MDCG 2025-5

Questions & Answers regarding performance studies of in vitro diagnostic medical devices under regulation (EU) 2017/746

June 2025

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Abbreviations

CE	CE marking
CPSP	Clinical Performance Study Plan
CTR	Clinical Trial Regulation – Regulation (EU) 536/2014 on clinical trials for medicinal products for human use
EU	European Union
EUDAMED	European Database on Medical Devices
GSPR	General Safety and Performance Requirements
IFU	Instructions for Use
ISO	The International Organization for Standardization
IVD	In Vitro Diagnostic Medical Device
IVDD	In Vitro Diagnostic Medical Device Directive – EU Directive 98/79/EC
IVDR	In Vitro Diagnostic Medical Devices Regulation – Regulation (EU) 2017/746 on in vitro diagnostic medical devices
MDR	Medical Devices Regulation – Regulation (EU) 2017/745 on medical devices
PMPF	Post-Market Performance Follow-up
RUO	Research Use Only
SAE	Serious Adverse Events

Introduction

This document is intended for sponsors of performance studies of in vitro diagnostic medical devices (IVDs) conducted within the scope of the Regulation (EU) 2017/746 (IVDR). It also contains information of relevance to manufacturers providing IVDs for use in performance studies that may be sponsored by other actors, and sponsors of combined studies[1].

Throughout this document, the term 'in vitro diagnostic medical device' (IVD) is used with the same meaning as in Article 2(2) of the IVDR, i.e., *in vitro* diagnostic medical devices and accessories for *in vitro* diagnostic medical devices.

Note that the IVDR regulates in vitro diagnostic medical devices, and also applies to performance studies concerning such devices and accessories conducted in the union. The IVDR does not regulate clinical or laboratory methods describing, e.g., workflows or operating procedures of a device in the laboratory. Thus, the scope of performance studies is device performance.

Further, the term “performance study” is used throughout with same meaning as in the Article 2(42) of the IVDR, where it is defined as “a study undertaken to establish or confirm the analytical or clinical performance of a device”.

Further, the sponsor needs to be aware that the IVDR does not specify details about ethics review of performance studies. It is thus necessary to check national requirements in relation to submission to the ethics committee and where possible make sure that the ethics committees and competent authorities have access to the same versions of updated documents.

This guidance document is not exhaustive, and cannot be used as the only source of information. Additional legal requirements, standards and guidance documents which are relevant to IVDs and performance studies also need to be taken into consideration. This document may be supplemented in due course with further questions and answers.

[1] Combined studies can be understood as studies that involve the simultaneous investigation of a medicinal product, an IVD and/or medical device which are subject to the requirements of the clinical trial regulation (CTR), the IVDR and/or the medical devices regulation (MDR). A combined study may also involve more than one medicinal product or more than one medical device/IVD. Examples of combined studies are a clinical trial of a medicinal product in parallel with a performance study of an IVD, or a clinical trial of a medicinal product in parallel with a clinical investigation of a medical device.

General

1. What is a performance study according to the IVDR?

A performance study is a study that falls within the definition of a performance study according to Article 2(42) of the IVDR. The article defines a performance study as a study undertaken to establish or confirm the analytical or clinical performance of an IVD.

All performance studies should have endpoint(s)[2] which establish or confirm the analytical and/or clinical performance of the device. The IVDR does not regulate clinical or laboratory methods, e.g., describing workflows or operating procedures of a device in the laboratory. Thus, a performance study should generate performance data for a device.

Performance studies of a device may not always require fresh specimens from human subjects, e.g., the source of data may be a curated database, registry or previously collected patient data or material. Contrived (artificial sample) may also be used for some performance studies.

2. What are analytical performance studies?

Analytical performance studies establish or confirm the ability of an IVD to detect or measure a particular analyte[3]. 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[4]. Data generated by analytical performance studies are necessary to demonstrate compliance with the relevant general safety and performance requirements (GSPR) in Annex I of the IVDR with respect to analytical performance.

3. What are clinical performance studies?

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[5]. 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[6].

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

[2] Endpoints (outcome measures) mean the specific response parameters that are defined and used to measure and evaluate the study objective.
[3] Article 2(40) and Article 2(42) IVDR and sections 3.3 and 3.4 EN ISO 20916:2024.
[4] Section 9(1)(a) Annex I IVDR.
[5] Article 2(41) and Article 2(42) IVDR and sections 3.10 and 3.11 EN ISO 20916:2024.
[6] Section 9(1)(b) Annex I IVDR.

and/or previous experience gained by routine diagnostic testing. This information is used to demonstrate compliance with the relevant GSPR 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[7].

4. Is it always required to perform both analytical and clinical performance studies?

As a general rule, analytical performance must always be demonstrated on the basis of analytical performance studies[8].

Demonstration of the clinical performance of a device must be based on one or a combination of the following sources:
— clinical performance studies;
— scientific peer-reviewed literature;
— published experience gained by routine diagnostic testing.

Clinical performance studies must be performed unless due justification is provided for relying on other sources of clinical performance data[9].

MDCG 2022-2 provides guidance on general principles of clinical evidence for IVDs.

5. Which performance studies are regulated by the IVDR?

The IVDR regulates all studies which fulfil the definition of "performance study" as defined by the regulation, regardless of who is performing the activities, i.e., regardless of who the sponsor[10] is. All performance studies are regulated by Article 57 of the IVDR. Article 57 identifies general requirements with regards to

- The device for performance study complying with the GSPR set out in Annex I of the IVDR, 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 patient, user and other persons.
- The circumstances for performing performance studies.
- Protection of subjects.
- The data generated.
- Data protection.

[7] Section 2.1 Part A, Annex XIII IVDR.
[8] Section 1.2.2 Annex XIII IVDR.
[9] Article 56 and Section 1.2.3 Annex XIII IVDR.
[10] '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 (Article 2(57) IVDR).

