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

Clinical investigations – Guidance on Dossier Content

This document aims at providing specific guidance on the content of a dossier for clinical investigations under MDR from a national point of view.

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Document revision history

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26.04.2021 – version 1.0	First publication
07.06.2021 – version 2.0	- Update section 3.1 – addition of invoice address and VAT number in cover letter - Update of section 3.2 - additional clarifications on the requirements in Belgium for several documents listed - Addition of section 3.8 – clinical evaluation plan (CEP) - Update section 3.19 – The clinical investigation agreement may be provided as a draft version - Addition of section 3.20 - Expert panel opinion / scientific advice

Contents

1. Definitions and abbreviations

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

Adverse event (AE): 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. (MDR Article 2(57))

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.

CEP: Clinical evaluation plan stated at annex XIV part A, is a document gathering different information related to the development of your investigated medical device to collect clinical data with the aim to demonstrate and confirm performance, including clinical benefit for the patients, and the safety of your medical device.

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

CIP: Clinical investigation plan or protocol, is a document that states the rationale, objectives, design and pre-specified analysis, methodology, organization, monitoring, conduct and record-keeping of the clinical investigation.

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 (DD): 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

DOI: Declaration of Interest

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

Harm: injury or damage to the health of people, or damage to property or the environment. [SOURCE: ISO/IEC Guide 63:2019, 3.1]

Hazard: potential source of harm. [SOURCE: ISO/IEC Guide 63:2019, 3.2]

Hazardous situation: circumstance in which people, property or the environment is/are exposed to one or more hazards.

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).

ICF: Informed consent form

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 (IFU): 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

Intended purpose: the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements and as specified by the manufacturer in the clinical evaluation.

Manufacturer: means a natural or legal person who manufactures or fully refurbishes a device or has a device designed, manufactured or fully refurbished, and markets that device under its name or trademark.

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".

NB: Notified Body

Post-market clinical follow-up (PMCF) investigation: a study carried out following the CE marking of a device and intended to answer specific questions relating to clinical safety or performance (i.e. residual risks) of a device when used in accordance with its approved labelling.

Serious adverse event (SAE): 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:
    i. life-threatening illness or injury,
    ii. permanent impairment of a body structure or a body function,
    iii. hospitalisation or prolongation of patient hospitalisation,
    iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

v. chronic disease,

c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect

Severity: measure of the possible consequences of a hazard.

SIN: Single identification number

Sponsor: any individual, company, institution or organisation which takes responsibility for the initiation, for the management and setting up of the financing of the clinical investigation**.**

Subject: means an individual who participates in a clinical investigation.

2. Introduction

All clinical investigations need to follow a regulatory pathway with the involvement of the Ethics Committee (EC) and/or Belgian competent authority (FAMHP). Depending on the status of the investigational medical device the submission procedure can be different. Please refer to our "Guideline on Submission Processes of Clinical Investigations according to MDR in Belgium" to determine which regulatory pathway needs to be followed for your clinical investigation and which documents need to be submitted with your dossier.

In this guidance we aim to explain, in detail, the specific requirements of each document as to provide the best submission dossier to the FAMHP and EC and avoiding questions related to the completeness of your dossier.

Please, take into consideration that the MDR is very strict regarding deadlines and completeness of the dossier. Only one round of questions is possible during the validation phase and one round of questions during the assessment phase of the process. Note that for PMCF studies with burdensome and/or invasive procedures (regulatory pathway: validation FAMHP and opinion EC) no questions are possible.

3. Documents related to initial applications

Below you can find a list of documents that, depending on the regulatory pathway followed, must be included in the submission package of initial applications to the FAMHP.

Please apply the PDF file format to all documents where possible (except for list of submitted documents, this **must** be a **WORD** file, see below). Certificates, licenses, authorizations and other documents with a signature can be scanned with optical character recognition (OCR). Digital signatures are also accepted. Some general requirements for the preparation of these PDF documents:

- The files must allow "copy/paste" and search functions.
- The layout should be clear, if possible a detailed table of contents must be included in order to quickly find specific sections of text.
- Files should not be locked with a password.
- Each part of the application dossier should be a separate file.

3.1. Cover Letter

The applicant should submit a signed (electronic signature is accepted) cover letter with the application dossier. Its subject line should contain the title of the trial and the invariable sponsor protocol number and, if available, the single identification number (SIN)[1] of the investigation.

The cover letter should give a very brief description of the investigational device and clinical investigation. Attention should be drawn to any peculiarities of the investigation if applicable, for example specific features of the investigation population, first-in-human investigation, unusual investigation design or particular investigational device features. Please also disclose any

[1] In absence of EUDAMED access to the sponsor, the FAMHP will provide you an Eudamed number, as was done under the directive. this number will be used as the single identification number (SIN) for your clinical investigation within the EU. It is requested to mention this number in any exchange with the competent authority.

connections to ongoing or previous clinical investigation applications and/or clinical trial applications if applicable.

It should be clearly mentioned which Belgian regulatory pathway is applicable: validation FAMHP and opinion EC, consolidated opinion FAMHP and EC or separate opinion FAMHP and EC (refer to our "Guideline on Submission Processes of Clinical Investigations according to MDR in Belgium" for more information).

