HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to
Performance Studies Conducted in Ireland

AUT-G0176-2
15 June 2022
This guide does not purport to be an interpretation of law and/or regulations and is for guidance purposes only.

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1 SCOPE

The purpose of this guide is to provide an overview of legislation and key concepts relevant to performance studies (PS) involving *in vitro* diagnostic medical devices (IVDs). In addition, information is provided on how to submit applications or notifications to the Health Products Regulatory Authority (HPRA).

This guide is targeted at PS sponsors (e.g. manufacturers, academic groups, clinical research organisations) who wish to conduct PS involving IVDs in Ireland. The information may also prove useful for ethics committees and other stakeholders.

This guidance does not purport to be the definite interpretation of the law and/or regulations and is for guidance purposes only. Relevant legislation relating to *in vitro* diagnostic medical devices should be consulted in addition to this guide (see Appendix 1 for examples).

2 INTRODUCTION

Regulation (EU) 2017/746 (referred to as the IVDR in the remainder of this guide) is the legislation underpinning the regulation of the safety and marketing of IVDs throughout the European Union. The IVDR was published in the Official Journal of the European Union in 2017 and is applicable from 26 May 2022 for elements related to PS. The IVDR introduced a number of changes with respect to the ethical and scientific review of PS. This guide aims to help sponsors and other stakeholders prepare to implement the requirements of the IVDR with regards to PS.

Performance studies are considered to be conducted in the Republic of Ireland where either the study:
- site is based in the Republic of Ireland, or
- participants/specimens originate from the Republic of Ireland.

In general, under the IVDR some PS conducted in Ireland require an application, or a notification to the HPRA. Further details can be found in section 3 below. It is worth noting that some PS require two forms of review, one from a National Competent Authority for *in vitro* diagnostic medical devices and another from a relevant Research Ethics Committee. In Ireland an ethics opinion can be sought from the National Office for Research Ethics Committees; further information can be found on the NREC website (www.nrecoffice.ie).

The IVDR describes the operation of an electronic database underpinning a number of functions within the regulation of IVDs in Europe (known as 'EUDAMED'). The modules of EUDAMED that are applicable to PS are not yet functional. The contingency measures that will be used by the HPRA pending deployment of the PS modules of EUDAMED are detailed throughout this guide.

ISO 20916:2019 is a useful reference when planning your PS. This is an international standard that addresses good clinical practice for the design, conduct, recording and reporting of PS carried out using specimens from human subjects to assess the safety or performance of medical devices for regulatory purposes.

3 TYPES OF PERFORMANCE STUDIES

The term 'performance study' (PS) is defined in the IVDR as a study undertaken to establish or confirm the analytical or clinical performance of a device. It should be noted that this definition includes the use of non-CE marked and CE marked devices. Specific articles of the IVDR detail the expectations for different types of PS.

3.1 Article 58 – Requirements for certain performance studies

The additional requirements specified in Article 58 apply to PS conducted for one or more of the purposes specified in Article 58(1-2), that is a study:

- in which surgically invasive sample-taking[1] is done only for the purpose of the performance study;
- which is an interventional clinical performance study as defined in point (46) of Article 2[2];
- where the conduct of the study involves additional invasive procedures or other risks for the subjects of the studies; or
- involving a companion diagnostic[3].

Sponsors of PS being undertaken for the purposes listed above, for devices of all risk classes (Class A to Class D), should apply to the HPRA before conducting the PS in Ireland. The requirements and expectations for these PS are detailed in Articles 58-77 of the IVDR, along with Annex XIII and XIV.

See section 4 below for further details.

[1] MDR Annex VIII Chapter 2.2 provides a definition for a surgically invasive device
'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

[2] IVDR Art 2.(46) '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;

[3] Studies involving companion diagnostics are subject to the same requirements under Article 58(2) as studies under Article 58(1). Where the study involves a companion diagnostic using left over samples only, see section 3.2.

