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Directorate-General PRE authorisation
Research and Development Division (human use)

Guideline on the Submission Processes for Performance Studies according to the IVDR in Belgium

This document aims at providing guidance for the different submission processes for performance studies under the IVDR from a national point of view.

Version 6.0, 15JAN2025

Document revision history

Date of publication	Revision description
12.05.2022 – version 1.0	First publication
09.06.2022 – version 2.0	- Section 5.1: dossier structure added - Section 6.3: adapted, notification not legally required - Annex I: Fees: table updated - Annex II: validation date of table extended by one month - Small updates and clarifications throughout the document
04.07.2022 – version 3.0	- Sections 5.1, 5.2 and 5.3: planning document added to list of documents to be submitted. - Annex II: update of tables for classification for additional burdensome or invasive procedures for Belgium.
30.03.2023 – version 4.0	- Small corrections and clarifications throughout the document. - Sections 5.5 and 6.4: clarification concerning the conclusion "Authorized subject to conditions" - Annex I: Indexation of fees for 2023 - Annex IV added: Overview of deadlines for each regulatory pathway.
01.07.2024 – version 5.0	- Clarifications and corrections throughout the document. - Section added on specific cases: combined studies and biomarkers for exploratory analysis (section 5) - Update of Section 8 – Safety Reporting: reference to MDCG guidance. - Update of fees to index 2024 (Annex I) - Update Annex II – Classification for additional burdensome or invasive procedures for Belgium
15.01.2025 – version 6.0	- Section 5.1: information on the synchronized submission procedure for combined studies added. Additional information on substantial modifications of combined studies added. - Sections 6.5 and 7.4: information on withdrawals added - Annex I: indexation of fees 2025 - Small clarifications and corrections.

Contents

1. Introduction

On May 26, 2022, the EU Regulation for *In vitro* Diagnostic Medical Devices (EU 2017/746) (IVDR) came into force. The IVDR introduced a major update of the regulatory framework in the European Union and brought about several changes to the scope of performance studies that must be notified or submitted for approval, the submission processes for performance studies and their substantial modifications, submission dossier contents and safety reporting.

The IVDR sets out the rules for the contents of the application, for the assessment by EU Member States and Ethics Committees and the obligations for sponsors in terms of conduct and reporting. However, the IVDR itself does not provide sufficient information for its application into practice. Therefore, in Belgium, a dedicated law and royal decree have been approved on 15.06.2022[1] and 25.10.2022[2] respectively, including general practical information for performance studies and their evaluation.

Finally, the unavailability of the Eudamed database brings uncertainties for all actors. This guidance also aims to clarify how the different exchanges will be done until Eudamed becomes available.

[1] FR link: https://www.ejustice.just.fgov.be/eli/loi/2022/06/15/2022032523/justel
NL link: https://www.ejustice.just.fgov.be/eli/wet/2022/06/15/2022032523/justel
[2] FR link: https://www.ejustice.just.fgov.be/eli/arrete/2022/09/25/2022042240/justel
NL link: https://www.ejustice.just.fgov.be/eli/besluit/2022/09/25/2022042240/justel

2. Definitions and abbreviations

All definitions provided in this section are compliant with the definitions stated in the IVDR.

Adverse Device Effect (ADE): Any adverse event related to the use of a device for performance study or a comparator. See ISO 20916

Adverse Event (AE): 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. See IVDR Article 2(60)

AoR: Acknowledgement of Receipt

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

CESP: Common European Submission Portal – see link

Combined clinical studies: studies that involve the simultaneous investigation of a medicinal product, an IVD and/or MD which are subject to the requirements of the CTR, IVDR and/or MDR.

Companion diagnostic (CDx): a device which is essential for the safe and effective use of a corresponding medicinal product to:

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

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

CPSP: Clinical Performance Study Plan – a document that describes the rationale, objectives, design methodology, monitoring, statistical considerations, organization and conduct of a performance study (see section 2.3.2 of Annex XIII of IVDR)

CT-College: an independent organ that coordinates the working of the Ethics Committees and is responsible for their quality assurance. It also acts as single point of contact between Ethics Committees and the FAMHP (see website).

Device deficiency (DD): 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

Device for performance study: a device intended by the manufacturer to be used in a performance study

EC: Ethics Committee – depending on the regulatory pathway the investigation is evaluated by an ethics committee accredited following the law of 07 May 2004 or the law of 07 May 2017

FAMHP: the federal agency for medicines and health products as defined in the law of 20 July 2006 related to the creation and functioning of the federal agency for medicines and health products – Belgian competent authority

IB: Investigator's Brochure, contains the clinical and non-clinical information on the investigational device that is relevant for the investigation and available at the time of application (see IVDR section 2 and 4.6 of Annex XIV)

In-house device: a device that is manufactured only within a health institution established in the Union, that meets all conditions set in Article 5(5) of the IVDR and is used only within that same health institution

Instructions for use: 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

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

***In vitro* diagnostic medical device (IVD):** 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:

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

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

IVDD: *In vitro* Diagnostic medical devices Directive – EU Directive (98/79/EC)

IVDR: *In vitro* Diagnostic medical devices Regulation (EU 2017/746)

Left-over sample: Unadulterated remainder of human derived samples collected as part of routine clinical practice and after all standard analysis has been performed. Such specimens/samples would be otherwise discarded as there is no remaining clinical need for them. This can include specimens collected for research or other purposes not connected to

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

MDCG: The EU Medical Device Coordination Group (MDCG) deals with key issues from the medical devices sector, from Notified Body oversight or standardisation to market surveillance, passing by international matters, new technologies and clinical investigation. All MDCG endorsed documents and guidelines can be found here.

Medical device: any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
- providing information by means of *in vitro* examination of specimens derived from the human body, including organ, blood and tissue donations,

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

The following products shall also be deemed to be medical devices:

- devices for the control or support of conception;
- products specifically intended for the cleaning, disinfection or sterilisation of devices as referred to in MDR Article 1(4) and products listed in Annex XVI of the MDR.

PEP: Performance Evaluation Plan – see section 1.1 of Annex XIII of IVDR for more information on the content

Performance study (PS): a study undertaken to establish or confirm the analytical or clinical performance of a device

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

Post-market surveillance: all activities carried out by manufacturers in cooperation with other economic operators to institute and keep up to date a systematic procedure to proactively collect and review experience gained from devices they place on the market, make available on the market or put into service for the purpose of identifying any need to immediately apply any necessary corrective or preventive actions

PMPF: Post-Market Performance Follow-up

RFI: Request for information

RUO: Research Use Only

Serious Adverse Device Effect (SADE): an adverse device effect that has resulted in any of the consequence characteristics of a serious adverse event

Serious Adverse Event (SAE): 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:
    - life-threatening illness or injury,
    - permanent impairment of a body structure or a body function,
    - hospitalisation or prolongation of patient hospitalisation,
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
    - chronic disease,
d. foetal distress, foetal death or a congenital physical or mental impairment or birth defect

Specimen: any 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 body fluid or tissue

Subject: an individual who participates in a performance study and whose specimen(s) undergo *in vitro* examination by a device for performance study and/or by a device used for control purposes

3. Transition period

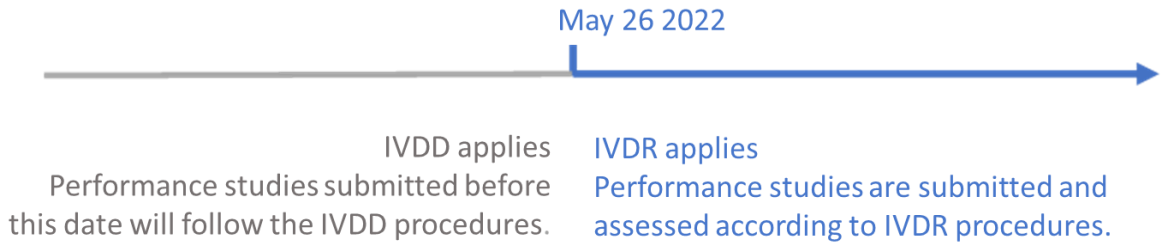

Figure 1. Timeline indicating the applicable legislation.

