MDCG 2024-5

guidance on content of the Investigator's Brochure for clinical investigations of medical devices

April 2024

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Abbreviations

AE	Adverse Event[1]
ARRIVE	Animal Research: Reporting of In Vivo Experiments
ASMF	Active Substance Master File
CE	Marking on a product to signify that it meets the legal requirements to be sold on the extended Single Market in the European Economic Area (EEA).
CEP	Certificate of suitability to the monographs of the European Pharmacopoeia
CS	Common Specification
DD	Device deficiency[2]
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency
EU	European Union
EUDAMED	European Database on Medical Devices
Eudralex	The collection of rules and regulations governing medicinal products in the European Union.
FMEA	Failure mode and effects analysis
FTA	Fault tree analysis
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GSPR	General Safety and Performance Requirements
HAZOP	Hazard and Operability
IB	Investigator's Brochure
IFU	Instructions for use
IMDRF	International Medical Device Regulators Forum
IMP	Investigational Medicinal Product
ISO	International Organization for Standardization
IVD	In vitro diagnostic
MDCG	Medical Device Coordination Group
MDR	Medical Device Regulation – Regulation (EU) 2017/745 on medical devices
MIR	Manufacturer Incident Report

[1] Defined in article 2(57) of the MDR.
[2] Defined in article 2(59) of the MDR.

Ph Eur	European Pharmacopoeia
PMF	Plasma Masterfile
PMSR	Post Market Surveillance Report
PSUR	Periodic Safety Update Report
SADE	Serious Adverse Device Effect[3]
SAE	Serious Adverse Event[4]
TSE	Transmissible Spongiform Encephalopathy

[3] Any adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. An adverse device effect is any adverse event related to the use of an investigational device or a comparator, if the comparator is a medical device.
[4] Defined in article 2(58) of the MDR.

1. Introduction

When a sponsor of a clinical investigation shall submit an application according to article 70(1) of the MDR, the application shall be accompanied by the documentation referred to in Chapter II of Annex XV of the MDR. The Investigator's Brochure (IB) is part of the required documentation and is one of the means by which the sponsor is to fulfil the requirement in section 2.7 of Chapter I of Annex XV of the MDR which states that the investigator shall have access to technical and clinical data regarding the device that is being investigated. This includes the intended purpose(s), design, the basic fundamental scientific principles behind the design and the level of objective evidence already in place, to assure its safety and functionality during the investigation. For the purpose of this guidance document, medical devices, accessories for medical devices, and products listed in Annex XVI shall hereinafter be referred to as 'devices'.[5]

Section 2 of Chapter II of Annex XV of the MDR describes the required content of the IB. Please note that by submitting complete applications and documents that contain all the required content, this helps competent authorities in assessing the application, which facilitates the review process. Prior to submission of the IB, sponsor is recommended to complete the checklist in Appendix A of this guidance, to ensure the IB meets the minimum requirements for validation of the application per article 70 of the MDR. The checklist, if used, should be included together with the IB in the submission.

When preparing the IB, sponsors are encouraged to review the full details of the regulation as well as the normative Annex B of the international standard ISO14155:2020 Clinical investigation of medical devices for human subjects - Good clinical practice.

This guidance document is intended to support sponsors in developing their IB by describing in greater detail what type of information is expected in the respective IB sections, in order to pre-empt questions from the competent authorities during the assessment of the clinical investigation application. The guidance is based on the requirements of both the MDR and ISO14155:2020 as well as experience from the competent authorities.

Note that any updates to the IB or other relevant information that is newly available shall be brought to the attention of the investigators in a timely manner[6]. Further, when the IB is updated, the sponsor needs to notify the member states concerned within one week[7]. Changes made to the IB shall be clearly identifiable.

Note that the scope of this guidance is IBs written for clinical investigations as defined by the MDR, and it is not intended to be applied for performance study IBs under the IVDR.

2. Content of the Investigator's Brochure

The IB shall contain the clinical and non-clinical information on the investigational device that is relevant for the investigation and available at the time of application. The information shall be presented in a concise, simple, objective, balanced, and non-promotional form that enables a potential investigator and the investigation site team, to understand it and make his/her own

[5] Article 1.4 of the MDR.
[6] Section 2, Chapter II, Annex XV of the MDR.
[7] Per article 70.2 of the MDR.

unbiased benefit-risk analysis of the appropriateness of exposing study participants to the investigational device. Further the IB should contain sufficient information to allow safe and correct use of the device.

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, then a clear reference should be made in the IB and the annexes enclosed with the application. The reference in the IB should clearly state the title of the referenced document and the section in which the information is given. A summary of the referenced document should still be provided in the IB, as the IB should be possible to read as a stand-alone document.

Administrative details

The IB shall be clearly identified. The first page(s) should contain a proper identification of the IB with the name of the investigational device, a document reference number, version and 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.

The page number and total number of pages of the document should be indicated on each page of the IB.

2.1. Investigational device information

According to section 2.1, chapter II, Annex XV of the MDR, the IB should include identification and description of the device, including information on the intended purpose, the risk classification and applicable classification rule of the regulation, design and manufacturing of the device and reference to previous and similar generations of the device.

This investigational device information should include the following elements, if applicable:

2.1.1. Identification of the device

If several names are used for the same device, this should be explained, and care taken to use consistent terminology throughout the study documentation, to avoid confusion.

2.1.2. Intended purpose

State the intended purpose[8] with a clear specification of the indications, contra-indications, the patient target group or groups, and the intended users, as appropriate[9].

If there is a known difference between the intended purpose in the clinical investigation (due to development stage, study design or other reasons) and the planned intended purpose when the device will be placed on the market, this difference should be clearly stated.

[8] Article 2(12) of the MDR.
[9] Aligned with section 23(4)b in Annex I of the MDR.

If the device has already been CE-marked and placed on the market, it should be explained whether the intended purpose of device in the clinical investigation is different from the intended purpose for which the device has been CE marked, or if it is to be further assessed within the scope of its intended purpose. This should be clearly specified.

2.1.3. Intended clinical performance[10]

Describe in clinical terms the performance that the device is intended to achieve. I.e. describe how (the mechanisms through which) the device is able to achieve its intended purpose as claimed by the manufacturer, thereby leading to a clinical benefit for patients, when used as intended by the manufacturer.

The 'clinical benefit' means the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health[11].

Describe the intended clinical benefits to patients with relevant and specified clinical outcome parameters. The clinical benefit could be resulting from any direct or indirect medical effects which stem from the technical or functional characteristics of the device, including diagnostic characteristics.

For products without an intended medical purpose that are covered by Annex XVI of the MDR, the requirement to demonstrate a clinical benefit shall be understood as a requirement to demonstrate the performance of the device[12].