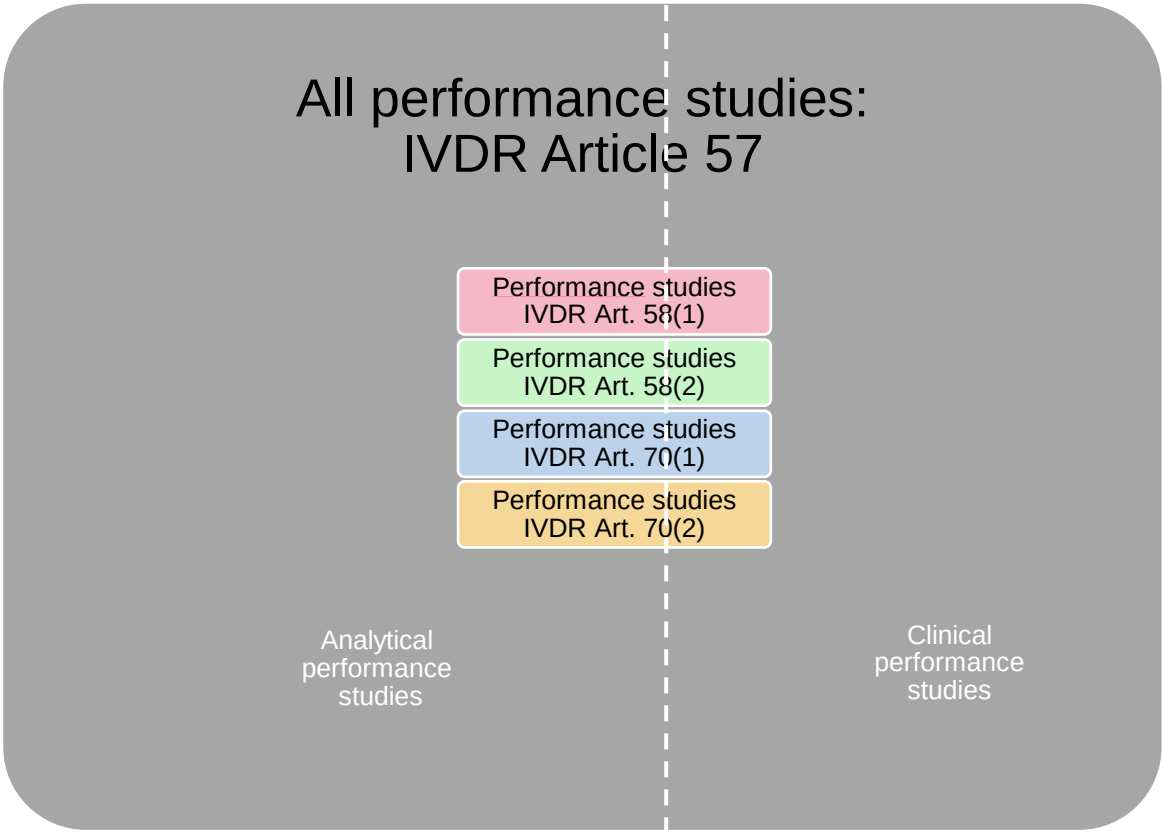


Figure 1. Performance studies regulated by the IVDR.

Both analytical and clinical performance studies are subject to the requirements of Article 57 in the IVDR. Additional requirements apply to certain performance studies according to Article 58(1), Article 58(2), Article 70(1) and Article 70(2) in the IVDR.

Note that there are performance studies covered by Article 57 (the larger box) which are not subject to any of the requirements in Articles 58(1-2) or 70(1-2) (each symbolized by the smaller boxes)

If there is additional risk for subjects introduced by the performance study, the study would either fall under Article 58(1), Article 58(2) for non-CE marked products or under Article 70 for CE marked products. More details on which performance studies are governed by these articles are provided in figure 2.

Further, it should be noted that unlike the MDR, the IVDR does not distinguish between studies conducted for conformity assessment purposes and other studies[11].

[11] In Article 62(1) of the MDR, there is a reference made to conformity assessment, but there is no similar wording in the IVDR.

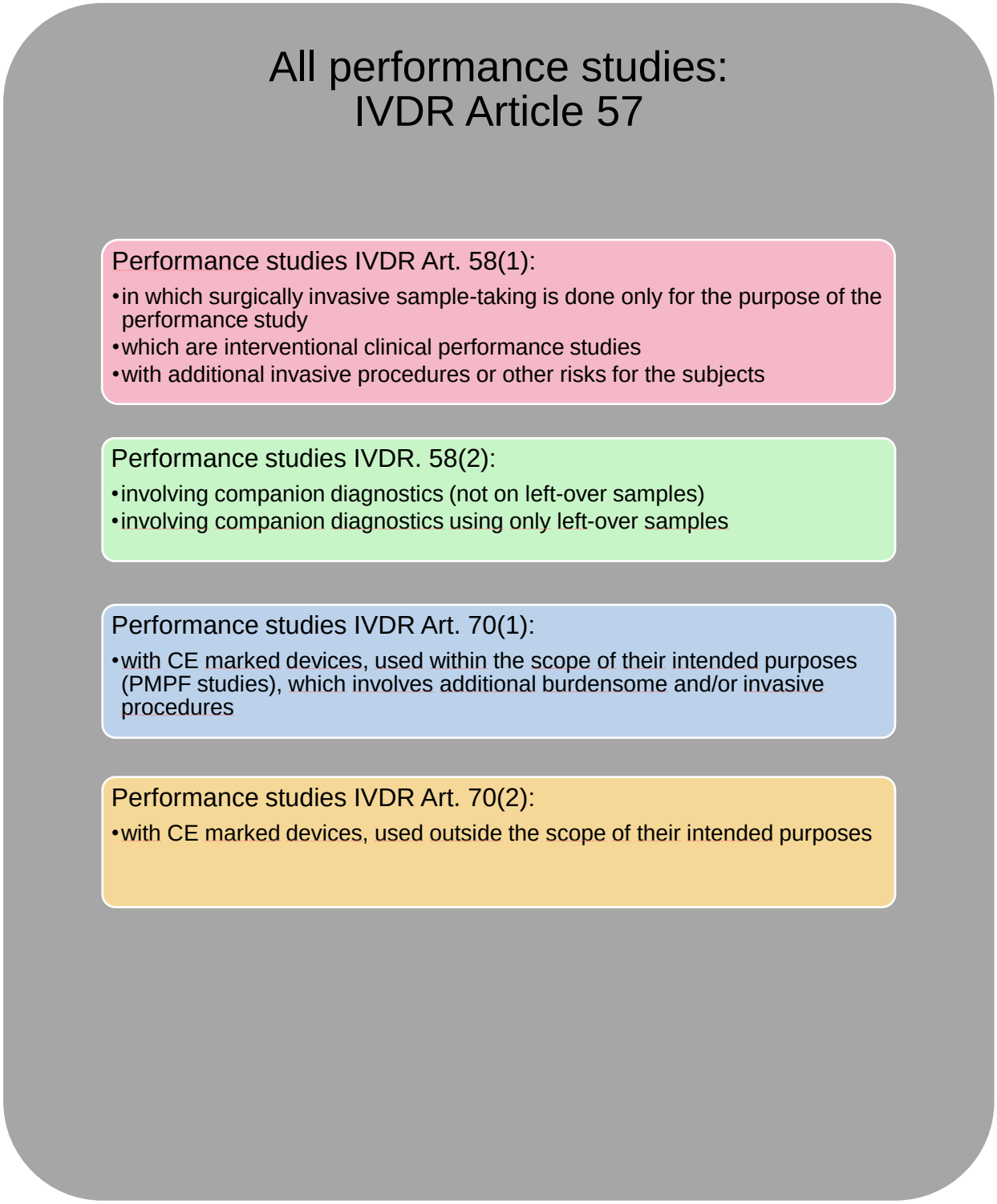


Figure 2. Detail of figure 1 with explanatory text about the types of performance studies that are governed by the different articles.

