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GUIDELINES ON MEDICAL DEVICES

GUIDELINES FOR COMPETENT AUTHORITIES FOR MAKING A VALIDATION/ASSESSMENT OF A CLINICAL INVESTIGATION APPLICATION UNDER DIRECTIVES 93/42/EEC and 90/385/EEC

Note

The present Guidelines are part of a set of Guidelines relating to questions of application of EC-Directives on medical Devices. They are legally not binding. The Guidelines have been carefully drafted through a process of intensive consultation of the various interested parties (competent authorities, Commission services, industries, other interested parties) during which intermediate drafts where circulated and comments were taken up in the document. Therefore, this document reflects positions taken by representatives of interest parties in the medical devices sector. These guidelines incorporate changes introduced by Directive 2007/47/EC amending Council Directive 90/385/EEC and Council Directive 93/42/EEC.

MEDICAL DEVICES DIRECTIVES
CLINICAL INVESTIGATION

GUIDELINES FOR COMPETENT AUTHORITIES FOR MAKING A VALIDATION/ASSESSMENT OF A CLINICAL INVESTIGATION APPLICATION

Index

0. PREFACE:

These guidelines on the validation/assessment of a clinical investigation application are part of a set of Medical Device Guidelines that, according to the relevant Annexes of the Medical Devices Directives, promote a common approach in clinical investigation validation and assessment procedures by Competent Authorities charged with safeguarding public health.

The guidelines are regularly updated according to regulatory developments. The latest version of the guidelines should always be used. This revision of the previous version has:

- modified the structure to align with the structure of other Medical Device Guidelines and to better reflect the relevant Directives and take note of the harmonized standard EN ISO 14155;
- provided some basic criteria to promote a harmonized approach in clinical investigation assessment among Member States and further the understanding of the requirements of Directive 93/42/EEC concerning medical devices and Directive 90/385/EEC relating to active implantable medical devices as amended by Directive 2007/47/EC;
- rephrased some paragraphs to reflect the above listed changes;
- introduced new Appendices to standardize specific procedures or provide checklists.

These guidelines are not legally binding. It is recognised that under given circumstances, for example as a result of scientific developments, an alternative approach may be possible or appropriate to comply with the legal requirements.

Nevertheless, due to the participation of the aforementioned interested parties and of experts from National Competent Authorities, it is anticipated that the guidelines will be followed within the Member States and, therefore, support uniform application of relevant EU Directive provisions and common practices within Member States.

However, only the text of the Directives constitutes legal requirements. On certain issues not addressed in the Directives, national legislation may be different from these guidelines.

1. INTRODUCTION

These guidelines are addressed to Competent Authorities responsible for validation/assessment of clinical investigation applications referred to in article 10 of Council Directive 90/385/EEC[1] and in article 15 of Council Directive 93/42/EEC[2], as amended.

However roles of Competent Authorities (CAs) may vary between Member States, and other bodies, such as Ethics Committees, are involved in the assessment/approval process of clinical investigations mentioned above, according to national regulations. Competent Authorities shall encourage the use of these guidelines by all the Ethics Committees and other possible national bodies involved in the assessment of clinical investigational application, according to national law.

Competent Authorities shall ensure that the information submitted in the application pursuant to annex 6 of Directive 90/385/EEC or annex VIII of Directive 93/42/EEC, contains the items listed below (if appropriate) and is adequate in detail.

It is also important to ensure that the clinical investigation plan shall include documented procedures and a study design in accordance with the provisions of Section 2 of Annex 7 of Directive 90/385/EEC or Section 2 of Annex X of Directive 93/42/EEC. Furthermore it is important that the clinical investigation plan correctly reflects the clinical evaluation as planned by the manufacturer/sponsor.

[1] Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, last amended by Directive 2007/47/EC of the European Parliament and of the Council.

[2] Council Directive 93/42/EEC concerning medical devices, last amended by Directive 2007/47/EC of the European Parliament and of the Council.

It is equally important to note that any substantial modifications to the clinical investigation plan or other substantial amendments and updates to the original documents, also need to be submitted in a timely manner to the Competent Authorities in accordance with applicable national legislation.

The clinical investigations described above are generally expected to be designed, conducted and reported in accordance with harmonized standard EN ISO 14155 – Clinical investigation of medical devices for human subjects- good clinical practice- or to comparable standards, and in compliance with the Declaration of Helsinki and national regulations.

2. SCOPE

The primary purpose of this document is to provide guidance to **Competent Authorities** when validating/assessing a clinical investigation application according to Article 10 of Directive 90/385/EEC or Article 15 of Directive 93/42/EEC provided by manufacturers/sponsors from the initial application up to the end of the investigation.

This document provides guidance on:

- description of the documents to be validated and/or assessed;
- criteria to be applied for general validation/assessment;
- description of events that may occur during the carrying out of the investigation and possible measures to be adopted;
- specific aspects of assessment (criteria in Appendices).

The guidance contained within this document is intended to apply to medical devices generally and the device component of combination products. It is not intended to cover *in vitro* diagnostics.

Furthermore, the guidance is intended to provide advice on the format and content of the information to be submitted in an application for clinical investigations and for substantial modifications.

NOTE: Post market clinical follow-up studies (PMCF-studies), where the IMD is a CE-marked medical device according to Directive 93/42/EEC and is used within it's intended purpose and the study is not considered interventional as per national regulations, shall be excluded from the scope of this MEDDEV and are covered by MEDDEV 2.12/2.

3. REFERENCES

European Legislation

Council Directive 90/385/EEC of 20 June 1990 concerning active implantable medical devices
Council Directive 93/42/EEC of 14 June 1993 concerning medical devices
Commission Regulation (EU) No 722/2012 - OJ 212/3 of 9.08.2012 concerning medical devices manufactured utilising tissues of animal origin
Commission Decision of 19 April 2010 No. 2010/227/EU on the European Databank on Medical Devices (EUDAMED)

Harmonized and International standards

EN ISO 14155:2011	*Clinical investigation of medical devices for human subjects – Good clinical practice*
EN ISO14971:2012	*Medical devices – application of risk management to medical devices.*

European guidance documents

MEDDEV 2.7/1	*Clinical Evaluation: a guide for manufacturers and notified bodies*
MEDDEV 2.7/3	*Clinical investigations: serious adverse event reporting*
MEDDEV 2.7/4	*Guidelines on Clinical investigations: a guide for manufacturers and notified bodies*
MEDDEV 2.12/2	*Guidelines on post-market clinical follow up studies: a guide for manufacturer and notified body*
MEDDEV 2.1/3	*Borderline products, drug-delivery products and medical devices incorporating, as integral part, an ancillary medicinal substance or an ancillary human blood derivative*
MEDDEV 2.1/2	*Field of application of directive "active implantable medical devices"*
MEDDEV 2.1/2.1	*Field of application of directive "active implantable medical devices" Treatment of computers used to program implantable pulse generators*
MEDDEV 2.1/6	*Qualification and Classification of stand alone software*
MEDDEV 2.4/1	*Classification of medical devices*
	Manual on borderline and classification in the Community regulatory framework for medical devices

4. DEFINITIONS[3]

Adverse Event: any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1: This definition includes events related to the investigational medical device or the comparator.
NOTE 2: This definition includes events related to the procedures involved.
NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse Device effect: adverse event related to the use of an investigational medical device.

NOTE 1: this definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE 2: this definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Clinical Data: safety and/or clinical performance information that are generated from the use of a medical device in humans.

Clinical Evaluation: a methodologically sound procedure to collect and analyse clinical data pertaining to a medical device and to assess whether there is sufficient clinical evidence to confirm compliance with relevant essential requirements for safety and performance.

Clinical Evidence[4]: clinical data of an amount and quality as to prove the validity and accuracy of a claim or a statement.

Clinical Evaluation Report: the documentation of the clinical evaluation.

Clinical Investigation: any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety or performance of a medical device.

NOTE: “Clinical Trial” or “clinical study” are synonymous with “clinical investigation”.

[3] Definitions to be adjusted when revision of MEDDEV 2.7.1 is finalised.
[4] Definition to be adjusted when revision of MEDDEV 2.7.1 is finalised.

Clinical Investigation Plan CIP: document that state(s) the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation.

NOTE: The term “protocol” is synonymous with “CIP”. However, protocol has many different meanings, some not related to clinical investigation, and these can differ from county to country. Therefore, the term CIP is used in this MEDDEV.

Clinical Performance: behaviour of a medical device or response of the subject(s) to that medical device in relation to its intended use, when correctly applied to appropriate subject(s).

Clinical Safety: freedom from unacceptable risk, when using the device according to the manufacturer’s Instructions for Use.

Conformity Assessment: the systematic examination of evidence generated and procedures undertaken by the manufacturer, under requirements established by the Regulatory Authority, to determine that a medical device is safe and performs as intended by the manufacturer and, therefore, conforms to the Essential Requirements.

Device Deficiency: inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

NOTE Device deficiencies include malfunctions, use errors, and inadequate labelling.

Ethics Committee (EC): independent body whose responsibility it is to review clinical investigations in order to protect the rights, safety and well-being of human subjects participating in a clinical investigation.

NOTE: For the purposes of this MEDDEV, “ethics committee” is synonymous with “research ethics committee”, “independent ethics committee” or “institutional review board”. The regulatory requirements pertaining to ethics committees or similar institutions vary by country or region.

Feasibility Study: a clinical investigation that is commonly used to capture preliminary information on a medical device (at an early stage of product design) to adequately plan further steps of device development, including needs for design modifications or parameters for a pivotal study.

Investigator: individual member of the investigation site team designated and supervised by the principal investigator at an investigation site to perform critical clinical-investigation-related procedures or to make important clinical-investigation-related decisions.

NOTE: An individual member of the investigation site team can also be called “sub-investigator” or “co-investigator”.

Investigator’s brochure (IB): compilation of the current clinical and non-clinical information on the investigational medical device(s) relevant to the clinical investigation.

Pivotal study: a clinical investigation adequately designed and powered to collect definitive evidence of benefits to the patients, clinical risks, clinical performance, and/or clinical aspects of the usability of a device for a specified intended use.

Principal Investigator: qualified person responsible for conducting the clinical investigation at an investigation site.

NOTE 1: If a clinical investigation is conducted by a team of individuals at an investigation site, the principal investigator is responsible for leading the team.

NOTE 2: Whether this is the responsibility of an individual or an institution can depend on national regulations.

Serious Adverse Event: an adverse event that

a) led to death;
b) led to serious deterioration in the health of a subject, that either resulted in:
    1. a life threatening illness or injury, or
    2. a permanent impairment of a body structure or body function;
    3. in-patient hospitalisation or prolongation of existing hospitalisation
    4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function;
c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Harmonised Standards: standards, the titles of which are published by the European Commission deemed to offer a presumption of conformity to the Essential or other Requirements of the Directives.

5. ETHICAL CONSIDERATIONS

In their sections 2.2 of Annex 7/Annex X, directives 90/385/EEC and 93/42/EEC require that: "Clinical investigations must be carried out in accordance with the Helsinki Declaration adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, as last amended by the World Medical Assembly. It is mandatory that all measures relating to the protection of human subjects are carried out in the spirit of the Helsinki Declaration. This includes every step in the clinical investigation from first consideration of the need and justification of the study to publication of the results."

