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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.

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Contents

1. Introduction

As of May 26, 2021, the European Regulation (EU) 2017/745 on Medical Devices (MDR) comes into force. The MDR introduces a major update of the regulatory framework in the European Union and brings 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 has been approved on 22/12/2020[1] 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 on 26 May 2021 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. Definitions and abbreviations

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

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 guidance for submission via CESP

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.

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).

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

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. Transition period

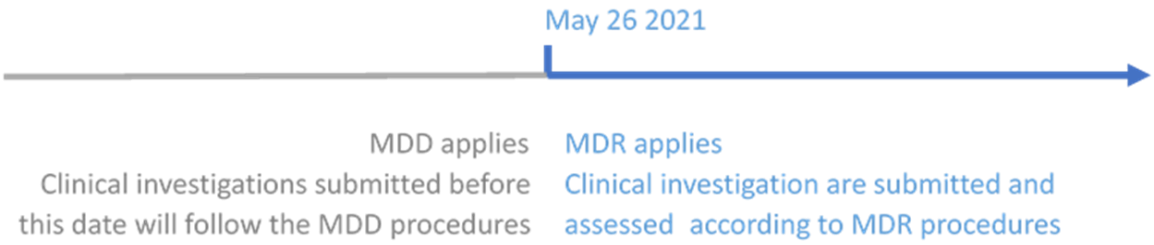

Figure 1. Timeline indicating the applicable legislation.

As depicted in the figure above, submissions with a date of reception up until May 25, 2021, will be handled in accordance with Directives 90/385/EEC or 93/42/EEC (MDD) and their dedicated Belgian laws[2]. Clinical investigation submissions received from May 26, 2021 will be 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.

- Clinical investigations planned to start before May 26, 2021 and which will be ongoing after the MDR comes into force, may implement the safety reporting from the beginning of the clinical investigation, according to the MDR if described as such in the protocol and approved. Note that this is a Belgian provision, in case of a multinational investigation, please check with the other competent authorities for their point of view.

[2] 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.

4. Regulatory pathways

All clinical investigations, need to follow a regulatory pathway with the involvement of the Ethics Committee (EC) and/or Belgian competent authority (FAHMP). 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.