Note that a performance study can be covered by several of the articles, they are not mutually exclusive.

A decision tree to determine the applicable regulatory pathway for a performance study is available in Appendix I: Performance studies under the IVDR – regulatory pathways

6. At what stage does an assay become an IVD, in the sense that IVDR provisions must be considered for performance studies?

A product is considered an IVD when the manufacturer assigns an intended purpose to a product that fulfils the definition of an IVD according to Article 2(2) of the IVDR. An assay should be understood as a testing method, and some of the products used in an assay may be IVDs. Where a sponsor[10] assigns a medical purpose to a product in a way that fulfils the definition of an IVD according to Article 2 of the IVDR, the sponsor may assume the role of a manufacturer under the IVDR. Refer also to Q7.

7. Who is responsible for assigning the "intended purpose" of the IVD?

The intended purpose of an IVD is determined by the manufacturer[12] of the device, in accordance with the requirements laid out in the IVDR.

Where a sponsor assigns a medical purpose to a product in a way that fulfils the definition of an IVD according to Article 2(2) of the IVDR, the sponsor may assume the role of a manufacturer under the IVDR. If a new intended purpose is assigned to an existing IVD, e.g., in the context of a clinical study[13], it might be necessary to use it as a device for performance study, and for the sponsor to assume the role as responsible for the manufacture of the device for performance study per section 4.1 in chapter I, Annex XIV of the IVDR.

8. At what stage of device development do the performance study requirements apply to a study of an IVD?

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 the clinical performance is being investigated, are not to be considered performance studies. Studies for validation of the design are considered as performance studies where they seek to establish or confirm analytical or clinical performance.

9. Do performance studies for IVDs manufactured and used only within health institutions established in the Union need to be conducted according to the IVDR performance study requirements?

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 GSPR set out in Annex I of the IVDR.

[12] Article 2(23) IVDR.
[13] Clinical trial, clinical investigation, performance study or other clinical study.

Data that needs to be collected for demonstration of GSPR compliance has to be collected before an IVD qualifies as an in-house device[14]. 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:

- 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, 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 Article 58 do not apply.

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

10. Could “research use only” (RUO) products be used in performance studies?

They could be. The scope of the IVDR is clearly delimited from other products, such as medical devices, general laboratory products and RUO products. 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 a RUO product. It consequently becomes regulated under the IVDR. Where a sponsor[10] (or another party) does assign such an in vitro diagnostic medical purpose to what was initially a RUO product, the

[14] In some cases, it might be possible to justify in the declaration described in Article 5(5)(f)(iii) of the IVDR that not all GSPR can be met, e.g., in situations where individual patient needs can be met at an adequate level without a preceding performance study.

sponsor (or the other party) needs to assume the role of a manufacturer[15] 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 only for research purposes (no medical purpose as defined by the IVDR in Article 2(2)) 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 planned performance study. The product is no longer a RUO product. It is in scope of the IVDR and relevant IVDR requirements apply to it (i.e., requirements for performance study, conformity assessment and CE marking or in-house manufacturing).

11. Who can be the investigator of a performance study?

According to Article 2(48) of the IVDR, an 'investigator' means an individual responsible for the conduct of a performance study at a performance study site.

In a performance study, there may be separate specimen collection sites and separate analysis sites (refer to Q20). All sites need to have a responsible investigator in accordance with Article 2(48) of the IVDR.

According to the IVDR, the investigator must be a person exercising a profession which is recognised in the Member State concerned, as qualifying for the role of investigator on account of having the necessary scientific knowledge and experience in patient care or laboratory medicine.

12. Who is the investigator of the performance study in combined studies?

If a combined study[1] is conducted at a site, the sponsor can either appoint separate investigators for the performance study and the clinical trial/clinical investigation or appoint the same investigator for both the performance study and the clinical trial/clinical

[15] Either as manufacturer per the definition in Article 2(23) of the IVDR, with the obligations outlined in Article 10 and Article 57(1) of the IVDR, or as the natural or legal person responsible for the manufacture of the device for performance study per section 4.1 in chapter I Annex XIV of the IVDR, stating that the that the device in question conforms to the GSPR laid down in Annex I of the IVDR 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, user and other persons.

investigation. The appointed investigator would need to have the necessary qualifications as specified by the respective legislation[16].

13. What are the safety reporting requirements for performance studies?

Safety reporting requirements are described in the guidance document MDCG 2024-4, which includes a safety reporting form MDCG 2024-4 Appendix.

14. Should ongoing performance studies that commenced under EU Directive (98/79/EC) (IVDD) be resubmitted under the IVDR?

No. The IVDR requirements with regard to authorisation or notification of performance studies do not apply to performance studies that have been approved or have started before 26 May 2022. However, any serious adverse event (SAE) or device deficiencies[17] that may lead to a SAE occurring in a performance study after 26 May 2022, regardless of when the performance study started, should be reported in accordance with Article 76 of the IVDR.

Note that national requirements may apply to performance studies that commenced under the IVDD.

Requirements to apply for/notify performance studies

15. Do all performance studies need to be submitted to the competent authority?

No. According to the IVDR, performance studies that are in scope of Article 58(1), Article 58(2) or Article 70 need to be submitted (application or notification) to the competent authority. For an overview of when an application or a notification is needed, consult Appendix I: Performance studies under the IVDR – regulatory pathways. Additional details and support are provided in the questions below.

Note: It might be necessary to consider additional national legislation applicable to performance studies.

16. Which performance studies require an application to the competent authority according to the IVDR?

The IVDR states that an application is required if the performance study:

- Involves surgically invasive sample-taking which is done only for the purpose of the performance study[18].