2.1.4. Qualification and classification

Provide a rationale for why the device qualifies i.e. has regulatory status as a medical device, an accessory for a medical device or a product listed in Annex XVI. Compare the intended purpose to the applicable definition in article 2(1), 2(2) or annex XVI of the MDR, and state the applicable risk class according to Annex VIII of the MDR.

For borderline products (i.e. where there could be uncertainty whether the product is a device or a medicinal product), it is of particular importance to include the scientific rationale for the qualification as device, and to align with the MDCG 2022-5 guidance[13].

Further, if the study is a study combining device and medicinal product, clear information on the regulatory status of both device and drug components should be provided.

[10] Article 2(52) of the MDR.
[11] Article 2(53) of the MDR.
[12] Article 61(9) of the MDR.
[13] MDCG 2022-5 Guideline on borderline between medical devices and medicinal products under Regulation (EU) 2017/745 on medical devices.

For classification, relevant guidance is available in MDCG 2021-24[14], MDCG 2019-11[15] and MDCG 2023-5[16]. Classification under previous legislation, i.e. for legacy devices may be mentioned as supplementary information.

2.1.5. Literature and evaluation supporting the rationale for the design and intended use of the investigational device

Provide a summary of the literature, previous research and evaluation supporting the rationale for the design and intended use of the investigational device, if available.

2.1.6. General description of the device:

2.1.6.1. Design

The IB shall contain a description of the critical and fundamental design (e. g. the technical or scientific principles applied) of the relevant components/parts of the device, so that the device, when used according to the instructions, will be able to achieve the intended purpose. The description should be as clear and fundamental as reasonably possibly, not assuming that all intended readers are already experts in the field. Describe the operation of the device and its mode of action, along with supporting scientific literature if available.

2.1.6.1.1. Description of the key functional elements

Include a general description of the key functional elements, e.g. its parts/components (including software if appropriate), its formulation[17], its composition, its functionality and, where relevant, its qualitative and quantitative composition. Where appropriate, this should include labelled pictorial representations (e.g. diagrams, photographs, and drawings), clearly indicating key parts/components, including sufficient explanation to understand the drawings and diagrams.

Often, animations or recordings are made to clarify the mechanism of action and specific features of a device; if this is the case, a copy or link to these can be provided in or together with the IB as a supporting way to explain the design and working principles of complex devices; nevertheless, these are considered complementary and do not fully replace a written description of the mechanism of action in the IB.

2.1.6.1.2. Overview of materials used

A clear overview of materials used in the device should be provided, preferably in a tabular format.

In addition, detailed information for all materials coming into contact with the human body (i.e., in contact with tissues or body fluids of a patient, health care professional, or other user, even if

[14] MDCG 2021-24 Guidance on classification of medical devices.
[15] MDCG 2019-11 Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 - MDR and Regulation (EU) 2017/746 - IVDR.
[16] MDCG 2023-5 Guidance on qualification and classification of Annex XVI products - A guide for manufacturers and notified bodies.
[17] Relevant for substance based devices.

contact is only brief, occasional or indirect) should be provided in a separate section on biocompatibility and biological safety. Refer to section 2.3.2.3.2 below for further guidance.

If relevant, details of any medicinal substances, non-viable human or animal tissues or their derivates, or other biologically active substances must also be included. See also section 2.6 below.

2.1.6.1.3. Technical specifications

Technical specifications, such as features, dimensions and performance attributes, of the device and any variants/configurations and accessories that would typically appear in the device specification made available to the user, for example in brochures, catalogues and similar publications should be provided. This concerns the variants/configurations and accessories to be used in the clinical investigation.

2.1.7. Summary of relevant manufacturing processes

The IB should contain information on how the manufacturing process has been designed to ensure sufficient device quality and robustness, considering e. g. known or foreseeable variability inherent to biological materials and other critical components or raw materials which may cause challenges that might jeopardize device performance unless they are sufficiently controlled.

Provide a summary of relevant manufacturing processes and the corresponding quality controls (including verifications and validations as well as final testing) applied 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.

2.1.8. Reference to previous and similar generations of the device

An overview of the previous and similar versions of the device (e.g., in table format) is recommended, if applicable. This overview should specifically focus on the devices used clinically and in confirmatory pre-clinical testing, i.e. the late stages of development. 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.

2.1.9. Overview of identified equivalent or, if any, similar devices available

As background for the evaluation of clinical data (refer to section 2.4 in chapter II Annex XV of the MDR as well as section 2.4 in this guidance document) and for the assessment of anticipated benefits per article 62(4e) of the MDR, the sponsor should provide an overview of identified equivalent if any, or relevant similar devices available in the Union or international markets. A brief description of similar devices including the key features and their intended purpose(s) focusing on the novelty of the current device when compared to other is sufficient.

2.2. Labels and instructions for use

According to section 2.2, chapter II, Annex XV of the MDR, the IB should include manufacturer's instructions for installation, maintenance, maintaining of hygienic standards and use of the investigational device, including any necessary storage and handling requirements, as well as, to the extent that such information is available, information to be placed on the label, and instructions for use to be provided with the device. In addition, information relating to any relevant training required is to be included.

Sponsor needs to check national legislation, which may require labelling and instructions for use to be in national language.

2.2.1. Instructions for use

For devices which do not bear CE marking, "Instructions for Use" (IFU) document(s) should be included in the application dossier, as part of the IB or as a separate document referenced from IB. Instructions for use should contain:

- The information to be provided with the device when placed on the market according to the requirements listed in chapter III, Annex I of the MDR,to the extent that such information is available,
- Instructions on the use and operation of the device need to be sufficiently detailed to prevent user errors and should allow the reader to understand how the device is to be operated without having an actual device at hand. Graphic illustrations are recommended.
- Information on preparation for use and any intended re-use (e.g., cleaning, sterilization), any pre-use safety or performance checks and any precautions to be taken after use (e.g., disposal), if relevant.
- Instructions for installation and maintenance of the device, including any precautions to be taken into consideration prior to installation and service, to ensure user and patient safety.
- Storage and handling requirements as well as shelf life (when appropriate) of the investigational device should be specified.

If the investigational device already bears the CE-marking and is to be used outside the intended purpose of the CE mark during the clinical investigation study specific IFU document(s) should be included in the application dossier, as part of the IB or as a separate document referenced from IB. Moreover:

- A description of how the device will be used differently during the clinical investigation must be included in the IB. There may be situations when the difference in use vs the CE mark is minimal and there may be situations where the difference is significant. Only where there are minimal differences of use, it may be sufficient that the clarification of the use difference is provided in the IB itself. Provided that safe and effective use of the device can be ensured without a study specific IFU, the CE marked IFU does not need to be updated.
- The manufacturer's IFU, covered by the CE mark, should be provided, in addition.