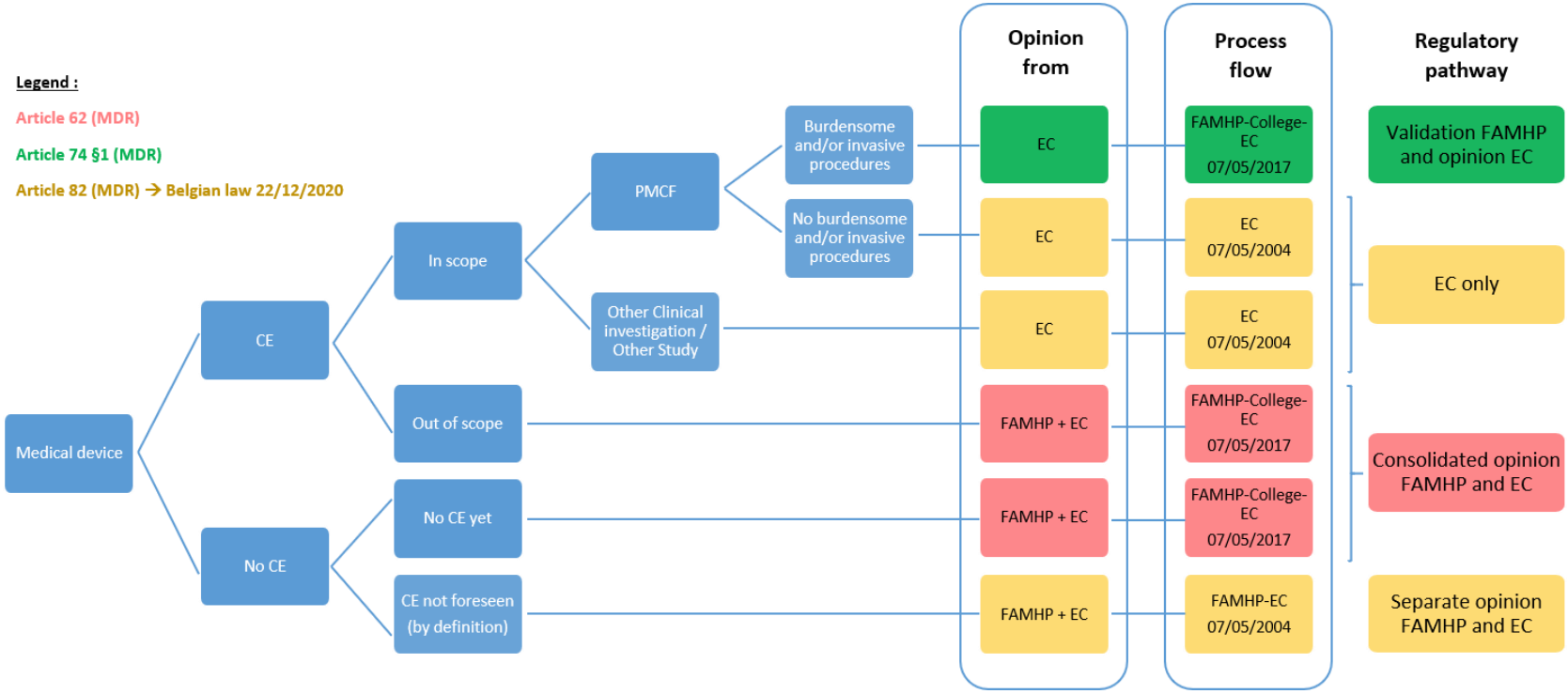

Figure 2. Different regulatory pathways. Different process flows and regulatory pathways are possible depending on the status of the investigational medical device and clinical investigation properties. PMCF studies with burdensome and/or invasive procedures are validated by the FAMHP but assessed only by an independent EC. Other clinical investigations with a CE labelled device used 'in scope' are only assessed by the EC. Clinical investigations with CE marked investigational devices used 'out of scope' or without a CE label are assessed by both the FAMHP and an independent EC, one consolidated opinion is issued. In case of in-house or custom made investigational medical devices, where no CE mark is foreseen by definition, the assessment by the FAMHP and EC is done separately (in parallel) and two separate opinions are issued.

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 5.

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 and/or functionalities 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.