As a general principle, "the rights, safety and wellbeing of clinical investigation subjects shall be protected consistent with the ethical principles laid down in the Declaration of Helsinki" (EN ISO 14155).

It is ethically important when deciding to conduct a clinical investigation that it should generate new data and answer specific safety and/or performance questions that remain unanswered by the current body of knowledge.

The desire to protect human subjects from unnecessary or inappropriate experimentation must be balanced with the need to protect public health through the use of clinical investigations where they are indicated. In all cases, however, care must be taken to ensure that the necessary data are obtained through a scientific and ethical investigational process that does not expose subjects to undue/avoidable risks or discomfort. The rights, safety and well-being of subjects are paramount and appropriate clinical investigation design and conduct is essential to generate meaningful data.

The following procedures/documents/information will have primary - but not exclusive- importance for validation and decision making with regard to ethical considerations:

- seeking research ethics committee favourable opinion;
- the confirmation of insurance of subjects for the purpose of the study;
- the process and documents used to obtain informed consent (usually CAs request these documents to be (also) available in national language(s));
- procedures with regard to protection of vulnerable groups and individuals;
- justification of the clinical investigation under ethical and scientific aspects;
- appropriate risk management and benefit/risk determination;
- qualification of Clinical Investigators and suitability of clinical investigation sites;
- appropriate choice of control group(s);

National and/or regional regulations usually play a major role in ethical considerations.

6. VALIDATION

The Validation of a clinical investigation application as an administrative review has to assure whether:

- the investigational product falls under one of the medical device directives 90/385/EEC or 93/42/EEC (qualification);
- a notification (preferably in an up-loadable format) is present with basic information on the clinical investigation to be uploaded to the EUDAMED database and to provide the correct CIV ID code; (see Appendix 7)
- a rationale is given for the classification of the investigational medical device (under Directive 93/42/EEC only: class III or implantable or long-term-invasive device under classes IIa or IIb);
- the statement together with the relevant documentation requested in Annex 6 respectively. VIII are present, according to national provisions;
- relevant information in accordance with additional national requirements has been provided.

Validation should be based on the following considerations:

6.1. Information to be supplied in applications

6.1.1. Cover letter

The applicant should submit and sign a letter with the application cover. Its heading should contain the sponsor protocol number with a title of the clinical investigation. The text should draw attention to any special issues related to the application such as special clinical investigation populations, first-in-human investigation, high-risk medical device, unusual clinical investigation designs, sub-group analyses etc.

In addition, it should be mentioned whether an application for a clinical investigation with the same medical device has previously been submitted in that or any other Member State.

6.1.2. An application form

Containing basic data on clinical investigations, to be included in the EUDAMED CI module by the MS, will have to be provided and should be preferably in an xml-format, to facilitate the upload by MS. A template is provided in Appendix 7 (MSs may require additional data in their own national application forms in accordance with national regulations)

Decision 2010/227/EU requests the following information to be provided:

a) manufacturer, where applicable authorised representative:
   (i) Name; (ii) Street; (iii) Locality; (iv) Postcode; (v) Country; (vi) Phone and E-mail; (vii) Role.
b) device:
   (i) Internationally recognised nomenclature code;
   (ii) Device Name/Make or, where not available, generic name.
c) title of investigation;
d) protocol number;
e) primary objective.

6.1.3. Additional documents/information usually required for the application dossier:

1 sponsor's and manufacturer's name (if the manufacturer is not the sponsor) and contact points for communication (similarly for authorised representative in the EEA if applicable);

2 whether first submission or resubmission[5];
3 if resubmission with regard to same device, previous date(s) and reference number(s) of earlier submission(s);
4 Member States and other countries participating in this clinical investigation as part of a multicentre/multinational study at the time of filing and the opinion available of the Member State or other countries;
5 a EUDAMED Clinical Investigation identification number (CIV ID), when available;
6 the application form signed by the sponsor confirming that:
- the information provided is complete;
- that submitted documents contain an accurate account of the information available;
- that the clinical investigation will be conducted in accordance with the clinical investigation plan;
- that serious adverse events, device deficiencies and related updates will be reported, in accordance with the applicable legislation (see MEDDEV 2.7.3);
- that appropriate safety measures have been taken for study participants/users and other persons;
- that the applicable fee for submission is accepted.

7 copy of the Ethics committee opinion as soon as available according to national requirements;
8 title of the clinical investigation;
9 other relevant documentation according to national requirements;
10 description of the current legal status of the investigational medical device and its intended use within the clinical investigation:
- CE marked and within intended use[6] (esp. Directive 90/385/EEC or if national provision); manufacturer should give indication on amount and time of market exposure since first placing on the market;
- CE marked and not within intended use;
- not CE marked;
- if national provisions allow: simplified dossier, if the investigational medical device has previously been part of a clinical investigation in the Member State and investigational medical device and its use have not been modified since then at all.

6.1.4. Rationale for Qualification (both Directives) and Classification (Directive 93/42/EEC only):

A rationale must be given, that the device under investigation falls under Directive 93/42/EEC resp. Directive 90/385/EEC.

Reference concerning **qualification** must address Art.1 of Directive 90/385/EEC resp. Directive 93/42/EEC. Helpful Guidance is contained in relevant MEDDEVs (e.g. MEDDEV 2.1/3) and the Manual on borderline and classification in the Community Regulatory framework for medical devices.

For **Classification** rationale, Art. 9 and Annex IX of Directive 93/42/EEC provide the legal basis; helpful guidance may be found in relevant MEDDEVs (e.g. 2.4/1) and in the "Manual on borderline and classification in the community regulatory framework for medical devices".

6.1.5. Statement and Documentation according to Annex 6 of Directive 90/385/EEC respectively Annex VIII of Directive 93/42/EEC:

Directives 90/385/EEC and 93/42/EEC request specific information to be provided or made available to CAs by manufacturers or Authorised Representatives, serving as sponsors. MS

[5] "Resubmission": application of a clinical investigation previously submitted reporting the same title, the same identification number/code and same EUDAMED code (CIV ID) where the previous one has been rejected or withdrawn.
[6] See note in chapter 2

may vary in their requests to provide the content of the **statement** or the **documentation** mentioned below without further notice at the time of application or may have a policy to request the content of the statement immediately and the more detailed information of the documentation if needed in the specific cases[7]. Subsequent information requests may trigger clock-stop procedures, according to national provisions.

Annex 6 of Directive 90/385/EEC and Annex VIII of Directive 93/42/EEC request the following content of a **statement** for devices intended for clinical investigations covered by Annex 7 (MDD 90/385/EEC), respectively Annex X (MDD 93/42/EEC) to be provided:

- data allowing identification of the device in question;
- the clinical investigation plan;
- the investigator's brochure;
- the confirmation of insurance of subjects;
- the documents used to obtain informed consent (usually CAs request translation into national language(s));
- a statement indicating whether or not the device incorporates, as an integral part, a substance or human blood derivative referred to in Section 10 of Annex 1 of Directive 90/385/EEC respectively section 7.4 of Annex I of Directive 93/42/EEC;
- a statement indicating whether or not the device is manufactured utilising tissues of animal origin as referred to in Commission Regulation 722/2012/EC;
- the opinion of the ethics committee concerned and details of the aspects covered by its opinion8;
- the name of the medical practitioner or other authorized person and of the institution responsible for the investigations;
- the place, starting date and scheduled duration for the investigation;
- a statement that the device in question conforms to the essential requirements apart from the aspects covered by the investigation and that, with regard to these aspects, every precaution has been taken to protect the health and safety of the patient.

For devices intended for clinical investigations, annex 6 of Directive 90/385/EEC and annex VIII of Directive 93/42/EC request that the **documentation** must contain:

- a general description of the product and its intended use;
- design drawings, methods of manufacture envisaged, in particular as regards sterilisation, and diagrams of components, sub-assemblies, circuits, etc.;
- the descriptions and explanations necessary to understand the abovementioned drawings and diagrams and the operation of the product;
- the results of the risk analysis and a list of the standards referred to in Article 5, applied in full or in part, and descriptions of the solutions adopted to meet the essential requirements of this Directive if the standards referred to in Article 5 have not been applied;
- if the device incorporates, as an integral part, a substance or human blood derivative referred to in Section 10 of Annex 1 of Directive 90/385/EEC resp. Section 7.4 of Annex I of Directive 93/42/EEC, the data on the tests conducted in this connection which are required to assess the safety, quality and usefulness of that substance or human blood derivative, taking account of the intended purpose of the device;
- if the device is manufactured utilising tissues of animal origin as referred to in COM Regulation 722/2012/EC, the risk management measures in this connection which have been applied to reduce the risk of infection;
- the results of the design calculations, and of the inspections and technical tests carried out, etc.

The relevant annexes mentioned above also request that:

"The manufacturer must take all the measures necessary to ensure that the manufacturing process produces products which are manufactured in accordance with the documentation referred to in the first paragraph of this Section."

[7] MSs should make available that information to sponsors prior to the submission.
[8] Some MSs accept parallel submission.

"The manufacturer must authorise the assessment, or audit where necessary, of the effectiveness of these measures."

"The information contained in the declarations concerned by these Annexes mentioned above[9] shall be kept for a period of time of at least five years. In the case of implantable devices the period shall be at least 15 years."[10]

6.1.6. Specific information may be added to the application/notification **based on national regulations**, mainly on ethical or local issues (e.g. on qualification of clinical investigators or suitability of clinical investigation sites; liability issues; protection of vulnerable subjects etc).[11]

6.1.7 A **checklist for validation** is provided in **Appendix 8.**

6.2 Outcome of the Validation:

Validation usually leads to a statement of the CA to the Sponsor/manufacturer/Authorised Representative that:

- a valid application has been submitted and (if applicable) the clock is ticking for the assessment phase within a certain time frame[12], according to national provisions; or
- a valid application has been submitted and the Sponsor/MF/AR now may commence the clinical investigation, on condition that the relevant Ethics Committee has issued a favorable opinion, if the Member States has so decided; or
- an incomplete/invalid application has been submitted, which must be completed/adjusted (possibly within a time frame); or
- an incomplete/invalid application has been submitted, which has not been completed/adjusted within a legal time frame or after (a) reasonable attempt(s) of the CA to have the application repaired, and the clinical investigation is rejected; or
- no favorable opinion of a relevant Ethics Committee, according to national regulations, has been obtained, and the clinical investigation is rejected; or
- the application submitted does not fall under the medical device regime.

7. ASSESSMENT:

7.1. General aspects:

Assessment is a detailed ethical, technical, scientific and clinical review of documents/ and information submitted in an application (possibly after a further information request) and of other relevant information, usually performed by experts, to ascertain, whether

- the Essential Requirements, applicable to the investigational medical device in question, apart from those, which are to be examined in this clinical investigation, are correctly identified and fulfilled, e.g. by use of relevant harmonized standards or equivalent solutions (see Appendices 1a and 1b, with templates as a help to outline this information),
- all applicable safety measures and risk mitigation have been taken with regard to the aspects under investigation (under consideration of the risk management provisions in Annexes 1/I, point I.2 of the Directives and the harmonized standard EN ISO 14971),

[9] Necessary adjustment.
[10] MS may have deviating time frames.
[11] Usually indicated at homepages of CAs; list of relevant CA contact points at URL: http://ec.europa.eu/growth/sectors/medical-devices/contacts/index_en.htm
[12] In the case of devices under Directive 90/385/EEC or devices falling within Class III and implantable and long-term invasive devices falling within Class IIa or IIb of Directive 93/42/EEC, the manufacturer may commence the relevant clinical investigation at the end of a period of 60 days after notification, unless the competent authorities have notified him within that period of a decision to the contrary based on considerations of public health or public policy.