As depicted in the figure above, submissions with a date of reception up until May 25, 2022, will be handled in accordance with EU Directive (98/79/EC) (IVDD) and its dedicated Belgian law[3]. Performance study submissions received from May 26, 2022 will be handled according to the IVDR procedures and its dedicated Belgian law. No other transition is foreseen in the IVDR regarding performance studies.

Ongoing performance studies approved under IVDD may continue to be conducted following IVDD legislation. For these studies substantial modifications do not need to be approved by the FAMHP and no SAE reporting is requested even after May 26, 2022.

[3] Directive (98/79/EC) was converted to Belgian law by the Royal Decree dated 14 November, 2001 governing medical devices for *in vitro* diagnostics.

4. Regulatory pathways

Performance studies that fall within the scope of the IVDR need to follow a regulatory pathway with the involvement of the Ethics Committee (EC) and/or the Belgian competent authority (FAMHP). Depending on the type of performance study the submission procedure can be different. The different types of performance studies, respective process flows and regulatory pathways are depicted in Figure 2.

The decision tree in Figure 3 and corresponding decision steps below will guide towards the correct regulatory pathway. The specific procedures of each regulatory pathway are discussed in more detail in section 0.

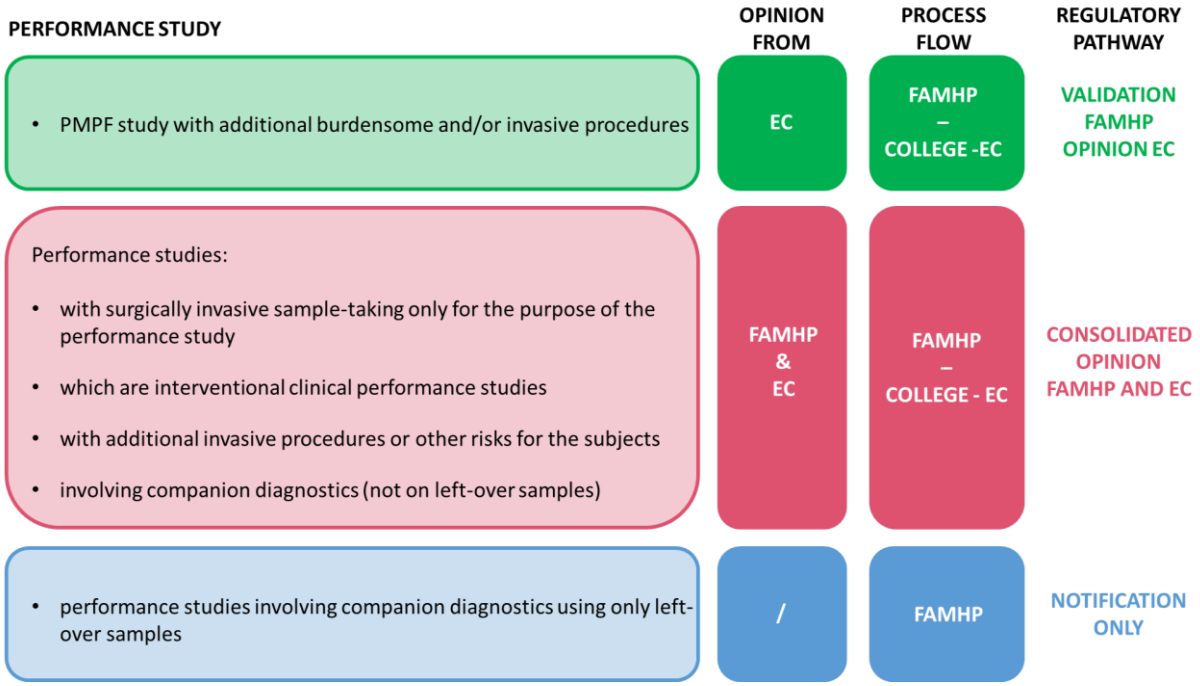

Figure 2. Different regulatory process flows and regulatory pathways are possible depending on the type of performance study.

Note that as per national provisions in Belgium, the **in-house IVDs** follow the same approach as not in-house IVDs. If one of the conditions of IVDR Art. 58.1 or Art. 58.2 are fulfilled within the study, an IVDR performance study application is required according to Chapter 3 of the Royal Decree of 25/09/2022 on performance studies and Art. 57 of the Belgian law of 15/06/2022 relative to in-vitro diagnostic medical devices.

This means that if any aspect of the performance study is interventional or includes additional burdensome and/or invasive procedures for the participants, the study may fall under the IVDR and should be submitted following the correct regulatory pathway.