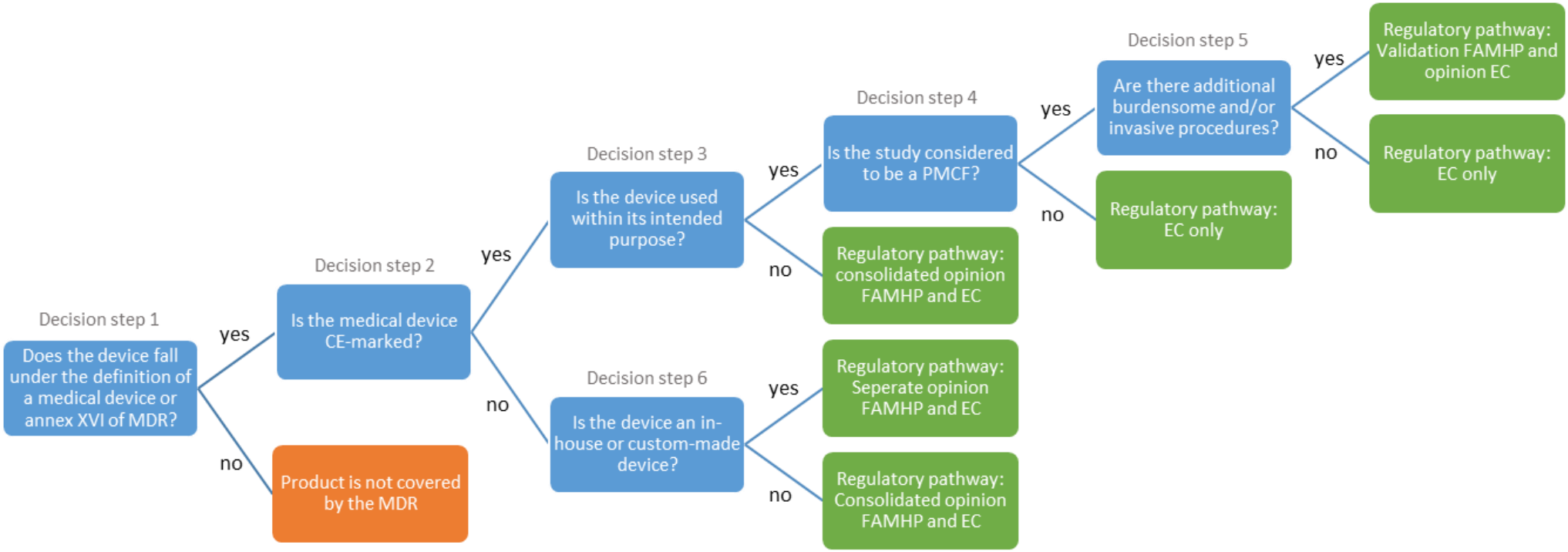

Figure 3. Decision tree

Decision step 1

If the product is a medical device according to the definition provided by the Regulation (EU) 2017/745 (see definitions) or if the product belongs to a group of products without an intended medical purpose that is listed in Annex XVI[3] of the Regulation (see list below), you can proceed to decision step 2.

If the product is not a device according to the definition or does not belong to a group of products listed in Annex XVI, then it is not covered by the Regulation 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.

It is up to the sponsor of the clinical investigation to assess whether a product is to be regarded as a medical device or belongs to the group of products listed in MDR Annex XVI.

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

[3] Be aware that additional products could be added to the list of product stated in annex XVI of MDR, following EU commission decision.

Decision step 2

If the product is a medical device, according to the definition outlined in this document, and has a valid CE label you can proceed to decision step 3.

If the product is a medical device, according to the definition outlined in this document, and does not have a CE label you can proceed to decision step 6.

Decision step 3

In this step, it is necessary to understand what the intended purpose 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. 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.

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 4.

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.

Decision step 4

A post-market clinical follow-up (PMCF) investigation, initiated by the manufacturer (sponsor), 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. 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 5.

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.

Decision step 5

In the scope of PMCF studies an additional procedure which could be considered as burdensome or invasive for the subject 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.

Examples include (non-exhaustive list):

- Additional imaging examination
- Patient questionnaires, which take time for the patient to complete, or which concern questions having an impact on the psychological and/or physical integrity of the subject.
- Completing extensive diaries in written or electronic formats
- Additional clinic or hospital visits, or a change in frequency of standard clinical follow up
- Additional functional testing, for example an additional 6 minute walk test
- The collection of additional data which includes activities which must be completed by the patient, for example wearing a holter monitor for more than a few days
- Changes or restrictions to diet, fasting or lifestyle modifications

Procedures which are invasive include penetration inside the body through the surface of the body, including through mucous membranes of body orifices, penetration of a body cavity via a body orifice or radiation which penetrates body structures.

Examples include (non-exhaustive list):

- Venepuncture,
- Invasive type imaging, for example a trans-oesophageal echo

Please note that the above definitions of additional burdensome and invasive procedures are broad and not final. We are working at European and national levels for further guidance on this topic.

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”.

Decision step 6

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, 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”.

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.

5. 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 and communicated together with the validation status of the dossier.

For a detailed description of each dossier document we kindly refer to our guidance on dossier content: " Clinical investigations – Guidance on Dossier Content", which will be available on our website soon.

5.1. 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 competent authority at least 30 days prior to its commencement**.

Following documents must be included in the notification package:

- Cover letter
- List of documents submitted (WORD document – see template on website)
- Application form
- Clinical Investigation Plan (Protocol)
- Technical documentation
- PMCF plan
- Proof of insurance
- Instructions for use (if not included in technical documentation)
- Documents used to obtain informed consent, including the patient information sheet and the informed consent document.
- CV of principal investigator(s)
- Suitability of clinical sites
- Description of the arrangements to comply with the applicable rules on the protection and confidentiality of personal data.

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 and notify the applicant of its completeness and as to whether the clinical investigation does indeed fall within PMCF investigations involving additional burdensome or invasive procedures. **Note that the procedure does not allow any validation questions to be asked, if the dossier is missing for example the PMCF plan the investigation will be refused 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.

5.2. 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. The EC will assess the dossier and the final opinion will be communicated within 45 calendar days of the date of reception. You can check on our website to which EC you can apply for such clinical investigations.

