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

Guideline Submission Processes of Clinical Investigations according to MDR in Belgium

This document aims at providing guidance for the different submission processes for clinical investigations under the new regulation from a national point of view.

Version 9.0, 24.02.2023

Document revision history

Date of publication	Revision description
03.03.2021 – version 1.0	First publication
07.05.2021 – version 2.0	- Update of SAE definition in the CIP (section 3) - Clarification on the handling of substantial modifications for investigations approved under MDD (section 3 and 6). - Update of list of documents to be included in the submission package (sections 5.1, 5.3 and 5.4) - Annex I – table specifying the different deadlines for each regulatory pathway was added - Annex II – Fees
18.05.2021 – version 3.0	- Figure 3: addition of decision step 7
07.06.2021 – version 4.0	- Figure 3: decision step 7 altered and decision step 8 added. - Update of documents needed for each regulatory pathway. - Section 5.2: Clarification that EC procedure can differ depending on type of clinical investigation. - Annex II: table with fees updated - Annex III added: Classification for additional burdensome or invasive procedures for Belgium
08.07.2021 – version 5.0	- Update figure 2: for custom-made and in-house devices a distinction is made between investigations which will be used for conformity assessment and investigations which will not be used for conformity assessment. - Update section 6 concerning the reporting of non-substantial modifications. - Update section 7: Clarification concerning SAE reporting for PMCF investigations. - Update annex I: clarification concerning separate opinion FAMHP and EC
26.10.2021 – version 6.0	- Correction of timeline for the regulatory pathway “separate opinion FAMHP and EC” for both initial submissions and substantial modifications (sections 5.4, 6.4 and annex I). - The option “rejected” was added to the conclusion sections (section 5.5 and 6.5). - Clinical evaluation plan was added to the list of documents needed for the consolidated and separate opinion FAMHP and EC pathway (section 5.3 and 5.4). -
17.03.2022 – version 7.0	- General update of whole document - Section concerning ongoing investigations and transition period updated and moved to end of document, now section 8. - Section 3 added: clinical investigations under MDR - Section 4.1 on dossier structure added - Update Section 7: clarification concerning safety reporting rules and materiovigilance - Annex II: Fees updated - Annex IV added: decision table for safety reporting

04.07.2022 – version 8.0	- Sections 4.1, 4.2 and 4.4: planning document added to list of documents to be submitted. - Annex III: update of tables for classification for additional burdensome or invasive procedures for Belgium.
24.02.2023 – version 9.0	- Corrections and clarifications throughout the document. - Section 4.6 and 5.5: clarification on approval with conditions - Section 6: links to newest versions of the MDCG 2020-10/1 guidance on SAE reporting and the new safety report form. Clarifications added on how to use the new form. - Annex II: indexation of fees

Contents

1. Introduction

As of May 26, 2021, the European Regulation (EU) 2017/745 on Medical Devices (MDR) came into force. The MDR introduced a major update of the regulatory framework in the European Union and brought about several changes to the scope of investigations that must be submitted for approval, the submission processes for clinical investigations and their substantial modifications, submission dossier contents and safety reporting.

The MDR sets up 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 MDR itself does not provide sufficient information for its application into practice. Therefore, in Belgium, a dedicated law and royal decree have been approved on 22.12.2020[1] and 18.05.2021[2] respectively, including general practical information for clinical investigations and evaluation. For example, different regulatory pathways were developed according to the type of clinical investigation.

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

[1] FR link: http://www.ejustice.just.fgov.be/cgi/article_body.pl?language=fr&pub_date=2021-01-18&caller=summary&numac=2021030071
NL link: http://www.ejustice.just.fgov.be/cgi/article_body.pl?language=nl&pub_date=2021-01-18&caller=summary&numac=2021030071
[2] Link: http://www.ejustice.just.fgov.be/mopdf/2021/05/25_1.pdf#Page41

2. Definitions and abbreviations

All definitions provided in this section are compliant with the definitions stated in the regulation 2017/745.

AoR: Acknowledgement of Receipt

AE: Adverse events are any untoward medical occurrence, 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 clinical investigation, whether or not related to the investigational device.

Note:

a. This definition includes events that are anticipated as well as unanticipated events.

b. This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved. For the purpose of safety reporting all activities related to the use of a medical device may be considered procedures.

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 guideline

Clinical investigation: any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance (including clinical benefits) of a medical device.

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

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).

Custom-made device: any device specifically made in accordance with a written prescription of any person authorised by national law by virtue of that person's professional qualifications which gives, under that person's responsibility, specific design characteristics, and is intended for the sole use of a particular patient exclusively to meet their individual conditions and needs.

However, mass-produced devices which need to be adapted to meet the specific requirements of any professional user and devices which are mass-produced by means of industrial manufacturing processes in accordance with the written prescriptions of any authorised person shall not be considered to be custom-made devices.

Device deficiency: any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer

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 MDR Annex XV, Chapter II, point 2).

IMD: Investigated medical device

In-house device: a medical device manufactured or modified in-house by health institutions to address, on a non-industrial scale, the specific needs of target patient groups which cannot be met at the appropriate level of performance by an equivalent device available on the market. They must comply with the rules laid out in Article 5.5 of Regulation (EU) 2017/745.

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

MDD: Medical Device Directives 90/385/EEC or 93/42/EEC

MDR: European Regulation (EU) 2017/745 on Medical Devices

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.

Please note that when a medical device is in the development phase, for example a prototype, the prototype may be tested on subjects in order to validate certain parts of the medical device. Although the prototype may not fulfil its intended medical purpose yet, the product nevertheless already qualifies as a medical device, since that is the potential aim of the product. Other products are solely developed to demonstrate a working principle for academic purposes, without the aim of transforming the product itself into a medical device. In those cases, the product does not qualify as a medical device".

PMCF: Post-market clinical follow-up investigation

RFI: Request for information

SADE: An adverse device effect is an adverse event (ADE) related to the use of an investigational device. A **serious adverse device effect** is an adverse device effect that has resulted in any of the consequence characteristics of a serious adverse event.