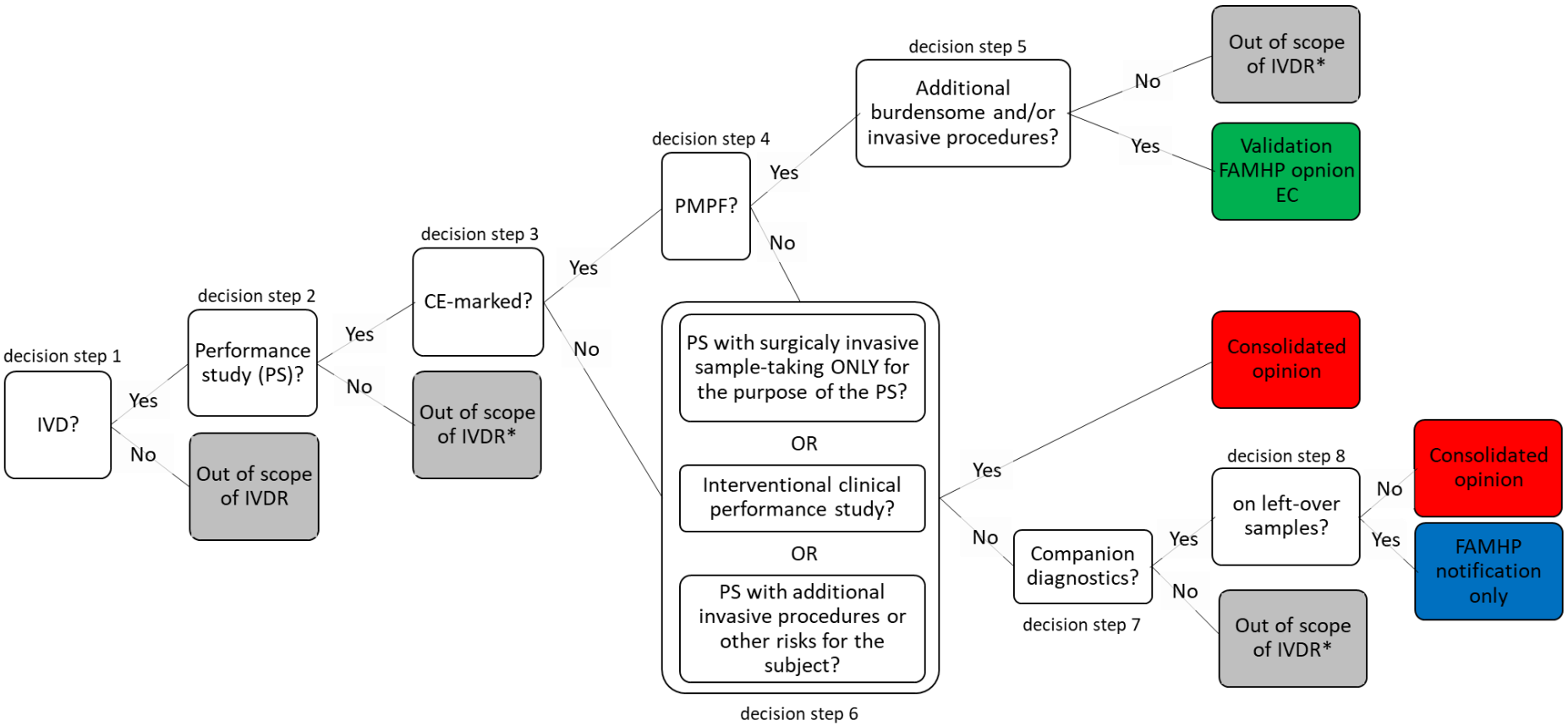

Figure 3. Decision tree to determine the regulatory pathway for the submission of a performance study. Please refer to the text below for a description of each decision step. (PS) = Performance study. (*) = If the study is not covered by the IVDR and does not need to be submitted to the FAMHP, approval of the EC may still be required following the national law of 07/05/2004.

Decision step 1

If the product is an *in vitro* diagnostic medical device (IVD) according to the definition provided by IVDR Art.2.2 (see definitions), you may proceed to decision step 2.

If the product is not an IVD according to the definition, then it is not covered by the IVDR and does not need to be submitted to the FAHMP. Approval of the EC may however still be required following the national law of 07/05/2004.

Decision step 2

If the study is a performance study according to the definition provided by the IVDR Art.2.42 (see definitions), you may proceed to decision step 3.

Please note that the IVDR regulates IVD devices (products) and not assays/tests (methods). A performance study should thus always generate performance data for a device.

If the study is not a performance study according to the definition, then it -does not need to be submitted to the FAHMP. Approval of the EC may however still be required following the national law of 07/05/2004.

Decision step 3

If the device for performance study has a valid CE label, you can proceed to decision step 4.

If the device for performance study does not have a valid CE label, you can proceed to decision step 6.

Decision step 4

A post-market performance follow-up (PMPF) study is conducted to further assess a CE-marked IVD within its intended purpose to proactively collect clinical data which would confirm the safety and/or performance. If the performance study is considered to be a PMPF study you can proceed to decision step 5.

If the investigation is not considered as a PMPF study, you can proceed to decision step 6.

Decision step 5

In the scope of PMPF studies an additional procedure which could be considered as burdensome or invasive for the subject is a procedure which is not foreseen by the manufacturer in the instructions for use or not foreseen in the clinical practice following state of the art.

Please refer to Annex II for a list of procedures which are considered to be burdensome or invasive and for a list of procedures which are specifically not considered burdensome or invasive.

If additional procedures are foreseen during the PMPF investigation which are considered to be burdensome and/or invasive, a positive advice from the EC needs to be obtained through the **"validation FAMHP, opinion EC" regulatory pathway**.

If there are no invasive or burdensome additional procedures foreseen during the PMPF study, the study does not need to be submitted to the FAHMP. Please note that approval of the EC may however still be required following the national law of 07/05/2004.

Decision step 6

In this step the following types of performance studies should be considered: performance studies with CE-labelled IVDs which are not PMPF studies (e.g. performance studies outside the scope of the intended purpose of a CE-labelled IVD) and performance studies on non-CE labelled IVDs, including performance studies on in-house IVDs.

If the performance study meets at least one of the below mentioned study characteristics the **"consolidated opinion FAMHP and EC" regulatory pathway** should be followed.

- A performance study in which surgically invasive sample-taking is done **only** for the purpose of the performance study.

- A performance study that is an interventional clinical performance study.

- A performance study where the conduct of the study involves additional invasive procedures or other risks for the subject of the study (see annex II)

If the performance study meets none of the above described study characteristics you may proceed to decision step 7.

Decision step 7

If the performance study involves companion diagnostics you may proceed to decision step 8. If your performance study does not involve companion diagnostics the study is not covered under the IVDR and does not need to be submitted to the FAHMP. Please note that approval of the EC may however still be required following the national law of 07/05/2004.

Decision step 8

For performance studies involving companion diagnostics using **only** left-over samples a notification to the FAMHP is sufficient, this can be done through the **"FAMHP notification only"** regulatory pathway.

Other performance studies involving companion diagnostics must be submitted through the **"consolidated opinion FAMHP and EC" regulatory pathway.**

5. Specific cases

5.1. Combined studies

According to the "MDCG 2022-10 - 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" (Question 7):

Where a non-CE marked IVD is used for a medical purpose in a clinical trial the IVD must either be

- a device for performance study (it is not acceptable to use an investigational IVD without evaluating its performance), or
- an in-house IVD.

This means it is not possible to use a non-CE marked IVD or CE-marked IVD but used out of scope (which is not an in-house IVD) within a clinical trial without performing a combined performance study on the investigational IVD.

When submitting an **initial application** of a performance study which is a combined study with a clinical trial, please take into account the following:

- For combined studies both clinical trial (CTR) and performance study (IVDR) need to be submitted and approved before the study can start.
- Parallel submission of the clinical trial and performance study is not obligatory but highly recommended.
- For combined studies the CT-College will appoint the same independent EC to both the clinical trial within the CTR procedure and performance study within the IVDR procedure. For this purpose, please clearly indicate in the cover letter of both procedures that it concerns a combined CTR/IVDR clinical study (with references to the EudraCT/Eudamed numbers if available).
- It is important to always provide the most recent versions of the ICF, even if it is still a draft version. This to prevent the EC from having to ask for the same adaptions twice, once within each procedure.

Since the beginning of 2025 a pilot is running for a **synchronized submission procedure** of initial applications of combined CTR-IVDR studies in Belgium. This concerns a synchronization of two separate procedures running in parallel through their respective submission procedures. The synchronization makes it possible to send out validation questions and Requests for Information (RFI) at the same time, streamline the process and enables alignment of approved documents within both applications. If you are interested in submitting your combined study through this pathway please contact us at ct.rd@fagg-afmps.be for more information.