- the benefit/risk estimation has been correctly performed and is acceptable according to the state of the art in medicine (see MEDDEV 2.7.1),
- scientific aspects and methodology have been duly considered and warrant, that the clinical data generated will be robust and reliable and are appropriate with regard to the clinical evaluation plan,
- ethical requirements of the Declaration of Helsinki and, if applicable, relevant national requirements are met (see chapter 5).

This assessment is usually primarily based on the information delivered in the **Clinical Investigation Plan (CIP)** and the **Investigators Brochure (IB)**, which are extensively covered by the harmonized Standard EN ISO 14155:2011, in its Annexes A and B. **Considerations for the review of the CIP and IB as given by the Annexes to the harmonized standard are given below under points 7.2 and 7.3.**

NOTE: The following is a list of items that should be covered although the information may be provided in different documents or in different formats, as required by individual Competent Authorities. Competent Authorities may also require additional documentation for their assessment needs.

NOTE: Where the harmonized Standard EN ISO 14155:2011 is not followed or only partly followed, a justification for that and for the alternative solutions taken should be provided.

Ethical Considerations are usually covered by the documentation discussed under chapter 5. Depending on national provisions, the roles of EC and the CA in this detailed ethical, technical and scientific review will have to be considered.

A tentative checklist of relevant points to consider for assessment can be found in Appendix 9.

7.2. Clinical Investigation Plan (CIP):

N.B.: The numbering follows the one in Annex A of EN ISO 14155:2011 for easy reference and coherence and adds comments or additional specific considerations.

A.1.3: The following information should be considered under Annex A.1.3 of EN ISO 14155:2011

Consideration: Name(s), address(es) and contact points for communication of the Sponsor and Manufacturer (if the manufacturer is not the sponsor). Similarly for the Authorised Representative, if applicable[13].

A.2: the following information should be considered under Annex A.2 of EN ISO 14155:2011

Consideration: When the handling of the specific device is complex or unfamiliar to the investigator: Have risks associated with learning been properly mitigated (such as training prior to the first use, support during the first cases). In addition, when inadequate handling of a complex or unfamiliar device can cause serious adverse events (SAE): Supervision of every investigator by an experienced person during the first use(s) should be foreseen and properly described in the CIP (or IB)

A.3: the following information should be considered under Annex A.3- of EN ISO 14155:2011

Consideration: There should be a clear reference to the Clinical Evaluation and the position and justification of this clinical investigation within, based on a proper scientific literature

[13]This would normally be checked during validation

review, the related gap analysis, the benefit/risk estimation before the background of the state of the art in medicine in the relevant field (see MEDDEV 2.7.1). It should be made clear in the rationale for the clinical investigation whether the current application is for an exploratory (eg. FIM, feasibility, pilot or proof of concept clinical investigation) or a confirmatory (pivotal) clinical investigation or a combined one. These may have different risk management and statistical approaches and procedures, e.g. see considerations under A.4. Also the possible conclusions from the clinical investigation with regard to demonstration of safety and clinical performance and to creation of clinical evidence will differ.

A.4: the following information should be considered under Annex A.4 of EN ISO 14155:2011

Considerations: The sponsor should review a subject's relevant clinical data, relevant information related to the device (functioning, method, usability) and continuously evaluate the risk/benefit of the study and potential remediation through the SAE's or USADE's process. If deemed necessary by the sponsor, a temporary suspension, interval time of exposure may be decided.

In light of this and considering FIM-studies, especially for high-risk devices, it shall be shown how unexpected risk will be addressed and mitigated and whether a need for improvement is identified before the next subject is treated, allowing a sufficient interval of time between treatment/exposure of subsequent subjects:
a. the sponsor should review a subject's relevant clinical data, relevant information related to the device (functioning, method, usability) and evaluate the need for improvement before the next subject is exposed to the device.
b. clear definition of the scope of an exploratory study: how many devices/subjects should reasonably be taken into account for this phase. This will certainly impact and limit the time for product development.

In FIM studies, the existing experience e.g. with the specific kind of technology, design, materials used or application shall be considered.
Consideration: Blended trials (exploratory/confirmatory; especially FIM/pivotal): FIM and pivotal phases normally should not be combined unless the sponsor presents adequate justification for the need to do so and explains how to mitigate the foreseen risks (special attention should be given to high risk class devices).

a) the sponsor should always properly separate a FIM-cohort, and produce an interim report of FIM patients that includes an adequate duration of follow-up. Based on FIM experience, the sponsor shall analyse if clinical development can be continued as originally planned or if there is a need to adapt the device or the CIP;
b) CAs should consider to request the sponsor to send the FIM report to the CA and/or the ethics committee for evaluation before recruitment is extended to the pivotal cohort with or without CIP/IB and possibly other document (informed consent, case report forms) modifications as a result of the FIM. (as part of an approval with conditions);
c) combining FIM and pivotal phases in one investigation should not be permissible for devices with significant high or unknown risks.

Consideration: description and justification of hazards caused by procedures that are specifically required by the clinical investigation, in particular with regard to invasive and innovative ones (if applicable).

A.6.1: the following information should be considered under Annex A.6.1 of EN ISO 14155:2011

Consideration: Is the duration of the follow up sufficient?

a) long enough to gather data necessary for ensuring the safety of participating subjects and take remedial action if necessary, under consideration of the specific standards, to the type of studies and to the shelf life of the medical device;
b) long enough to fully achieve study objectives;

c) observations should cover at least entire duration of clinical healing phase/ recovery phase connected to use of investigational devices. Longer observations are necessary if required by a or b (e.g. for implants if long term side-effects can be expected).

A.6.4: the following information should be considered under Annex A.6.4 of EN ISO 14155:2011

Considerations for implants:

a) retrieval analyses: Retrievals (failed implants removed in a revision intervention) should be collected and assessed in a structured process by the manufacturer;
b) comprehensive documentation should be available for inspection;
c) retrieval collection and analysis plan including further investigation scheduled for retrievals in case of failure, including in-house possibilities/capabilities and external expertise (conflict of interest);
d) workflow of retrieval assessment, including forms for documentation, and institutions involved;
e) arrangements for long-term follow-up of subjects beyond primary endpoint e.g. for long term implantable devices.

Consideration: Description and justification of hazards caused by procedures that are specifically required by the clinical investigation, in particular with regard to invasive and innovative ones (if applicable).

A.7: the following information should be considered under Annex A.7 of EN ISO 14155:2011

Consideration: Patients lost to follow-up

a) there should be clear procedures on how patients lost to follow-up are handled.
b) if study endpoints include death or outcomes that can cause disability / loss of autonomy:
    - if a study subject cannot be contacted, the procedure should foresee that the centre should contact other persons or institutions (in certain countries the family doctor). Such contacts should take place rapidly, especially in FIM studies of devices with relevant risks, in order to enable the sponsor to promptly identify undue risks and take measures that are necessary for preserving the health and safety of study subjects (i.e. temporary stop of recruitment in order to review the design of the device);
    - the consent form should name the persons or institutions to be contacted and clearly state that the subject allows exchange of medical information with these persons or institutions. (see also 4.7.4.j of *EN ISO 14155:2011*).

A.11: the following information should be considered under Annex A.11 of EN ISO 14155:2011

Consideration: what provisions, if any have been made by the manufacturer for the recovering of the device (if applicable, i.e. implantable devices, multiple use devices) and subsequent prevention of unauthorised use.

A.13: the following information should be considered under Annex A.13 of EN ISO 14155:2011

Consideration: besides the process described in A.13 the copy of informed consent or the draft informed consent intended for the Ethics Committee shall be examined. Persons responsible for reviewing the (draft) informed consent should be clarified.

NOTE: These can be separate documents.

Check for a reference to insurance coverage in case of injury: confirmation that the sponsor has an insurance in place for the study to cover the patients enrolled as per the CIP.

A.14: the following information should be considered under Annex A.14 of EN ISO 14155:2011

Consideration: principles applied to clarify relationship of events to investigational procedures should be captured.

A.17: the following information should be considered under Annex A.17 of EN ISO 14155:2011

Consideration: the Chapter "Research Registration" and "Publication and Dissemination of Results" (points 35 and 36) of the Declaration of Helsinki shall be considered here, as this is mandated by the Directives' reference to the Declaration of Helsinki.

7. 3.Investigator's Brochure (IB):

N.B: the numbering follows the one in Annex B of EN ISO 14155:2011 for easy reference and coherence and adds comments or additional specific issues

B.2: the following information should be added to/considered under Annex B.2 of EN ISO 14155:2011

Devices Identification

2.1 details allowing device(s) to be identified;
2.2 trade name of device(s);
2.3 generic name of device(s);
2.4 model name of device(s) and/or trade name or generic name of the investigational device(s);
2.5 model number(s) including revision number(s), if any (or reference from apparent model number if appropriate);
2.6 copy of device(s) labels and IFU(s) [including version nr and date of issue] including risks, contraindications and warnings (if available);
2.7 A description of the device including a list of accessories, principles of operation and block or flow diagrams of major components, together with a brief description of other devices designed to be used in combination for the purpose of the investigation, if applicable;
2.8 identification of any features of design that are different from a previously similar marketed product (if relevant);
2.9 details of any new or previously untested features of the device including, where applicable, function and principles of operation;
2.10 description of software, functionality and constraints, version (if relevant);
2.11 design drawings, if necessary for the understanding of the functioning of the device;
2.12 identification of any special manufacturing conditions required and if so, how such requirements have been met.

Consideration: device(s) classification: the rationale for device classification could also be provided as a separate document, see chapter 6 Validation.

B.3: the following information should be added to/considered under Annex B.3 of EN ISO 14155:2011

3.1 description of materials coming into contact with the body, body fluids, rationale for choice of materials and which standards apply (if relevant);

3.2 identification of any medicinal substance or human blood derivatives incorporated into the device with description of intended purpose and previous experience with the use of substance(s) (see Appendix 2);

3.3 method of sterilisation and its validation (method, justification, if ETO-residuals) (if applicable) and methods for cleaning, disinfection and sterilisation for devices indicated as reusable (see Appendix 3);
3.4 identification of any tissues of animal origin incorporated within the device together with information on the sourcing and collection of animal tissue(s) prior to manufacturing operation and other relevant information on the origin of tissue(s) (e.g.: copy of "TSE certificate of suitability", if available); and details with regard to validation of manufacturing procedures employed for the reduction or inactivation of (un)conventional agents as well as details concerning the manufacturer's risk analysis and risk management process and the justification for the use of animal tissues or derivatives, taking into consideration lower risk tissues or synthetic alternatives. This is also applicable in circumstances of genetically produced material (see Appendix 6). In case of devices falling under Commission Regulation (EU) No 722/2012 the relevant requirements have to be observed.