Please also include the invoice address and VAT number in the cover letter for invoicing purposes.

In case of a resubmission the applicant should highlight the changes as compared to the previous submission in each document.

The covering letter may be addressed to:

Federal Agency for Medicines and Health Products
Division R&D - Medical Device Unit
Avenue Galilée - Galileelaan 5/03
1210 BRUSSELS
Belgium

3.2. List of documents submitted

Applicants are requested to provide the filled-out list of documents submitted in the application package. This list contains the full document name, version and date of the respective documents.

When an approval is issued this list of approved documents will be attached to the approval letter. It is thus important that the applicant keeps this list of documents up to date, it must be **resubmitted it at each change** (validation questions, response to RFI, etc.) **with a clear indication of which documents have been updated/added.**

This is a European document approved by the MDCG. Below you can find additional clarifications on the requirements in Belgium for several documents listed.

- Statement of conformity – not mandatory as a separate document in Belgium as a statement of conformity is included at the end of the application form.
- Risk management documentation – can be included in the IB or provided as separate document(s).
- Test reports – can be included in the IB or provided as separate document(s).
- Recruitment procedures and advertising materials – can be included in the CIP but should for clarity reasons also be provided as separate documents in a dedicated folder (see section 3.15).
- Documents to obtain informed consent, informed consent procedure, all written information to participants, payments and compensation of participants – can be included in the CIP but should for clarity reasons also be provided as separate documents in a dedicated folder (see section 3.15).

3.3. Application Form

The application form for initial submissions can be found on our website (available soon). Please include a correctly filled-out and signed form in the application dossier. The form must be saved in the PDF file format and allow copy/paste. Electronic signature is accepted, alternatively the file may be sent as an unsigned PDF document in parallel with a scan of the signed document.

3.4. Synopsis Clinical Investigation Plan

An overall synopsis of the clinical investigation plan (CIP) should be provided as a separate document. The document must be provided in English and at least in the official national language(s) of the region(s) where the investigation is conducted, except in German.

3.5. Clinical Investigation Plan (CIP)

A protocol, also called clinical investigation plan (CIP), is a document which gathers information regarding the study: background information, the rationale, objectives, outcomes, design, pre-specified analysis, methodology, monitoring conduct, safety and follow-up and record-keeping of the clinical investigation data.

The full details of the CIP content are provided in annex A of ISO 14155:2020. In summary, the content of a standard protocol is described below.

3.5.1. General introduction

The general introduction should include the title of the clinical investigation, the invariable CIP reference number, version and date of the CIP, a summary of the revision history in case of modifications, abbreviations and acronyms and an overall synopsis of the clinical investigation. The name and contact details of the following should be stated:

- sponsor
- local representative (if applicable)
- principle investigator(s)
- coordinating investigator(s) (if applicable)
- investigational sites in which the clinical investigation will be conducted
- external organizations (such as laboratories, CRO's, consultants) involved in the clinical investigation (if applicable)

A brief description of how the clinical investigation is financed and a brief description of the agreement between the sponsor and the site(s) must also be included.

3.5.2. Identification and description of the investigational device

This section should include the information listed below, if applicable. If appropriate, references to the IB and/or IFU can be made. In case a comparator device is used the information below should **also** be provided for the comparator.

- Summary description of the investigational device.
- Details concerning the manufacturer of the investigational device.
- Name or number of the model/type, including software version and accessories to permit full identification.
- Description as to how traceability will be achieved during and after the clinical investigation, for example, by assignment of lot numbers, batch numbers or serial numbers.
- Intended purpose of the investigational device in the clinical investigation.
- The populations and indications for which the investigational device is intended.
- A detailed description of the investigational device, including a list of all materials which will be in contact with tissues or body fluids. Also any medicinal substances, human or animal tissues or their derivates, or other biological active substances incorporated in the device must be defined.
- Summary of the necessary training and experience needed to use the investigational device based on risk assessment.
- Description of the specific medical or surgical procedures involved in the use of the investigational device.

3.5.3. Justification for the design of the clinical investigation

This section includes a justification for the design of the clinical investigation. It should comprise an evaluation of the results of the relevant pre-clinical and clinical data, if applicable, to justify the use of the investigational device in human subjects. If appropriate a description of the clinical developmental stage can be included.

3.5.4. Benefits and risks

At first, a description is required of (1) all incremental risks to which subjects will be exposed by participating in the clinical investigation, related to the investigated medical device and procedures (i.e.; risk characterization) and (2) of the manner(s) used to minimize these risks (i.e.; risk mitigation). It is not necessary to include specific mitigations for hypothetical risks that are not supported by scientific evidence or risks that are determined to be negligible due to a low probability of occurrence and low severity of harm. It is, however, recommended to identify all possible risks.

In particular, for risk characterization, the following factors should be considered, individually and in aggregate: types of risk (taking account of the study design as well), their likelihood and duration along with the severity. Also consider the risk factors for health care personnel, family members or caregivers, if any, and the risks related to the interpretation of the study data. In specific, the risk of drawing a false conclusion based on clinical data obtained, and the risk of data which are inconclusive or difficult to interpret.

