is om de analytische prestatie te beoordelen van het IVD. Tijdens een geplande bloedafname voor standaardzorg wordt één extra buisje bloed afgenomen voor de klinische studie.

- Toetsing onder de IVDR? In het algemeen: nee
- Zo ja, welk artikel? Nvt
- Toelichting: een extra afname uit een geplande afname voor standaardzorg wordt niet gezien als chirurgisch invasieve handeling onder de IVDR. Hierdoor valt de studie niet onder IVDR artikel 58.1a. Wanneer IVDR artikel 58.1b en 58.1c ook niet van toepassing zijn hoeft de studie niet door een METC getoetst te worden. De studie moet wel voldoen aan IVDR artikel 56 en 57.

Casus 2
Binnen een klinische studie wordt een IVD gebruikt voor het meten van reuma factor. Het doel is om de analytische prestatie te beoordelen van het IVD. Tijdens een geplande bloedafname voor standaardzorg wordt relatief veel bloed afgenomen voor de klinische studie.

- Toetsing onder de IVDR? Wellicht
- Zo ja, welk artikel? 58.1c
- Toelichting: een extra afname uit een geplande afname voor standaardzorg wordt niet gezien als chirurgisch invasieve handeling onder de IVDR. Hierdoor valt de studie niet onder IVDR artikel 58.1a. Echter de hoeveelheid bloed die wordt afgenomen kan in bepaalde gevallen wel een risico vormen voor de (kwetsbare) onderzoeksdeelnemer. In dat geval kan IVDR artikel 58.1c van toepassing zijn en moet de studie door een METC getoetst worden. Dit is een afweging die door de sponsor gemaakt moet worden eventueel in overleg met de METC. De studie moet sowieso wel voldoen aan IVDR artikel 56 en 57.

Casus 3
Binnen een klinische studie wordt een IVD gebruikt voor het meten van reuma factor. Het doel is om de analytische prestatie te beoordelen van het IVD. Specifiek voor deze studie worden onderzoeksdeelnemers gezocht en er wordt één buisje bloed afgenomen.

- Toetsing onder de IVDR? Ja
- Zo ja, welk artikel? 58.1a
- Toelichting: een afname specifiek voor de prestatiestudie wordt gezien als chirurgisch invasieve handeling onder de IVDR. Hierdoor valt de studie onder IVDR artikel 58.1a en moet worden getoetst door een METC.

Casus 4
Binnen een klinische studie wordt een IVD gebruikt voor het meten van reuma factor. Het doel is om de analytische prestatie te beoordelen van het IVD. Tijdens een geplande bloedafname voor standaardzorg wordt één extra buisje bloed afgenomen voor de klinische studie. De uitkomst van het IVD heeft invloed op de behandeling van de onderzoeksdeelnemer.

- Toetsing onder de IVDR? Ja
- Zo ja, welk artikel? 58.1b
- Toelichting: in deze studie wordt een IVD gebruikt en de uitkomst van het IVD heeft invloed op de behandeling of patiëntmanagement in de studie. Hierdoor moet het worden getoetst onder IVDR artikel 58.1b en beoordeeld door een METC.

Casus 5
Binnen een klinische studie wordt een IVD gebruikt voor het meten van CRP (een belangrijke ontstekingsmarker) uit een bestaande bloedafname. Deze uitkomst geldt als in- of exclusie criteria voor deelname aan de studie.

- Toetsing onder de IVDR? Ja
- Zo ja, welk artikel? 58.1b
- Toelichting: in deze studie wordt een IVD gebruikt en de uitkomst van het IVD heeft invloed op de behandeling of patiëntmanagement in de studie. Hierdoor moet het worden getoetst onder IVDR artikel 58.1b en beoordeeld door een METC.

Casus 6
Binnen een klinische studie wordt een IVD gebruikt voor het meten van CRP (een belangrijke ontstekingsmarker) uit een bestaande bloedafname. De uitslag wordt niet gebruikt voor diagnostiek of medische beslissingen in de studie. In alle onderzoeksdeelnemers wordt CRP gemeten en daarna worden de deelnemers willekeurig verdeeld over de studiearmen.

- Toetsing onder de IVDR? Nee
- Zo ja, welk artikel? -
- Toelichting: in deze studie wordt wel een IVD gebruikt, maar de uitkomst van het IVD heeft geen invloed op de behandeling of patiëntmanagement in de studie. Ondanks de CRP meting worden de onderzoeksdeelnemers willekeurig verdeeld. Hierdoor hoeft het niet te worden getoetst onder IVDR artikel 58.1b. De studie moet wel voldoen aan IVDR artikel 56 en 57. De CRP assay kan hier ook een research-use-only assay zijn.