SAE: a **serious adverse event** is any adverse event that led to any of the following:

a. death,
b. serious deterioration in the health of the subject, 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,
c. foetal distress, foetal death or a congenital physical or mental impairment or birth defect (MDR Article 2(58)).

3. Clinical investigations under MDR

3.1. Does the study fall within scope of MDR?

For a study to fall within scope of the MDR, the investigational device must fall under the definition of a medical device and the study must qualify as a clinical investigation (MDR art. 1). The flowchart below can be used to help determine if both conditions are met. The steps in the flowchart are explained below.

Note, for more information concerning the qualification (and classification) of **software** in the context of the MDR the "Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR" can also be consulted.

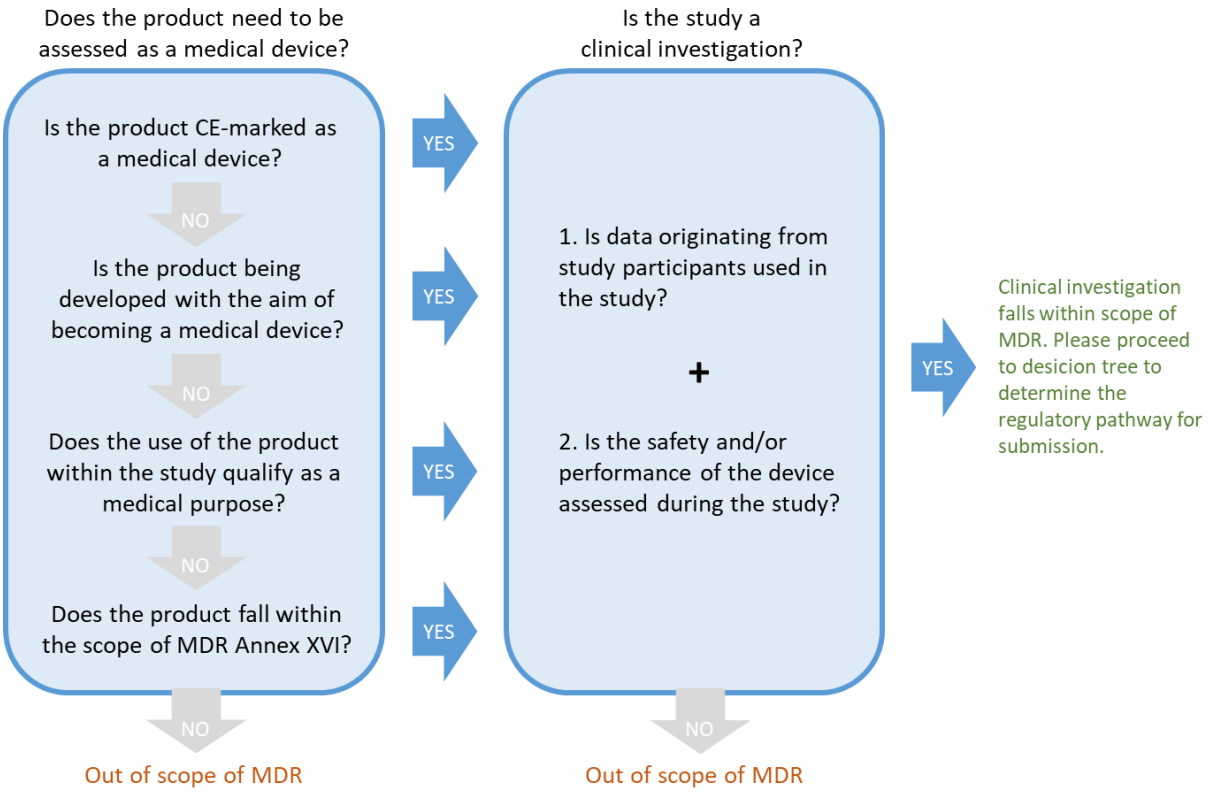

Figure 1. Does the study fall within scope of MDR?

In a first step (first blue box), it needs to be determined if the product is to be assessed as a medical device following its intended purpose.

- **Is the product CE-marked as a medical device?**
  A product is CE-marked as a medical device if the manufacturer claims that the intended purpose is a medical purpose. The product thus qualifies as a medical device under the definition and should be assessed as such. The product should in

this case have a valid CE-mark according to the MDD, AIMD or MDR.

- **Is the product being developed with the aim of becoming a medical device?**
  When a medical device is in the development phase, for example a prototype, the prototype may be tested on subjects in order to validate certain parts of the medical device. Although the prototype may not fulfil its intended medical purpose yet, the product nevertheless already needs to be assessed as a medical device.

- **Does the use of the product within the study qualify as medical purpose?**
  If a product is used within a clinical investigation for a medical purpose, it qualifies as a medical device and should be assessed as such. Devices which are for example marketed without a medical purpose but used with a medical purpose within the clinical investigation should be assessed as a medical device.

- **Does the product fall within the scope of MDR Annex XVI?**
  MDR Annex XVI lists products without an intended medical purpose whose risk profiles are however considered to be similar to analogous medical devices. Therefore, the products listed in Annex XVI are also to be considered and assessed as medical devices.

MDR ANNEX XVI LIST OF GROUPS OF PRODUCTS WITHOUT AN INTENDED MEDICAL PURPOSE

1. Contact lenses or other items intended to be introduced into or onto the eye.
2. Products intended to be totally or partially introduced into the human body through surgically invasive means for the purpose of modifying the anatomy or fixation of body parts with the exception of tattooing products and piercings.
3. Substances, combinations of substances, or items intended to be used for facial or other dermal or mucous membrane filling by subcutaneous, submucous or intradermal injection or other introduction, excluding those for tattooing.
4. Equipment intended to be used to reduce, remove or destroy adipose tissue, such as equipment for liposuction, lipolysis or lipoplasty.
5. High intensity electromagnetic radiation (e.g. infra-red, visible light and ultra-violet) emitting equipment intended for use on the human body, including coherent and non-coherent sources, monochromatic and broad spectrum, such as lasers and intense pulsed light equipment, for skin resurfacing, tattoo or hair removal or other skin treatment.
6. Equipment intended for brain stimulation that apply electrical currents or magnetic or electromagnetic fields that penetrate the cranium to modify neuronal activity in the brain. 5.5.2017 L 117/173 Official Journal of the European Union EN

If you answer “no” to all of the above questions, your product falls out of scope of the MDR and should not be assessed as a medical device.