B.4: the following information should be added to/considered under Annex B.4 of EN ISO 14155:2011

4.1 summary of experience with any similar devices made by same manufacturer including length of time on market and a review of safety and clinical performance related problems and complaints together with any corrective or preventive actions taken to address these issues;
4.2 summary of existing clinical data, in particular:
- of the relevant scientific literature available relating to the safety, clinical performance, design characteristics and intended purpose of the device and/or of equivalent devices;
- of previous clinical investigations, relating to the device in question and/or to equivalent devices, if available;

4.3 reference should be made as to how experience with previous device models has affected the current iterations of design, if applicable. The modifications should be described, documented and improvement evaluated against the expected effect.

B.5: the following information should be added to/considered under Annex B.5 of EN ISO 14155:2011

5.1 benefit/risk analysis to include identification of hazards and estimated risks associated with the manufacture (including factors relating to device choice, choice of materials, software) and the use of the device, together with the description of what actions have been taken to minimise or eliminate the identified risks. (NOTE: may also be included in the clinical investigation plan);
5.2 description of how biocompatibility and biological safety have been addressed including identification of the risks and hazards associated with the use of the device and how these have been addressed;
5.3 list of applicable Essential Requirements and of relevant Standards applied in full or in part, or description of solutions adopted to meet the essential requirements of the Directive if relevant standards have not been fully applied (Appendices 1a and 1b show examples of lists with all relevant elements. Competent authorities may encourage manufacturers to use the templates).

8. DECISION ON APPROVAL/AUTHORIZATION

Based on the outcome of Validation and/or Assessment by the entitled parties (primarily CA, EC[14]), the following decisions may be taken according to national provisions:

1. Approval of the Clinical Investigation;
2. Approval with conditions;
   (1+2: See template letter of no objection in 8.1)

[14] others, e.g. hospital owners, health insurance providers, according to national provisions, may also play a role.

3. Tacit approval;
4. Rejection of/Objection to the Clinical Investigation
   (4: See template letter of objection in 8.2)

8.1. Letter of no objection

Letters of no objection/decisions of Competent Authorities should contain the following information:

1. the name of the sponsor of the Clinical Investigation (according to national provisions);
2. the name of the authorised representative, if applicable;
3. the name of the manufacturer of the investigational device (if the manufacturer is not the sponsor);
4. the title of the clinical investigation, the CIP code and version date;
5. the name of the investigational device(s);
6. the EUDAMED CIV-ID;
7. the date;
8. the decision;
9. any conditions imposed (i.e. recruitment limited to a subgroup (e.g. FIM cohort), need to submit an interim report in order to extend recruitment beyond the subgroup, approval from the Ethics Committee;
10. summary of duties (such as serious adverse event reporting, reporting of serious violations of the CIP, amendments, reports required as a condition of approval.

8.2. Letter of objection

Letters of objection/decisions of Competent Authorities should contain the following information:

1. the name of the sponsor;
2. the name of the authorised representative, if applicable;
3. the name of the manufacturer of the investigational device (if the manufacturer is not the sponsor);
4. the title of the clinical investigation, the CIP code and version date;
5. the name of the investigational device(s), if available;
6. the EUDAMED CIV-ID;
7. the date;
8. the decision;
9. detailed reason(s) for the objection – to include all grounds for objection being raised;
10. description of legal remedies open to the applicant under national legislation, including timelines.
11. Specific information required in a resubmission in order to address the grounds for objection.

9. ACTIONS TO BE PERFORMED DURING THE CONDUCT OF A CLINICAL INVESTIGATION AND AT THE END

9.1 Suspension of a clinical investigation

After the commencement of the investigation, the Competent Authority may call for a significant modification or temporary interruption of a clinical investigation where it has objective grounds for considering that the conditions in the authorisation are not being met or has doubts about the safety or scientific validity of the clinical trial, due to suspicion of an

unacceptable risk to subjects arisen during the clinical investigation[15]. Before they reach their decision, they must inform the manufacturer, or the sponsor when this does not coincide with the manufacturer, except where there is imminent risk for the subjects involved, and ask the sponsor and/or the investigator for their opinion. The sponsor should immediately investigate the grounds for suspension and provide a report/response addressing the issues raised in a timely manner. A preliminary report may be requested by the MS and be provided within one week.

When the Competent Authority suspends a trial, they must inform the ethics committee concerned and the other Competent Authorities concerned about its action and the grounds for the actions taken.

To restart the trial following a suspension, the sponsor should make the request as a substantial amendment to the Competent Authority and the Ethics Committees concerned providing evidence that it is safe to restart the clinical investigation.

If the sponsor decides not to recommence a temporarily halted clinical investigation he should notify the Competent Authorities and the ethics committees concerned within 15 days of his decision and provide a brief explanation of the reasons for ending the investigation early.

9.2 Termination, Temporary Halt, Clinical Investigation Report

The manufacturer/sponsor shall notify the Competent Authorities of the Member States concerned and the Ethics committee involved the termination of the clinical investigation.

The manufacture/sponsor should also make a report of the clinical investigation preferably within one year after the termination of the investigation and keep it at the disposal of the competent Authorities according to Annex 7 and Annex X of Directives 90/385/EEC and 93/42/EEC. A guidance to produce a clinical investigation report is contained in the ISO 14155:2011 (Annex D) and, for some aspects in the MEDDEV 2.7/1.

If the manufacture/sponsor halts the clinical investigation temporarily he should notify immediately the competent Authorities concerned and at least within 15 days from when the clinical investigation is halted. This should be notified as a substantial amendment and clear explanations should be provided.

Whenever a clinical investigation is terminated early the sponsor must notify the Competent Authorities and the Ethics committees concerned immediately and at least within 15 days from the premature termination. This time frame will be shorter for halt or termination for safety reasons.

9.3 Follow-up

If a new event occurs after the termination of the investigation that is likely to change the risk/benefit analysis of the medical device and could still have an impact on the investigation participants, the sponsor should notify the Competent Authority and ethics committee concerned and provide a proposed course of action.

The following Appendices are provided as guidance. The format or document stated in the Appendices can be modified, according to MS provisions.

[15] Doubts about the validity of the ongoing investigation may arise from SAE reports, new data from human experience with the investigational medical device, new interpretation of existing data from human experience with the investigational medical device or type of medical devices, results from other trials, data demonstrating lack of efficacy.

APPENDIX 1a:

List of the standards applied in full or in part

Investigational device (name, size, model):
Manufacturer:
Date:

Standard (identifier and title)	Version/ Year	Compliance (with the exception of clinical requirements that will be assessed during the clinical investigation)		
		Full	Partial	Description of all deviations and of the alternative solutions adopted to meet the essential requirements of directive 90/385/EEC or 93/42/EEC
		☐	☐	
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APPENDIX 1b:

Matrix of Essential Requirements[16], being applicable or not to an Investigational Medical Device, with rationale

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
I. GENERAL REQUIREMENTS				
1. The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety. This shall include: • reducing, as far as possible, the risk of use error due to ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety), and • consideration of the technical knowledge, experience, education and training and where applicable the medical and physical conditions of intended users (design for lay, professional, disabled or other users).				