If the investigational device and/or comparator device already bears the CE-marking, and is to be used within the intended purpose of the CE-mark during the clinical investigation, the manufacturer's IFU, covered by the CE mark, must be provided.

2.2.2. Labels

Labels of the investigational device should contain, to the extent that such information is available, the information to be provided with the device when placed on the market[18], according to the requirements listed in chapter III, Annex I of the MDR. Note in particular the specific requirement which is applicable if the investigational device is intended for clinical investigation only; to include the text 'exclusively for clinical investigation" on the labels. Sponsor needs to check national legislation, which may require labels to include 'exclusively for clinical investigation" in national language.

It is recommended to include the graphic presentation of the device labels, either in the IB or as separate documents which are referenced from the IB.

Note that the requirements for labelling apply also to investigational software devices.

2.2.3. Training

Training needs and plans for training should be described in the IB.

2.2.4. Implant card

In the case of a clinical investigation with an implantable device, it is recommended that a study implant card is provided to the patient for safety reasons. Refer to article 18 of the MDR for detailed requirements on content of the implant card, and to MDCG guidance documents MDCG 2019-8[19] and MDCG 2021-11[20] for additional guidance.

2.3. Pre-clinical evaluation

According to section 2.3, chapter II, Annex XV of the MDR, the IB should include a pre-clinical evaluation based on relevant pre-clinical testing and experimental data, in particular in-design calculations, in vitro tests, ex vivo tests, animal tests, mechanical or electrical tests, reliability tests, sterilisation validation, software verification and validation, performance tests, evaluation of biocompatibility and biological safety, as applicable.

2.3.1. General recommendations regarding pre-clinical evaluation

Note that it is a requirement of the MDR that the investigational device(s) conform(s) to the applicable general safety and performance requirements (GSPR) set out in Annex I of the MDR

[18] Investigational devices are not required to include UDI labelling.
[19] MDCG 2019-8 Guidance document Implant Card relating to the application of Article 18 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices
[20] MDCG 2021-11 Guidance on Implant Card – 'Device types'

apart from the aspects covered by the clinical investigation and that, with regard to those aspects, every precaution has been taken to protect the health and safety of the subjects. This includes, where appropriate, technical and biological safety testing and pre-clinical evaluation, as well as provisions in the field of occupational safety and accident prevention, taking into consideration the state of the art.[21]

As a general principle, pre-clinical tests have to be completed before a clinical investigation application is made. Testing would at least have to be completed to an extent that supports the planned use of the device in the clinical investigation. As an example, if the exposure to the device in the clinical investigation is shorter than the planned exposure of the final marketed device, it might be sufficient to provide the data that ensures that the characteristics and performance of the device is not adversely affected during the time the device is used in the clinical investigation. The level of objective evidence of compliance available versus planned should be easily accessible through the GSPR information (refer also to section 2.7 below).

In situations where some aspects of pre-clinical testing have not been completed, this should be clearly highlighted and justified. If equivalence is claimed as a reason for not performing some of the pre-clinical testing, clarify the technical, biological, and clinical grounds for this[22].

The IB should include a summary of the pre-clinical testing that has been performed on the investigational device, together with an evaluation of the results of such testing, justifying its use in/on human subjects.

Pre-clinical testing should be made according to relevant standards and common specifications, unless a justification based on scientific grounds is provided to not conduct certain tests or not adhering to standards and/or common specifications.

Any deviations from acceptance criteria need to be justified.

Test summaries could preferably be provided in tabular format and should include:

- Reference standard or common specification
- Reference to test report for traceability[23]
- For each test, information on:
    - Specific reference in the standard applied
    - GLP status when relevant (if non-GLP, this should be justified)
    - Acceptance criteria
    - Test method
    - Sample (including type and size) and its rationale
    - Brief summary of results
    - Conclusion (e.g. pass/not pass)

[21] Article 62(4)l of the MDR
[22] MDCG 2020-5 (Clinical Evaluation - Equivalence A guide for manufacturers and notified bodies)provides guidance on equivalence.
[23] Indicating the identifier of the report, in order to allow tracking and requests for particular reports.

- The applicant should either confirm that the device used was identical to the investigational device for clinical use (including e.g., sterilization) or detail any differences between the device used tested pre-clinically (e.g., mechanical testing, fatigue testing, reliability testing, animal studies, biocompatibility studies) and used clinically. If the device that will be used in the clinical investigation differs from the device used in pre-clinical studies, a justification of the transposability of the pre-clinical results should be provided.
- It should be clearly indicated whether the test has been performed on parts of, or the entire device.

Note that during assessment of the clinical investigation application, the full study reports of any pre-clinical study may be requested; to reduce the overall time to clinical investigation approval (take into consideration there is only one possible round of questions following MDR), the applicant may consider submitting the full study reports of certain critical studies (such as animal tests, if applicable) at the time of the initial application along with a justification for doing so. Please note that even if full pre-clinical study-reports are submitted, there is an obligation to include a summary of the pre-clinical studies in the IB. This summary should provide an overview of the scope, results and evaluation of the results, accessible also to non-experts.

Note that if references are made to separate reports, the reference should point to the sections of interest in the referenced document.

2.3.2. Specific recommendations regarding pre-clinical evaluation

2.3.2.1. In design calculations

In design calculations may support the design and mechanical strength of the device.

2.3.2.2. Bench testing - “horizontal” tests (valid for any device)

2.3.2.2.1. Performance tests

The primary objective of performance[24] testing is to evaluate whether the device achieves the intended purpose as stated by the manufacturer. The manufacturer should establish (i.e. define, document, and implement) the clinical performance requirements of the device and the corresponding device performance specifications for the intended use and device claims.

Provide information on conducted performance tests. If no performance testing has been conducted, this should be explicitly justified (e.g. when there is a previous version of the device with the same intended purpose and function, for which performance has been evaluated, that is already placed on the market, and the current investigational device does not implement any significant change that might impact performance).

[24] Article 2(22) of the MDR.

Discuss whether it is possible and relevant to perform in vitro, ex vivo or animal testing in order to demonstrate performance of the device.

2.3.2.2.2. Reliability tests

Reliability could be defined as the probability that a device, system, or service will perform its intended function adequately for a specified period of time, or will operate in a defined environment without failure.

Describe how durability of the device has been evaluated, to ensure the occurrence of device deficiencies during the lifetime of the device, or at least during its use in the clinical investigation, will be kept at an acceptable level. Summarize results of stability testing and simulations, accelerated tests (may be necessary for devices that will be used for longer time periods), aging tests to evaluate wear after repeated use and reprocessing etc.