If you answer “yes” to at least one of the above questions your product should be assessed as a medical device and you can proceed to the next step (2nd blue box) where you have to determine if the study qualifies as a clinical investigation.

According to the MDR a clinical investigation is any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance (including clinical benefits) of a medical device. This means, more specifically, that you need to answer “yes” to both of the following questions for your investigation to qualify as a clinical investigation.

- **Is data originating from study participants used in the study?**
  During a clinical investigation clinical data is collected, used and/or analyzed. For a study to qualify as a clinical investigation this clinical data must be originating from study participants. Please note that the MDR does not make any distinction between prospective or retrospective studies, a retrospective study may also qualify as a clinical investigation.

- **Is the safety and/or performance of the device assessed during the study?**
  If the assessment of the safety and/or performance of the device, including clinical benefits, is included in one or more endpoints of the study, the study may qualify as a clinical investigation.

Examples:

- *A clinical study assessing the performance of a CE-marked device by gathering clinical data in a retrospective way qualifies as a clinical investigation and falls within the scope of the MDR.*

- *A study assessing the performance of a medical device software does not qualify as a clinical investigation if “fake datasets” are used for the analyses. Although the software should be assessed as a medical device and the performance of the device is an endpoint of the study, the data does not originate from study participants so the study falls out of scope of the MDR.*

3.2. Regulatory pathways

If the investigational device needs to be assessed as a medical device and the study qualifies as a clinical investigation, it falls within scope of the MDR. All clinical investigations within the scope of the MDR need to follow a regulatory pathway with the involvement of an Ethics Committee (EC) and/or Belgian competent authority (FAMHP). Depending on the status of the investigational medical device, the submission procedure can be different. The different process flows and regulatory pathways are depicted in Figure 2.

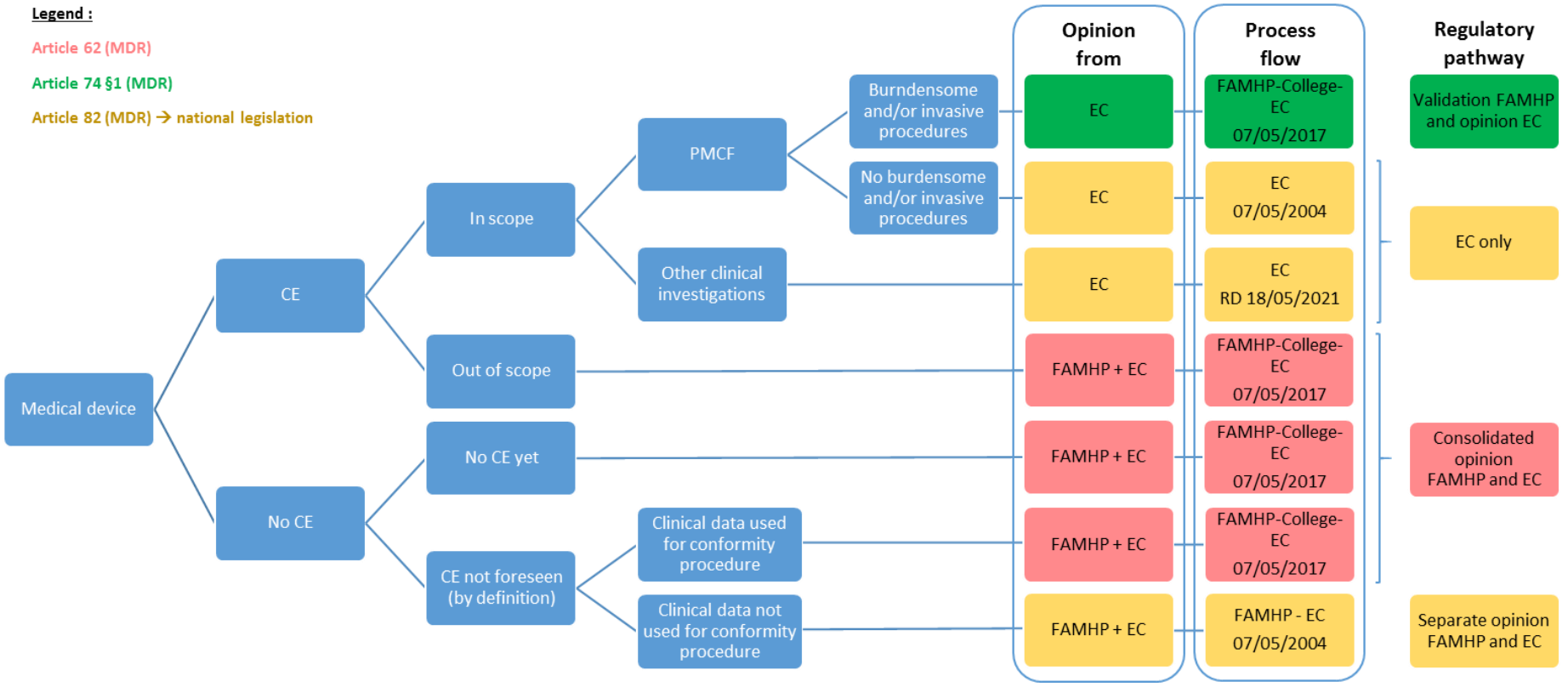

Figure 2. Different regulatory pathways. Different process flows and regulatory pathways are possible depending on the status of the investigational medical device and clinical investigation properties.