3.2 Article 58(2) – PS involving a companion diagnostic using left over samples only

Performance studies conducted in Ireland involving a companion diagnostic IVD where the study is performed using left over samples only are required to be notified to the HPRA. Further details, including appropriate forms, are available on the performance studies webpage on the HPRA website.

3.3 Article 70(1) – PS within the intended purpose of an IVD bearing a CE mark

Where a device CE marked under the IVDR is used within its intended purpose in a PS, the IVDR requires that sponsors assess whether subjects will be submitted to additional procedures that are deemed invasive or burdensome. Where this is the case, the sponsor is expected to notify the HPRA of their intention to undertake that PS and is expected to include, along with the notification, the documentation referenced in Article 70(1) of the IVDR. The sponsor must notify the HPRA at least 30 days prior to commencing the study in Ireland.

3.4 Article 70(2) – PS outside the intended purpose of an IVD bearing a CE mark

Where a PS is to be conducted to assess a device, CE marked under the IVDR where the study is outside the scope of the device's intended purpose, in accordance with Article 70(2), Articles 58-77 also apply. See section 3.1 above.

3.5 Determining whether an application or notification is required

In all cases the general requirements outlined in Article 57 apply to performance studies. To assist you in determining which requirements apply to your study we have included a decision tree in Figure 1.

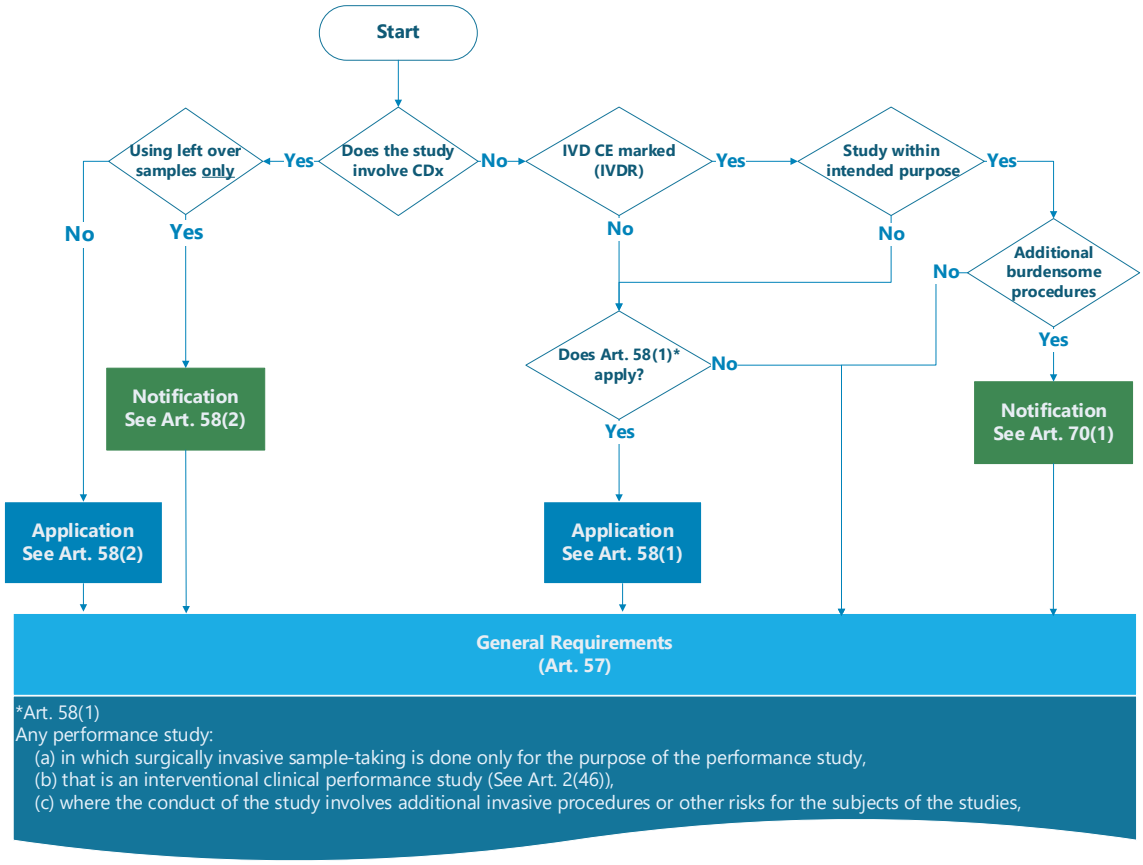

Figure 1: Decision tree to assist in determining performance study application/notification requirements