There are specific requirements regarding reliability for some device types, e.g.:

- For devices with a measuring function[25], summarize tests which document that the device has sufficient accuracy, precision and stability for the intended purpose. Indicate the limits of accuracy.
- Interoperability and compatibility with other devices[26] needs to be addressed in relation to reliability, if applicable. Provide summary of evidence supporting that the device is reliable and safe when operated together with other devices or products. Refer to section 2.3.2.2.3 for further details.
- If the device incorporates an electronic programmable system, including software and software that are devices in themselves, the manufacturer shall ensure repeatability, reliability and performance in line with the intended use[27]. Summarize how repeatability, reliability and performance have been tested to ensure that it is in line with the intended use. The reliability of the energy source for active implantable devices[28] has to be ensured. Describe how this has been tested.
- Devices for use by lay persons shall, where appropriate, include a procedure by which the lay person is warned if the device has failed to provide a valid result[29].

2.3.2.2.3. Interoperability and compatibility tests

When a device, including software, is intended to be operated together with other devices or products, from the same manufacturer or from different manufacturers, it shall be designed and manufactured in such a way that the interoperability and compatibility are reliable and safe.

The (natural or legal) person who is responsible for the combination of devices, has to verify:

- that the combination is done compatibly with the intended purposes of the devices, i.e. within the limits of use specified by their manufacturers (in the instructions for use).

[25] Section 15.1 in Annex I of the MDR.
[26] Section 14.5 in Annex I of the MDR.
[27] Section 17.1 in Annex I of the MDR.
[28] Section 19.2 in Annex I of the MDR.
[29] Section 22.3 in Annex I of the MDR.

- the mutual compatibility between the device and other devices or products, i.e. the devices have to perform as intended, have to integrate and operate without any modification or adaptation and have to be used without conflict/interference or adverse reaction.
- the interoperability of the devices, i.e. the ability to exchange information and use information that has been exchanged for the correct execution of a specified function without changing the data and/or to communicate with each other and/or work as intended.

A summary of the evidence produced to demonstrate the compatibility and interoperability of combined devices should be provided.

For a clear understanding of the interoperability and compatibility test results, a detailed description of the types of elements to be combined (e.g. CE marked devices, CE marked IVD devices, other products which are in conformity with legislation that applies to them), the types of connection, the type of established data exchange and any restrictions on use applying to such combination should also be provided.

Specific risks related to interoperable devices and cybersecurity should be considered, please refer to section 2.3.2.3.4 on cybersecurity testing.

2.3.2.2.4. Usability tests

Usability is defined in the European standard EN 62366-1[30] as the characteristic of the user interface that establishes effectiveness, efficiency, ease of user learning and user satisfaction in the intended use environment.

All aspects of usability, including effectiveness, efficiency, and user satisfaction, can either increase or decrease safety of a medical device. Usability is created by characteristics of the user interface that facilitate use, i.e., to make it easier for the user to perceive information presented by the user interface, to understand and to make decisions based on that information, and to interact with the medical device to achieve specified goals in the intended use environments. Many of these factors can influence safety and performance[31] to various extents.

Usability test is defined as a method for exploring or evaluating a user interface with intended users within a specified intended use environment[32]. Usability tests may be preclinical or clinical depending on the test design. In situations where the usability test fulfils the definition of a clinical investigation[33], the test is to be reported in the Existing clinical data section of the IB, while the pre-clinical usability tests are to be presented in the Preclinical evaluation section.

[30] EN 62366-1 Medical devices - Part 1: Application of usability engineering to medical devices (IEC 62366-1:2015) section 3.16
[31] The words ”and performance” have been added vs the text in standard EN 62366-1
[32] EN 62366-1 Medical devices - Part 1: Application of usability engineering to medical devices (IEC 62366-1:2015) section 3.19.
[33] Additional guidance available in MDCG 2021-6.

2.3.2.3. Bench testing - “Vertical”tests (depending on the device type)

2.3.2.3.1. Mechanical, electrical safety and electromagnetic compatibility tests

Mechanical and electrical safety tests are important to ensure that the investigational device is safe for users and patients. The extent of testing required varies depending on type of device, and may include tests of both materials, parts, and the final device.

There are specific standards for some types of devices, and the manufacturer is expected to adhere to those that are relevant, or describe the measures taken and procedures used to achieve at least the same requirement level as described in the relevant standard.

As an example, the IEC 60601 standard series is applicable to electrical devices.

2.3.2.3.2. Biocompatibility and biological safety

To address the compatibility between an investigational device and biological tissues, cells and body fluids, a biological risk assessment should be carried out according to ISO 10993 standard series.

ISO 10993 part 1 provides the general principles for a risk-based approach to biological safety evaluation and material characterization. The other parts of the ISO 10993 standard series cover tests methods for different aspects of biocompatibility and biological safety.

The extent of biocompatibility and biological testing will depend on the intended purpose, available information, and demonstration of equivalence to other devices. Guidance on equivalence is provided in MDCG 2020-5.

Results from the evaluation of biocompatibility and biological safety shall be summarized in the IB. The following information will have to be provided, at a minimum,

- Overview of the material composition of the device, focussing on body-contacting materials (both direct and indirect). Preferably, the information is provided in a tabular format. Detailed information about materials should be available upon request, such as generic name, brand name and if applicable, the grade, quality, specification or standard adhered to and if anything has been added such as additives or colorants.
- The nature, degree, frequency, and duration of the exposure.
- Criteria for determining the acceptability of the material for the intended purpose and if applicable demonstration of equivalence to other devices.
- Rationale for test strategy (selection and/or waiving of tests) and test samples. Material characterization according to ISO 10993-18 is expected, and when applicable toxicological risk assessment according to ISO 10993-17. Further, there are special requirements in point 12, Annex I of MDR for devices incorporating a substance considered to be a medicinal product and devices that are composed of substances or of combinations of substances that are absorbed by or locally dispersed in the human body.
- Test methods used, acceptance criteria, results, and conclusion. Preferably presented in table format.
- Separate and specific discussion of substances which are carcinogenic, mutagenic, toxic to reproduction, or endocrine disrupting, according to point 10.4.1, Annex I of MDR.
- Overall biocompatibility and biological safety conclusion in relation to the foreseen exposure to the device due to the clinical investigation.

2.3.2.3.3. Software verification and validation

For devices that incorporate software or for software that are devices in themselves, describe the software design and development process and evidence of the validation of the software, as used in the finished device. This information should typically include the summary results of all verification, validation and testing performed both in-house and in a simulated or actual user environment prior to final release. It should also address all of the different hardware configurations and, where applicable, operating systems identified in the information supplied by the manufacturer.