[16] For Directive 93/42/EEC

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
2. The solutions adopted by the manufacturer for the design and construction of the devices must conform to safety principles, taking account of the generally acknowledged state of the art. In selecting the most appropriate solutions, the manufacturer must apply the following principles in the following order: • eliminate or reduce risks as far as possible (inherently safe design and construction), • where appropriate take adequate protection measures including alarms if necessary, in relation to risks that cannot be eliminated, • inform users of the residual risks due to any shortcomings of the protection measures adopted.				
3. The devices must achieve the performances intended by the manufacturer and be designed, manufactured, and packaged in such a way that they are suitable for one or more of the functions referred to in Article 1 (2) (a), as specified by the manufacturer.				
4. The characteristics and performances referred to in Sections 1, 2 and 3 must not be adversely affected to such a degree that the clinical conditions and safety of the patients and, where applicable, of other persons are compromised during the lifetime of the device as indicated by the				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use.				
5. The devices must be designed, manufactured and packed in such a way that their characteristics and performances during their intended use will not be adversely affected during transport and storage taking account of the instructions and information provided by the manufacturer.				
6. Any undesirable side effect must constitute an acceptable risk when weighed against the performances intended.				
6a. Demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X.				
II. REQUIREMENTS REGARDING DESIGN AND CONSTRUCTION				
7. Chemical, physical and biological properties				
7.1 The devices must be designed and manufactured in such a way as to guarantee the characteristics and performances referred to in Section I on the 'General requirements'. Particular attention must be paid to: • the choice of materials used, particularly as regards toxicity and, where appropriate, flammability, • the compatibility between the materials used and biological tissues, cells and body fluids, taking account of the				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
intended purpose of the device. • where appropriate, the results of biophysical or modelling research whose validity has been demonstrated beforehand.				
7.2 The devices must be designed, manufactured and packed in such a way as to minimize the risk posed by contaminants and residues to the persons involved in the transport, storage and use of the devices and to the patients, taking account of the intended purpose of the product. Particular attention must be paid to the tissues exposed and to the duration and frequency of exposure.				
7.3 The devices must be designed and manufactured in such a way that they can be used safely with the materials, substances, and gases with which they enter into contact during normal use or during routine procedures; if the devices are intended to administer medicinal products they must be designed and manufactured in such a way as to be compatible with the medicinal products concerned according to the provisions and restrictions governing these products and that their performance is maintained in accordance with the intended use.				
7.4 Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product as defined in Article 1 of Directive 2001/83/EC				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
and which is liable to act upon the body with action ancillary to that of the device, the quality, safety and usefulness of the substance must be verified by analogy with the methods specified in Annex I to Directive 2001/83/EC. • For the substances referred to in the first paragraph, the notified body shall, having verified the usefulness of the substance as part of the medical device and taking account of the intended purpose of the device, seek a scientific opinion from one of the competent authorities designated by the Member States or the European Medicines Agency (EMA) acting particularly through its committee in accordance with Regulation (EC) No 726/2004 (*) on the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the substance into the device. When issuing its opinion, the competent authority or the EMA shall take into account the manufacturing process and the data related to the usefulness of incorporation of the substance into the device as determined by the notified body.				
• Where a device incorporates, as an integral part, a human blood derivative, the notified body shall, having verified the usefulness of the				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
substance as part of the medical device and taking into account the intended purpose of the device, seek a scientific opinion from the EMEA, acting particularly through its committee, on the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the human blood derivative into the device. When issuing its opinion, the EMEA shall take into account the manufacturing process and the data related to the usefulness of incorporation of the substance into the device as determined by the notified body.,				
• Where changes are made to an ancillary substance incorporated in a device, in particular related to its manufacturing process, the notified body shall be informed of the changes and shall consult the relevant medicines competent authority (i.e. the only involved in the initial consultation), in order to confirm that the quality and safety of the ancillary substance are maintained. The competent authority shall take into account the data related to the usefulness of incorporation of the substance into the device as determined by the notified body, in order to ensure that the changes have no negative impact on the				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
established benefit/risk profile of the addition of the substance in the medical device.				
• When the relevant medicines competent authority (i.e. the one involved in the initial consultation) has obtained information on the ancillary substance, which could have an impact on the established benefit/risk profile of the addition of the substance in the medical device, it shall provide the notified body with advice, whether this information has an impact on the established benefit/risk profile of the addition of the substance in the medical device or not. The notified body shall take the updated scientific opinion into account in reconsidering its assessment of the conformity assessment procedure.				
7.5 The devices must be designed and manufactured in such a way as to reduce to a minimum the risks posed by substances leaking from the device. Special attention shall be given to substances which are carcinogenic, mutagenic or toxic to reproduction, in accordance with Annex I to Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labeling of dangerous substances.				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
• If parts of the device (or device itself) intended to administer and/or remove medicines, body liquids or other substances to or from the body, or devices intended for transport and storage of such body fluids or substances, contain phthalates which are classified as carcinogenic, mutagenic or toxic to reproduction, of category 1 or 2, in accordance with Annex 1 to Directive 67/548/EEC, these devices must be labelled on the device itself and/or on the packaging for each unit, or, where appropriate, on the sale packaging as a device containing phthalates.				
• If the intended use of such devices includes treatment of children or treatment of pregnant or nursing women, the manufacturer must provide a specific justification for the use of these substances with regard to compliance with the essential requirements, in particular of this paragraph, within the technical documentation and within the instructions of use information on residual risks for these patient groups and, if applicable, on appropriate precautionary measures.				
7.6 Devices must be designed and manufactured in such a way as to reduce, as much as possible, risks posed by				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
the unintentional ingress of substances into the device taking into account the device and the nature of the environment in which it is intended to be used.				
8 Infection and microbial contamination				
8.1 The devices and manufacturing processes must be designed in such a way as to eliminate or reduce as far as possible the risk of infection to the patient, user, and third parties. The design must allow easy handling and, where necessary, minimize contamination of the device by the patient or vice versa during use.				
8.2 Tissues of animal origin must originate from animals that have been subjected to veterinary controls and surveillance adapted to the intended use of the tissues. Notified bodies shall retain information on the geographical origin of the animals. Processing, preservation, testing, and handling of tissues, cells, and substances of animal origin must be carried out so as to provide optimal security. In particular, safety with regard to viruses and other transmissible agents must be addressed by implementation of validated methods of elimination or viral inactivation in the course of the manufacturing process.				
8.3 Devices delivered in a sterile state must be designed, manufactured,				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
and packed in a non-reusable pack and/or according to appropriate procedures to ensure that they are sterile when placed on the market and remain sterile, under the storage and transport conditions laid down, until the protective packaging is damaged or opened.				
8.4 Devices delivered in a sterile state must have been manufactured and sterilized by an appropriate, validated method.				
8.5 Devices intended to be sterilized must be manufactured in appropriately controlled (e.g. environmental) conditions.				
8.6 Packaging systems for non-sterile devices must keep product without deterioration at the level of cleanliness stipulated and, if the devices are to be sterilized prior to use, minimize the risk of microbial contamination; the packaging system must be suitable, taking account of the method of sterilization indicated by the manufacturer.				
8.7 The packaging and/or label of the device must distinguish between identical or similar products sold in both sterile and non-sterile condition.				
9 Construction and environmental properties				
9.1 If the device is intended for use in combination with other devices or equipment, the whole combination, including the connection system must				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
be safe and must not impair the specified performances of the devices. Any restrictions on use must be indicated on the label or in the instructions for use.				
9.2 Devices must be designed and manufactured in such a way as to remove or minimize as far as is possible: • the risk of injury, in connection with their physical features, including the volume/pressure ratio, dimensional and, where appropriate, ergonomic features; • risks connected with reasonable foreseeable environmental conditions, such as magnetic fields, external electrical influences, electrostatic discharge, pressure, temperature or variations in pressure and acceleration, • risks of reciprocal interference with other devices normally used in the investigations or for the treatment given, • risks arising where maintenance or calibration is not possible (as with implants), from aging of materials used or loss of accuracy of any measuring or control mechanism.				
9.3 Devices must be designed and manufactured in such a				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
way as to minimize the risks of fire or explosion during normal use and in single fault condition. Particular attention must be paid to devices whose intended use includes exposure to flammable substances or to substances that could cause combustion.				
10 Devices with a measuring function				
10.1 Devices with a measuring function must be designed and manufactured in such a way as to provide sufficient accuracy and stability within appropriate limits of accuracy and taking account of the intended purpose of the device. The limits of accuracy must be indicated by the manufacturer.				
10.2 The measurement, monitoring and display scale must be designed in line with ergonomic principles, taking account of the intended purpose of the device.				
10.3 The measurements made by devices with a measuring function must be expressed in legal units conforming to the provisions of Council Directive 80/181/EEC.				
11 Protection against radiation				
11.1 General				
11.1.1 Devices shall be designed and manufactured in such a way that exposure of patients, users, and other persons to radiation shall be reduced as far as possible compatible with the intended purpose,				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
while not restricting the application of appropriate specified levels for therapeutic and diagnostic purposes.				
11.2 Intended radiation				
11.2.1 Where devices are designed to emit hazardous levels of radiation necessary for a specific medical purpose the benefit of which is considered to outweigh the risks inherent in the emission, it must be possible for the user to control the emissions. Such devices shall be designed and manufactured to ensure reproducibility and tolerance of relevant variable parameters.				
11.2.2 Where devices are intended to emit potentially hazardous, visible and/or invisible radiation, they must be fitted, where practicable, with visual displays and/or audible warnings of such emissions				
11.3 Unintended radiation				
11.3.1 Devices shall be designed and manufactured in such a way that exposure of patients, users and other persons to the emissions of unintended, stray or scattered radiation is reduced as far as possible.				
11.4 Instructions				
11.4.1 The operating instructions for devices emitting radiation must give detailed information as to the nature of the				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
emitted radiation, means of protecting the patient and the user and on ways of avoiding misuse and of eliminating the risks inherent in installation.				
11.5 Ionizing radiation				
11.5.1 Devices intended to emit ionizing radiation must be designed and manufactured in such a way as to ensure that, where practicable, the quantity, geometry and quality of radiation emitted can be varied and controlled taking into account the intended use.				
11.5.2 Devices emitting ionizing radiation intended for diagnostic radiology shall be designed and manufactured in such a way as to achieve appropriate image and/or output quality for the intended medical purpose whilst minimizing radiation exposure of the patient and user.				
11.5.3 Devices emitting ionizing radiation intended for therapeutic radiology shall be designed and manufactured in such a way as to enable reliable monitoring and control of the delivered dose, the beam type and energy and where appropriate the quality of radiation.				
12 Requirements for devices connected to or equipped with an energy source				
12.1 Devices incorporating electronic programmable systems must be designed to ensure the repeatability,				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
reliability, and performance of these systems according to the intended use. In the event of a single fault condition (in the system) appropriate means should be adopted to eliminate or reduce as far as possible consequent risks. 12.1a. For devices which incorporate software or which are medical software in themselves, the software must be validated according to the state of the art taking into the account the principles of development lifecycle, risk management, validation and verification.				
12.2 Devices where the safety of the patients depends on an internal power supply must be equipped with a means of determining the state of the power supply.				
12.3 Devices where the safety of the patients depends on an external power supply must include an alarm system to signal any power failure.				
12.4. Devices intended to monitor one or more clinical parameters of a patient must be equipped with appropriate alarm systems to alert the user of situations which could lead to death or severe deterioration of the patient's state of health.				
12.5. Devices must be designed and manufactured in such a way as to minimize the risks of creating electromagnetic fields which could impair the operation of other devices or equipment in the usual environment.				
12.6. Protection against electrical				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
risks: Devices must be designed and manufactured in such a way as to avoid, as far as possible, the risk of accidental electric shocks during normal use and in single fault condition, provided the devices are installed correctly.				
12.7. Protection against mechanical and thermal risks				
12.7.1. Devices must be designed and manufactured in such a way as to protect the patient and user against mechanical risks connected with, for example, resistance, stability and moving parts.				
12.7.2. Devices must be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from vibration generated by the devices, taking account of technical progress and of the means available for limiting vibrations, particularly at source, unless the vibrations are part of the specified performance.				
12.7.3. Devices must be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from the noise emitted, taking account of technical progress and of the means available to reduce noise, particularly at source, unless the noise emitted is part of the specified				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
performance.				
12.7.4. Terminals and connectors to the electricity, gas or hydraulic and pneumatic energy supplies which the user has to handle must be designed and constructed in such a way as to minimize all possible risks.				
12.7.5. Accessible parts of the devices (excluding the parts or areas intended to supply heat or reach given temperatures) and their surroundings must not attain potentially dangerous temperatures under normal use.				
12.8. Protection against the risks posed to the patient by energy supplies or substances				
12.8.1. Devices for supplying the patient with energy or substances must be designed and constructed in such a way that the flow-rate can be set and maintained accurately enough to guarantee the safety of the patient and of the user.				
12.8.2. Devices must be fitted with the means of preventing and/or indicating any inadequacies in the flow-rate which could pose a danger. Devices must incorporate suitable means to prevent, as far as possible, the accidental release of dangerous levels of energy from an energy and/or substance source.				
12.9. The function of the controls and indicators must be clearly specified				