When submitting a **substantial modification** of a performance study which is a combined study with a clinical trial, please take into account the following:

- Substantial modifications to documents that are applicable to both clinical trial (CTR) and performance study (IVDR) need to be submitted and approved through both procedures before the modification can be implemented.
- As an exception, in Belgium, for substantial modifications of patient facing documents such as the ICF a submission and approval as a substantial modification through one of the two procedures (CTR or IVDR) is sufficient. Please note:
    - This only accounts for patient facing documents which are common for both IVDR and CTR applications of the combined study. Updates of any other documents need to submitted as a substantial modification through both procedures.
    - The ICF version approved by CTIS must be identical to the one notified within the IVDR procedure.
    - In case the substantial modification has been approved through CTR, a notification of a non-substantial modification, by e-mail to ct.rd@fagg-afmps, needs to be done as soon as possible for the IVDR dossier. This notification must include the updated version of the ICF in clean and track-changes and the confirmation by the sponsor that this version has been approved through CTIS. The updated ICF can only be implemented once you have the approval through CTIS **AND** have notified the non-substantial modification for the IVDR part.
    - In case the substantial modification has been approved through IVDR, a notification of a non-substantial modification needs to be done as soon as possible through CTIS. The updated ICF can only be implemented once you have the approval through IVDR **AND** have notified the non-substantial modification through CTIS.

5.2. Biomarkers for exploratory analysis

Performance studies or clinical trials may include a sub-protocol or section where next to the investigational IVD and/or IMP other biomarker analyses are included. These analyses may be purely exploratory for scientific research only and do not have any impact on screening, enrollment or treatment decisions.

When an IVD is used “for research use only” it is called a RUO product. For RUO products there cannot be a single link to a medical purpose or any reference to certain diseases or diagnostic procedures. Also note that when a medical purpose has been established based on sufficient and broadly agreed upon scientific, diagnostic and clinical evidence, then the product must comply with the requirements of the IVDR even if it used for research use only. For example it will not be possible for a manufacturer to market a SARS-CoV-2 test as an RUO product, even when the test is only used during research on SARS-CoV-2, and not for diagnostics purposes.

RUO products fall outside the scope of the IVDR, for these products no performance study is needed.

Note that the cover letter should include a list of all IVDs that will be used within the performance study (and clinical trial if a combined study). This includes biomarkers for exploratory analysis. Next to the name of the IVD the list must also include the samples that they will analyze and whether they are CE-marked or not (if CE-marked, whether they will be used within their intended purpose or not). If the products are considered to be RUO, please justify within the cover letter.

6. Initial submissions

Please note that as long as Eudamed is not available all submissions must be done via CESP. Response documents can also be submitted via CESP. A unique Eudamed number will be generated by the FAMHP upon dossier submission and communicated together with the status of the dossier. Alternatively, the Eudamed number can also be requested by the sponsor before submission. In this case please send an e-mail to ct.rd@fagg-afmps.be including the following details of the performance study:

- Title
- Protocol code
- Manufacturer name and address
- Primary objective(s)
- Name of investigational device(s)
- Intended purpose of investigational device(s) within the clinical investigation

6.1. Dossier structure

A zip-folder with the dossier structure, including all relevant templates, is available on our website. The table below indicates which documents should be saved in each folder, if applicable. We highly recommend to adapt this folder structure for all initial applications.

Name folder	**Contents (if applicable)**
A. COVER	- Cover letter *The cover letter should include all details that need to be present on the invoice: company name, postal address, e-mail (not mandatory), VAT-number (or EIN-number), purchase order number (if applicable) or any other relevant information.* *The cover letter should include a list of all IVDs that will be used within the performance study (and clinical trial if a combined study). This includes biomarkers for exploratory analysis. Next to the name of the IVD the list must also include the samples that they will analyse and whether they are CE-marked or not (if CE-marked, whether they will be used within their intended purpose or not). If the products are considered to be RUO, please justify.* - List of submitted documents (WORD document) - Planning document

	- Any other supportive information (e-mails, letters, tables,…)
B. APPLICATION FORM	- signed application form for initial performance study applications *Note that the list of sites should include all clinical sites and not the site(s) of the lab.*
C. CPSP	- Clinical Performance Study Plan (CPSP) - Any CPSP addenda or annexes - CPSP synopsis as separate documents in English and at least in the official national language(s) of the region(s) where the investigation is conducted, except in German.
D. IB	- IB - Any IB annexes including test reports, risk assessment reports, … - List of GSPR
E. IFU	- Manufacturer's instructions for use
F. CE CERTFIFICATE	- CE certificate of investigational device
G. PEP - PMPF	- Performance evaluation plan or; - PMPF plan in case of post-market performance study
H. COMPARATOR	- Instructions for use of comparator - CE certificate of comparator - Any other relevant information on the comparator
I. OTHER MS	- If multinational investigation, list of other participating EU Member States including the status on submission procedure(s). - Approval and/or refusal letters from other EU member states
J. LABELLING	- Example of labels. *According to section 20.2 of IVDR Annex I, the following three elements should be included on the labels: ID device, manufacturer's name & address and "Exclusively for use in performance study".*
K. RECRUITMENT	- Recruitment arrangements - Advertising materials
L. ICF AND PROCEDURE	- Recruitment and ICF procedure

	- ICF - Questionnaires, participation card, diaries or other patient documents
M. SUITABILITY PI	- CV of PI at each site - DOI of PI at each site
N. SUITABILITY SITE	- Site Suitability Template (see Folder Structure on website for most recent template) *One Site Suitability Template must be present for each participating Belgian clinical site.* *Note that for combined studies the Site Suitability Template must also refer to the performance study and not only the clinical trial.*
O. INSURANCE	- Proof of insurance cover or identification *The certificate should state that it is in compliance with all relevant national legislation (specific listing of law of 15 June 2022 no longer obligatory).*
P. FINANCIAL ARRANGEMENTS	- Description of compensation for participants - Performance study agreement - Any other agreements
R. DATA PROTECTION	- Statement that data will be collected and processed in accordance with the GDPR

The sections below list all necessary documents per regulatory pathway.

6.2. Regulatory pathway: validation FAMHP and opinion EC

➔ *PMPF studies involving additional burdensome or invasive procedures.*
➔ *Validation by FAMHP and Assessment by EC, one decision issued.*

According to Art. 70 of IVDR, where a performance study is to be conducted to further assess, within the scope of its intended purpose, a device which already bears the CE marking in a PMPF study, and 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 and/or burdensome, the sponsor shall **notify the FAMHP at least 30 days prior to its commencement**.