Manner(s) in which risks will be minimized may include:

- Protective measures, e.g.; physical protective measures; staged enrolment and interim pre-specified subject safety assessment; pre-specified stopping rules; narrow study population with more favourable benefit-risk profile; performance of study at trained/specialized sites or investigators meeting certain criteria; study oversight (monitoring committees); frequent reporting of SAEs; accurate recording of AEs, including

the timing and clinical context and a description of any medical interventions provided and the associated outcomes.

- Communication of safety information and residual risks, e.g.; through labelling or informed consent, training of investigational staff, optimizing communication among sites, communicating safety data and residual risks with ethics committee(s) and competent authority to determine if any additional subject protection measures are needed.

A list of anticipated A(D)E, SA(D)E, DD, including those considered critical, must be prepared.

Secondly, a description should be provided of the anticipated benefits of the proposed clinical investigation. This concerns the direct benefit(s) to the study subjects, but may also cover the benefit(s) to others.

In particular, regarding the direct benefit(s) to the study subject, the following factors should be considered, individually and in aggregate: (a) type of benefit(s) and magnitude of the benefit(s); (b) if possible, probability evaluation of the participant experiencing one or more benefits, or identification of subgroups more likely to experience a benefit; (c) duration of the benefit(s), i.e.; how long the benefit can be expected to last for the participant; (d) medical necessity, if a medical device provides benefits or addresses needs unmet by other medical devices or therapies. Benefit considerations should also include an assessment of whether another medical device or therapy could be used in substitution, and the availability of that other medical device or therapy.

Benefit(s) to others include(s) benefits to caregivers or family members and health care personnel, and public health.

Other information providing useful context is appreciated and may include: consideration of patient preference information (when available) characterizing the subjects' perspective on benefit, i.e.; the value that the patients place on the use of the medical device, as well as information characterizing subjects' tolerance for risk.

3.5.5. Objectives and hypotheses

This section describes:

- The purpose of the clinical investigation, claims for clinical performance, effectiveness or safety of the investigational device that are to be verified.

- Objectives, primary and secondary, described as 'superiority', 'non-inferiority', or 'equivalence', if applicable.

- Scientific justification and clinical relevance for effect sizes, non-inferiority margins or equivalence limits, where applicable.

- Primary and secondary hypothesis, if applicable.

- Risks and anticipated adverse device effects that are to be assessed.

3.5.6. Design of the clinical investigation

The design should be sufficiently detailed with evidence of its robustness and validity. Information is required on study type (e.g.; exploratory, confirmatory), phase of device development, subject number, endpoints, selection criteria, representativeness of the investigation population in relation to the target population, vulnerable subjects involved (if applicable), clinical procedures and

diagnostic tests used in the course of the clinical investigation, any deviation from normal clinical practice, the investigational device, any comparator or other device or medication used, and thus any concomitant treatments permitted or prohibited, number of medical devices and comparators (if applicable) used per subject, symptoms, parameters and/or results to be studied, details of measures taken to minimize bias, follow-up provided, and expected (total and per subject) duration of the investigation. Where possible, a schematic overview of study assessments and visits is included.

Justification of follow-up duration is recommended. The extent and nature of monitoring activities for the proper conduct of the investigation in accordance with the clinical investigation plan should be described and, conform MDR article 72, be based on objective(s) and methodology and degree of deviation of the intervention from normal clinical practice.

Use of either single arm or (choice of) comparator or other (historically) controlled design and the concept of blinding and unblinding, or running open label need to be covered, with rationale and justification.

Overall, the investigation has to be designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects. For that, a rationale in relation to the available preclinical data and results of clinical evaluation may be recommended.

3.5.7. Statistical design and analysis

This section describes and justifies the statistical design and analysis of the clinical investigation and should cover following points, if applicable:

- Analysis population and procedures that take into account all the data.
- Descriptive statistics of baseline data, treatments, safety data and where applicable, primary and secondary endpoints.
- Analytical procedures including measures of precision such as confidence intervals.
- Sample size calculation and justification.
- The rationale for the number of procedures to be performed by a single user as part of the learning curve and how these data are to be analysed.
- Pass/fail criteria to be applied to the results of the clinical investigation.
- The provision for an interim analysis, criteria for the termination of the clinical investigation on statistical grounds.
- Management of bias and, when randomization, matching, or blinding are applied, plan of assessment of success thereof.
- Management of potential confounding factors (e.g. adjustment, stratification, or stratified randomization).
- Description of procedures for multiplicity control and adjustment of error probabilities.
- The specification of subgroups for analysis or if response to treatment is expected to be different in these groups.
- Management, justification, and documentation of missing, unused or spurious data, including drop-outs.

- Exploratory analysis and sensitivity analysis (e.g. to explore robustness of results of primary and secondary analysis with respect to different methods used for handling missing data).

- Procedures for reporting any deviations(s) from the original statistical plan.

- For multicentre clinical investigations, a strategy for handling the potential imbalance of the numbers of subjects across investigation sites.

- A strategy for pooling data.