Casus 7
Binnen een klinische studie wordt een IVD gebruikt voor het meten van CRP (een belangrijke ontstekingsmarker) uit een bestaande bloedafname. In alle onderzoeksdeelnemers wordt CRP gemeten en daarna worden de deelnemers verdeeld over de studiearmen op basis van de CRP uitkomsten.

- Toetsing onder de IVDR? Ja
- Zo ja, welk artikel? 58.1b
- Toelichting: in deze studie wordt een IVD gebruikt en de uitkomst van het IVD heeft invloed op de behandeling of patiëntmanagement in de studie. Hierdoor moet het worden getoetst onder IVDR artikel 58.1b en beoordeeld door een METC.

Casus 8
Binnen een klinische studie wordt een IVD gebruikt voor het meten van CRP (een belangrijke ontstekingsmarker) uit een bestaande bloedafname. In alle onderzoeksdeelnemers wordt pas aan het einde van de studie CRP gemeten.

- Toetsing onder de IVDR? Nee
- Zo ja, welk artikel? -
- Toelichting: in deze studie wordt wel een IVD gebruikt, maar de onderzoeksdeelnemers worden pas aan het einde van de studie gemeten. Een zogenaamde eindpunt-analyse. De uitkomst heeft geen invloed meer op de behandeling binnen de studie. Hierdoor is alleen artikel 56 en 57 van kracht. De CRP assay kan hier ook een research-use-only assay zijn.

Casus 9
Binnen een klinische studie wordt een IVD gebruikt als inclusiecriterium voor een geneesmiddelenstudie. Hiervoor wordt gearchiveerd tumorweefsel gebruikt.

- Toetsing onder de IVDR? Ja
- Zo ja, welk artikel? 58.1b
- Toelichting: doordat het IVD als inclusiecriterium wordt gebruikt heeft het invloed op de behandeling of patiëntmanagement in de studie. Ondanks dat er restmateriaal wordt gebruikt heeft de uitkomst direct invloed op de studie. Hierdoor moet het worden getoetst onder IVDR artikel 58.1b en worden beoordeeld door een METC.

Casus 10
Binnen een retrospectieve klinische studie wordt gearchiveerd tumorweefsel gebruikt (restmateriaal) voor het ontwikkelen van een IVD.

- Toetsing onder de IVDR? Nee
- Zo ja, welk artikel? -
- Toelichting: in deze studie wordt restmateriaal gebruikt voor het ontwikkelen van een IVD. De uitkomsten hebben geen invloed meer op de studie. De studie moet wel voldoen aan IVDR artikel 56 en 57. Wanneer het specifiek het ontwikkelen van de CDx betreft is een notificatie aan de CCMO verplicht (IVDR artikel 58.2).

Casus 11
In een laboratorium (in het ziekenhuis) wordt een test ontwikkeld voor het meten van een auto-antilichaam. De onderzoekers voeren een studie uit om te onderzoeken of het auto-antilichaam in de bloedmonsters van patiënten gedetecteerd kan worden. Tijdens een geplande bloedafname voor standaardzorg wordt één extra buisje bloed afgenomen voor de klinische studie.

- Toetsing onder de IVDR? Nee
- Zo ja, welk artikel? -
- Toelichting: Dit is een wetenschappelijke studie om te onderzoek of de auto-antilichamen gedetecteerd kunnen worden. Er is hier nog geen sprake van een IVD.

Casus 12
In een laboratorium (in het ziekenhuis) wordt een IVD ontwikkeld voor het meten van een auto-antilichaam. De onderzoekers voeren een studie uit om de sensitiviteit en specificiteit van het IVD te bepalen. Specifiek voor deze studie worden onderzoeksdeelnemers gezocht en er wordt één buisje bloed afgenomen.

- Toetsing onder de IVDR? ja
- Zo ja, welk artikel? 58.1a
- Toelichting: Dit is geen wetenschappelijke studie meer. Er wordt nu specifiek onderzoek gedaan naar de analytische prestatie van het IVD. Omdat er specifiek bloed wordt afgenomen geldt IVDR artikel 58.1a en moet de studie door een METC worden beoordeeld.

Casus 13
In een laboratorium (in het ziekenhuis) wordt een IVD ontwikkeld voor het meten van een auto-antilichaam. De onderzoekers voeren een studie uit om de sensitiviteit en specificiteit van het IVD te bepalen. Tijdens een geplande bloedafname voor standaardzorg wordt één extra buisje bloed afgenomen voor de klinische studie.

- Toetsing onder de IVDR? nee
- Zo ja, welk artikel?
- Toelichting: Dit is geen wetenschappelijke studie meer. Er wordt nu specifiek onderzoek gedaan naar de analytische prestatie van het IVD. Echter, een extra afname uit een geplande opname voor standaardzorg wordt niet gezien als chirurgisch invasieve handeling onder de IVDR. Hiervoor hoeft de studie niet te worden getoetst door een METC. De studie moet wel voldoen aan IVDR artikel 56 en 57.