Following documents must be included in the notification package:

- *Cover letter – including address and VAT for invoicing purposes*
- *List of documents submitted (WORD document – see template on website)*
- *Application form (see template on website)*
- *Planning document containing a table indicating each Belgian site, the principle investigator per site and the estimated amount of patients to be included per site.*
- *Clinical Performance Study Plan (CPSP) – see section 2.3.2 of Annex XIII of IVDR for more information on the content of the CPSP.*
- *CPSP synopsis as separate documents in English and at least in the official national language(s) of the region(s) where the investigation is conducted, except in German.*
- *CE certificate*
- *Technical documentation*
- *PMPF plan – see section 5 of Annex XIII of IVDR for more information on the content of the PMPF plan.*
- *Proof of insurance*
- *Manufacturer's instructions for use (if not included in technical documentation)*
- *CV and Declaration of Interest (DOI) of principal investigator(s) – see templates in ZIP folder*
- *Suitability of clinical sites – see templates in ZIP folder*
- *Patient related documents:*
    - *documents used to obtain informed consent, including the patient information sheet and the informed consent document*
    - *separate document describing the procedure and materials used for recruitment of patients*
    - *separate document describing the compensation for investigation participants*
    - *any other written information provided to the subjects*
- *Description of the arrangements to comply with the applicable rules on the protection and confidentiality of personal data.*
- *The performance study agreement and proposed compensation to the investigation site or principle investigator.*
- *CE certificate and manufacturer's instructions for use of any comparator device used in the performance study*

The complete dossier must be submitted via CESP to the FAMHP, according to the steps outlined in our CESP guidance document. The FAMHP will validate the dossier within 5 days of reception. **Note that the procedure does not allow any validation questions to be asked, if the dossier is missing one of the above listed documents it will be rejected automatically.**

If complete, the dossier will be dispatched to an independent EC (accredited following law of 07/05/2017) by the CT-College. The EC will assess the dossier and the final opinion will be communicated within 30 calendar days of the date of reception.

An invoice will be sent to the sponsor at the end of the process for the payment of fees (see Annex I).

6.3. Regulatory pathway: consolidated opinion FAMHP and EC

➔ *Performance studies:*
- *with surgically invasive sample-taking only for the purpose of the performance study*
- *which are interventional clinical performance studies*
- *with additional invasive procedures or other risks for the subjects*
- *involving companion diagnostics (not on left-over samples)*

➔ *Assessment by FAHMP and EC, one consolidated decision is issued.*

These performance studies are assessed jointly by the competent authority and an independent ethics committee, accredited through the law of 07/05/2017. Only one submission is needed through the national contact point (FAMHP) and only one joined opinion will be issued.

The complete dossier must be submitted, via CESP, to the competent authority. The dossier must contain the following documents (if applicable):

- *Cover letter – including address and VAT for invoicing purposes*
- *List of documents submitted (WORD document – see template on website)*
- *Application form (see template on website)*
- Planning document containing a table indicating each Belgian site, the principle investigator per site and the estimated amount of patients to be included per site.
- *Clinical Performance Study Plan (CPSP) – see section 2.3.2 of Annex XIII of IVDR for more information on the content of the CPSP.*
- *CPSP synopsis as separate documents in English and at least in the official national language(s) of the region(s) where the investigation is conducted, except in German.*
- *Performance evaluation plan (PEP) - see section 1.1 of Annex XIII of IVDR for more information on the content of the PEP.*
- *Investigator's Brochure (IB) - see section 2 and 4.6 of Annex XIV of IVDR for more information on the content of the IB.*
- *Example of labels (IVDR Annex I, Chapter III, 20.2)*
- *CE certificate (if applicable)*
- *Manufacturer's instructions for use*
- *List of general safety and performance requirements that have already been met, including motivation (template available on our website) – see template in ZIP folder*
- *Proof of insurance*
- *CV and DOI of principal investigator(s) – see templates in ZIP folder*
- *Suitability of sites (see template on website) – see template in ZIP folder*
- *Patient related documents:*

    - *documents used to obtain informed consent, including the patient information sheet and the informed consent document*
    - *separate document describing the procedure and materials used for recruitment of patients*
    - *separate document describing the compensation for investigation participants*
    - *any other written information provided to the subjects*
- *Description of the arrangements to comply with the applicable rules on the protection and confidentiality of personal data.*
- *The performance study agreement and proposed compensation to the investigation site or principle investigator.*
- *If multinational, status on submission procedure(s) in other countries, including any approval or refusal letter if applicable.*
- *CE certificate and manufacturer's instructions for use of any comparator device used in the performance study*

Within 10 days of receiving the application, the FAMHP will notify the sponsor as to whether the performance study falls within the scope of the IVDR and as to whether the application is complete. If incomplete, validation questions will be asked. For validation questions a clock-stop of maximum 10 days will be installed with a possible extension of 20 days if specifically requested by the sponsor. If complete, an Acknowledgement of Receipt (AoR) letter will be sent notifying the official T0 and including the specific timetable of the procedure.

On T28, at the latest, the assessment reports of the EC and FAMHP will be consolidated and requests for information (RFIs), if any, will be sent to the sponsor. In this case a clock-stop of maximum 20 days is installed. The clock is restarted when the agency receives the response from the sponsor via mail or CESP. Only one round of questions is allowed. The FAMHP and EC will issue one consolidated decision on T45 at the latest, an official authorization, or refusal, letter will be sent to the sponsor.

The competent authority may extend the legal deadline of 45 days (starting from T0) by a further 20 days for the purpose of consulting experts. If this is the case, the sponsor will be notified of this deadline extension by the FAMHP. Consequently RFIs will be communicated at the latest on T48 and the one consolidated decision will be notified at the latest on T65.

An invoice will be sent to the sponsor at the end of the process for the payment of fees (see Annex I).

NOTE

Article 66 (7) (a) of the IVDR states that the sponsor may start a performance study in which surgically invasive sample-taking is done only for the purpose of the performance study immediately after the validation date of the application, unless otherwise stated by national

law. In Belgium, it was decided to fully assess all performance studies that fall under Article 58 of the IVDR. The process and timelines described above are thus applicable for all performance studies described under Article 58 of the IVDR.

6.4. Regulatory pathway: notification only

➔ *Performance studies involving companion diagnositcs using only left-over samples.*
➔ *Notification only, no official approval issued*

NOTE: if the performance study is regarding a companion diagnostics using left over sample, but this study implies one the three criteria stated at article 58 from IVDR (include invasive sample-taking, interventional, invasive procedure or other risks for the subjects); the stricter regulatory pathway will be followed, so the consolidated opinion.

The manufacturer, sponsor or its delegated representative, of these performance studies must submit the dossier to the FAMHP, electronically via CESP. The dossier must contain following items:

- Cover letter – including address and VAT for invoicing purposes
- Application form (see website)
- Clinical Performance Study Plan (CPSP) – see section 2.3.2 of Annex XIII of IVDR for more information on the content of the CPSP.
- All documents used to obtain informed consent, including the patient information sheet and the informed consent document, if applicable.

If the notification dossier is found to be complete, an acknowledgement of receipt (AoR) letter will be sent within 10 days of reception.

6.5. Withdrawal

A sponsor may decide to withdraw an ongoing application. Withdrawal of the application is possible at any time between the date of submission of the date the final decision is issued.

To withdraw an ongoing application a letter of withdrawal must be sent by e-mail to the FAMHP at ct.rd@fagg-afmps.be containing following elements:

- Title and Eudamed number of the performance study
- Date of withdrawal
- Brief description of reason for withdrawal
- Signature of the sponsor or his representative

If the application is withdrawn after validation has been completed a full fee will be applicable. If the application is withdrawn before validation has been completed the reduced fee of a "rejection before validation" will be applicable (see Annex I).