3.5.8. Data management

In the clinical investigation plan, a description should be provided of the procedures implemented which can guarantee that the data generated in the clinical investigation is reliable and robust. For that, arrangements for data collection, protection, monitoring (accounting for data accuracy, data completeness, resolving of queries, and the presence or absence of a data safety monitoring board) and retention but also statistical approaches with sample size determination require careful consideration. Conform MDR article 72, all clinical investigation information shall be recorded, processed, handled, and stored by the sponsor or investigator, as applicable, in such a way that it can be accurately reported, interpreted and verified while the confidentiality of records and the personal data of the subjects remain protected in accordance with the applicable law on personal data protection. In addition, appropriate technical and organizational measures should be installed to protect information and personal data processed against unauthorized or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss, in particular where the processing involves transmission over a network.

3.5.9. Amendments to the CIP

It should be clear from the clinical investigation plan that, once approved, the competent authority shall be notified of all proposed changes to the approved 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, and that the response of no objection will be awaited, in accordance with ISO 14155 and the procedure as laid down in MDR article 75.

3.5.10. Deviations from the CIP

There should be a statement specifying that the investigator is not allowed to deviate from the CIP. Except if to protect the rights, safety and well-being of human subjects under emergency circumstances may the investigator deviate without prior approval of the sponsor.

Procedures for recording, reporting and analysing CIP deviations should be described, including notification requirements and time frames. Also, corrective and preventive actions and principal investigator disqualification criteria can be included.

3.5.11. Device accountability

Adequate procedures for the accountability and traceability of the investigational device should be incorporated in the CIP, in particular control of access to and adequate storage of the device, follow-up in relation to the device used in the clinical investigation and the return of unused, expired or malfunctioning devices. Further, conform MDR article 72 the sponsor should establish a procedure for emergency situations which enables the immediate identification and, where necessary, an immediate recall of the devices used in the investigation.

3.5.12. Statements of compliance

Following statements should be included:

- Statement specifying that the clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.
- Statement specifying compliance with the national and European legislation.
- Statement specifying that the clinical investigation shall not begin until the required approval/favourable opinion from the EC and regulatory authority have been obtained, if appropriate.
- Statement specifying that any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.
- Statement specifying the type of insurance that shall be provided for subjects, if appropriate.
- Statement addressing the financing of the clinical investigation including a description of the agreement between the sponsor and investigation site(s), and where applicable with the investigator(s) if not addressed in a separate agreement.

3.5.13. Informed consent process

This includes a description of the general process for obtaining informed consent, including the process for providing subjects with new information and process for incentives for subjects, as needed. If applicable, the description of the process in circumstances where the subject is unable to give informed consent (e.g. for emergency treatment) must also be included.

3.5.14. Adverse events, adverse device effects and device deficiencies

This sections describes the definitions of adverse events (AE), averse device effects (ADE), device deficiencies (DD), serious adverse events (SAE) including serious health treat and serious adverse device effects (SADE).

A list of non-reportable adverse events should be given, including a rationale. Also, a list of foreseeable adverse events and anticipated adverse device effects, together with their likely incidence, mitigation, or treatment must be specified.

Details of the process for reporting adverse events and device deficiencies should be described, including the time period in which the principal investigator must report to the sponsor and, where

appropriate, the sponsor must report to the competent authority. Emergency contact details for reporting serious adverse events and serious adverse device effects must be specified.

For Belgium it must be specified that the reporting of SAE must be done to the FAMHP at ct.rd@fagg.be, by using the European form.

Please consult the guidance on safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 (May 2020) and our Submission Guidance for more information on the reporting of SAE.

3.5.15. Vulnerable population

If applicable, this section describes the vulnerable population that is included in the clinical investigation. The specific screening process to identify and protect the vulnerable population and the informed consent process must be defined. Finally, the medical care, if any, that will be provided for the subjects after the clinical investigation has been completed must also be given. (MDR Art. 64-68)

3.5.16. End, suspension or premature termination of the clinical investigation

The clinical investigation plan should consider appropriate subject and study stopping criteria as well as procedures for the follow-up (care) of subjects following the end or temporary halt of the investigation, for follow-up of subjects who have withdrawn their consent and for subjects lost to follow-up.

Further, it must be clear from the clinical investigation plan that the competent authority shall be notified of the end of the clinical investigation, and that a justification shall be provided in case of a temporary study halt or early termination. In accordance with MDR article 77 study end reporting is mandatory within 15 days (but 24 hours if based on safety grounds). In addition, a clinical investigation report needs to be submitted within one year of the end of the clinical investigation or within three months of the early termination or temporary halt. The end of a clinical investigation shall be deemed to coincide with the last visit of the last subject unless another point in time for such end was set out in the clinical investigation plan.

3.5.17. Publication policy

Following statements must be included:

- Statement that the clinical investigation will be registered in a publicly available database.
- Statement indicating that the results of the clinical investigation will be made publicly available.
- Statement indicating the conditions and timeframes under which the results of the clinical investigation will be offered for publication including the role of the sponsor and criteria for authorship.

3.5.18. Bibliography

List of bibliographic references relating to the clinical investigation.