[16] For clinical trials of medicinal products, Article 49 of the CTR outlines investigator qualifications, and for clinical investigations of medical devices, the investigator qualifications are outlined in Article 62(6) of the MDR. Note that there may be additional national legislation regarding investigator qualifications, both in relation to the IVDR, the CTR and the MDR.
[17] Article 2(62) IVDR.
[18] Article 58(1)(a) IVDR.

- Is an interventional study of clinical performance[19], which in the IVDR means that the test results may influence patient management decisions and/or may be used to guide treatment. Note that the term interventional study has a different meaning in the context of clinical trial legislation for medicinal products. Further note that specimens used in interventional studies cannot be considered as left-over samples (as they will have clinical relevance for the performance study subjects). Refer further to Q30 on left-over samples.
- Involves additional invasive procedures or other risks for the study subjects, even if these are not related to the sample collection[20].
- Involves companion diagnostics[21] but not using left-over samples only[22].

17. Which performance studies require a notification to the competent authority according to the IVDR?

The IVDR states that a notification is required in the following cases:

- Performance studies involving companion diagnostics[21] using left-over samples[22] only. See Q30 for more explanations on what can be considered a left-over sample.
- Performance studies with CE marked IVDs conducted within the scope of their intended purpose, and where the performance study would involve submitting subjects to procedures additional to those performed under the normal conditions of use of the devices and those additional procedures are invasive or burdensome (refer to Q32)[23].

Further, national requirements may apply regarding notifications of performance studies. Please check the national legal basis or the information published by the competent authority.

18. Is a comparison of CE marked IVDs a performance study that requires notification or application for authorisation to the competent authority?

If the comparison fulfils the criteria of a performance study (as per the definition in Article 2(42) of the IVDR), a notification may be required depending on the study characteristics.

Article 70(1) specifies that a notification is required for a performance study conducted with a CE marked device within the scope of its intended purpose (PMPF study) and where such study would involve submitting subjects to procedures additional to those performed under normal conditions of use of the device and those additional procedures are invasive or burdensome.

[19] Articles 58(1)(b) and 2(46) IVDR.
[20] Article 58(1)(c) IVDR.
[21] Article 2(7) IVDR.
[22] Article 58(2) IVDR.
[23] Article 70(1) IVDR.

Each performance study with CE marked IVDs will have to be assessed by the sponsor in order to determine if the performance study fulfils the condition for a notification according to Article 70(1) of the IVDR. In this process, the wording related to study characteristics present in Article 70(1) needs to be checked. The decision tree in Appendix I of this document can be consulted for guidance.
Note that if a performance study is conducted to assess a CE marked device outside the scope of its intended purpose, then Articles 58-77 apply[24].

19. Do performance studies initiated by researchers within academia require notification/application to the competent authority?

The same requirements for application/notification apply, regardless of sponsor identity.

20. In IVD performance studies, specimen collection and specimen analysis may occur in different Member States. Given this context, which Member States are considered concerned and need to receive an application, when the wording in Article 66 of the IVDR states "submit an application to the Member State(s) in which the performance study is to be conducted"?

In a performance study, both locations where specimens are collected and locations where specimens are analysed are considered investigational sites[25]. The performance study is considered to be "conducted" at both types of sites. The applicability of performance study requirements should be assessed for both types of sites.

For example, Article 57 applies to all sites including both specimen collection and specimen analysis sites. However, the criteria for performance studies to which additional requirements apply[26], that are listed in Article 58(1) all relate to the study subjects and Article 66 is therefore applicable only to sites where specimen collection is performed.

Therefore, an application for authorisation of a performance study should be submitted for all Member States where subjects are included. In contrast, an application is not necessary for Member States where only analysis sites are located but no specimens are collected from study subjects.

The same reasoning can be applied to the notification of performance studies falling under Article 70(1) of the IVDR.

21. What kind of studies are meant in Annex XIII part A - 3. "Other performance studies"? Is any application/notification to the competent authority required?

The header of section 2 in part A of Annex XIII of the IVDR refers to clinical performance studies and thus section 3 "Other performance studies" should be understood as relevant

[24] Article 70(2) IVDR.
[25] Section 3.25 EN ISO 20916:2024.
[26] The performance studies meeting any of the criteria listed in in point (a), (b) or (c) in Article 58(1) of the IVDR shall, addition to meeting the requirements set out in Article 57 and Annex XIII, be designed, authorised, conducted, recorded and reported in accordance with Article 58 and Articles 59 to 77 and Annex XIV of the IVDR.

for non-clinical performance studies such as analytical performance studies. Note that the provisions in Article 58(1), Article 58(2) and Article 70 in the IVDR do not differentiate between analytical and clinical performance studies. Thus, these Articles and the flow-chart in Appendix I: Performance studies under the IVDR – regulatory pathways, should be consulted to determine whether an application or notification of the performance study is required.

22. If a specimen collected in an EU Member State for a performance study is sent outside the EU for analysis, what are the requirements on the IVD used for the analysis?

In addition to possible local provisions outside EU, the IVD for the performance study 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.

Additional requirements for certain performance studies

23. 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[27] 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. Furthermore, 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"[28].

Examples of surgically invasive sampling:

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

[27] Section 2.2 chap. I Annex VIII EU Regulation 2017/745.
[28] According to section 2.2 chap. I Annex VIII EU Regulation 2017/745.

24. 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 **not** 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[29] 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) point (b) or point (c).

25. With reference to Article 66(7), what factors need to be considered when deciding whether sample-taking could represent a major clinical risk to the study subject?

What could be considered a major clinical risk depends on the situation. Factors that need to be considered are, e.g., the study population and the clinical status of the subjects, as well as the number, volume and type of collected samples. Sponsors are encouraged to document their assessments and justification about clinical risk in the application.

[29] e.g., a risk assessment of the volume of blood to be collected from an individual subject vs the subject's sensitivity to reduction in blood volume will have to be made. Sponsors are encouraged to document their assessments and justification of why a performance study does not fulfil any of the criteria in Article 58(1).

26. 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[30].

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.

27. 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 (see also Q32).

28. With reference to Article 58(2), what are "performance studies involving companion diagnostics"?

Article 58(2) applies to performance studies conducted with a device which has been assigned an intended purpose as a companion diagnostic in line with the definition in Article 2(7)[31] of the IVDR.

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.

This means that an application is required[32], unless the performance study uses only left-over samples and where the results are not used for interventional purposes, in which case a notification is required to the competent authority.

30 Article 2(46) IVDR.

31 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.