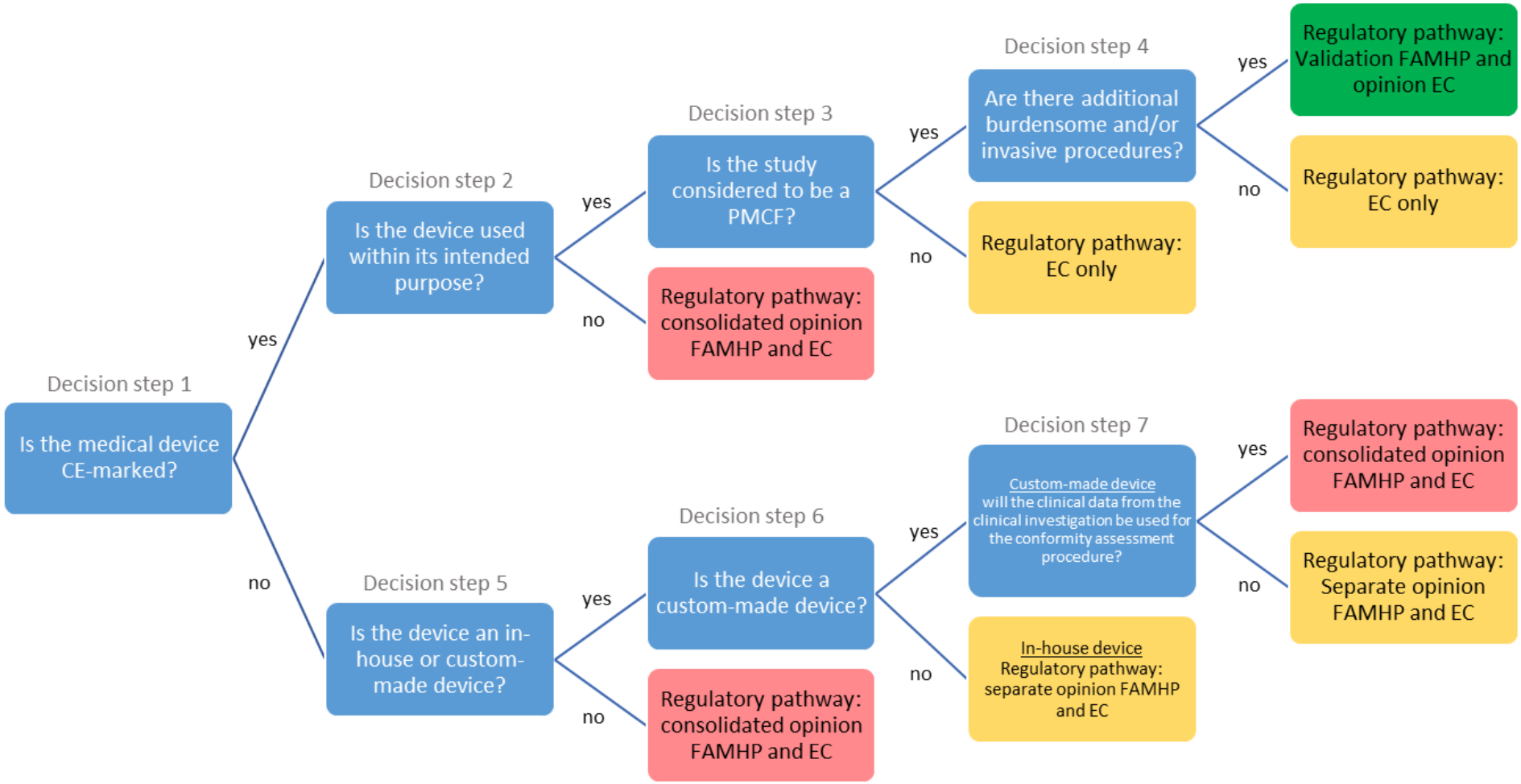

Figure 3. Decision tree

As described above, if the investigational device needs to be assessed as a medical device and the study qualifies as a clinical investigation, it falls within scope of the MDR. The decision tree in Figure 3 and corresponding decision steps below will guide you towards the correct regulatory pathway. The specific procedures of each regulatory pathway are discussed in more detail in section 4.

Decision step 1

If the investigational medical device has a valid CE label you can proceed to decision step 2.

If the investigational medical device does not have a CE label you can proceed to decision step 5.

Decision step 2

In this step, it is necessary to understand:

- what the intended purpose [3]of the device covered by the CE mark is, and
- to check if the planned use in the clinical investigation is covered by this intended purpose.

If the planned use in the clinical investigation is covered by the intended purpose, then the device is considered to be used *"in scope", meaning that the investigated medical device will be used as it would be used outside the clinical investigation including in regards of procedures linked to its use*. In this case, you can proceed to decision step 3.

If the planned use in the clinical investigation is not covered by the intended purpose, then the device is considered to be used *"out of scope*". In this case a consolidated positive advice needs to be obtained from the FAMHP and EC, "Regulatory pathway: consolidated opinion FAMHP and EC" needs to be followed.

Examples:

- *Consider a prospective, multicentre clinical investigation with a CE approved cochlear implant. The aim of the study is to investigate the incremental change of the software functionality and the concept of a new signal processing method. As the investigational device is not used with the CE-approved software during the investigation, it is used*

[3] The intended purpose means the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use, other promotional and sales materials or statements and as specified by the manufacturer in the clinical evaluation.

"out of scope" and thus needs to be submitted though the "Regulatory pathway: consolidated opinion FAMHP and EC".

- *The manufacturer of a "self-expandable metal stent" CE-marked to be used for the treatment of pancreatic pseudocysts wants to conduct a feasibility study to investigate the safety and technical performance of this stent used during endo-echoscopic gall bladder drainage in patients with acute cholecystitis. As the investigational device is used for an indication which is not covered by its CE-mark it is used "out of scope" during this clinical investigation and needs to be submitted though the "Regulatory pathway: consolidated opinion FAMHP and EC".*

Decision step 3

A post-market clinical follow-up (PMCF) investigation is conducted to further assess a CE-marked medical device within its intended purpose to proactively collect clinical data which would confirm the safety and/or performance following a PMCF plan. Further information can be found in Annex XIV, Part B of Regulation (EU) 2017/745 and related guidance on PMCF. If the investigation with the medical device is considered to be a PMCF investigation you can proceed to decision step 4.

If the clinical investigation with a CE-marked medical device, that is used within its intended purpose, is not considered to be a PMCF, only positive advice from the relevant EC(s) is necessary and "Regulatory pathway: EC only" needs to be followed. Examples of such studies are studies not covered by the definition of a clinical investigation or studies without any aim regarding the collection of clinical data that would be used to confirm the safety and/or performance of the medical device. These are not planned in the PMCF plan and will not be taken into account in the PMCF report or in the updates of conformity assessment.