4 MAKING AN APPLICATION OR NOTIFICATION

4.1 Performance study applications

An application for a PS consists of the following:

- a completed 'Application for a performance study' form available at www.hpra.ie
- any required documentation as per Annex XIV of the IVDR
- the relevant fee (see the 'Guide to Fees for Human Products')

Prior to submission of an application, the HPRA strongly encourages manufacturers or sponsors to arrange a pre-submission meeting with the HPRA's performance studies review team to discuss the proposed PS.

Further information on pre-submission meetings or the procedure for submitting an application/notification to the HPRA is available on the performance studies webpage.

4.2 Changes or modifications to the performance study

Modifications to PS that have been previously approved by the HPRA should be notified in line with Article 71 of the IVDR. Until the relevant functionality of EUDAMED is established, these notifications should be made to the HPRA via CESP (Common European Submission Portal) following the steps as detailed on the performance studies webpage.

The IVDR requires that changes to the relevant documentation are clearly identifiable. The HPRA expects that, in addition to the relevant application form, any substantial modifications are notified in the format provided in Appendix 2 of this guide and include a description of the changes, justification of the changes and their potential impact on the performance, effectiveness, safety or other endpoints, and identification of the affected documents.

It should be noted that prior to the implementation of any proposed modifications, a review and positive opinion from the relevant Research Ethics Committee may also be required.

4.3 Performance study notifications

A performance study notification to the HPRA consists of the following:
- a completed notification form available on the performance studies webpage
- any additional required documentation, where relevant.
- the relevant fee (see the 'Guide to Fees for Human Products')

When notification to the HPRA is required, the sponsor should complete the relevant form and submit this along with the relevant documents via CESP. The sponsor should also send an email to devices@hpra.ie to advise that a notification has been submitted via CESP and supply the reference number provided by the CESP system. Following receipt of the notification, the HPRA will issue a letter to the sponsor.

5 PROCESS FOR HPRA REVIEW OF PERFORMANCE STUDIES APPLICATIONS

On receipt of an application to undertake a PS, the application is validated to check that all the required documentation is present and that the proposed PS falls within the scope of the IVDR.

At that time, a HPRA reference number is assigned to the application, and this should be quoted in all future correspondence with the HPRA. All PS undertaken in Europe should also be assigned a CIV ID. If you have already been issued with a CIV ID for the same PS being conducted in another Member State, please provide this to the HPRA on the application form.

Once validated, the application then undergoes a preliminary review to determine if external experts are required to assist with the review. If external experts are required, they will have signed a confidentiality agreement with the HPRA that incorporates a declaration of conflicts of

interest. All external experts are required to return submitted documentation to the HPRA or confirm destruction post review.

Article 66(7a) of the IVDR outlines that in the case of PS applications under Article 58(1), where the specimen collection does not represent a major clinical risk to the subjects of the study, the study can commence after validation. In all other cases, the study cannot commence until the sponsor has been notified of the HPRA's authorisation as per Article 66(7b).

For studies where the specimen collection does not represent a major clinical risk, a detailed justification must be provided in the application form. The HPRA reserves the right to seek additional clarification from the sponsor in relation to any justification provided as part of the dossier completeness check outlined in Article 66. The HPRA may decide that the justification provided is not sufficient; in such cases the study cannot commence until authorised by the HPRA in line with Article 66(7b).