Note that it is not possible to "withdraw" a performance study for which the final decision already has been issued. In this case a notification of early termination needs to be provided (see section 9.2).

6.6. Conclusions

After notification and/or evaluation of the dossier according to one of the above described procedures a final conclusion is provided to the sponsor by the FAMHP and/or EC. Following final conclusions can be issued:

- **"Acknowledgement of receipt":** performance studies notified under the "notification only" regulatory pathway will receive an acknowledgement of receipt letter if the dossier is complete, the performance study can now start.
- **"Rejected":** the notification or application is rejected after validation if the performance study does not fall within scope of the IVDR, if the dossier is incomplete or if the response to the validation questions was not received within the legal deadlines. The applicant is provided with a brief explanation detailing the grounds on which the notification or application is rejected. The performance study may not start. In case of a rejection the (completed or amended) dossier can be re-submitted at any time.
- **"Authorised"**: the performance study can start immediately.
- **"Authorised with recommendation(s)"**: the performance study can start immediately, it is however advised to take into consideration the recommendation(s) provided.
- **"Authorised subject to conditions":** the performance study can start however the approval is subject to the conditions mentioned in the approval letter. The approval letter will clearly state how the conditions should be fulfilled. This could be by submitting the requested adaptions/information as a substantial modification (as soon as possible) or by submitting the adaptions/information as a non-substantial modification (together with the next substantial modification).
- **"Refused"**: the clinical performance study cannot start. The applicant is provided with a brief explanation detailing the grounds on which the application is refused. In case of refusal, the dossier can be re-submitted. In this case, the sponsor is asked:
    - to adapt the dossier (to answer the objections given in the refusal letter);
    - to add the refusal letter to the dossier;
    - to add a description of the changes compared to the previous submission.

7. Substantial modifications

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, are considered substantial modifications and must be approved by the FAMHP and/or EC before implementation.

Non-substantial modifications need to be notified to the FAMHP but do not require a formal approval before implementation. Non-substantial modifications can be notified in one of the following ways:

- Together with the next substantial modification(s): the non-substantial modification(s) must be submitted along with the substantial modification(s). Please also briefly describe the non-substantial modification(s) in the cover letter and provide the adapted documents in a clean and track-change version.

- After one year: if no substantial modification has occurred or is foreseen within one year, the non-substantial modification(s) must be notified via CESP or e-mail (ct.rd@fagg-afmps.be). Please describe the non-substantial modification(s) briefly in a cover letter and provide the adapted documents in a clean and track-change version.

- At the end of the study: please submit all non-substantial modifications that have not yet been notified together with the notification of the end of the performance study (see section 8.1). Please describe the non-substantial modification(s) briefly in a cover letter and provide the adapted documents in a clean and track-change version.

As for the initial application of the study, the submission procedure for **substantial modification** depends on the status of the device for performance study. The decision tree (Figure 3) and corresponding decision steps explained in section 4 of this guidance will guide you towards the correct regulatory pathway.

7.1. Substantial modification regulatory pathway: validation FAMHP and opinion EC

➔ *PMPF studies involving additional burdensome or invasive procedures.*
➔ *Validation by FAMHP and Assessment by EC, one decision issued.*

The complete dossier must be submitted, via CESP, to the competent authority. The dossier must contain following documents:

- Cover letter – **including address and VAT for invoicing purposes**
- List of documents submitted (WORD document – see template on website)
- Rationale or justification of the changes (point by point)
- Application form **for substantial modifications** – see template on website
- Amended documents in **track change** and **clean version**
- Any other documents that may be relevant for the assessment of the modification.

The agency will validate the dossier within 5 days of reception and notify the applicant of its completeness. Note that the procedure does not allow any validation questions to be asked, if important documents are missing, the substantial modification will be rejected. The approval (or rejection) will be communicated within 38 calendar days of date of reception.

An invoice will be sent to the sponsor at the end of the process for the payment of fees (see Annex I).

7.2. Substantial modification regulatory pathway: consolidated opinion FAMHP and EC

➔ *Performance studies:*
  - *with surgically invasive sample-taking only for the purpose of the performance study*
  - *which are interventional clinical performance studies*
  - *with additional invasive procedures or other risks for the subjects*
  - *involving companion diagnostics (not on left-over samples)*

➔ *Assessment by FAHMP and EC, one consolidated decision is issued.*

Substantial modifications of these performance studies are assessed jointly by the competent authority and an independent ethics committee. Only one submission is needed through the national contact point (FAMHP) and only one joined opinion will be issued.

The complete dossier must be submitted, via CESP, to the competent authority. The dossier must contain following documents:

- Cover letter – **including address and VAT for invoicing purposes**
- List of documents submitted (WORD document – see template on website)
- Rationale or justification of the changes (point by point)
- Application form **for substantial modifications** – see template on website
- Amended documents in **track change** and **clean version**
- Any other documents that may be relevant for the assessment of the modification.

The date of reception is considered as T0 and within 3 days of receiving the substantial modification, the agency will notify the sponsor as to whether the application is complete. If incomplete, validation questions will be asked for which a clock-stop is installed.

On T24, at the latest, the assessment reports of the EC and FAMHP will be consolidated and requests for information (RFIs), if any, will be sent to the sponsor. In this case a clock-stop of maximum 20 days is installed. Only one round of RFI is allowed. The clock is restarted when the agency receives the response from the sponsor via mail or CESP. The FAMHP and EC will issue one consolidated decision on T38 at the latest, an official approval, or refusal, letter will be sent to the sponsor.

The competent authority may extend the legal deadline of 38 days by a further 7 days for the purpose of consulting experts. If this is the case the sponsor will be notified of this deadline extension by the FAMHP. Consequently RFIs will be communicated at the latest on T31 and authorization will be notified at the latest on T45.

An invoice will be sent to the sponsor at the end of the process for the payment of fees (see Annex I).

7.3. Regulatory pathway: notification only

➔ *Performance studies involving companion diagnositcs using only left-over samples.*
➔ *Notification only, no official approval issued*

Substantial modifications for performance studies falling under the "notification only" regulatory pathway legally do not need to be notified or approved by the FAMHP.

We however ask sponsors to keep us updated on any substantial modifications by providing us the modified documents through CESP or via ct.rd@fagg-afmps.be. No official "Acknowledgement of Receipt" (AoR) letter will be sent.

This notification is free of any charge.

7.4. Withdrawal

A sponsor may decide to withdraw an ongoing application of a substantial modification. Withdrawal of the application is possible at any time between the date of submission of the substantial modification of the date the final decision is issued.

Please refer to section 6.5 for more information.