Example:

Consider an academic clinical investigation comparing two different types of implants used to treat the same medical condition. Both implants are CE-marked and used according to the instructions for use. This study is considered to be an "other clinical study" (figure 2) and should be submitted following the "Regulatory pathway: EC only".

Decision step 4

In the scope of PMCF studies an **additional** procedure is a procedure additional to those performed under the normal conditions of use of the device.

Procedures which are **burdensome** can include a wide variety of different interventions which may include procedures which may cause pain, discomfort, fear, disturbances of lives and

personal activities or otherwise unpleasant experiences. It 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.

In annex III you can find two tables establishing whether an additional procedure should be considered burdensome or invasive. Attention, the first table list procedures which are NOT considered to be invasive or burdensome in Belgium. The second table lists procedure which should be considered as burdensome or invasive in Belgium.

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

If there are no invasive or burdensome additional procedures foreseen during the PMCF investigation, a positive advice from the EC needs to be obtained through "Regulatory pathway: EC only".

Example:

A clinical investigation aims at investigating a surgically invasive CE-marked medical device used within its intended purpose. This investigation is designed by the manufacturer as part of its PMCF plan to evaluate the medical device's performance in a real-life situation. An extra CT-imaging will be performed from the onset of the follow-up and repeated every two years for a period of six years. According to Annex III of this guidance the CT-imaging is to be considered an additional burdensome procedure additional to the normal conditions of use of the medical device. The investigation should thus be submitted via the "Regulatory pathway: validation FAMHP and opinion EC".

Decision step 5

If the medical device falls under the definition of a custom-made device or an 'in house' device, according to the definitions outlined in this document, you can proceed to decision step 6.

If the medical device is not a custom-made or 'in-house' device, a consolidated positive advice needs to be obtained from the FAMHP and EC, "Regulatory pathway: consolidated opinion FAMHP and EC" needs to be followed.

Examples

- *Consider a non-randomized feasibility study in which a prototype of a medical device is tested. The primary outcome parameters are the feasibility and the safety. As this investigational device is not CE-marked it must be submitted via the "Regulatory pathway: consolidated opinion FAMHP and EC".*

- *Similarly, a telemedicine study using a non- CE labelled smartphone based telemonitoring and a digital support platform for the monitoring of heart failure must also be submitted via the "Regulatory pathway: consolidated opinion FAMHP and EC".*

Decision step 6

If the medical device is a custom-made device you may proceed to decision step 7.

If the medical device is an 'in-house' device a positive advice from the EC and FAMHP needs to be obtained, a parallel submission of the dossier must be done as explained in "Regulatory pathway: separate opinion FAMHP and EC".

Example

Consider a clinical investigation of an in-house developed and used, stand-alone software intended to be used for psychoeducation. Based on information following from generic questionnaires, the patients and personnel are provided with several psychotherapies, feedback, and tools for relapse prevention. The aim of the investigation is to investigate the efficacy and outcomes of the software. As this is an in-house developed and used software the study may be submitted via the "Regulatory pathway: separate opinion FAMHP and EC".

Decision step 7

For clinical investigations with custom-made devices a distinction must be made between investigations which will be used for conformity assessment (although products are not CE marked) and investigations which will not be used for conformity assessment.

If the clinical data from the clinical investigation may be used for the conformity assessment, then, a consolidated positive advice needs to be obtained from the FAMHP and EC: "Regulatory pathway: consolidated opinion FAMHP and EC" needs to be followed.

If the clinical data from the clinical investigation is not used for the conformity procedure, a positive advice from the EC and FAMHP needs to be obtained: a parallel submission of the dossier must be done as explained in "Regulatory pathway: separate opinion FAMHP and EC".

Example

A manufacturer aims to place his new custom-made orthopaedic shoes on the market. To demonstrate the required general safety and performance he first wishes to compare his shoes to the standard of care in a clinical investigation. As the investigational device is a custom-made medical device and the data will be used for conformity assessment the study must be submitted via the "Regulatory pathway: consolidated opinion FAMHP and EC".

4. Submission procedures for clinical investigations (initial applications)

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 of the initial application and communicated together with the status of the dossier.

4.1. 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 - List of submitted documents - Planning document - Any other supportive information (e-mails, letters, tables,…) Proof of parallel application to the EC (only for Regulatory pathway: separate opinion FAMHP and EC)
B. APPLICATION FORM	- signed application form for initial applications
C. CIP	- CIP - Any CIP addenda or annexes - CIP synopsis
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. CEP - PMCF	- Clinical evaluation plan or; - PMCF plan in case of post-market clinical study
H. COMPARATOR	- Instructions for use

	- CE certificate - 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
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	- Written statement for each site
O. INSURANCE	- Proof of insurance cover or identification
P. FINANCIAL ARRANGEMENTS	- Description of compensation for participants - Clinical investigation 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. For a detailed description of each dossier document we kindly refer to our guidance on dossier content: "Clinical Investigations – Guidance on Dossier Content" on our website.

4.2. Regulatory pathway: validation FAMHP and opinion EC

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

Where a clinical investigation is to be conducted to further assess, within the scope of its intended purpose, a device which already bears the CE marking in a PMCF investigation, and where the investigation would involve submitting subjects to procedures additional to those performed under the normal conditions of use of the device and those additional procedures are invasive and/or burdensome, the sponsor shall **notify the FAMHP at least 30 days prior to its commencement**. The FAMHP validates the dossier after which an independent EC is appointed by the CT-College for assessment of the dossier.

Following documents must be included in the notification package:

- Cover letter
- 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 Investigation Plan (CIP)
- CIP synopsis
- CE certificate
- Technical documentation
- PMCF plan
- Proof of insurance
- Manufacturer's instructions for use (if not included in technical documentation)
- CV and Declaration of Interest (DOI) of the principal investigator of each site.
- Suitability of each clinical site
- 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 clinical investigation agreement and proposed compensation to the investigation site or principle investigator.
- CE certificate and manufacturer's instructions for use of any comparator device used

The complete dossier must be submitted via CESP to the agency, 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 any of the above described documents it will be rejected automatically.**

If complete, the dossier will be dispatched to an independent EC (accredited following the law of 07/05/2017) who will evaluate the dossier within 30 calendar days of the date of reception. If the EC has no objections to the start of the investigation, the FAMHP will provide the sponsor with an "Acknowledgement of Receipt" (AoR) letter formally stating the absence of any objections. If the EC has major objections to the start of the investigation the application will be rejected.