3.6. Investigator's Brochure (IB)

The IB is a compilation of the current clinical and non-clinical information on the investigational medical device relevant to the clinical investigation. It also provides a benefit/risk assessment for the intended purpose of the device in the study. The content is technical and scientific. The full details of the content are provided in annex B of ISO 14155, a summary is given below.

Note that it is preferred for all necessary information to be included in the IB. However, if it is decided to move part of the information to annexes (or other referenced documents), then a clear reference should be made in the IB and the respective documents must be submitted together with the IB as part of the initial data package accompanying the clinical investigation application.

3.6.1. General introduction

The first page(s) should contain a proper identification of the IB with the name of the investigational device, a document reference number, version or date of the IB, if appropriate a confidentiality statement, a summary of the revision history and table of contents.

The name and address of the sponsor of the clinical investigation should be given, and of the manufacturer of the investigational device, if different from the sponsor.

3.6.2. Investigational device information

In this section detailed information is given concerning the investigational device, it must contain following elements, if applicable:

- Summary of the literature and evaluation supporting the rationale for the design and intended use of the investigational device.

- Statement concerning the regulatory classification of the investigational device including a justification based on the classification rules. The classification rules can be found in Annex VIII of the MDR.

- A detailed description of the investigational device and its components. A clear overview of materials used in the device should be provided. For more complicated devices, this can be accompanied by an annotated drawing or photograph of the device. Especially for all human (patient, clinician, …) contacting materials, sufficient detail should be provided, even if contact is only brief or occasional. The information provided should be sufficiently specific and should include the supplier, supplier product code, generic name, brand name and if applicable, the grade, quality, specification or standard adhered to. Preferably, the information is provided in a tabular format.
  Details of any medicinal substances, human, or animal tissues or their derivates, or other biologically active substances must also be included.

- Summary of relevant manufacturing processes and related validation processes, to demonstrate that the investigational devices are manufactured and verified under a controlled process according to the applicable regulations. This can be done by means of a manufacturing flowchart. In-process controls should be described and acceptance criteria for these tests should be clearly defined.

- Description of the mechanism of action of the investigational device, along with supporting scientific literature.

- Manufacturer's instructions for installation, maintenance of hygienic conditions and use of the investigational device, including any necessary storage and handling requirements, preparation for use and any intended re-use (e.g. sterilization), any pre-use safety or performance checks and any precautions to be taken after use (e.g. disposal), if relevant.

- Reference to the examples of investigational device labelling (see section3.13) and instructions for use (see section3.7). Information on any specific training, if required, should be given here.

- Description of the intended clinical performance.

- An overview of the design history of the medical device (e.g. in table form) is recommended and appreciated. This overview should specifically focus on the devices used clinically and in confirmatory preclinical testing. Preferably, this table contains for each iteration the version number, a photograph/drawing and a brief overview and rationale of changes with regards to the previous iteration.

3.6.3. Preclinical testing

This section contains a summary of the preclinical testing that has been performed on the investigational device, together with an evaluation of the results of such testing, justifying its use in human subjects.

In the summaries of the non-clinical studies, the applicant should either confirm that the device used was identical to the device for clinical use (including e.g. sterilization) or detail any differences between the device used preclinically (e.g. mechanical testing, fatigue testing, reliability testing, animal studies, biocompatibility studies) and clinically. If the device that will be used in the clinical differs from the device used in preclinical studies, a justification for not using the final, clinical design of the device should be provided.

Note that all preclinical tests must be completed before a clinical investigation application can be assessed and approved.

Note that during assessment of the clinical investigation application, the full study reports of pivotal preclinical studies may be requested; to reduce the overall time to clinical investigation approval (take into consideration there is only one possible round of question following MDR), the applicant may consider submitting the full study reports of these studies at the time of the initial application (however, this does not negate the obligation to include a summary of pivotal preclinical studies in the IB).

This section must include following information, when applicable:

- Design calculations

- *In vitro* tests

- Mechanical and electrical safety tests

- Reliability tests

- Validation of software relating to the function of the device

- Performance tests

- *Ex vivo* tests

- *In vivo* animal tests

    - Animal study summaries should be included in the IB (a reference to external documents is not sufficient) and should contain sufficient information, including: species, breed, number of animals, age of animals, GLP status, version of the device used and an overview of the analyses performed. Any notable findings should be mentioned and discussed.
    - Study design choices including species used, study duration and choice or absence of comparator should be explicitly justified.
    - In case of non-GLP studies, applicants are recommended to follow the ARRIVE guidelines (to the extent that this is possible) in the preparation of the study report.

- Evaluation of biological safety.
    - A (justified) categorization in line with ISO 10993-1 should be provided. A brief summary of each evaluation required by ISO 10993-1, Annex A should be provided. It should be clear from this summary whether actual testing or an evaluation based on literature data was performed and where applicable, test results should be provided (e.g. for cytotoxicity testing, it is recommended to report the specific assay used and the % cell viability observed, rather than simply stating "passed").
    - For investigational devices with extensive clinical data or for devices that differ only little (in their material composition, design and anatomical target site) from devices with extensive clinical experience, the section on biocompatibility evaluation can be kept brief and may be limited to an overview table.
    - If a device is CE marked but investigated for an non-CE marked indication and if the categorization according to Annex A of ISO 10993-1 does not change, no further information on biocompatibility evaluation is required (other than the justified classification of the medical device in line with ISO 10993-1, Annex A in view of the new indication).