For software, a number of standards are available. Three standards are elaborated upon underneath, but this list is not exhaustive, and it should be noted that other standards can also be applicable.

IEC 62304:2006 Medical device software – Software life cycle processes, covers both software as a component of a medical device and standalone software (a medical device in its own right).

IEC 82304-1:2017 Health Software – Part 1: General requirements, provides requirements for the safety and security of health software products.

IEC 60601-1:2005 Medical electrical equipment – Part 1: General requirements for basic safety and essential performance, contains a section specifically on programmable electrical medical systems.

For the choice of methods and standards used for software verification and validation, the manufacturer should provide a rationale.

2.3.2.3.4. Cybersecurity tests

For devices that incorporate software or for software that are devices in themselves, the software should be designed and manufactured in accordance with the state of the art, considering the principles of the development life cycle, risk management, including information security, verification and validation[34].

A description of how testing for verification and validation of security was performed should be provided. Methods can include security feature testing, fuzz testing, vulnerability scanning and penetration testing. Additional security testing can be done by using tools for secure code analysis and tools that scan for open source code and libraries used in the device, to identify components with known issues. Please refer to MDCG 2019-16 Guidance on Cybersecurity for medical devices for further details.

2.3.2.3.5. Validation of cleaning, disinfection and sterilization

The sterilization method, cleaning and disinfection used should be stated and justified in the IB. A broad range of standards are available for disinfection and sterilisation methods, such as radiation, ethylene oxide, dry and moist heat. For sterilization, a validation report should be provided[35]. Validation reports for cleaning and disinfection are not expected with the submission, but need to be summarised in the IB and referenced in relation to the overview of GSPR (section

[34] Section 17.2, Annex I of the MDR.
[35] Article 71(3f) of the MDR.

2.7). Compatibility of the method used and the device should be discussed, if applicable. Clearly state the validated method for reprocessing reusable devices. Should ethylene oxide be used as sterilizing agent, please specify whether testing for residuals is performed and provide the results and conclusions of these tests[36]. For invasive devices please specify how endotoxin levels have been tested[37] and which acceptance criteria[38] have been used.

2.3.2.3.6. Packaging validation

Packaging systems need to be validated for both sterile and non-sterile devices. Describe how the ability of the packaging has been validated to ensure the device maintains its integrity and, when applicable, sterility, considering its distribution and storage (as specified by the manufacturer).

In cases of sterile packaging, validation of the packaging's ability to maintain sterility is important. Packaging validation may also be necessary for other packaging situations, e.g. mechanical and thermal stability.

2.3.3. Animal tests

If applicable, include a summary of all *in vivo* animal tests that have been conducted (a reference to external documents is typically not sufficient). Each summary should include information on the laboratory where the test has been performed, as well as study design choices including:

- Species used, breed
- Number of animals per group
- Age of animals
- GLP status (if non-GLP, this should be justified)
- Version of the device used
- Choice or absence of comparator, with justification
- Duration of exposure
- Standard applied, if any
- Results
- Evaluation of results

An overview of the analyses performed should be provided. Acceptance criteria, results, any deviations and conclusions should be presented. Any notable findings should be mentioned and discussed.

In case of non-GLP studies, it is expected that study reports (which may be requested by the competent authority) are compliant with the ARRIVE guidelines[39] or equivalent (to the extent that this is possible).

In addition to the summaries provided in the IB, sponsors are recommended to submit the referenced full study reports from preclinical animal tests to the competent authority.

[36] Refer to standard ISO 10993-7.
[37] Such as ISO standard 11737-3 "Sterilization of health care products — Microbiological methods — Part 3: Bacterial endotoxin testing".
[38] Often available in pharmacopoeia.
[39] https://arriveguidelines.org/arrive-guidelines .

2.4. Existing clinical data

According to section 2.4, chapter II, Annex XV of the MDR, the IB should include existing clinical data, in particular:

- from relevant scientific literature available relating to the safety, performance, clinical benefits to patients, design characteristics and intended purpose of the device and/or of equivalent or similar devices.
- other relevant clinical data available relating to the safety, performance, clinical benefits to patients, design characteristics and intended purpose of equivalent or similar devices of the same manufacturer, including length of time on the market and a review of performance, clinical benefit and safety-related issues and any corrective actions taken.

If applicable an overview of ongoing and completed clinical investigations with the investigational device should be provided. Tabular presentation of clinical investigation information is recommended, including number of subjects, indication for use, endpoints, etc. In addition, it might be relevant to provide such information on devices that have similar characteristics, as well as information on studies with the investigational device that relate to other indications for use. If equivalence with previous generations of the device or competitor devices based on the same technology is claimed, the demonstration of equivalence should be done in line with the provisions in Section 3 of Annex XIV of the MDR and the MDCG guidance 2020-5 Clinical Evaluation - Equivalence. A guide for manufacturers and notified bodies.

The overview must provide sufficient and clear information on the previous clinical investigation(s), including sites/centres, safety and performance results and an analysis of adverse device effects, serious adverse events (SAE) and any history of modification or recall of the investigational device.

In case the clinical investigation has a phased approach, and the study is expanded to other sites that were not involved in the initial phase, it is recommended to review and update, if necessary, the IB with a summary or interim analysis of the current status discussing any notable information such as SAEs. Ensure that interim analyses are based on clean data.

For CE-marked devices evaluated outside the intended purpose as well as in situations where there are previous marketed generations of the device, please provide a summary of the latest Periodic Safety Update Report (PSUR) for class II-III devices or Post Market Surveillance Report (PMSR) for class I devices.

If applicable any compassionate use of the device should be described, with information on the extent of use and any relevant finding if available.

2.5. Risk management of the investigational device

According to section 2.5, chapter II, Annex XV of the MDR, the IB should include a summary of the benefit-risk analysis and the risk management, including information regarding known or foreseeable risks, any undesirable side-effects, contraindications, and warnings.

Sponsors conducting clinical investigations of CE marked devices which are being investigated outside the intended purpose for which they have been CE-marked, need to make sure that the differences in use (e.g. different duration, location, user or patient population) and any new risks that arise from them have been appropriately addressed in the risk management and that this is described in the IB. The risk management process needs to be described. It should describe risk

analysis, risk evaluation and risk control/mitigation (this last part includes benefit-risk analysis). It should also describe the levels used for assigning probabilities and severities of harm and the risk-acceptability criteria that are used (in other words: When do the benefits outweigh the risks?).

Refer to ISO 14971:2019[40] and ISO/TC 24971:2020[41] for more info on the application of risk management to medical devices and Annex H in ISO 14155:2020 on the application of ISO 14971 to clinical investigations.