7.5. Conclusions

After notification and/or evaluation of the dossier according to one of the above described procedures a final conclusion is provided to the sponsor by the FAMHP and/or EC. Following final conclusions can be issued:

- **"Acknowledgement of receipt":** substantial modifications notified under the "notification only" regulatory pathway will receive an acknowledgement of receipt letter if the dossier is complete, the substantial modification may now be implemented.
- **"Rejected":** the notification or application is rejected after validation if the dossier is incomplete or if the response to the validation questions was not received within the legal deadlines. The applicant is provided with a brief explanation detailing the grounds on which the notification or application is rejected. The substantial modification may not be implemented. In case of a rejection the (completed or amended) dossier can be re-submitted at any time.
- **"Authorised"**: the substantial modification can be implemented immediately.
- **"Authorised with recommendation(s)"**: the substantial modification can be implemented immediately, it is however advised to take into consideration the recommendation(s) provided.
- **"Authorised subject to conditions"**: the modifications can be implemented however the approval is subject to the conditions mentioned in the approval letter. The approval letter will clearly state how the conditions should be fulfilled. This could be by submitting the requested adaptions/information as a new substantial modification (as soon as possible) or by submitting the adaptions/information as a non-substantial modification (together with the next substantial modification).
- **"Refused"**: the substantial modification cannot be implemented. The applicant is provided with a brief explanation detailing the grounds on which the modification is refused. In case of refusal, the dossier can be re-submitted. In this case, the sponsor is asked:
    - to adapt the dossier (to answer the objections given in the refusal letter);
    - to add the refusal letter to the dossier;
    - to add a description of the changes compared to the previous submission.

8. Safety reporting

Safety reporting in clinical performance studies should be done in line with the requirements of IVDR Article 76.

For detailed information, please consult the MDCG 2024-4 guidance on safety reporting in performance studies of *in vitro* diagnostic medical devices under Regulation (EU) 2017/746 available on the website of the European Commission should also be consulted in addition to the information below. As Eudamed is not yet available and fully functional, this guidance outlines the procedures for safety reporting in the absence of Eudamed.

8.1. Scope

Serious adverse event reporting is mandatory for performance studies. The rules for reporting depend on the regulatory pathway the performance study needs to follow, see annex III for a summary.

NOTE

- In situations where a performance study has started using a non-CE marked IVD, and the right to bear the CE marking has been obtained before the end of the performance study, the SAE reporting continues using the SAE reporting procedures of performance studies as described here, until completion of the investigation.

- For performance studies involving CE marked comparator IVDs used within their intended purpose, SAEs occurring in or to subjects that are in the comparator arm of the performance study must also be reported according to the SAE reporting procedures of performance studies as described here. Please note that vigilance reporting remains necessary.

- SAEs concerning CE marked IVDs which meet the vigilance reporting criteria also need to be handled under the post-market surveillance/vigilance system.

8.2. Reportable events

In general the following events are considered **reportable events**:

a. any serious adverse event (SAE)[4] that has a causal relationship with the device[5], the comparator[6] 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).

From the definition above, it also follows that SAEs related to a CE marked IVD which is part of a PS with an IVD for PS (for example a CE marked comparator IVD or a CE marked IVD that is used during the study procedure) are reportable if there is a causal (or reasonably possible) relationship to that IVD. The reporting procedures described in this guide should then be followed by the PS sponsor, in addition to the normal vigilance reporting for CE marked devices by the manufacturer (double reporting is certainly possible).

For multinational performance studies this includes the reporting of SAEs occurring in other member states or even in 3rd countries when these studies are performed under the same clinical performance study plan (same protocol code). It is acknowledged that the same PS can be conducted under different versions of the same PSP code in different MS, e.g. with country specific adaptations, and in those cases the SAE reporting can normally be combined for all the versions of the PSP for the same PS.

Reportable events occurring before the PS is authorised to start in a MS will be reported to this MS upon authorization in this MS.

Both the relationship between the occurrence of each adverse event and the use of the device (device for performance study and comparator), and the relationship between the occurrence of each adverse event and the study procedure (including the medical and surgical procedure), must be assessed and categorized. For the purpose of harmonizing reports each SAE must be classified according to four different levels of causality:

- not related
- possible
- probable
- causal relationship

[4] SAE ≠ SADE. Please see section 2 'definitions'. SAE is a broader term than SADE.
[5] Device= device for performance study.
[6] A comparator might be: other CE-marked IVD, reference method, gold standard,…

Only the causality level "not related" is excluded from reporting. If either the sponsor or the investigator has assigned a higher causality level than "not related", the event should be reported.

Specifically for PMPF studies with burdensome and/or invasive procedures, only SAEs where a **causal relationship** between the serious adverse event and the preceding performance study has been established are considered reportable events.
Additionally the IVDR provisions related to vigilance apply.

8.3. How to report SAEs

8.3.1. Reporting form

Once Eudamed is available and fully functional SAE reporting will have to be done through the Eudamed web form. Until then, the new template for safety reporting should be used to report SAEs. This tabular form can be found in the Appendix of the MDCG 2024-4 guidance and needs to be filled in/updated for each reportable event or for new findings/updates to already reported events.
Guidelines on how to complete the form can be found in section 11 of the MDCG 2024-4 guidance.
The reporting form is study specific and covers only a given PS, defined by a distinct PSP. English is the recommended language for the reporting form. The reporting form needs to be compatible with Microsoft Excel when sent. Sponsors who generate the excel report file by automated processes may implement other technical features in their systems for excel file generation to ensure the preferred terms listed in metadata are used.
The template form contains inserted filters and functionalities to facilitate the use of **preferred terminology** in the reporting. These are **important for the analysis and should be maintained**.
The table gives a **cumulative** overview of the reportable events per PS and will be updated and transmitted to participating NCAs each time a new reportable event or a new finding to an already reported event is to be reported.

8.3.2. Reporting timelines

- For all reportable events as described in section 6 which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: **immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.**
  This includes events that are of significant and unexpected nature such that they become alarming as a potential public health hazard. It also includes the possibility of multiple deaths occurring at short intervals.
  These concerns may be identified by either the NCA or the sponsor.

- Any other reportable events as described in section 6 or a new finding/update to it: **immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.**

8.3.3. Report to whom

Reportable events must be reported all at the same time to all national competent authorities where the performance study is authorized to start or has commenced.

In Belgium the SAE reporting form may be sent to the R&D division of the FAMHP by e-mail at ct.rd@fagg-afmps.be or through CESP.
If you send it directly by email to ct.rd@fagg-afmps.be, please mention the following in the subject line: "SAE notification – Performance study *Eudamed number*" (use the Eudamed number provided on the approval letter).

9. End of performance study, temporary halt or early termination

9.1. End of the performance study

A performance study ends with the last visit of the last subject unless another endpoint is specifically set out in the performance study plan.

> The sponsor must notify the FAMHP of the end of the performance study. This notification must be made **within 15 days** of the end of the study in Belgium. We ask to send an official signed letter by email to ct.rd@fagg-afmps.be , please mention the following in the subject line: "End of performance study notification – *Eudamed number*" (use the Eudamed number provided on the approval letter).

For multinational studies the sponsor must notify the FAMHP of the end of the performance study in Belgium and a second notification must be made to the FAMHP when the performance study ends in all Member States. Both notifications must be made **within 15 days**.

9.2. Temporary halt or early termination

The sponsor must notify the FAMHP in case of a temporary halt or early termination of the performance study. This notification must be made **within 15 days** of the temporary halt or early termination, providing a justification of the event.

In the event that the sponsor has temporarily halted or terminated early the performance study on safety grounds, the FAMHP must be informed **within 24 hours** of the event.