- Validation of procedures for cleaning, disinfection or sterilization.
    - The sterilization method used should be stated and a sterilization validation report should be provided. Compatibility of the sterilization method and the device materials should be discussed, if applicable. In case ethylene oxide is used as sterilizing agent, please specify whether testing for residuals is performed and provide the results of these tests.

3.6.4. Existing clinical data

If applicable an overview of ongoing and finished clinical investigations with the investigational device should be provided. Medical devices that have similar characteristics, including such characteristics that relate to other indications for use of the investigational device can be included. The overview must provide sufficient and clear information on the protocol of each investigation, sites/centres, safety and performance results and an analysis of adverse device effects, serious adverse events and any history of modification or recall.

In case the clinical investigation has a phased approach and Belgium was not involved in the initial phase we ask for a summary or interim analysis of the current status discussing any notable information such as SAE.

If applicable this section can also contain any information on the extent and findings of compassionate use of the device.

3.6.5. Risk management of the investigational device

This section includes a summary of the benefit-risk analysis including the identification of residual risks. Contra-indications and warnings for the device must also be stated.

We request to provide a table with the Anticipated SAE's and SADE's. The following table is an example of what we request and gives an example of the characteristics of the event we would like to see featured in such a table.

Harm/event	Related to device or procedure	Probability of occurrence	Severity	Risk Level	Reference (basis of these nrs)

The risk management process needs to be described here. It should describe risk analysis, risk evaluation and risk control/mitigation (this last part includes benefit-risk analysis). It should also describe the risk-acceptability criteria that are used (in other words: When do the benefits outweigh the risks?).

See ISO 14971-2020 for more info on the application of risk management to medical devices.

Some examples of types of risk analyses:

- HAZOP: Hazard and Operability (https://en.wikipedia.org/wiki/Hazard_and_operability_study)
- FMEA: Failure mode and effects analysis (https://en.wikipedia.org/wiki/Failure_mode_and_effects_analysis)
- FTA: Fault tree analysis (https://en.wikipedia.org/wiki/Fault_tree_analysis)
- Procedure analysis

Detail what information was used to estimate the risks. For example:

- Published standards or articles about similar devices
- Expert assessment
- Tests
- Simulation
- …

Describe the estimation scales that are used for probability and severity estimations. For example, is it a risk matrix of 3 x 3, a 4 x 5, a 5 x 5 …?

- Attention, matrices with more than five levels can require significantly more data to be able to distinguish between the various levels and to avoid overlap of the levels. Rationales for the selection of matrices and their outcome scores should be documented. Note that matrices with three levels might not always be sufficiently accurate for adequate decision making. While the above examples were 3 × 3 and 5 × 5, there is no need that these matrices be balanced. For example, a 4 × 5 matrix could be appropriate for a given application.

When available it is preferred to include the full Risk Analysis Table, Risk Management Plan and/or Risk Management Report in the submission package.

3.6.6. Regulatory and other references

This section includes:

- A list of applicable international standards, if any, complied with, in full or part.
- Statement of conformity with national regulations, where appropriate.
- List of references, if relevant.

Note that not all elements described above are applicable for all investigational devices.

- For PMCF studies the IB may be replaced by the technical information document containing all technical information on the device and a discussion of the clinical evaluation.
- For studies with CE-labelled devices used "out of scope" the technical information document containing all technical information on the device and a discussion of the clinical evaluation may be provided as an alternative for the IB. Please make sure that the new intended purpose, investigated within the clinical investigation, is well covered by the information provided.

3.7. Manufacturer's Instructions for Use

For non-CE labelled devices a separate "Manufacturer's Instructions for Use" (IFU) document must be included in the dossier, if available. If no IFU is available a very detailed description of the medical and/or surgical procedure and handling of the device must be provided in the CIP.

If the investigational device and/or comparator device concerns a CE-labelled medical device, the official manufacturer's instructions for use, covered by the CE-label, must be provided. If during the clinical investigation the medical device is used "out of scope" of the CE label a description of how the device will be used differently during the trial must be included.

3.8. Clinical evaluation plan (CEP)

According to the MDR (annex XIV) it is necessary as a manufacturer or developer of a medical device to establish and update a clinical evaluation plan (CEP). The CEP describes the strategy of, not just one clinical investigation, but of the clinical evaluation process **as a whole**. It should identify the gaps in information and associated steps that need to be taken to provide answers to the unanswered questions. The CEP can be updated with new information from previous clinical investigations. The aim of this CEP is to increase the quality of the clinical evaluations and clinical investigations.