When needed, the competent authority may request that the full Risk Analysis Table, Risk Management Plan and/or Risk Management Report as well as actual data and evaluations from specific tests are provided. If these documents are referenced in the IB, the references to the sections of interest in the documents should be provided in the IB.

Some examples of types of risk analyses:

- HAZOP: Hazard and Operability
- FMEA: Failure mode and effects analysis
- FTA: Fault tree analysis
- Procedure analysis

The risk management methods and techniques listed above should normally be used in combination so that all reasonably foreseeable risks are identified and managed.

Detail what information was used to estimate the risks. For example published standards or articles about similar devices, expert assessments, tests or simulations.

It might be useful to 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. Note that 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. It is also to be noted that matrices with three levels might not always be sufficiently accurate for adequate decision making. There is no need that these matrices be balanced. For example, a 4 × 5 matrix could be appropriate for a given application. Regarding probabilities levels such as 1:10, 1:100 may be used. The levels of severity should be selected based on what is relevant for the device, its intended use and users.

Risk control measures should be taken to reduce any identified risks as far as possible. Risk control measures are generally divided into three broad categories, in order of priority:

- Risk elimination/reduction through safe design and manufacture, e.g. identifying risks through pre-clinical testing and pre-clinical evaluation and making changes in design or manufacturing in advance of the clinical investigation; completion of bench testing, pre-clinical evaluation, and verification and validation of design prior to commencement of the clinical investigation application; designing the clinical investigation to be conducted in accordance with relevant international standards, consensus guidance, and good clinical practice; performance of the study at specialised clinical sites only, with investigators meeting specific specialist criteria.
- Protective measures, e.g.; physical protective measures of the device; in the context of a clinical investigation, measures such as staged enrolment and interim pre-

[40] Medical devices – Application of risk management to medical devices (ISO 14971:2019).
[41] ISO/TR 24971:2020 Medical devices — Guidance on the application of ISO 14971.

specified subject safety assessment, pre-specified stopping rules, narrow study population with more favourable benefit-risk profile, independent study oversight (such as data monitoring committees, clinical events committees), frequent and accurate reporting and investigation of SAEs and device deficiencies (DDs), accurate recording of AEs/SAEs/DDs, 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 patient information sheet; training of investigational staff on residual risks; provision of warnings, precautions, and contra-indications on labelling, in the instructions for use, and in the IB; optimizing communication among sites in order to rapidly communicate and informs sites of any emerging risks; communicating safety data and residual risks with ethics committee(s) and competent authority(ies) to determine if any additional subject protection measures are needed.

Please provide, in the IB, information on any identified residual risks, including risk-benefit analysis of these residual risks. Please provide a list of warnings, precautions, and contra-indications for the investigational device.

2.5.1. Anticipated Serious Adverse Events (SAEs) and Serious Adverse Device Effects (SADEs)

Based on their internal risk management documents sponsors are expected to assess anticipated frequency of occurrence of serious adverse events (SAEs) and serious adverse device effects (SADEs). The outcomes of this assessment could preferably be presented in a tabular format in the IB.The following table is an example of recommended characteristics of the events to include.

Anticipated SAE/SADE	Related to device or procedure	Probability of occurrence	Reference (basis of these numbers)

Such a table will help the sponsor with its duties regarding the risk assessment of the device and the procedures. It could also be used by the competent authorities for the assessment of the risk-benefit of the clinical investigation and safety follow up during the conduct of study. When the same source is used, it can reduce the risk of divergent interpretation between sponsor and competent authorities.

In the safety analysis of the SAE reports, the table would help determine whether the benefit/risk ratio of the clinical investigation has changed due to the reported SAE/SADE. When a SAE/SADE is reported it can be compared to the table to determine whether it was listed among the anticipated SAEs/SADEs and the observed/reported frequency of SAEs/SADEs can be compared to the expected/previously reported frequency.

Sponsors are reminded that if new data arises that is likely to substantially impact the safety, health or rights of the subjects or the robustness or reliability of the clinical data generated by the clinical investigation, it shall notify within one week the member states in which the clinical investigation is being conducted[42]. The new data needs to be reflected in updated documents included with the notification of substantial modification to the competent authorities. When updating the IB during the conduct of the clinical investigation, the sponsor is expected to revise the table with up-to-date information including safety reports arising from the ongoing clinical investigation.

Sponsors are further encouraged to link information in the anticipated SAE table to the IMDRF codes[43] that will be used in the future European database on medical device (EUDAMED)[44], and which are already used in the manufacturers incidents report (MIR)[45]. This will support the device community (manufacturer, competent authorities, notified body) to get a global view of the safety of a device throughout its lifecycle.

2.6. Devices that incorporate a medicinal substance, including a human blood or plasma derivative or devices manufactured utilising non-viable tissues or cells of human or animal origin, or their derivatives

According to section 2.6, chapter II, Annex XV of the MDR, the IB should include detailed information on the medicinal substance or on the tissues, cells or their derivatives, and on the compliance with the relevant general safety and performance requirements and the specific risk management in relation to the substance or tissues, cells or their derivatives, as well as evidence for the added value of incorporation of such constituents in relation to the clinical benefit and/or safety of the device.
Note that methods specified in Annex I to Directive 2001/83/EC shall be used to verify the quality, safety and usefulness of substances which, if used separately, would be considered to be a medicinal product within the meaning of point (2) of Article 1 of that directive.[46]

For CE-marked devices which are unaltered but used outside the intended purpose, the quality aspects in section 2.6.2 may be considered as appropriately addressed during the conformity assessment by the Notified Body, and the evidence submitted may be adapted accordingly.

2.6.1. General requirements

For medicinal substances the chemical name, chemical and structural formula should be presented.

In case a medicinal product is included in the device, it could be relevant to reference that a Marketing Authorization has already been obtained in EU (e.g. the number of the authorization for placing the medicinal product on the market). Also, the general information that can be provided for the medicinal product is the name of the medicinal product. i.e. both the common

[42] Article 75 Substantial modifications to clinical investigations.
[43] Terminologies for Categorized Adverse Event Reporting (AER): terms, terminology and codes | International Medical Device Regulators Forum (imdrf.org).
[44] Medical Devices – EUDAMED (europa.eu).
[45] Manufacturer incident report 2020 and Questions and Answers document regarding the Implementation of the new Manufacturer Incident Report (MIR) Form.
[46] Section 12.1, Annex I of the MDR.

name, which is the international non-proprietary name (INN) as well as the trade mark ; qualitative and quantitative composition; pharmaceutical form (e.g. tablet, capsule, cream, ointment, solution for injection etc).