Annex I gives a detailed overview of the different deadlines for each regulatory pathway.

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

4.3. Regulatory pathway: EC only

- ➔ *PMCF investigations without additional burdensome or invasive procedures.*
- ➔ *Other clinical investigations involving CE-marked devices used within their intended purpose.*
- ➔ *Advice from the EC needs to be obtained.*

These clinical investigations only need a positive advice from the EC, accredited through the law of 07/05/2004, approval from the competent authority is not needed. The dossier must be submitted directly to the EC according to their specific submission procedure. Please note that depending on the type of investigation, the specific EC procedure and timelines can differ. For PMCF investigations without additional burdensome or invasive procedures the timeline for approval is maximum 28 days as these investigations fall entirely under the law of 07/05/2004. Other clinical investigations involving CE-marked devices used within their intended purpose are also regulated under the Royal Decree of 18 May 2021 and as such a timeline of 45 days is applicable. Please contact your EC for more detailed information.

You can check on our website to which EC you can apply for such clinical investigations.

4.4. Regulatory pathway: consolidated opinion FAMHP and EC

- ➔ *Other clinical investigations involving CE-marked devices used outside their intended purpose*
- ➔ *Other clinical investigations involving devices without a CE mark which are not 'in-house' devices.*
- ➔ *Clinical investigations (including those involving custom-made devices) of which the data will be used for conformity assessment.*
- ➔ *Assessment by FAMHP and EC, one consolidated decision is issued.*

These clinical investigations 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 following documents (if applicable):

- Cover letter
- 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 investigation plan (CIP)
- CIP synopsis
- Clinical evaluation plan
- Investigator's Brochure (IB)
- Example of labels
- 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).
- Proof of insurance
- CV and DOI of principal investigator of each site
- Suitability of each site (see template on website)
- 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 clinical investigation 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

Within 10 days of receiving the application, the agency will notify the sponsor as to whether the clinical investigation falls within the scope of the Regulation on medical devices and as to whether the application is complete. If incomplete, validation questions will be asked. 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 approval, 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.

Annex I gives a detailed overview of the different deadlines for each regulatory pathway.

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

NOTE

Article 70 (7) (a) of the MDR states that the sponsor may start the clinical investigation in case of investigational class I devices or in case of non-invasive class IIa and class IIb devices immediately after the validation date of the application, unless otherwise stated by national law. In Belgium, it was decided to fully assess each clinical investigation application regardless of classification of the medical device. The process and timelines described above are thus applicable for all classes of devices.

4.5. Regulatory pathway: separate opinion FAMHP and EC

➔ *Other clinical investigations involving 'in-house' devices or custom-made devices of which data will not be used for conformity assessment.*
➔ *Parallel assessment by FAMHP and EC, two separate approvals are issued.*

These clinical investigations are assessed separately by the competent authority and the ethics committee(s). Two parallel submissions are needed:

- Submission and approval of the dossier directly to the EC(s) according to their specific submission procedure. The EC(s) is/are accredited through the law of 07/05/2004, you can check on our website to which EC(s) you can apply for such clinical investigations.
- Submission (and approval) of the dossier to the FAMHP according to the procedure described below. The deadlines provided below are only considered for the FAMHP, and not for EC(s).

The manufacturer, sponsor or its delegated representative, must submit the dossier electronically via CESP.

The dossier submitted to the FAMHP must contain following documents, if applicable:

- Cover letter
- List of documents submitted (WORD document – see template on website)
- Application form (see template on website)
- Clinical Investigational Plan (CIP)
- CIP synopsis
- Clinical evaluation plan
- Investigator's Brochure (IB)
- Manufacturer's instructions for use
- List of general safety and performance requirements that have already been met, including motivation (template available on our website).
- Proof of insurance
- Proof of parallel application to EC
- Informed consent forms
- CV of principal investigator(s)
- Example of labels
- Description of the arrangements to comply with the applicable rules on the protection and confidentiality of personal data.
- The clinical investigation agreement
- 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

Within 10 days of receiving the application, the agency will notify the sponsor as to whether the clinical investigation is complete. If incomplete, validation questions will be asked. 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, 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 RFI is allowed. The FAMHP will issue its decision on T45 at the latest.

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.

Note that the FAMHP must get the final approval from the EC (separate submission in parallel) before giving its final approval. We therefore ask the sponsor to provide us the EC approval by mail as soon as available.

Annex I gives a global overview of the different deadlines for each regulatory pathway.

From FAMHP perspective, an invoice will be sent to the sponsor at the end of the process for the payment of fees (see Annex II).

4.6. Conclusions

After 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:

- **"Rejected":** the application is rejected during validation if the application does not fall under the scope of the MDR, if the response to the validation questions was not received within the legal deadlines or if the application is incomplete. The applicant is provided with a brief explanation detailing the grounds on which the application is rejected. In case of a rejection the (completed) dossier can be re-submitted at any time.

  For PMCF studies involving additional burdensome and/or invasive procedures the notification can also be rejected if the independent EC issues a negative opinion.

- **"Authorised"**: the clinical investigation can start immediately.

- **"Authorised with recommendation(s)"**: the investigation can start immediately, it is however advised to take into consideration the recommendation(s) provided.

- **“Authorised subject to conditions”**: the investigation 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 as a substantial modification (as soon as possible) or by submitting the adaptions as a non-substantial modification (together with the next substantial modification).

- **“Refused”**: the clinical investigation 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.

5. Substantial modifications

Modifications to a clinical investigation 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 investigation, are considered substantial modifications. Also, changes made to patient information documents (ICF, flyers, brochures,…) are considered substantial modifications. All substantial modifications must be approved by the FAMHP and/or EC before implementation using one of the regulatory pathways described below.