This CEP must include:

- an identification of the general safety and performance requirements that require support from relevant clinical data (see section 3.9);
- a specification of the intended purpose of the device;

- a clear specification of intended target groups with clear indications and contra-indications;
- a detailed description of intended clinical benefits to patients with relevant and specified clinical outcome parameters;
- a specification of methods to be used for examination of qualitative and quantitative aspects of clinical safety with clear reference to the determination of residual risks and side-effects;
- an indicative list and specification of parameters to be used to determine, based on the state of the art in medicine, the acceptability of the benefit-risk ratio for the various indications and for the intended purpose or purposes of the device;
- an indication how benefit-risk issues relating to specific components such as use of pharmaceutical, non- viable animal or human tissues, are to be addressed if applicable; and
- a clinical development plan indicating progression from exploratory investigations, such as first-in-man studies, feasibility and pilot studies, to confirmatory investigations, such as pivotal clinical investigations, and a PMCF. It is expected to get an indication of the major milestones and a description of potential acceptance criteria to go with the next steps of your clinical development.

3.9. List of General Safety and Performance Requirements

According to the MDR a medical device must meet the general safety and performance requirements set out in Annex I which apply to it, taking into account its intended purpose, to be able to be put on the market. Clinical evaluation is performed to demonstrate conformity with the general safety and performance requirements. Clinical investigations may be done to gain data/evidence useful for the clinical evaluation.

For each clinical investigation we ask to provide us with the list of general safety and performance requirements that have already been met for the investigational device, including a motivation, and describe which safety and/or performance requirements will be studied during this particular clinical investigation. For this purpose a template list of general safety and performance requirements, available on our website, can be used.

This document may be provided as a separate document or can be included in the CEP (see section 3.8).

3.10. Notified Body Certificates

If the investigational device and/or comparator device used during the clinical investigation concerns a CE-labelled medical device, a valid copy of the CE-certificate issued by a notified body must be provided.

3.11. Proof of Insurance

The certificate provided must specify the amount insured and reference to the Belgian law of 22 December 2020, art. 32.

3.12. Suitability of Sites

A written statement from the site on its suitability to conduct the investigation needs to be provided.

This document is crucial for the completeness of the submission dossier as only one ethics committee (independent of the participating sites) will evaluate the application dossier. It is thus important to contact the sites as soon as possible in order to obtain this document in due time for the submission.

The written statement template, available on our website, can be used as a guidance.

3.13. Example of Labels

An example of the investigational device labelling must be provided. According to section 23.2 of annex I of the MDR, following elements should be present on the label:

- name and address of the manufacturer
- identification of the medical device and/or contents of the package
- the statement "for clinical investigation use only"
- the statement "sterile", if applicable
- where appropriate, the sterilization method
- expiration date, if applicable
- the statement "for single use only", if applicable
- the statement "custom-made device", if applicable
- any special conditions for storage and / or handling, if applicable
- any specific instructions for use, if applicable
- any warnings and / or precautions to be taken, if applicable
-
- where appropriate, a statement that a human blood derivative is incorporated into the device as an integral part

Note that in case of software, where physical labelling is not possible, a "digital label" should be provided on the opening page or start page of the software, containing the required elements described above.

3.14. Decisions from other Countries

In case of a multinational clinical investigation a document listing all other EU Member State countries and third countries involved should be provided. The current approval status (to be submitted, submitted, approved or refused) of the clinical investigation must be clearly indicated for each country. If applicable the respective approval and/or refusal letters must also be included.

3.15. Patient Related Documents

- Informed consent form (ICF), including the patient information sheet.
    - Provide the ICF at least in the official national language(s) of the region(s) where the investigation is conducted (Dutch, French and/or German).
    - The ICF version number and date must be clearly mentioned on each page (in header or footer), all pages must be numbered.
    - When electronic informed consent forms are used, the Guidance on e-consent for interventional clinical trials can be used as a guide.
    - The ICF template for interventional clinical trials with IMP in adult patients can be a guidance to develop the ICFs for clinical investigations with medical devices. The ICF template for CTAs has been developed to be in line with the GDPR and was accepted by the Belgian ECs.
    - Both the ICF template and the Guidance on e-consent are available on www.ct-college.be.

- Procedure and materials used for recruitment of patients.
    - Description of the procedures that will be used to effectively recruit the study population defined in the protocol: where, how, by whom.
    - The "Recruitment and Informed consent procedure template" developed for clinical trial applications can be used as a guidance and is available in the zip-folder with the "Dossier structure" on the FAMHP webpage for the clinical trial regulation: https://www.famhp.be/en/human_use/medicines/medicines/research_development/clinical_trials
    - Any recruitment materials used (poster, folder, flyer, advertisement, website, etc.…) must also be included.

- A description of the compensation for investigation participants.
    - If participants receive any compensation, financial or other, for investigation participation, this should be clearly described in the dossier.
    - The template "Compensation for trial participants" developed for clinical trial applications can be used as a guidance and is available in the zip-folder with the "Dossier structure" on the FAMHP webpage for the clinical trial regulation: https://www.famhp.be/en/human_use/medicines/medicines/research_development/clinical_trials

- In addition to the above documents, any other written information to be provided to subjects should be added to the application.