Then main physical, chemical, pharmaceutical, toxicological and pharmacokinetic properties of the substance as well as available clinical data should be summarised. It is necessary to elaborate not only on the safety, quality and effectiveness of the active substance itself, but also on possible interactions between the substance and the materials used in devices and/or other substances. Note that where relevant, the pharmacodynamics, pharmacokinetics, toxicity and local tolerance of the substance may need to be specifically addressed during the pre-clinical evaluation and should be covered in the relevant subsection(s) under 2.3 above.

Justify the inclusion of the medicinal substance, human blood or plasma derivative, non-viable tissues or cells of human or animal origin (or their derivatives) in relation to the intended clinical use and clinical benefit of the device. If there is already a scientific opinion[47] issued on the quality and safety of the substance, tissues or cells of human or animal origin or their derivates, this opinion should be summarized and referenced in the IB, and a copy of the scientific opinion should be provided with the application to the Competent Authority.

2.6.2. Quality aspects

Sponsors are encouraged to provide the detailed information on quality aspects required for the competent authority's assessment in a separate document, e.g. for commercial confidentiality or readability reasons, and to provide a summary in the IB which is relevant to the investigators.

Sponsors are further recommended to consult the EMA guidances on Investigational Medicinal Product Dossiers[48,49], which provides information on expected content and structure for quality documentation related to the incorporated medicinal substance, human blood or plasma derivatives, non-viable tissues or cells of human or animal origin, or their derivatives. It is expected that relevant aspects of EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines[50] are applied.

- The manufacturer of the medicinal substance[51] should be stated and compliance to EU-GMP or a relevant quality system verified. A GMP certificate, manufacturing authorisation or similar should be referenced in the IB if available and copies included with the application to the Competent Authority. The date of the last inspection should be indicated.
- A sufficiently detailed description of the manufacturing process to allow assessment of the specification with regards to e.g. impurities.
- A specification for the medicinal substance should be provided together with descriptions of the analytical methods used as well as verification of their suitability (unless references to Ph Eur methods are given). Results from batch analysis should be presented.
- The container/closure systems used for storage should be described.
- A shelf-life and a storage condition should be proposed and supported by stability data.

[47] Refer to sections 5.2, 5.3 and 5.4 in Annex IX of the MDR.
[48] Guideline on the requirements for the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (europa.eu).
[49] Guideline on quality for biological IMPs (europa.eu).
[50] EudraLex – Volume 4 (europa.eu).
[51] Also relevant for human blood or plasma derivatives, non-viable tissues or cells of human or animal origin, or their derivatives even in situations where they may not be considered medicinal substances.

For chemical medicinal substances a Certificate of suitability to the monographs of the European Pharmacopoeia issued by the European Directorate for the Quality of Medicines (EDQM) or an Active Substance Master File (ASMF) could be referred to. Note that when reference is made to a EDQM Certificate of suitability to the monographs of the European Pharmacopoeia (CEP), the certificate should be included in the application. If reference is made by the device manufacturer to the substance manufacturer's documentation, a Letter of Access is required.

If no certificate of suitability or ASMF is available, complete documentation of the substance is required. Note that for substances of biological origin, it is not possible to refer to a certificate of suitability or ASMF.

2.6.2.1. Information on incorporation of the medicinal substance in the device

The IB needs to contain sufficient information to allow evaluation of the quality of the medicinal substance after it has been incorporated in the device.

The incorporation process, including sterilisation may impact the quality of the medicinal substance. If the substance is chemically modified, mixed with excipients and/or solvents during the process, this should be described, even if the excipients or solvents used are not present in the final device. Information on the quality and purpose of excipients should be provided. The complete composition of the final device must be provided.

The methods to verify the amount/activity and release of medicinal substance from the final device should be presented and data from these tests should be provided.

2.6.2.2. Information on the final investigational device[52]

- The manufacturer should be stated and compliance to EU-GMP or a relevant quality system (ISO) verified. The date of the last inspection should be indicated.
- A complete composition of the investigational device should be provided.
- A detailed description of the manufacturing process including details about the sterilisation process, in-process controls and control of all raw materials and intermediates.
- A specification for the investigational device together with descriptions of the analytical methods used (unless references to Ph Eur methods are given). Results from batch analysis should be presented.
- The container/closure system used should be stated.

A shelf-life and storage condition should be proposed and supported by stability data.

2.6.2.3. Specific requirements for starting materials, intermediates or substances of biological origin

- Information on the collection and control of starting material should be provided

[52] With incorporated medicinal substance, human blood or plasma derivatives, non-viable tissues or cells of human or animal origin, or their derivative.

- Information on the manufacturing process should include details relevant for inactivation of viral and bacterial contamination (reagents used, time, temperatures pH, irradiation dose etc.) should be provided.
- The EU Tissue Directive (2004/23/EC) and EU Blood Directive 2002/98/EC should be followed for tissues, cells and blood respectively

2.6.2.4. Specific requirements for adventitious agents

- A TSE statement confirming compliance to EN ISO 22442-3:2007 and the TSE guideline EMA/410/01[53] should be provided.
- A viral risk assessment in accordance with EN ISO 22442-1:2015 and Ph Eur 5.1.7 Viral safety should be provided. The risk assessment should also include information about the capacity of the manufacturing process to remove viral contamination.

2.6.2.5. Additional information required for substances from human plasma

- Information in accordance with the EMA guideline *EMA/CHMP/BWP/706271/2010 Guideline on plasma-derived medicinal products* is to be provided.

- Information regarding the contract that has been established between the supplier of the plasma derived product/substance and the manufacturer of the device to ensure that the traceability is maintained from donation to the device for at least 30 years and that the manufacturer of medical device and Competent Authorities would be informed if, in exceptional circumstances, post collection information would lead to measures regarding the product.[54]

- If a product licensed in an EU country is used for the manufacture of the device, please state which product, the country(ies) where it is authorised and include information on whether the human plasma used for the medicinal product in question is covered by an EMA certified PMF (Plasma Master File).

2.6.2.6. Substance of animal origin

The source countries for collection of the substance should be stated together with information about the health status of the animals.

2.7. Fulfilment of General Safety and Performance Requirements

According to section 2.7, chapter II, Annex XV of the MDR, the IB should include a list detailing the fulfilment of the relevant GSPR set out in Annex I of the MDR, including the standards and any common specifications applied, in full or in part, as well as a description of the solutions for fulfilling the relevant GSPRs, in so far as those standards and common specifications have not or have only been partly fulfilled or are lacking.

The IB should provide an overview of which GSPRs are applicable for the investigational device and a rationale for any GSPRs indicated as not applicable. Further, it should be clearly indicated

[53] Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3) (europa.eu).
[54] EMA/CHMP/BWP/706271/2010 Committee for medicinal products for human use (CHMP) Guideline on plasma-derived medicinal products.

which GSPRs that have already been addressed by objective evidence and which GSPRs that will be addressed in the proposed study. Reference can be made to the relevant GSPR documentation.