ESSENTIAL REQUIREMENT (ER)		Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
	on the devices. Where a device bears instructions required for its operation or indicates operating or adjustment parameters by means of a visual system, such information must be understandable to the user and, as appropriate, to the patient.				
13.	**Information supplied by the manufacturer**				
13.1.	Each device must be accompanied by the information needed to use it safely and properly, taking account of the training and knowledge of the potential users, and to identify the manufacturer. This information comprises the details on the label and the data in the instruction for use. As far as practicable and appropriate, the information needed to use the device safely must be set out on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging. If individual packaging of each unit is not practicable, the information must be set out in the leaflet supplied with one or more devices. Instructions for use must be included in the packaging for every device. By way of exception, no such instructions for use are needed for devices in Class I or IIa if they can be used completely safely without any such instructions.				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
13.2. Where appropriate, this information should take the form of symbols. Any symbol or identification color used must conform to the harmonized standards. In areas for which no standards exist the symbols and colors must be described in the documentation supplied with the device.				
13.3. The label must bear the following particulars:				
(a) the name or trade name and address of the manufacturer. For devices imported into the Community, in view of their distribution in the Community, the label, or the outer packaging, or instructions for use, shall contain, in addition, the name and address of the authorized representative where the manufacturer does not have a registered place of business in the Community.				
(b) the details strictly necessary to identify the device and the contents of the packaging especially for the users;				
(c) where appropriate, the word ‘STERILE’;				
(d) where appropriate, the batch code, preceded by the word ‘LOT’, or the serial number;				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
(e) where appropriate, an indication of the date by which the device should be used, in safety, expressed as the year and month;				
(f) where appropriate, an indication that the device is for single use. A manufacturer's indication of single use must be consistent across the Community				
(g) if the device is custom-made, the words 'custom-made device';				
(h) if the device is intended for clinical investigations, the words 'exclusively for clinical investigations';				
(i) any special storage and/or handling conditions;				
(j) any special operating instructions;				
(k) any warnings and/or precautions to take;				
(l) year of manufacture for active devices other than those covered by (e). This indication may be included in the batch or serial number;				
(m) where applicable, method of sterilization.				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
(n) in the case of a device within the meaning of Article 1(4a), an indication that the device contains a human blood derivative				
13.4. If the intended purpose of the device is not obvious to the user, the manufacturer must clearly state it on the label and in the instructions for use.				
13.5. Whenever reasonable and practicable, the devices and detachable components must be identified, where appropriate in terms of batch, to allow all appropriate action to detect any potential risk posed by the devices and detachable components.				
13.6. Where appropriate, the instructions for use must contain the following particulars: (a) the details referred to in section 13.3, with the exception of (d) and (e);				
(b) the performances referred to in Section 3 and any undesirable side-effects;				
(c) if the device must be installed with or connected to other medical devices or equipment in order to operate as required for its intended purpose, sufficient details of its characteristics to identify the correct				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
devices or equipment to use in order to obtain a safe combination;				
(d) all the information needed to verify whether the device is properly installed and can operate correctly and safely, plus details of the nature and frequency of the maintenance and calibration needed to ensure that the devices operate properly and safely at all times;				
(e) where appropriate, information to avoid certain risks in connection with implantation of the device;				
(f) information regarding the risks of reciprocal interference posed by the presence of the device during specific investigations or treatment;				
(g) the necessary instructions in the event of damage to the sterile packaging and, where appropriate, details of appropriate methods of re-sterilization;				
(h) if the device is reusable, information on the appropriate processes to allow reuse, including cleaning,				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
disinfection, packaging and, where appropriate, the method of sterilization of the device to be re-sterilized, and any restriction on the number of reuses. Where devices are supplied with the intention that they be sterilized before use, the instructions for cleaning and sterilization must be such that, if correctly followed, the device will still comply with the requirements in Section I. If the device bears an indication that the device is for single use, information on known characteristics and technical factors known to the manufacturer that could pose a risk if the device would be re-used. If in accordance with Section 13.1 no instructions for use are needed, the information must be made available to the user upon request;				
(i) details of any further treatment or handling needed before the device can be used (for example, sterilization, final assembly, etc.):				
(j) in the cases of devices emitting radiation for medical				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
purposes, details of the nature, type, intensity and distribution of this radiation.				
The instructions for use must also include details allowing the medical staff to brief the patient on any contraindications and any precautions to be taken. These details should cover in particular:				
(k) precautions to be taken in the event of changes in the performance of the device;				
(l) precautions to be taken as regards exposure, in reasonably foreseeable environmental conditions, to magnetic fields, external electrical influences, electrostatic discharge, pressure or variations in pressure or acceleration, thermal ignition sources, etc.;				
(m) adequate information regarding the medicinal product or products which the device in question is designed to administer, including any limitations in the choice of substances to be delivered;				
(n) precautions to be taken against any special, unusual risks related to the				

ESSENTIAL REQUIREMENT (ER)	Does ER apply ? (Yes/ No)	Standards used in full or in part	Evidence of conformance to standard; documentation	Justification/comment in case of deviation
disposal of the device;				
(o) medicinal substances, or human blood derivatives incorporated into the device as an integral part in accordance with section 7.4;				
(p) degree of accuracy claimed for devices with a measuring function				
(q) date of issue or the latest revision of the instructions for use.				

APPENDIX 2:

Guidance Notes on Medical Devices Incorporating a Medicinal Substance or Human Blood Derivative Having Ancillary Action

Additional information may be required with regard to the medicinal substance and/or the human blood derivative:

- Information if it is an authorized medicinal substance, or not. If yes, it's authorized on the EU market? Since how long? The approved indication(s) must be mentioned and the EU SPC must be included; reference to applicable pharmaceutical legislation (EU, nationally).

- Intended purpose within the context of the device and the risk analysis.

- Source, product license (where applicable), quantity/dosage of the medicinal component, and the method by which the substance is incorporated into the device.

- Method of manufacture (solvents/reagents used in processing, residuals).

- Stability data in relation to the expected shelf-life/lifetime of the device.

Qualitative and quantitative tests carried out on the medicinal substances.

- Clinical documentation (clinical data demonstrating the usefulness of the medicinal substance).

Additional information required with regard to the medicinal substance only:

- Control of the starting materials

  - medicinal substance specifications e.g., summary of the European Drug Master File, reference to European Pharmacopoeia or national monograph of a European Member State.
  - Manufacturers may wish to cross-reference a granted Clinical Trial Authorisation (CTA)
  - Please refer to "The rules governing medicinal products in the European Community" volume III, Addendum II.

- Toxicological profile (summary of results of toxicity testing/biological compatibility).

  - This should include the effect on reproductivity, embryo/foetal and perinatal toxicity and the mutagenic/carcinogenic potential of the medicinal substance.

- Pharmacodynamics of the medicinal substance in relation to the device.

  Pharmacokinetic characteristics (local/systemic exposure patterns, duration and maximum exposure and the maximum plasma concentration peak taking into account individual variability, area under the curve (AUC), in the context of the device). Notably, for new active substances the release of the substance from the device, its subsequent distribution and elimination should be addressed.

- Local tolerance (particularly where the route of exposure is different to the conventional application) e.g., the results of EN/ISO 10993 testing, or a review of scientific literature.

NOTE: Reference is made to MEDDEV 2.1.3, Section C 3, which describes the documentation to be provided by the Notified Body to the Medicinal Product Competent

Authority for medicinal products as part of the consultation procedure, which may be helpful here also.

Additional information required with regard to the human blood derivative only:

- Control of the starting materials

  - Control of plasma source e.g. summary of the European Plasma Master File
  - Production of the blood derivative

For Appendices 3-5 reference is made to the harmonized standards applicable for each section in light of the presumption of conformity given by those standards with the Essential requirements, the intent of the appendices being to emphasize key considerations of the standards

APPENDIX 3: Guidance on medical devices which require sterilization

Additional information may be required for sterile devices, which are either provided sterile or sterilized at the point of use:

Documentation to demonstrate that the method of sterilization renders the device sterile.

If provided sterile, this should include where appropriate:

- the method of sterilization
- details of the sterilization facility, name, location, process
- proof of validation to demonstrate that the sterilization process can be delivered effectively and reproducibly to the specified devices in the sterilization load, e.g. results, certificates and justification for the choice of sterilization process
- details of the records for product release (indicator testing, dosimetric release, parametric release), this should include the results and outcomes
- data relating to bio burden, e.g. nature, frequency and outcome
- details of any environmental precautions undertaken on the device during manufacture or sterilization. Information to include; nature, frequency of monitoring and outcome
- details of any standards applied to any of the sterilization processes.

If devices are to be sterilized at the point of use, this should include where appropriate:

- a copy of the instructions for decontamination (i.e. cleaning, disinfection and/or sterilization) including details of any special precautions for handling
- appropriate validation data to demonstrate that the processes can be delivered effectively and reproducibly to the specified devices must be provided.

Important points to note

- documentation should be provided for **each** investigational device which requires sterilization. This includes any instruments or accessories.
- where devices are sterilized at the point of use, and specifically moist heat (steam) is chosen as the method of sterilization, particular attention should be taken with regards to the ‘standard sterilization parameters’ applicable within the country where the devices are to be processed and sterilized. The appropriate sterilization qualification and validation reports should take account of these ‘standard’ requirements and of relevant harmonized standards.

APPENDIX 4: Guidance on clinical investigations of active devices (excluding Software, see Appendix 5)

Additional information to support claims of compliance with the essential requirements of the Council Directive, e.g. 93/42/EEC or 90/385/EEC.

General

1. Essential requirements checklist detailing how these requirements have been addressed, including references to harmonised standards as appropriate.

Note: The application of harmonised standards is voluntary and applicants may choose alternative methods of demonstrating compliance with the essential requirements. For example, compliance with international, national or in-house standards. This should be supported by a risk benefit analysis, preferably to EN ISO 14971.

2. Documentary evidence supporting compliance with any of the standards referenced. This may include certification by an independent body, or test house. Alternatively, self-certification is acceptable, providing this is supported with evidence of design input and subsequent in-house verification.

3. For those applicants choosing self-certification against EN 60601-1 (which includes protection against electric shock hazards, mechanical hazards, fault conditions, constructional requirements etc.) a checklist for that standard, or equivalent, should be provided. This should be completed and signed by a competent engineer. Where clauses are considered not applicable, a justification should be given. Where measurements of leakage currents are made, the values should be recorded.

4. When the medical device is to be used with other devices as part of a system, e.g. connection to laptop computers, etc. an additional EN 60601-1-1 checklist or equivalent covering the whole system under investigation should also be provided.

Specialist technologies including: infra-red, laser, microwave, MRI, RF ultrasound, ultraviolet, X-ray etc.

5. Details of how this technology has been incorporated in the design and what steps have been taken to assure the safe application in the device. Information pertaining to output power, justification of safety limits used and reference to appropriate standards should be included, e.g. the relevant part 2 of the EN 60601 series.

Active Implants

6. A summary of the Failure Mode, Effects [and Criticality] Analysis (FMEA/FMECA).

7. The results of animal studies.

8. Performance statistics and adverse incident data of earlier model, when device is the next generation of an earlier design.

APPENDIX 5: Software and programmable devices

Where the device includes a software component or is software the following should be addressed in the notification:

Describe any standards used in the development of the software (e.g. IEC 62304, IEC 80002, IEC 80001-1).

Describe the role of the software including whether:

- the normal operation, initial setting up, maintenance, calibration, adjustment, or monitoring of the medical device, depend on software;
- the correct operation of the medical device depends on the execution of the software within a limited time i.e. real time software is used;
- any part of the medical device's software can be run independently on hardware not directly connected to the medical device.

Describe the relationship of software to safety including:

- whether essential performance depends on software (essential performance is the performance whose absence would pose a threat of harm to the patient);
- which risk control measures depend on software;
- what opportunities there are for informed intervention by clinical staff or the patient to prevent harm in the event of a software failure.

Describe the risk management of software including:

- a risk management process that includes software items;
- identification of causative sequences of events that includes software defects;
- whether hardware risk control measures are used to prevent the consequences of software defects;
- whether the software development process is used as a risk control measure;
- whether software verification or software validation is used as a risk control measure (verification = 'did we do the right thing right', validation = 'did we do the right thing?').

Describe the software development processes including:

- whether the system and software architecture is documented in such a manner that it is possible to reason about the contribution of each component and software item to safety;
- whether software units (the lowest level of software decomposition) were tested before being integrated into larger software items.

Describe the purpose of the clinical investigation with regard to:

- whether the clinical investigation is intended to evaluate the performance and/or safety of the software or to evaluate the fitness for clinical purpose of any part of the software and, if so, how this will be done;
- detail of any specific protocols designed to evaluate the operation of the software in the clinical context.

Describe the human interface including:

- the user interfaces (mechanisms intended to allow humans to interact with the software) that the software has (including user interfaces for the patient, clinical technician, physician, service engineer, etc.);
- the target population for each type of user interface (for example, age, expertise, language etc.) and whether this is documented;
- the tests that have been done prior to the clinical investigation to evaluate the effectiveness of the user interfaces for each target population, or how this will be evaluated in the study;
- the measures used to ensure that only appropriate people are allowed to operate each different type of user interface.