3.16. CV and DOI of Principal Investigator(s)

- For each principal investigator, one per investigational site, the curriculum vitae (CV) and a declaration of interest (DOI). In the CV the diploma's should be listed and the clinical study experience relevant to the submitted clinical investigation should be documented.

- The "Investigator CV template" and the "Declaration of Interest template" developed for clinical trial applications can be used as a guidance and is available in the zip-folder with the "Dossier structure" on the FAMHP webpage for the clinical trial regulation: https://www.famhp.be/en/human_use/medicines/medicines/research_development/clinical_trials

3.17. Compliance with Rules on Data Protection

This stand-alone document includes a description of the arrangements to comply with the applicable rules on the protection and confidentiality of personal data.

This document should at least contain:

"[name of sponsor] confirms that collection and processing during clinical trials is done in full compliance with the European Regulation 2016/679 of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (GDPR)"

3.18. PMCF plan

This document is only relevant for PMCF investigations. A PMCF plan specifies the methods and procedures set up by the manufacturer, to proactively collect and evaluate clinical data from the use in or on humans of a CE marked medical device, placed on the market or put into service within its intended purpose, as referred to in the relevant conformity assessment procedure.

Detailed information on the PMCF plan and a template can be found in the PMCF Plan Template.

3.19. Clinical Investigation Agreement

The agreement between the sponsor and the principal investigator(s)/investigation site(s) and any other relevant parties (e.g. investigators, CRO(s), and core laboratories), the responsibilities of each party in the clinical investigation should be defined. The agreement shall identify instances where, by participating in a clinical investigation, the parties share regulatory responsibilities with the sponsor. In addition, a brief description should be given of how the clinical investigation is financed and of any proposed compensation to the investigation site or principal investigator.

This agreement may be provided in as an unsigned, draft version. If this is the case the final, signed version must be submitted together with the first substantial modification after approval of the study.

3.20. Expert panel opinion / scientific advice

If an opinion was obtained from an expert panel (MDR Art 106) or scientific advice was obtained from a national competent authority we ask you to include the advice documents in the dossier.

3.21. Proof of Parallel Application to the EC

Proof of parallel application to the EC is only needed in case the regulatory pathway "separate opinion FAMHP and EC" is followed for non-CE marked in-house or custom-made devices. In this

case the application dossier is submitted to the FAMHP and EC in parallel and proof of submission to the EC must be provided to the FAMHP. This can be a copy of an e-mail, confirmation of receipt or any other relevant document.

4. Documents related to substantial modifications

Below you can find a list of documents that, depending on the regulatory pathway followed, must be included in the submission package of substantial modifications to the FAMHP.

Please apply the PDF file format to all documents where possible. Certificates, licenses, authorizations and other documents with a signature can be scanned with optical character recognition (OCR), digital signature are also accepted. Some general requirements for the preparation of these PDF documents:

- The files must allow "copy/paste" and search functions.
- The layout should be clear, if possible a detailed table of contents must be included in order to quickly find specific sections of text.
- Files should not be locked with a password.
- Each part of the application dossier should be a separate file.

4.1. Cover letter

The applicant should submit a signed (electronic signature is accepted) cover letter with the application dossier. Its subject line should contain the title of the trial, the invariable sponsor protocol number (if available), the single identification number/Eudamed number of the initial application and the number of the substantial modification (Ex: SM001, SM002, …).

The cover letter should give a brief description of the substantial modifications.

It should be clearly mentioned which Belgian regulatory pathway is applicable: validation FAMHP and opinion EC, consolidated opinion PAMHP and EC or separate opinion FAMHP and EC (refer to our "Guidance on submission of clinical investigations according to MDR in Belgium" for more information).

In case of a resubmission the applicant should highlight the changes as compared to the previous submission in each document. Please also add the refusal letter to the dossier.

The covering letter may be addressed to:

Federal Agency for Medicines and Health Products
Division R&D - Medical Device Unit
Avenue Galilée - Galileelaan 5/03
1210 BRUSSELS
Belgium

4.2. List of documents submitted – substantial modification

Applicants are requested to provide the filled-out list of documents submitted in the application package. This list contains the full document name, version and date of the respective documents.

When an approval is issued this list of approved documents will be attached to the approval letter. It is thus important that the applicant keeps this list of documents up to date, it must be **resubmitted it at each change** (validation questions, response to RFI, etc.) **with a clear indication of which documents have been updated/added.**

4.3. Application form substantial modification

The application form for substantial modifications can be found on our website (available soon). Please include a correctly filled-out and signed form in the application dossier. The form must be saved in the PDF file format and allow copy/paste. Electronic signature is accepted, alternatively the file may be sent as an unsigned PDF document in parallel with a scan of the signed document.

4.4. Description of the substantial modification(s)

To have a clear overview of the modifications we ask following documents to be provided:

- An extract from the amended document or the amended document itself, showing previous and new wording in track changes.

- An extract from the amended document or the amended document itself, only showing the new wording (clean version).

- A summary of all the modifications including a point by point justification.

4.5. Supporting information

If applicable, any extra information supporting the substantial modification(s) may be provided. This can be for example an extra justification of the changes, a new benefit-risk analysis, references to literature, interim analysis report, full test reports,…