After validation of an application the HPRA will assess and provide an outcome of its assessment within 45 calendar days. Where the HPRA needs to consult with an expert during the period of assessment, an additional 20 calendar days is added to the time available for assessment by the HPRA. During the assessment period, the HPRA may request additional information from the sponsor of the PS. Any time taken by the sponsor to provide this additional information is not included within the assessment timeframe described above. This process applies to all risk classes of IVD medical devices, i.e. Class A to D.

Where a response is not provided to the issues raised by the HPRA within the timeframe this may result in rejection or refusal of the application due to incomplete data being available to support the application.

6 REFUSAL OF AUTHORISATION OF A PERFORMANCE STUDY

The HPRA may refuse to authorise the PS if, after consideration of all the evidence provided by a manufacturer or sponsor, the grounds for authorisation of the PS are not met or there are grounds for refusal. The reasons for a refusal to authorise a PS will be provided in written form to the sponsor.

Following receipt of the notification of refusal to authorise a PS, the applicant has the right to appeal the decision as per the procedure detailed in the 'Guide to Refusals and Appeals', available at www.hpra.ie.

7 REPORTING OF ADVERSE EVENTS

Safety reporting of adverse events in PS should be made to the HPRA. This applies to all performance studies conducted in Ireland including studies which commenced prior to the date

of application of the IVDR. Safety reporting of adverse events does not apply to studies conducted in line with Article 70(1) of the IVDR; in such cases vigilance reporting applies.

Serious adverse events and device deficiencies are defined in the IVDR[4] and the following events are considered reportable in accordance with IVDR Article 76(2):

(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).

Until such a time as the PS modules of EUDAMED are fully functional, the HPRA expects sponsors to submit relevant event reports to the HPRA to devicesafety@hpra.ie stating the HPRA reference number assigned to the PS.
The MDCG has published guidance on the reporting of serious adverse events and device deficiency in clinical investigations under the MDR. In the absence of IVDR specific guidance, sponsors should take into account the principles of this guidance. This document provides practical information about definitions, timelines, reporting methods and reportable events.

8 END OF PERFORMANCE STUDY IN IRELAND

The HPRA expects that sponsors undertaking a PS in Ireland will submit a notification to the HPRA within 15 days of the end of the PS.

This notification should be followed by the submission of a report to the HPRA on the PS, within one year of the end of the PS. The requirements for this report can be found in Annex XIII of the IVDR. Where a PS has been terminated early or where a temporary halt has occurred, the PS report should be submitted to the HPRA within three months.

[4] IVDR article 2(61): '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,
(c) 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,
(d) foetal distress, foetal death or a congenital physical or mental impairment or birth defect;

Until such a time as the PS modules of EUDAMED are fully functional, the HPRA expects sponsors to submit this notification and subsequent report to devices@hpra.ie along with the reference number assigned to the PS.

9 ADMINISTRATIVE DETAILS

This guide and associated documents can be found under the publications and forms section of www.hpra.ie.

Alternatively, they can be obtained from the HPRA directly as follows:
Telephone: +353-1-6764971
Email: devices@hpra.ie

The HPRA encourages communication with the medical device sector. Should you have specific queries please address them to the Medical Devices department of the HPRA who will endeavour to be of assistance.

APPENDIX 1 REFERENCES

1 Regulation (EU) 2017/746 of the European Parliament and of the Council on *in vitro* diagnostic medical devices

2 ISO Standard 20916: 2019 In vitro diagnostic medical devices — Clinical performance studies using specimens from human subjects — Good study practice

3 MDCG 2020 10/1 Guidance on safety reporting in clinical investigations

APPENDIX 2 TEMPLATE FOR NOTIFYING MODIFICATIONS

Format of document identifying proposed modifications to approved PS:

Document and location reference	Original text	Amended text	Rationale
e.g. PSP001 Page 2 Section 1.11	The study will be performed at the following sites: Hospital A Hospital B	The study will be performed at the following sites: Hospital A Hospital B Hospital C	An additional study site will be added due to….