Describe how the software is protected including:

- protection from accidental or unauthorised change;
- identification of roles which have the authority to make software changes during the clinical trial;
- the rationale and/or measures that are in place to ensure that software changes do not adversely affect the clinical investigation.

APPENDIX 6: Devices utilizing animal tissue which is rendered non-viable or non-viable products derived from animal tissue:

Regulation No. 722/2012/EC lays down particular requirements in relation to the placing on the market and/or putting into service of medical devices, including active implantable medical devices, manufactured utilizing animal tissue which is rendered non-viable or non-viable products derived from animal tissue. This Regulation applies to animal tissues, as well as their derivatives, originating from bovine, ovine and caprine species, deer, elk, mink and cats. It does not apply to certain tallow derivatives, processed under conditions at least as vigorous as those laid down in Section 3 of Annex I of that Regulation nor to medical devices, which are not intended to come into contact with the human body or which are intended to come into contact with intact skin only.

For devices intended for clinical investigation which fall under that Regulation, the statement of the manufacturer or of his authorized representative and the documentation in accordance with Annex 6 to Directive 90/385/EEC or Annex VIII to Directive 93/42/EEC, respectively, shall also address compliance with the particular requirements set out in section 1 of Annex I to that Regulation.

Harmonized standard series EN ISO 22442 on medical devices utilizing animal tissues and their derivatives will be additionally useful in providing important information to support or assess applications for clinical investigations of that kind of devices.

APPENDIX 7:

Clinical Investigation Application form to National Competent Authority for Medical Devices

Member State concerned:

A. Clinical Investigation (CI):

A.1.First notification to an authority within the EEA: yes ☐ no ☐

A.1.1.EUDAMED CIV ID, when available:

A.2.Full title of the trial (local language/English):

A2.1.local language:

A2.2.english:

A.2.3. Short title:

A.2.4. Protocol number: A.2.4.1.version: A.2.4.2.date:

A.2.5. Is this a resubmission? yes ☐ no ☐

A.2.5.1. If Yes, indicate NCA's reference(s):

A.2.6. Objective of the investigation:

A.2.7. Inclusion criteria:

A.2.8. Exclusion criteria: [17]

A.2.9. Study-specific measures (procedures, medications, diagnostics):

A.2.10. Type of clinical investigation (CI):

A.2.10.1. First-in-Man (FIM) ☐

Pilot/proof-of-concept CI ☐

Confirmatory (pivotal) CI ☐

A.2.10.2. CI with medical device and medicinal product (combined study) ☐

A.2.10.2.1 If yes EudraCT number:

A.2.11. Mononational CI ☐ or multinational CI ☐

A.2.11.1 Other Member States concerned

A.2.12. Planned number of subjects to be enrolled:

In the Member State: In the EEA: Outside the EEA:

A.2.13. Planned number of sites:

In the Member State: In the EEA: Outside the EEA:

A.2.14. Planned start date DD/MM/YYYY: Planned end date DD/MM/YYYY:

B. Contact Information

B.1. Sponsor:

B.1.1. Name of organisation:

B.1.2. Name of the person to contact:

B.1.3. Address:

B.1.3.1. ZIP code/place:

B.1.3.2. country:

[17] A.2.7. and A.2.8. optional

B.1.4.Telephone number:

B.1.5. Fax number:

B.1.6. e-mail:

B.1.7. Status of the sponsor: commercial ☐ Non-Commercial ☐

B.2. Legal Representative of the sponsor in the Community for this trial (if different from the sponsor)

B.2.1. Name of organisation:

B.2.2. Name of the person to contact:

B.2.3. Address:

B.2.3.1. ZIP code/place:

B.2.3.2. country:

B.2.4. Telephone number:

B.2.5. Fax number:

B.2.6. e-mail:

B.3. Billing Address (if not identical with the Sponsor)

B.3.1. Name of organisation:

B.3.2. Name of the person to contact:

B.3.3. Address:

B.3.3.1. ZIP code/place:

B.3.3.2. country:

B.3.4. Telephone number:

B.3.5. Fax number:

B.3.6. e-mail:

C. Description of the Investigational Medical Device

C.1. Name:

C.2. Description and Type (local language/English)

C.2.1. local language:

C.2.2.english:

C.3. GMDN Code:

C.4. Information on the use of the device

C.4.1.Intended use(s) of the medical device in the CI:

C.4.2. Indication as defined by the manufacturer:

C.4.3. Contraindication(s) as defined by the manufacturer:

C.4.4. Patient population as defined by the manufacturer:

C.4.5. ☐ Medical device bears a CE mark

C.4.5.1.☐ and will be used in accordance with the intended use as given by the manufacturer[18][19]

[18] see NOTE in chapter 2 concerning PMCF-studies conducted with investigational CE-marked medical devices acc. to Directive 93/42/EEC, which are covered by MEDDEV 2.12/2

[19] MS may request data on countries where device is placed on the market and since when

C.4.5.2. ☐ and will **not** be used in accordance with the intended use as given by the manufacturer

C.4.5.3. ☐ the medical device and/or its intended use has been modified in relation to the CE mark

C.5. Manufacturer of the medical device:

C.5.1. Name of organisation:

C.5.2. Address:

C.5.2.1. ZIP code/place:

C.5.2.2. country:

Ca/b. Description of comparator devices, placebo or other comparator/control, if any

Ca.0. Description of comparator device, if applicable

Ca.1. Name of comparator device:

Ca.2. Description and Type (local language/English)

Ca.2.1. local language:

Ca.2.2.english:

Ca.3. GMDN Code:

Ca.4. Information on the use of the device

Ca.4.1.Intended use(s) of the medical device in the CI:

Ca.4.2. Indication(s) as defined by the manufacturer:

Ca.4.3. Contraindication(s) as defined by the manufacturer:

Ca.4.4. Patient population as defined by the manufacturer:

Ca.4.5. ☐ Medical device bears a CE mark

Ca.4.5.1.☐ and will be used in accordance with the intended use as given by the manufacturer

Ca.4.5.2. ☐ and will **not** be used in accordance with the intended use as given by the manufacturer

Ca.4.5.3. ☐ the medical device and/or its intended use has been modified in relation to the CE mark

Ca.5. Manufacturer of the medical device:

Ca.5.1. Name of organisation:

Ca.5.2. Address:

Ca.5.2.1. ZIP code/place:

Ca.5.2.2. country:

Cb.0. Description of other comparator/control than a device, including placebo, if any

Cb.1. Name of (non-device) comparator:

Cb.2. Description and Type (local language/English)

Cb.2.1. Local language:

Cb.2.2. English:

Cb.3. Information on the use of the non-device comparator:

Cb.3.1. Intended use(s) of the non-device comparator in the CI:

Cb.3.2. Indication(s) as defined by the manufacturer of the comparator:

Cb.3.3. Contraindication(s) as defined by the manufacturer:

Cb.3.4. Patient population as defined by the manufacturer:

Cb.4. Manufacturer of the non- device comparator:

Cb.4.1. Name of organisation:

Cb.4.2. Address:

Cb.4.2.1. Street Address:

Cb.4.2.2. Postcode:

Cb.4.2.3. Town/City:

Cb.4.2.4. Country:

Cb.4.3.. Telephone number:

Cb.4.4. E-mail:

Repeat if necessary, "add more" button should be available

D. Classification of the Medical Device

D.1. ☐ Active implantable medical device (AIMD) (device according to Directive 90/385/EEC)

D.2. ☐ Medical device by risk class (device according to Directive 93/42/EEC)

D.2.1 ☐ Class I according to rule ____ (Annex IX, Dir/93/42/EC)

D.2.2. ☐ Class IIa according to rule ____ (Annex IX, Dir/93/42/EC)

D.2.2.1. ☐ invasive, intended for long-term use

D.2.3. ☐ Class IIb according to rule ____ (Annex IX, Dir/93/42/EC)

D.2.3.1. ☐ invasive, intended for long-term use

D.2.4. ☐ Class III according to rule ____ (Annex IX, Dir/93/42/EC)

D.3. ☐ Medical device is an implant

D.3.1. if yes, which type:

D.3.2. is the implant intended to remain permanently in the patient yes ☐ no ☐

D.4. ☐ Medical device is manufactured using tissue of animal origin (COM RegNo. 722/2012/EC)

D.4.1. if yes, which:

D.5. ☐ Medical device contains human blood or blood plasma component(s) (Dir/2000/70/EC or Dir/2001/104/EC)

D.5.1. if yes, which:

D.6. ☐ Medical device contains/incorporates, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in Article 1 of Dir/2001/83/EC

D.6.1. if yes, which:

D.7. ☐ Medical device is used in combination with accessories

D.7.1. if yes, which:

D.8. ☐ Medical device contains medicinal product components with supportive function

D.8.1. if yes, which:

D.9. ☐ Specific additional software application is required for the medical device

D.9.1. if yes, which:

E. List of Investigational Sites

E.1.1. Investigator Coordinator:

E.1.2. Principal investigator:

E.1.3. Investigator:

E.2.1. Organisation:

E.2.2. Address:

E.2.3. Telephone number:

E.2.4. e-mail:

Repeat if necessary "add more" button should be available; a new site would get E.2.sequence fields

F. Ethics Committee

F.1. Concerned ethics committee:

F.1.1. Responsible for Investigational site(s):

F.2. Favourable Opinion yes ☐ no ☐ pending ☐

F.2.1. If no: Submission date:

Repeat if necessary "add more" button should be available; a new ethics committee would get F.2.sequence fields

G. The following documentation is contained in the dossier:

G.1. ☐ Clinical Investigation Plan/Protocol

G.2. ☐ Investigators Brochure

G.3. ☐ Manufacturer's instructions (*in appropriate local language*) for CE marked medical devices

G.4. ☐ Declaration of Compliance with Essential Requirements[20] or Declaration of Conformity by the manufacturer[21], as applicable

G.5. ☐ Certificate of the Notified Body/Bodies

G.6. ☐ Documentation on construction/manufacture (manufacturing process, sterilization etc.)

G.7. ☐ Results of studies or technical tests (i.e. Biocompatibility[22], electrical safety[23], etc.)