32 "in addition to meeting the requirements set out in Article 57 and Annex XIII, be designed, authorised, conducted, recorded and reported in accordance with this Article and Articles 59 to 77 and Annex XIV".

For help in determining whether an IVD is considered a companion diagnostic, please refer to Annex II of the MDCG 2020-16 rev.3 guidance on classification.

29. Are all performance studies involving companion diagnostics considered to be interventional clinical performance studies?

No. Examples of performance studies with companion diagnostic devices that are not considered interventional clinical performance studies are:

- analytical performance studies;
- clinical performance studies where, during the study, the results are not used to influence patient management decisions and are not used to guide treatment.

For definition of an interventional clinical performance study, refer to Q26.

30. What is the definition of left-over samples?

This term should be understood as unadulterated remnants of human derived specimens[33] 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[34].

Left-over samples can include specimen or sample[35] that are collected in the past and obtained from repositories (e.g., tissue banks, commercial vendor collections)[36].

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.

31. What are the submission requirements when only left-over samples are used for a performance study?

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 (refer to Q30).

A notification is required due to Article 58(2) of the IVDR for performance studies of companion diagnostics using left-over samples only.

When left-over samples are used for non-companion diagnostic performance studies, there might be situations[37] where Article 58(1) point (c) of the IVDR applies. If the study

[33] Section 3.47, EN ISO 20916:2024: "Specimen" - discrete portion of a body fluid or tissue taken for examination, study, or analysis of one or more quantities or characteristics to determine the character of the whole.
[34] Section 3.25, EN ISO 20916:2024.
[35] Section 3.42, EN ISO 20916:2024:" Sample" – one or more representative parts taken from a specimen, which are intended to provide information.
[36] Section 3.6, EN ISO 20916:2024.
[37] Examples could be performance studies where the subjects are exposed to other risks due to additional examinations that are part of the performance study (Article 58(1)(c)).

fulfils point (c) in Article 58(1), an application must be submitted to the competent authority.

Further, a notification per Article 70(1) of the IVDR is required when left-over samples are used for performance studies conducted to further assess, within the scope of its intended purpose, a CE marked device where the study involves exposing subjects to additional procedures which are burdensome or invasive.

Appendix I of this guidance can be consulted for an overview of regulatory pathways.

Note that when left-over samples are used for performance studies, Article 57 applies, including the need to follow applicable legislation on data protection, and that national requirements for ethics submission needs to be checked.

32. With reference to Article 70(1), what does burdensome mean?

Additional procedures which are burdensome can include a wide variety of different interventions. This may include procedures which may cause pain, discomfort, fear, potential risks or complications/side-effects, disturbances of lives and personal activities, or otherwise unpleasant experiences. It is mostly determined from the perspective of the person bearing the burden.

The understanding of what is considered to be burdensome is expected to develop over time. Sponsors are encouraged to document their assessment whether the additional procedures imposed by the clinical performance study plan (CPSP) are considered burdensome, and where appropriate, contact the relevant authority or ethics committee in the Member State(s) to discuss cases where the sponsor is uncertain.

33. Article 70(1) and Article 70(2) of the IVDR refer to CE marked devices. Does this include IVDs that have been CE marked according to the IVD Directive?

Yes. The provisions in Article 70(1) and Article 70(2) can be applied to IVDs that are CE marked either in accordance with the IVDD[38] or in accordance with the IVDR.

34. Are Article 58(1) and Article 58(2) applicable to performance studies with CE marked IVDs used within the scope of their intended purpose?

No, Articles 58(1) and 58(2) are only applicable for non-CE marked IVDs or CE marked IVDs used outside their intended purposes. Performance studies of IVDs conducted *within* the scope of its intended purpose are regulated by Article 70(1) and can fulfil the condition for notification[39]. These performance studies do not have to comply with the other obligations of 'additional requirements for certain performance studies' in Article 58

[38] Provided that "legacy devices" (devices previously CE marked under the IVDD) are duly placed on the market in compliance with the transitional provisions.
[39] Where the performance study 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.

such as an authorisation. They must in any case still comply with the general requirements regarding performance studies outlined in Article 57.

Application/Notification

35. What is considered the identification number of a performance study until EUDAMED is functional?

In the absence of performance study functionalities in EUDAMED, the CIV-ID[40] (which is generated by a competent authority using the old database, Eudamed2) should be used as Union-wide single identification number[41].

Until the EUDAMED module for performance studies is functional, national identification numbers may also be used by competent authorities.

36. What documentation should be included in the application for a performance study?

According to IVDR Article 66(1), each performance study application must be accompanied by the documentation referred to in Sections 2[42] and 3 of Annex XIII and in Annex XIV.

The guidance MDCG 2022-19 on performance study application/notification documents contains a series of performance study application/notification documents which have been created to support performance study procedures with respect to the IVDR. In addition, it is necessary to check the website of the relevant competent authority in the Member State where the performance study is to be conducted, for national requirements regarding the application content.

For the content of some of the required documents, additional guidance can be found in the annexes of the ISO 20916:2024.

Additional, supporting documents may be provided in order to show compliance with applicable requirements and to provide sufficient information on the proposed study and device(s) for performance study for the assessors to make a decision.

37. Does the performance evaluation plan need to be included in the application for a performance study?

No. The IVDR does not require the performance evaluation plan (PEP) to be included in the application. However, the PEP provides a useful overview of product development and how the current performance study contributes to collection of analytical and/or clinical evidence. The PEP shall be provided to the competent authority upon request.

[40] Sometimes referred to as PS-ID for performance studies.
[41] MDCG 2022-12– Guidance on harmonised administrative practices and alternative technical solutions until Eudamed is fully functional (for Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices).
[42] I.e., performance study plan as specified in section 2.3.2 Annex XIII IVDR.

38. What documentation should be included in the notification of a companion diagnostic performance study using only left-over samples (IVDR Article 58(2))?

As the IVDR does not specify any details on the notification required per Article 58(2), it is necessary for the sponsor to check with national competent authorities what documentation should be included.

39. Does the data used to support the compliance to the GSPR for the purpose of the performance study need to be the same information as the data included in the technical documentation as described in Annex II of the IVDR (for conformity assessment)?

No, full technical documentation is not required; however, compliance with the GSPR in Annex I of the IVDR must be documented to a level appropriate for the planned use in the performance study[43].

The full data/underlying reports demonstrating compliance to the relevant GSPR should be available to the competent authority upon request[44].

The data/underlying reports are the basis for the manufacturer to sign the statement of conformity for performance study, where the manufacturer signs the statement that the GSPR are fulfilled, apart from the aspects which are part of the performance study[45].