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 investigation: please submit all non-substantial modifications that have not yet been notified together with the notification of the end of the investigation (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 investigational medical device. The decision tree in figure 3 and corresponding decision steps explained in section 3 of this guidance will guide you towards the correct regulatory pathway.

For a detailed description of each dossier document we kindly refer to our guidance on dossier content: “Clinical Investigations – Guidance on Dossier Content” on our website.

Please note that substantial modifications to clinical investigations approved under MDD must still follow the MDD procedure for the approval of the modification.

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

➔ PMCF investigations involving additional burdensome or invasive procedures.
➔ Assessment by FAMHP and EC, one consolidated decision issued.

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

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

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 any of the above described documents, it will be rejected automatically.**

If complete, the dossier will be dispatched to an independent EC (accredited following the law of 07/05/2017) who will evaluate the dossier within 38 calendar days of the date of reception. If the EC has no objections to the substantial modification, the FAMHP will provide the sponsor with an "Acknowledgement of Receipt" (AoR) letter formally stating the absence of any objections. If the EC has major objections to the substantial modification the application will be rejected.

Annex I gives a global overview of the different deadlines for each regulatory pathway.

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

5.2. Substantial modification regulatory pathway: EC only

➔ PMCF investigations without additional burdensome or invasive procedures
➔ Other clinical investigations involving CE-marked devices used within their intended purpose.

The initial submission of this clinical investigation was not approved by the FAMHP, only approval of the EC is necessary. The dossier for substantial modifications must be submitted directly to the EC according to their specific submission procedure.

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

- ➔ *Other Clinical investigations involving CE-marked devices used outside their intended purpose*
- ➔ *Other clinical investigations involving devices without a CE mark which are not 'in-house' devices.*
- ➔ *Clinical investigations (including those involving custom-made devices) of which data will be used for conformity assessment.*
- ➔ *Assessment by FAMHP and EC, one consolidated decision is issued.*

Substantial modifications of these clinical investigations 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
- List of documents submitted (WORD document – see template on website)
- Rationale or justification of the changes (point by point)
- Application form
- 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 II).

5.4. Substantial modification regulatory pathway: separate opinion FAMHP and EC

➔ *Other clinical investigations involving 'in-house' devices or custom-made devices of which data will not be used for conformity assessment.*
➔ *Parallel assessment by FAMHP and EC, two separate approvals are issued.*

The complete dossier must be submitted, via CESP, to the competent authority and also in parallel to the EC according to their specific procedure. The dossier must contain following documents:

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

Within 10 days of receiving the application, the agency will notify the sponsor as to whether the clinical investigation is complete. If incomplete, validation questions will be asked. 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, 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 RFI is allowed. The FAMHP will issue its decision on T45 at the latest.

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.

Note that the FAMHP must get the final approval from the EC (separate submission in parallel) before giving its final approval. We therefore ask the sponsor to provide us the EC approval by mail as soon as available.

Annex I gives a global overview of the different deadlines for each regulatory pathway.

From FAMHP perspective, an invoice will be sent to the sponsor at the end of the process for the payment of fees (see Annex II).

5.5. Conclusions

After 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:

- **"Rejected":** the application is rejected after validation if the application does not fall under the scope of the MDR, if the response to the validation questions was not received within the legal deadlines or if the application is incomplete. . The applicant is provided with a brief explanation detailing the grounds on which the application is rejected. In case of a rejection the (completed) dossier can be re-submitted at any time.

  For PMCF studies involving additional burdensome and/or invasive procedures the notification of the substantial modification can also be rejected if the independent EC issues a negative opinion.

- **"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 substantial modification 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 as a substantial modification (as soon as possible) or by submitting the adaptions 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.

6. Safety reporting

Safety reporting in clinical investigations should be done in line with the requirements of the Regulation (EU) 2017/745 – Medical Device Regulation (MDR) Article 80.

For detailed information, please consult the MDCG 2020-10/1 guidance on safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 (May 2020). As Eudamed is not yet available and fully functional, this guidance outlines the procedures for safety reporting in the absence of Eudamed.

6.1. Scope

Serious adverse event reporting is mandatory for clinical investigations. The rules for reporting depend on the regulatory pathway the clinical investigation needs to follow. For a guiding decision table, please see Annex IV.

NOTE

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

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

- For clinical investigations that follow an EC only regulatory pathway, the sponsor is only obliged to send the SAE reports to the EC and not to ct.rd@fagg-afmps.be.

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

6.2. 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 investigational device, the comparator or the investigation 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).

For multinational clinical investigations this includes the reporting of SAEs occurring in other member states or even in 3rd countries.

Both the relationship between the occurrence of each adverse event and the use of the medical device (investigational device and comparator), and the relationship between the occurrence of each adverse event and the investigational 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

All causality assessments should be made guided by section 9 of the MDCG 2020-10/1 guidance. **Only 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.

When a CEC (or a Medical Safety Monitor or …) adjudicates a previously unreported adverse event as a reportable event and/or when this committee/monitor adjudicates a higher causality assessment to an event than the site or the investigator, the safety report needs to be updated and sent to the national Competent Authority (nCA). The reason(s) should be added to the cell in the column "Free description of event".

Specifically for post-market clinical follow-up (PMCF) investigations with burdensome and/or invasive procedures of CE-marked devices used within the intended use covered by the CE-marking, only SAEs where a **causal relationship** between the serious adverse event and the preceding investigational procedure has been established are considered reportable events.

[4] SAE ≠ SADE. Please see 2.Definitions and abbreviations. SAE is a broader term than SADE.

6.3. How to report SAEs

6.3.1. 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 2020-10/1 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 10 of the MDCG 2020-10/1 guidance.

We strongly encourage that only the IMDRF codes and not the terminology is entered in the columns "Device issue", "Clinical signs/symptoms" and "Clinical impact". Please only use ";" as a divider between the codes in a cell.

6.3.2. Reporting timelines

- For all reportable events which indicate an imminent risk of death, serious injury, or serious illness and that require 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.**

- Any other reportable events 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.**

6.3.3. Report to whom

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

In Belgium the completed 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 – Clinical investigation *Eudamed number*" (use the Eudamed number provided on the approval letter).