> Notifications must be sent to the FAMHP by email to ct.rd@fagg-afmps.be. Please mention the following in the subject line: "Temporary halt/early termination – Performance study: *Eudamed number*" (use the Eudamed number provided on the approval letter).

9.3. Performance study report

Within one year of the end of the performance study, the full final performance study report must be submitted to the FAMHP by email to ct.rd@fagg-afmps.be. Please mention the following in the subject line: "Performance study report – *Eudamed number*" (use the Eudamed number provided on the approval letter).

In case of a temporary halt or early termination this report must be provided **within 3 months**.

According to the IVDR (Art. 73.7) the final report must also be made publicly available. In absence of Eudamed this public version of the final report may be published on the company website. Please also notify the FAMHP of the location of this published final report.

Annex I – Fees

An invoice will be sent to the sponsor at the end of a process for the payment of fees. The table below indicates the fees according to the specific output. The total fees include the fees for the EC and the FAMHP.

The cover letter should include all details that need to be present on the invoice: company name, postal address, e-mail (not mandatory), VAT-number (or EIN-number), purchase order number (if applicable) or any other relevant information (also for substantial modifications).

Please note that non-commercial sponsors don't have to pay a retribution.

Fees - index 2025

Output – Regulatory pathway	**Total Fees** (EC + FAMHP fees)
Consolidated opinion FAMHP and EC – initial submission	€ 12.019,11
Consolidated opinion FAMHP and EC – substantial modification	€ 4.068,97
Validation FAMHP and opinion EC – initial submission	€ 8.744,04
Validation FAMHP and opinion EC – substantial modification	€ 3.010,58
Notification only – initial submission	€ 1.834,32
Notification only – substantial modification	/
Due fees if the application is not valid	€ 610,52

Annex II – Classification for additional burdensome or invasive procedures for Belgium

This list can be used for both MDR and IVDR studies if any of the procedures are applicable. The 2 tables below establish whether an additional procedure should be considered burdensome or invasive.

Additional procedures NOT considered burdensome or invasive (if applicable)
patient surveys, compilation of parameters for the assessment of quality of life, such as pain assessment, dietary assessment, etc.
semi-automatic or automatic data collection by apps
(self-)blood pressure monitoring
cardiac Holter monitoring; EEG and ECG measurements
ultrasound imaging **if no contrast agent must be administered**
thermography
consultation for clinical-physical examination
examinations regarding cognitive faculty
non-invasive collection of other material to be examined (saliva, hair)
use of surplus examination materials gathered during a diagnostic/therapeutic routine check-up
hearing and eye tests (ophthalmoscopy, tympanometry)
venous or capillary blood sampling by finger or heel prick
collection of urine and/or stool samples (e.g. by means of urine bags)
bio-impedance analysis
lung function tests, spirometry (without provocation test)

Additional procedures considered burdensome or invasive (if applicable) includes but is not limited to:
functional testing session with a risk of falling
(laser) ophthalmoscopy
magnetic resonance imaging
any application of radiation (including DEXA examination, x-ray imaging, CT scan, endoradiology examinations such as scintigraphy, …)
any biopsy (in the case of clinically indicated tissue)
lumbar puncture, bone marrow aspiration
invasive cardiac procedure (catheterization, stent, angioplasty)
ultrasound imaging **if contrast agent must be administered**
sedation, anxiolysis, general anesthesia
provocation tests: e.g., lung function examination, stress ECG, stress echo, sleep deprivation
blood test (venous puncture)
polysomnography
endoscopy/endoscopic ultrasound (bronchoscopy, gastroscopy, …)
oral glucose tolerance test
Procedures that impose a psycho-social burden within the context of the study

Note: if the additional procedures designed by the sponsor are not listed yet, the sponsor may take contact with the FAMHP.

Please keep in mind that the qualification for a procedure as burdensome and/or invasive is mostly determined from the perspective of the person bearing the burden. Whether a procedure is burdensome may vary according to age, health status and vulnerability of the subject and the duration, previous experience, repetition or accumulation of the procedure compared to standard of care.

Annex III – Decision table for reportable events (SAEs and incidents)

Regulatory pathway	Reportable events and definitions	How to report	To be reported by
Consolidated opinion FAMHP & EC	See 8.2 Reportable events	See 8.3 How to report SAEs, ct.rd@fagg-afmps.be	Sponsor
Validation FAMHP & opinion EC	1. All reportable events according to vigilance see IVDR articles 82-86 **AND** 2. ONLY for those SAEs where a **causal relationship** between the SAE and the **preceding investigational procedure**[7] has been established.	1. vigilance.meddev@fagg-afmps.be according to IVDR article 82-86 **AND** 2. See 8.3 How to report SAEs, ct.rd@fagg-afmps.be	1. Manufacturer[8] **AND** 2. Sponsor
FAMHP notification only	See 8.2 Reportable events	1. See 8.3 How to report SAEs, ct.rd@fagg-afmps.be	Sponsor
When only EC law 2004 is applicable	1. All reportable events according to vigilance see IVDR articles 82-86 **AND** 2. See 8.2 Reportable events	1. vigilance.meddev@fagg-afmps.be according to IVDR article 82-86 **AND** 2. EC	1. Manufacturer[5] **AND** 2. Sponsor

[7] The "preceding investigational procedure" is broader than only "the additional burdensome and/or invasive procedure(s)".

[8] Sponsors should make sure that the device manufacturer is notified about any incidents related to the device and the legal manufacturer of the device is responsible for the subsequent vigilance reporting.

Annex IV – Overview of deadlines for each regulatory pathway

Please note that the legal deadlines depicted in the table below are considered to be maximum deadlines.

	VALIDATION FAMHP OPINION EC		**CONSOLIDATED OPINION FAMHP AND EC**		**NOTIFICATION ONLY**	
	INITIAL	SUBSTANTIAL MODIFICATION	INITIAL	SUBSTANTIAL MODIFICATION	INITIAL	SUBSTANTIAL MODIFICATION
Reception of dossier	T0 = TS	T0 = TS	TS	T0 = TS	TS	/
Validation questions (if applicable)	/	/	TS +10d*	T3	/	/
Deadline response to validation questions	/	/	TS +20d**	T3bis°	/	/
Validation complete	T5	T5	T0 (=TS +25d***)	T6	TS + 10d	/
RFI sent to sponsor (if applicable)	/	/	T28 (or T48)	T24 (orT31)	/	/
Response to RFI	/	/	T28bis° (or T48bis°)	T24bis° (or T31bis°)	/	/
Final conclusion	T30	T38	T45 (or T65)	T38 (or T45)	/	/

* FAMHP may add 5d to the legal deadline of 10d to send validation questions, in this case this will be communicated to the sponsor by mail

** a legal extension of the deadline to respond to validation question of 20d can be granted upon request

*** FAMHP may add 5d to the legal deadline of 5d to assess the response to the validation questions, in this case this will be communicated to the sponsor by mail

( ) a legal extension of the deadlines by 20d is possible for initial applications and an extension of 7d for substantial modifications, this for the consultation with experts. In this case this will be communicated to the sponsor by mail.

° the sponsor has maximum 20d to respond to validation questions or RFI