The documentation should provide an overview of which of the GSPR that are applicable, which have already been addressed by objective evidence and which ones will be addressed by the proposed study.

40. What is expected regarding the requirement to list the technical and functional features of the device, indicating those that are covered by the performance study?

To fulfil the requirement to present this information in the CPSP[46], a tabular presentation of the relevant product characteristics of the device for performance study is expected with an indication of the associated product specifications and assignment of the expected clinical outcome.

It should be stated whether each characteristic relates to the safety or the performance of the device. The expected clinical performance outcomes should be specified according to the performance study endpoints.

[43] An example where less data is needed could be a situation where an IVD is only used/stored/shipped within certain temperature limits during the performance study. In that case, it would not be necessary to have data supporting stability of reagents outside these temperatures.
[44] Section 4(6), chapter I Annex XIV of the IVDR.
[45] Section 4(1), chapter I Annex XIV of the IVDR.
[46] Section 2.3.2(aa), Annex XIII of the IVDR.

41. Is it possible to have more than one device for performance study within one performance study?

Yes, 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[47] 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[48] all of 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.

42. For a performance study that requires application or notification (according to Articles 58(1-2) or Article 70) and where collection and analysis of specimens are performed in different countries, what are the submission requirements to the competent authority?

An application or notification is required for

- all Members States where subjects are included
- all Member States part of a performance study involving companion diagnostics using only left-over samples (notification according to Art. 58(2) regardless of whether the samples are sourced from an EU Member State or a non-EU country

In all other cases an application or notification under the IVDR is not required.

43. Is translation of the instructions for use needed into the languages of all Member States from which patients will be enrolled, when no analysis is occurring in those Member States?

Translation requirements for Instructions for Use (IFU) are governed by national legislation and should be confirmed with each Member State involved. While national regulatory requirements may vary, ensuring that the IFU is comprehensible to all users involved in the study is crucial, particularly for handling, pre-analytical, and operational steps aligned with the CPSP. This may imply that translations are necessary for Member States where sample collection occurs to ensure understanding among local site staff, even if analysis is conducted elsewhere. In such cases, a partial translation of the relevant sections of the IFU could be a viable option. Verification with each Member State's regulations is recommended to confirm whether full or partial translation of the IFU is required. Regardless of national regulatory requirements, comprehension of the manufacturer's IFU is one of the important aspects of the performance studies and the

[47] MDCG 2022-19.

[48] The documentation for several devices could in some cases be combined, while some documents are more suitable to provide separately per device; e.g., one investigator's brochure issued by the sponsor covering two devices used together with sufficient details on each device, while the statement of conformity may be two separate documents, one for each device and signed by the relevant party assuming responsibility for that particular device.

IVD medical device under investigation shall be used according to the CPSP and the IFU. This concerns also preanalytical phase and pre-handling of the samples. Therefore, the investigator's brochure shall contain manufacturer's instructions for installation, maintenance, maintaining hygiene standards and for use, including storage and handling requirements, as well as, to the extent that such information is available, information to be placed on the label, and IFU to be provided with the device when placed on the market. In addition, the investigator's brochure shall contain information relating to any relevant training required.[49]

The IFU may be divided over several sections, each describing a few steps of the procedure in which the device(s) is intended to be used. The section(s) describing how to correctly obtain, prepare and store specimens so that they will be suitable for the intended analysis are especially important for the sampling sites and the information must be suited for their needs.

Note that for performance studies with devices for self-testing or near-patient testing, the information supplied to the user should be easily understandable and provided in the official Union language(s) determined by the Member State in which the device is made available to the user or patient. Validation of the comprehensiveness and usability of the manufacturer's IFU is one of the important aspects of these studies.

Timeline considerations for performance studies

44. In case different Member States are involved in specimen collection and in performing the analysis, when can the performance study start?

The study can only start in a Member State when at least one of the collection sites within that Member State has the relevant authorisations[50] in place. Further, to ensure that subjects are not unduly exposed to risks related to specimen collection, the sponsor has to ensure that the analysis site is ready.

45. Which date is considered as the start date of a performance study?

In general, the start date is considered to be the first act of recruitment in the performance study in a Member State. The first act of recruitment should be specified by the sponsor and could be, for example, the date of initiation of the performance study in the first site or the date when the first study-specific advertisement is published. In any case, the performance study cannot start earlier than the authorisation date (or commencement date notified for PMPF studies and performance studies involving companion diagnostics using only left-over samples) or not later than the date recruitment starts. The start date of a performance study should be described in the performance study plan. For performance studies using only left-over samples, the start date could correspond to the date of the analysis of the first sample.

[49] Section 2.2 of chapter I in Annex XIV of the IVDR.
[50] Including ethical review not resulting in a negative opinion (Article 58(3) and Article 58(5)(b)).

46. Does the performance study notification need to be "authorised" or "acknowledged" by the competent authority prior to study start?

Notifications referred to in Article 58(2) and Article 70(1) are not required by the IVDR to be authorised by the Member States prior to study start. Rather, acknowledgement of receipt by the competent authority is sufficient but not necessary (check national requirements) to proceed, provided that the 30-day timeline applicable to Article 70(1) is respected. This is in contrast with an application for performance study under Article 66 where an explicit authorisation from the Member State is to be given.

Note that for performance studies conducted under Article 70(1) of the IVDR, points (b) to (l) and point (p) of Article 58(5) applies, which includes an ethical review by an ethics committee.

Substantial Modifications

47. How is a substantial modification defined?

A substantial modification of a performance study is a change to the performance study that is likely to have a substantial impact on the safety, health or rights of the subject, or on the robustness or reliability of data generated by the study. Modifications of the IVD or the performance study plan, investigator's brochure, the subject information sheet and other performance study documentation may or may not be considered as substantial modifications depending on whether or not they fulfil the above definition.

Sponsors should also take into consideration the fact that some modifications may impact the design or scientific outcome of the performance study to such an extent that this may require the initiation of a new performance study.

The procedure to notify a substantial modification is further described in Article 71 of the IVDR. A non-exhaustive list of modifications that may be interpreted as substantial can be found in Appendix II: Non-exhaustive list of modifications that may be deemed substantial.

It is the sponsor's responsibility to determine if the modification is substantial or not. However, if the sponsor is uncertain about the impact for a particular modification of a performance study, the national competent authority may be consulted prior notification.