5.3. Regulatory pathway: consolidated opinion FAMHP and EC

- ➔ *Clinical investigations involving CE-marked devices used outside their intended purpose*
- ➔ *Clinical investigations involving devices without a CE mark which are not custom made or 'in-house' devices.*
- ➔ *Assessment by FAHMP 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
- Clinical investigation 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 will be available on our website soon).
- Notified body certificates
- Proof of insurance
- Documents to be used to obtain informed consent, including the patient information sheet and the informed consent documents.
- CV of principal investigator(s)
- Suitability of sites
- Description of the arrangements to comply with the applicable rules on the protection and confidentiality of personal data.
- Example of labels
- Decisions from other countries
- The clinical investigation agreement between the manufacturer and the non-commercial sponsor (only applicable for non-commercial sponsors)

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.

An invoice will be sent to the sponsor at the end of the process for the payment of fees.

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.

5.4. Regulatory pathway: separate opinion FAMHP and EC

➔ *Clinical investigations involving in-house or custom-made medical devices.*
➔ *Parallel assessment by FAHMP 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
- Clinical Investigational Plan (CIP) or protocol
- Investigator's Brochure (IB)
- Manufacturer's instructions for use
- List of general safety and performance requirements that have already been met, including motivation (template will be available on our website soon).
- 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 between the manufacturer and the non-commercial sponsor (only applicable for non-commercial sponsors)

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 T30, 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 T60 at the latest.

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.

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

5.5. Approval

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:

- **“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 after the conditions have been fulfilled. The approval letter is sent at the time of the conditional approval. The sponsor is asked to answer the conditions as soon as possible. These conditions typically concern the availability of documents (such as study reports) or the modification of documents (such as the CIP). After reception of the answers to the conditions, the FAMHP and/or EC will assess these answers. When all conditions are met an email is sent to the sponsor to indicate that “the conditions are met and the investigation may start”. No additional approval letter is sent.

- **“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.

6. 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 and must be approved by the FAMHP and/or EC before implementation.

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 4 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", which will be available on our website soon.

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

➔ PMCF investigations involving additional burdensome or invasive procedures.
➔ Assessment by FAHMP 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 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 amendment will be refused. The approval (or refusal) 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.

6.2. 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.

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

- ➔ *Clinical investigations involving CE-marked devices used outside their intended purpose*
- ➔ *Clinical investigations involving devices without a CE mark which are not custom made or 'in-house' devices.*
- ➔ *Assessment by FAHMP 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 T28 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.

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

➔ Clinical investigations involving in-house or custom-made medical devices.
➔ Parallel assessment by FAHMP 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.

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, 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 a final decision on T38 at the latest.

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.

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

6.5. Approval

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:

- **"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 after the conditions have been fulfilled. The approval letter is sent at the time of the conditional approval. The sponsor is asked to answer the conditions as soon as possible. After reception of the answers to the conditions, the FAMHP and/or EC will assess these answers. When all conditions are met an email is sent to the sponsor to indicate that "the conditions are met and the substantial modification may be implemented". No additional approval letter is sent.
- **"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.

7. 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 will not be available and fully functional at the date of application of MDR this guidance outlines the procedures for safety reporting in the absence of Eudamed.

7.1. Scope

Serious adverse event reporting is mandatory for clinical investigations:

- conducted with non-CE marked medical devices
- conducted with CE marked medical devices used outside the intended use(s) covered by the CE-marking
- conducted with custom-made or in-house medical devices

For **post-market clinical follow-up (PMCF) investigations** of CE-marked devices used within the intended use covered by the CE-marking:

- SAEs reporting should be done following the materiovigilance rules;
- However for SAEs where a causal relationship between the serious adverse event and the preceding investigational procedure has been established must follow the SAE reporting procedures of clinical investigations as described here.

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.

7.2. Reportable events

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

a. any serious adverse event 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).

The relationship between the use of the medical device (investigational device and comparator), including the medical and surgical procedure, and the occurrence of each adverse event 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.

Specifically for post-market clinical follow-up (PMCF) investigations 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.

7.3. How to report SAEs

7.3.1. Reporting form

Once Eudamed is available and fully functional SAE reporting will have to be done through the Eudamed web form. Until then, as from May 26 2021 the new template for the Clinical Investigation Summary Safety Report Form 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.

7.3.2. Reporting timelines

- For all reportable events 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.**

- 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.**

7.3.3. 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).

Reportable events do not need to be sent to the EC, unless they specifically ask otherwise.

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

8.1. 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**.

8.2. 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).

8.3. 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.