Casus 14
In een laboratorium (in het ziekenhuis) wordt een IVD ontwikkeld voor het meten van een auto-antilichaam. De onderzoekers voeren een studie uit om de sensitiviteit en specificiteit van het IVD te bepalen. Tijdens een geplande bloedafname voor standaardzorg wordt één extra buisje bloed afgenomen voor de klinische studie. De resultaten worden teruggekoppeld en hebben invloed op de behandeling.

- Toetsing onder de IVDR? Ja
- Zo ja, welk artikel? 58.1b
- Toelichting: Dit is geen wetenschappelijke studie meer. Er wordt nu specifiek onderzoek gedaan naar de analytische prestatie van het IVD. Tevens hebben de uitkomsten nu invloed op de behandeling van de onderzoeksdeelnemers. Hiervoor moet de studie worden getoetst door een METC onder IVDR artikel 58.1b.

Casus 15
Voor een klinische studies worden wereldwijd deelnemers gerekruteerd, inclusief binnen Europese lidstaten. Er wordt een assay gebruikt als inclusie criterium binnen de studie. De assay is niet CE-gemarkeerd en wordt uitgevoerd in een centraal-lab in de US (CAP/CLIA gecertificeerd).

- Toetsing onder de IVDR? Ja
- Zo ja, welk artikel? 58.1b
- Toelichting: doordat het IVD als inclusiecriterium wordt gebruikt heeft het invloed op de behandeling of patiëntmanagement in de studie. De juridische status van het IVD in de US is niet geldig binnen de Europese Unie.

In de volgende casussen wordt een IVD gebruikt met een CE-markering.

Casus 16
Een laboratorium (in het ziekenhuis) wilt graag de intended use van een CE-IVD kit uitbreiden. Hiervoor wordt een studie opgezet waarbij uit een geplande opname een extra buis bloed wordt afgenomen. De uitkomst van het IVD heeft geen invloed op de behandeling.

- Toetsing onder de IVDR? Nee
- Zo ja, welk artikel? -
- Toelichting: in deze studie wordt wel een IVD gebruikt, maar de uitkomst van het IVD heeft geen invloed op de behandeling of patiëntmanagement in de studie. Daarnaast wordt een extra afname uit een geplande opname voor standaardzorg wordt niet gezien als chirurgisch invasieve handeling onder de IVDR. De studie moet wel voldoen aan IVDR artikel 56 en 57.

Casus 17
Een laboratorium (in het ziekenhuis) wilt graag de intended use van een CE-IVD kit uitbreiden. Hiervoor wordt een studie opgezet waarbij uit een geplande opname een extra buis bloed wordt afgenomen. De uitkomst van het IVD heeft invloed op de behandeling.

- Toetsing onder de IVDR? Ja
- Zo ja, welk artikel? 70.2
- Toelichting: de uitkomst van het IVD heeft invloed op de behandeling van de onderzoeksdeelnemer. Hierdoor moet de studie wel worden getoetst door een METC. Omdat het hier gaat om een IVD met een CE-markering (maar wordt gebruikt buiten de intended use) is artikel 70.2 van kracht. IVDR artikel 70.2 geeft aan dat de IVDR artikelen 58 tot en met 77 van toepassing zijn op de studie. Omdat de uitkomst van invloed is op de behandeling is artikel 58.1b van kracht.

Casus 18
Een laboratorium (in het ziekenhuis) wilt graag de intended use van een CE-IVD kit uitbreiden. Hiervoor wordt een studie opgezet waarbij uit een geplande opname een grote hoeveelheid bloed wordt afgenomen. De uitkomst van het IVD heeft geen invloed op de behandeling.

- Toetsing onder de IVDR? wellicht
- Zo ja, welk artikel? mogelijk 70.2
- Toelichting: Omdat het hier gaat om een IVD met een CE-markering (maar wordt gebruikt buiten de intended use) is artikel 70.2 van kracht. IVDR artikel 70.2 geeft aan dat de IVDR artikelen 58 tot en met 77 van toepassing zijn op de studie.

  Een extra afname uit een geplande afname voor standaardzorg wordt niet gezien als chirurgisch invasieve handeling onder de IVDR. Hierdoor valt de studie niet onder IVDR artikel 58.1a. Echter de hoeveelheid bloed die wordt afgenomen kan in bepaalde gevallen wel een risico vormen voor de (kwetsbare) onderzoeksdeelnemer. In dat geval kan IVDR artikel 58.1c van toepassing zijn en moet de studie door een METC worden getoetst. Dit is een afweging die door de sponsor gemaakt moet worden eventueel in overleg met de METC. De studie moet sowieso wel voldoen aan IVDR artikel 56 en 57.