48. When can a sponsor submit a substantial modification notification?

A notification of a planned substantial modification may be submitted in accordance with Article 71 of the IVDR as soon as a performance study is allowed to commence in accordance with the IVDR. Moreover, it is not recommended to submit a substantial modification while assessment of an already submitted substantial modification is still ongoing. It is also important to consider whether national procedures may apply regarding modifications to performance studies.

In some situations, it may be acceptable to submit changes to submitted study documentation (with an updated version control) prior to the completion of the application or notification process. These changes would not be considered substantial modifications. Changes in this manner would need to be agreed with the relevant competent authority.

49. Is a change to the device for performance study to be considered a substantial modification to the performance study or does it lead to the submission of a new performance study application?

In general, a change to the device for performance study is a substantial modification of the performance study. As an example, a change to the device which alters the risk profile or adds new risks is likely to have a substantial impact on the safety or health or rights of the subject and, thus, is a substantial modification. Some modifications to the device for performance study are so extensive in nature that the ongoing performance study should be terminated and a new performance study should be applied for. Modifications to the device which alter the suitability of the performance study design to provide evidence for the safety, performance or clinical benefit of the device may result in refusal of the modification and the submission of a new performance study application may be required.

50. According to Article 71(1) of the IVDR, if a sponsor intends to introduce modifications to a performance study, the sponsor has to notify the Member State(s) within 'one week'. From which point in time does this 'one week' start?

The 'one week' period starts from the date when the relevant documents (such as performance study plan, investigator brochure, subject information sheet and informed consent form) are issued in an updated version.

It is acknowledged that changes to, e.g., a CPSP may require subsequent changes to other documents such as subject information, and that these changes may be done on a different date. Such changes can be collected and submitted together when the last affected document is issued but note that the implementation of substantial modifications to the performance study cannot be done until the deadline in Article 71 of the IVDR has expired or an authorisation letter is issued by the competent authority, and/or ethics committee if this is required according to national provisions.

51. Can the sponsor start to implement the substantial modification after 38 days of the notification date to the Member State?

Yes, if the sponsor has not heard from the Member State after 38 calendar days, the substantial modification may be implemented, provided that an ethics committee in that Member State has not issued a negative opinion in relation to the substantial modification. This 38-day period, which starts when all the relevant documentation with clearly identifiable changes have been submitted in their entirety, may be extended by a further 7 calendar days by the Member States in order to consult with experts. The Member States will notify the sponsor if such a consultation is taking place. The substantial

modification can be implemented sooner if the Member State has authorised the substantial modification.

If the Member State has sent a request for information, there may be, depending on national provisions, a clock-stop, as long as the Member State has not received the additional information.

Further, the sponsor needs to ensure that updated documents in relation to a substantial modification are submitted to both the competent authority and the ethics committee where required. Note that there may be national provisions in place regarding, e.g., the notification and review of substantial modifications to the ethics committees.

Once a substantial modification is authorised in a particular Member State, the change can be implemented there, even if it is not yet authorised in other Member States.

52. Is it necessary to announce substantial modifications to competent authorities of a performance study that is conducted with companion diagnostics using left-over samples only?

No. Article 58(2) states that Article 58(1) does not apply to performance studies involving companion diagnostics using only left-over samples. As Article 58(1) refers to performance studies having to meet several requirements, including those to be designed, authorised, conducted, recorded, and reported in accordance with Article 58(1) and Articles 59-77 – this does not apply to performance studies involving companion diagnostics using only left-over samples. Article 71 on 'substantial modifications to performance studies' does therefore not apply to performance studies involving companion diagnostics using only left-over samples.

53. What notification requirements apply to 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. However, in the absence of EUDAMED, Member States have not yet harmonised their approach, and it is thus necessary to check the national requirements.

54. If there is a common CTR/IVDR document (e.g., Informed Consent Form) within a combined study with modifications, must this updated document be submitted through both regulatory pathways?

Depending on the nature of the modification, it might be considered a substantial modification according to the IVDR (see Q47) and/or the CTR.

Modifications to elements of a combined study, or documentation for the combined study, that are not likely to have a substantial impact on the safety, health, or rights of the subjects, or on the robustness or reliability of the data, may not require a notification of substantial modification regarding the performance study. Examples could include:

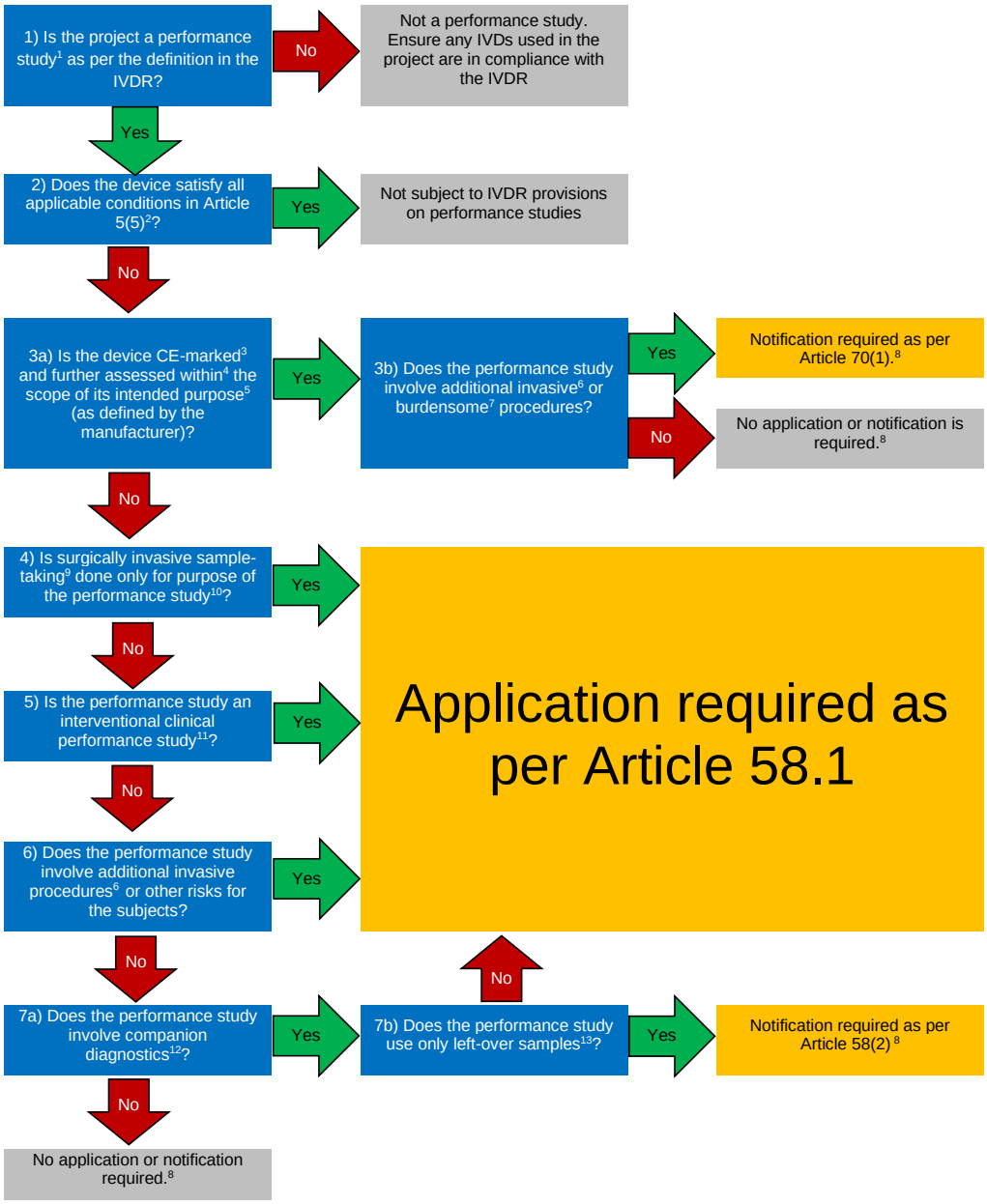
- Modifications to informed consent documents that are requested by ethics committees during review of the medicinal product clinical trial application and pertain only to explaining the risks of administration of the medicinal product.