For investigations approved under MDD and only approved by the EC, it is requested to continue to provide the SAE reporting directly to the EC and not to ct.rd@fagg-

afmps.be. The same is applicable for investigations approved under the MDR and approved through the EC only pathway.

7. End of clinical investigation, temporary halt or early termination

7.1. End of the clinical investigation

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

The sponsor must notify the FAMHP of the end of the investigation. This notification must be made **within 15 days** of the end of the clinical investigation 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 clinical investigation 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 clinical investigation in Belgium and a second notification must be made to the FAMHP when the clinical investigation ends in all Member States. Both notifications must be made **within 15 days**.

7.2. Temporary halt or early termination

The sponsor must notify the FAMHP in case of a temporary halt or early termination of the clinical investigation. 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 investigation 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 – Clinical investigation *Eudamed number*" (use the Eudamed number provided on the approval letter).

7.3. Clinical investigation report

Within one year of the end of the clinical investigation, the full final clinical investigation report must be submitted to the FAMHP by email to ct.rd@fagg-afmps.be. Please mention the following in the subject line: "Clinical investigation 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 MDR 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.

8. Ongoing clinical investigations approved under MDD

Clinical investigation submissions with a date of reception up until May 25 2021, were handled in accordance with Directives 90/385/EEC or 93/42/EEC (MDD) and their dedicated Belgian laws[5]. Clinical investigation submissions received after May 26 2021 are handled according to the MDR procedures and its dedicated Belgian law.

To enhance a smooth transition from MDD to MDR, several provisions were laid down:

- Clinical investigations which have been approved under MDD, may continue to be conducted after the date of application of the MDR following MDD legislation, but the reporting of SAE and device deficiencies must be carried out in accordance with the MDR requirements from 26 May 2021 and onwards as described in section 7 of this guidance.
    - Please note that the SAE definition changes under the MDR, we therefore ask that this definition is also changed in the CIP of ongoing studies. This can be done by changing the definition in the protocol itself or by creating a CIP addendum.

- Substantial modifications to clinical investigations approved under MDD must follow the MDD procedure for the approval of the modification, also after 26 May 2021.

[5] Directives 90/385/EEC and 93/42/EEC were converted to Belgian law by the Royal Decree dated July 15, 1997 governing the active implantable medical devices, by the Royal Decree dated March 18, 1999 governing medical devices and the Belgian law dated May 7, 2004 related to experiments on human people.

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

\# times depicted under "separate opinion FAMHP and EC" are only applicable for the FAMHP procedure. The dossier must also be submitted in parallel to the EC, the EC has a maximum of 28 days to provide an opinion (law of 07/05/2004).

* 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

Annex II – Fees

An invoice will be sent to the sponsor at the end of the process for the payment of fees. The table below indicates the fees according to the specific output. For clinical investigations submitted within the "validation FAMHP, opinion EC" or "consolidated opinion" regulatory pathways the total fees in the second column are applicable. These fees include the fees for the EC and the FAMHP. For clinical investigations submitted within the "separate opinion" regulatory pathway the fees in the third column are applicable. These are the FAMHP fees only as the EC opinion is applied for in a separate parallel pathway, independent of the FAMHP.

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

Fees - index 2023

Outputs	Total Fees (EC + FAMHP fees)	Fees for regulatory pathway: separate opinion (FAMHP fees only)
Request for a commercial clinical investigation with a medical device Class I or II	€ 11.410,23	€ 5.525,33
Request for a substantial modification of commercial clinical investigation with a medical device Class I or II	€ 4.425,15	€ 3.283,46
Request for a commercial clinical investigation with a medical device Class III	€ 16.407,72	€ 10.522,82
Request for a substantial modification of commercial clinical investigation with a medical device Class III	€ 4.479,12	€ 3.337,43
Notification of post market clinical investigation following article 74.1 of (EU) 2017/745	€ 8.069,67	
Notification of a substantial modification of post market clinical investigation following article 74.1 of (EU) 2017/745	€ 3.326,46	
Due fees if the application is rejected during validation	€ 519,97	€ 519,97

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

The 2 tables below establish whether an additional procedure should be considered burdensome or invasive. **They are both valid until 01/06/2023**.

Additional procedures NOT considered burdensome or invasive
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
functional testing session with a risk of falling
(laser) ophtalmoscopy
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

Note: if the additional procedures designed by the sponsor are not listed yet, the sponsor may contact the FAMHP at ct.rd@fagg-afmps.be.

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

Regulatory pathway	CE-marked?	Used within intended purposes?	Used for conformity assessment purposes?	In-house or custom-made?	PMCF?	Additional burdensome and/or invasive procedures?	Reportable events and definitions	How to report	To be reported by
Consolidated opinion FAMHP & EC	NO	-	YES	Incl. custom-made	NO	-	See 6.2 Reportable events	See 6.3 How to report SAEs, ct.rd@fagg-afmps.be	Sponsor
	NO	-	NO	NO	NO	-			
	YES	NO	-	-	NO	-			
Validation FAMHP & opinion EC	YES	YES	-	-	YES	YES	1. All reportable events according to vigilance see MDR articles 87-92 **AND** 2. ONLY for those SAEs where a **causal relationship** between the SAE and the **preceding investigational procedure** has been established.	1. vigilance.meddev@fagg-afmps.be according to MDR article 87-92 **AND** 2. See 6.3 How to report SAEs, ct.rd@fagg-afmps.be	1. Manufacturer[6] **AND** 2. Sponsor
Regulatory pathway EC only	YES	YES	-	-	YES	NO	1. All reportable events according to vigilance see MDR articles 87-92 **AND** 2. See 6.2 Reportable events	1. vigilance.meddev@fagg-afmps.be according to MDR article 87-92 **AND** 2. EC	1. Manufacturer[6] **AND** 2. Sponsor
	YES	YES	-	-	NO	-			
Separate opinion FAMHP and EC	NO	-	-	In-house	-	-	See 6.2 Reportable events	See 6.3 How to report SAEs, ct.rd@fagg-afmps.be **AND** EC	Sponsor
	NO	-	NO	Custom-made	-	-			

- : Not applicable

[6] 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.