The overview should indicate the means (e.g. standard, CS, internal procedure) to address each applicable GSPR and the corresponding evidence, e. g. by listing the report(s). It is not sufficient to list the standards only and it is not sufficient to list the file in which the report will be placed, e. g. the risk management file. It is also not appropriate to list the title of a report that is not yet available. The GSPR documentation should thus contain both a prospective and retrospective summary of compliance, and clearly show the evidence already evaluated.

With regard to the GSPRs that are not yet met but will be covered by the investigation, please identify them clearly and indicate how every precaution has been taken to protect the health and safety of the subjects and other users.

If some GSPRs are not relevant for the investigational device, this should be indicated and briefly justified.

All of the information above is preferably presented in the format of the checklist of GSPRs, standards, common specifications and scientific advice, which can be found as an annex in the MDCG 2021-8 guidance[55]. This template has two sections: Section A where standards, common specifications and scientific advice can be listed, and the level of compliance is indicated. Section B is a matrix for documenting the fulfilment of the GSPRs, referencing the applied standards or common specifications, as well as the evidence of conformance, documentation and justification/comment in case of deviation. If documenting the conformance with a particular requirement is the purpose of the current clinical investigation, this should be clearly indicated in the matrix.

In case CE-marked devices are investigated in the clinical investigation, fulfilment of the GSPRs for the intended purpose(s) covered by the CE-mark should be confirmed by providing the EU Declaration of Conformity[56] issued by the manufacturer and the certificate issued by the Notified Body[57] (if applicable, depending on device classification).

2.8. Procedures

According to section 2.8, chapter II, Annex XV of the MDR, the IB should include a detailed description of the clinical procedures and diagnostic tests used in the course of the clinical investigation and in particular information on any deviation from normal clinical practice.

All involved procedures may impact the overall risk assessment of the clinical investigation and the sponsor needs to ensure that risks associated with the planned use of the investigational device have been included in the risk assessment.

If the use of the investigational device deviates from normal clinical practice this should be highlighted. Note that it is appropriate to describe what is considered normal clinical practice in this section.

[55] MDCG 2021-08 Clinical investigation application/notification documents.
[56] Article 19 and Annex IV of the MDR.
[57] Article 56 and Annex XII of the MDR.

Specify any other devices or medicinal products to be used in combination with the investigational device and comment on their regulatory status. It is necessary to describe any potential new risks with such combinations and how these are managed. In addition, it is necessary to ensure that the combined use planned in the investigation does not impact the regulatory status of the other devices or medicinal products.

Appendix A

Cross-references between requirements in Annex XV chapter II of the MDR and the Clinical Investigation submission package

Prior to submission of the IB, sponsor may complete this checklist to ensure the IB meets the minimum requirements for validation of the application per article 70 of the MDR.

The checklist, if used, should be included together with the IB in the submission to facilitate the validation by the competent authority.

Cross-references between requirements in Chapter II Annex XV of the MDR and the Clinical Investigation submission package			
Requirement		**Description of requirement**	**Location within submission package**
Annex XV Chapter II (2): **Investigators Brochure** (information in IB or enclosed as separate documents with a summary provided in the IB.	2.1	Identification and description of the device	Document Page
	2.1	Identification of the device	Document Page
	2.1	Information on the intended purpose	Document Page
	2.1	The risk classification and applicable classification rule pursuant to Annex VIII	Document Page
	2.1	Design of the device	Document Page
	2.1	Manufacturing of the device	Document Page

Cross-references between requirements in Chapter II Annex XV of the MDR and the Clinical Investigation submission package			
Requirement		**Description of requirement**	**Location within submission package**
If enclosed as separate documents, a clear reference within the IB should be made to the enclosed documents)			
	2.1	Reference to previous and similar generations of the device.	Document Page
	2.2	Manufacturer's instructions for installation, maintenance, maintaining hygiene standards and for use, including storage and handling requirements	Document Page
	2.2	Information to be placed on the label	Document Page
	2.2	Instructions for use to be provided with the device.	Document Page
	2.2	Information relating to any relevant training required.	Document Page

Cross-references between requirements in Chapter II Annex XV of the MDR and the Clinical Investigation submission package			
Requirement		**Description of requirement**	**Location within submission package**
	2.3	Pre-clinical evaluation based on pre-clinical testing and experimental data in particular as applicable; in-design calculations, in-vitro test, ex-vivo test, animal test, mechanical test, electrical test, reliability test, sterilization validation, software verification and validation, performance test, evaluation of biocompatibility and biological safety. Summary and evaluation of pre-clinical/ non-clinical data	Document(s) Page
	2.4	Existing clinical data, in particular available literature or other clinical data available relating to safety, performance and clinical benefit	Document Page
	2.5	Summary of the benefit risk analysis and risk management	Document Page
	2.5	Information regarding known or foreseeable risks, any undesirable side effects, contraindications and warnings	Document Page

Cross-references between requirements in Chapter II Annex XV of the MDR and the Clinical Investigation submission package			
Requirement		**Description of requirement**	**Location within submission package**
	2.6	In case of devices that contains: **medicinal substance** Detailed information om the substance, and the risk management in relation to the substance, and evidence for the added value of incorporation of such constituents in relation to the clinical benefit and safety of the device	Document Page
	2.6	In case of devices that contains: **human blood / plasma or derivate** Detailed information om the substance, and the risk management in relation to the substance, and evidence for the added value of incorporation of such constituents in relation to the clinical benefit and safety of the device	Document Page
	2.6	In case of devices that contains **non-viable tissues or cells of human or animal origin, or their derivatives** Detailed information on the tissue/cell their derivate, and the risk management in relation to the tissue, cell or their derivate, and evidence for the added value of incorporation of such constituents in relation to the clinical benefit and safety of the device	Document Page
	2.7	List of fulfilment of the General Safety and Performance Requirements (GSPR).	Document Page

Cross-references between requirements in Chapter II Annex XV of the MDR and the Clinical Investigation submission package			
Requirement		**Description of requirement**	**Location within submission package**
		A list detailing the fulfilment of the relevant general safety and performance requirements set out in Annex I, including the standards and CS applied, in full or in part, as well as a description of the solutions for fulfilling the relevant general safety and performance requirements, in so far as those standards and CS have not or have only been partly fulfilled or are lacking.	
	2.8	A detailed description of the clinical procedures and diagnostic tests used in the course of the clinical investigation and in particular information on any deviation from normal clinical practice.	Document Page