- Modifications to the investigational medicinal product dossier or the investigator's brochure for the medicinal product that are unrelated to the performance study and to treatment decisions made on the basis of the IVD result.
- Modifications to the clinical trial protocol to add additional study visits, assessments and/or to clarify eligibility criteria, that are unrelated to the performance of the device.

If the modification is only concerning the medicinal product under investigation, and does not impact the performance study, it does not have to be notified and assessed as a substantial modification for the parallel performance study. Some Member States require that copies of updated documents for their records are provided for the performance study (regarded as non-substantial modifications).

Regarding possibilities for simplifying the process when substantial modifications are to be made according to the CTR and the IVDR in parallel by means of coordinated assessment procedures and number of ethics committees involved, there are different solutions to this applied in the Member States. The national differences are mainly related to the organisation at competent authority level and how the Member State has set up the ethics committees in relation to the medicinal product and device legislations.

Appendix I: Performance studies under the IVDR – regulatory pathways



[1] At the starting point of this decision tree it is already assumed that the device in question qualifies as an IVD (per the definition in article 2(2) of the IVDR), when used as planned in the project. 'Performance study' means a study undertaken to establish or confirm the analytical or clinical performance of a device (Article 2(42) of the IVDR).
[2] For performance studies of so called "in house" IVD, refer to Q9
[3] CE-marked according to EU directive 98/79/EC (IVDD) or EU regulation 2017/746.
[4] If further assessed outside the intended purpose, the answer to this question is "No"
[5] For guidance on the responsibility of assigning intended purpose, refer to Q7.
[6] For guidance on invasive procedures, refer to Q27
[7] For guidance on burdensome procedures, refer to Q32
[8] General requirements in Article 57 apply.
[9] For guidance on "surgically invasive sample-taking", refer to Q23.
[10] For guidance on "only for the purpose of the performance study", refer to Q24.
[11] '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 (Article 2(46) of the IVDR). Refer to Q26.
[12] For guidance on performance studies with companion diagnostics, please refer to Q28.
[13] For guidance on left-over samples, refer to Q30.

Appendix II: Non-exhaustive list of modifications that may be deemed substantial.

Modifications related to the performance study plan or subject information

1. Change to/addition of a primary or secondary endpoint;
2. Use of a new mode of measurement for the primary endpoint;
3. A change of performance study design which is likely to have a significant impact on the statistical analysis or the benefit/risk assessment;
4. A change in the definition of the end of the performance study;
5. A modification of the duration of the study and/or the follow up of subjects;
6. A modification of the sample taking and their preparation. E.g., method (whole blood/ serum/ plasma/ finger pricking, other tube additive, fixing solution, storage conditions, etc.);
7. Changes in the number of scheduled subject visits;
8. Change of a diagnostic or other assessment procedure which is likely to have a significant impact on the safety of the subject or the scientific value of the clinical data collected in the performance study;
9. Changes to the data monitoring committee which may affect, for example, the safety evaluation, or the independence and impartiality of the committee;
10. Amending the number of subjects to be included in the performance study, either due to an adaptation of the sample size calculation or to maintain a previously defined sample size calculation due to an increased unanticipated dropout rate;
11. Addition of an interim analysis not planned in the initial performance study plan;
12. Deletion of an interim analysis;
13. Content change in the subject information sheet and informed consent forms, or other information provided to the subject;
14. Change of inclusion or exclusion criteria if these changes are likely to have a significant impact on the safety of the subject or scientific value of the clinical data collected in the performance study.

Modifications related to the benefit/risk of the performance study

15. New technical or clinical data which is likely to impact on the benefit/risk assessment;
16. The revocation or suspension of the conformity assessment certificate or another certificate related to the devices used as calibrator or control of clinical performance or performance characteristics of the device for performance study.

Modifications related to the use of the device for performance study or the device itself

17. Change of testing modalities (modification of procedure, techniques, or instructions for use) of the device for performance study;
18. The type and/or duration of the investigator's training;
19. Changes to the device’s labeling or IFU;

20. Changes to the device's intended purpose;
21. Changes to the risk management plan likely to impact on the benefit/risk of the performance study;
22. Changes to the device's software or firmware.

Modifications of other information

23. Change of sponsor or the sponsor's legal representative;
24. Change/addition of a clinical investigation site;
25. Change of manufacturer;
26. New insurance policy[51];
27. Change in compensation paid to subjects and/or investigators/site;
28. Change/addition of new investigator(s).

Modifications related to the manufacturing process

29. Modification of the manufacturing site, process of manufacturing including change in supply chain (e.g., antibodies, material of human or animal origin suppliers or their sources, etc.). raw materials, reagent formulation, materials and coating of storage containers (such as tubes, plates and vials), production volume, sterilisation method, sterilisation or packaging.

[51] Renewal of an insurance certificate is considered a non-substantial modification, while a new insurance certificate with new policies and/or conditions is considered a substantial modification.