G.8. ☐ List of harmonized standards applied in full or in part/List of ER

G.9. ☐ Documentation on the safety of animal [24] or human[25] derived components, if applicable

G.10. ☐ Risk assessment

G.11. ☐ Agreements between Sponsor, Monitor and clinical investigator outlining their respective responsibilities

G.12. ☐ Documentation on Investigator Qualification

G.13. ☐ Informed Consent Form (*in local language*)

G.14. ☐ Insurance certificate

G.15. ☐ CRF, Case Report Form

G.16. ☐ Opinion of the ethics committee(s) concerned

G.17. ☐ further documentation: G.17.1. List documentation:

20 See Annex 6.2.2 of Directive 90/385/EEC resp. Annex VIII.2.2 of Directive 93/42/EEC
21 For CE-marked investigational devices
22 See EN ISO 10993
23 See standard series EN 60601
24 See COM Reg (EU) Nr. 722/2012
25 See Dir/2000/70/EC, Dir/2001/104/EC

H. Declaration and Signature

H.1. I hereby confirm that /confirm on behalf of the sponsor (delete which is not applicable) that:

- the information provided is complete
- the attached documents contain an accurate account of the information available
- the clinical investigation will be conducted in accordance with the protocol
- serious adverse events and result-related information will be reported, in accordance with the applicable legislation
- I confirm that the medical device(s) conform(s) to the essential requirements of all applicable directives and regulations except for those which are the scope of this CI
- I confirm that appropriate safety measures have been taken for study participants/users
- I accept the applicable fee(s)

H.2.1. Signature of the sponsor/legal representative:

H.2.2. Print name:

H.2.3. Date:

APPENDIX 8: Clinical Investigation Validation Checklist:

Checklist Validation (Verification of Submission requirements)
Comment: Validation check for presence of document only, unless stated differently)

- Application document in electronic form (xml or pdf-file; fields include EUDAMED required information)*(check for provision of required fields)*
- Clinical Investigation Plan
- Investigator's Brochure
- Patient Information and Informed Consent Form
- Case Report Forms (CRFs)
- Proof of qualification of the clinical investigator(s)
- Information on the device:
    - For CE-marked medical devices:
        - instructions for use
        - Certificate(s) of notified bodies
        - Declaration of conformity of the manufacturer
    - For non CE-marked devices: Written confirmation that the medical device complies with the essential requirements of the applicable Directive in all aspects except those that will be assessed in the clinical investigation
        - construction and manufacture of the device, especially sterilisation
        - Results of construction calculations, assessments, technical tests, preclinical and clinical studies etc.
        - Results of the risk analysis
- Rationale for Qualification (both Directives) and Classification (Directive 93/42/EEC only)
- List of standards applied in full or in part/List of applicable ER and how addressed
- Billing address (Company, contact, Street, ZIP code/place, country, Phone, Fax, Email)
- Documentation on the safety of animal [26] or human[27] derived components, if applicable
- Documentation on medicinal substances having ancillary action

Optional (depending on country specific requirements)

- Opinion of the competent ethics committee(s)
- Confirmation of insurance coverage for the subjects enrolled in the clinical investigation
- Written agreements or draft agreements between the sponsor, monitor, and clinical investigator establishing each party's responsibilities

Declaration and signature

[26] See COM Reg (EU) 722/2012
[27] See RL 2000/70/EG bzw. RL 2001/104/EG

APPENDIX 9: Clinical investigation assessment checklist (CIP, IB, Ethical aspects)

Investigational device :
Manufacturer/Sponsor:
Title of clinical investigation :
Date:
Version:
CIV/ID:

Clinical Investigation Plan (CIP)

Requirement	Fulfilled?	Comment
General		
Identification of CIP Title and ref.nr of CI; version/issue nr/date of CIP; summary revision history;	complete/sufficient Incomplete/insufficient	
Identification of sponsor, MF, AR, principal or other investigators; investigation sites	sufficient/adequate insufficient/inadequate provided elsewhere (eg IB)	
The justification for the need of the proposed CI	adequate/sufficient inadequate/insufficient	
Overall Synopsis of the clinical investigation	sufficient/adequate insufficient/inadequate	
Identification and description of the IMD		
Identification and description of the investigational device(s)	sufficient/adequate insufficient/inadequate provided elsewhere (eg IB)	
Benefit/risk considerations for CI and IMD		
Anticipated clinical benefits	adequate/sufficient inadequate/insufficient	
Anticipated ADE, SAE, SADE, DD, including those considered critical	adequate/sufficient inadequate/insufficient	
Results of risk analysis	adequate/sufficient inadequate/insufficient	
Steps to control or mitigate risks.	adequate/sufficient inadequate/insufficient	
Risk management according to EN ISO 14791?	Yes No	

	partly equivalent solutions provided	
Justification of the Design of the Clinical Investigation		
Rationale in relation to preclinical and clinical evaluation: based on evaluation of preclinical data to justify use on human subjects and on results of clinical evaluation to determine and justify optimal design of CI and help identify relevant endpoints and confounders	sufficient/adequate insufficient/inadequate	
General design aspects: Specification if the CI has been planned as exploratory, confirmatory study or a combined one; planned for CE-marking?; phase of device development; Type of CI with rationale; measures to avoid bias	sufficient/adequate insufficient/inadequate	
Investigational device and comparators: Exposure to IMD and comparator, if any; justification for choice of comparator(s); other concomitant treatments;	sufficient/adequate insufficient/inadequate	
Subjects: Inclusion-exclusion criteria; representative to target population? Criteria and procedures for subject withdrawal or discontinuation; expected duration of CI and for subjects; number of subjects	adequate/sufficient inadequate/insufficient	
Statistical considerations		
Design, method and analytical procedures	adequate/sufficient non adequate/insufficient	
Sample size, level of significance and power of the CI	adequate/sufficient non adequate/insufficient	
Particular justification for descriptive statistical analysis and small sample size (e.g. for exploratory, FIM study)	adequate/sufficient inadequate/insufficient	
Provisions for subgroup analysis or interim reports, if any	adequate/sufficient inadequate/insufficient NA	
Procedures for missing data, drop-outs and lost to follow-ups	adequate/sufficient inadequate/insufficient	
Objectives, endpoints and hypothesis		
Description of primary and secondary objectives and endpoints of CI, that must be consistent with the rationale of the CI and appropriate to the device; rationale for selection and measurement of endpoints; methods	adequate/sufficient inadequate/insufficient	

and timing for assessing, recording and analysing variables; equipment used for assessing		
Description of the hypothesis of the CI, that must be consistent with the selected objectives and with the statistical plan	adequate/sufficient inadequate/insufficient	
Identification of the variables to be evaluated and/or measured during the CI, in order to accept or reject the hypothesis of the CI	adequate/sufficient inadequate/insufficient	
Design of CI		
Description and justification of the type and of the design of the CI	adequate/sufficient inadequate/insufficient	
Choice of controls, if any (e.g., comparator, cohort, sham, historical)	adequate/sufficient inadequate/insufficient NA	
Description and identification of the comparator, if used, and justification of its choice	adequate/sufficient inadequate/insufficient NA	
Identification of any medical device, medical treatment or medication to be used during the CI	adequate/sufficient inadequate/insufficient NA	
Number of investigational medical devices and comparators (if applicable) to be used	adequate/sufficient inadequate/insufficient	
Expected duration of CI	adequate/sufficient inadequate/insufficient	
Expected duration of CI for each subject	adequate/sufficient inadequate/insufficient	
Procedures and follow-up		
Description of the medical/surgical procedures involved in the use of the investigational device and identification of the innovative aspects of these procedures; known or foreseeable factors to compromise outcome or interpretation of results	adequate/sufficient inadequate/insufficient	
Description of all the medical procedures that subjects undergo during the CI	adequate/sufficient inadequate/insufficient	
Proposed follow up: - long enough to demonstrate the	adequate/sufficient	

safety and performance of the investigational device and of the procedures - consistent with the objectives of the CI	inadequate/insufficient	
Description of procedures for follow up of subjects who have withdrawn their consent and for subjects lost to follow up	adequate/sufficient inadequate/insufficient	
Training of investigators		
Description of the training and experience of the investigator/s regarding the use of the investigational device	adequate/sufficient inadequate/insufficient	
Mitigation of the risks due to the learning curve. For FIM with high risk class, innovative, invasive device: - procedure supervision of each investigator by an experienced person during the first use(s). - sufficient interval between the treatment/exposure of each of study subjects to be able to evaluate need for improvement.	adequate/sufficient inadequate/insufficient	
Monitoring plan		
General description of the monitoring plan	sufficient /adequate non adequate /insufficient incomplete/absent	
Data management		
Description of procedures for data management	adequate/sufficient inadequate/insufficient	
A DSMB is presented, or its absence justified?	Yes No	
Deviation from or Amendments to the CIP		
Description of the procedures to manage, report and prevent the deviation from CI	adequate/sufficient inadequate/insufficient	
Statement that deviating without request from CIP is not allowed, except in justified emergency circumstances	adequate/sufficient inadequate/insufficient	
Description of the procedures to amend the CIP	adequate/sufficient inadequate/insufficient	
Device Accountability		
Procedures for device accountability	adequate/sufficient inadequate/insufficient	
Description of the procedures for the	adequate/sufficient	

traceability of the device during the CI (including before the use, example, storage and distribution circuit in the Centre) and after the CI;	inadequate/insufficient	
Statements of Compliance		
Ethical principles of DoH; conformity with relevant legislation; with relevant standards or equivalent; waiting for approval/favourable opinion and observing conditions acc. to nat. provisions; liability and insurance acc. to nat. provisions	adequate/sufficient inadequate/insufficient	
AE, SAE, ADE, SADE, DD		
Definition of terms (e.g. adverse events, adverse effects, SAE, SADE, adverse events related to investigational procedures, device deficiencies)	adequate/sufficient inadequate/insufficient	
List of foreseeable adverse events and anticipated device effects weighed on their likely incidence, mitigation or treatment	adequate/sufficient inadequate/insufficient	
Identification of anticipated adverse events related to IMDs	adequate/sufficient inadequate/insufficient	
Identification of anticipated adverse events related to investigational procedures.	adequate/sufficient inadequate/insufficient	
Procedures for recording and analysing AE, ADE and DD	adequate/sufficient inadequate/insufficient	
Procedures and time frames for reporting SAE, SADE, DD and updates	adequate/sufficient inadequate/insufficient	
Informed consent process		
Description of general process for obtaining the informed consent, specifying procedures for subjects unable to give it and for cases of emergency treatment.	adequate/sufficient inadequate/insufficient considered under Ethical Aspects	
Vulnerable population		
Description of vulnerable population to be included in CI, justification for including, and description of particular procedures and medical care planned for them	adequate/sufficient inadequate/insufficient considered under Ethical Aspects	
Suspension – premature termination of the CI		
Description of the procedure to suspend –terminate prematurely the CI	adequate/sufficient inadequate/insufficient	
Description of procedures for follow up of subjects following completion, suspension or early termination of the	adequate/sufficient	

clinical investigation .	inadequate/insufficient	
Publication policy and transparency		
Description of publication policy, that shall be in line with the provisions of Declaration of Helsinki	adequate/sufficient inadequate/insufficient	
Statement of compliance to DoH with regard to registration requirements in a public CI registry or database before commencing the CI	adequate/sufficient inadequate/insufficient	
Conclusions:		

Investigator's Brochure (IB)

Requirement	Fulfilled?	Comment
General requirements		
Identification of the IB	adequate/sufficient inadequate/insufficient	
Identification of Sponsor/MF/AR	adequate/sufficient inadequate/insufficient provided elsewhere (eg in CIP)	
Investigational device information		
Scientific rationale for design and intended use	adequate/sufficient inadequate/insufficient provided elsewhere (eg in CIP)	
Risk classification of IMD and application rule(s)	adequate/sufficient inadequate/insufficient	
Description of the device (included components, software, materials, substances used and accessories) together with its intended use in the study population	adequate/sufficient inadequate/insufficient	
Description of the intended clinical performance, mechanism of action, technical and functional features of the investigational device,	adequate/sufficient inadequate/insufficient	
Description of the manufacturing, related validation processes, maintenance, storage and handling of the device	adequate/sufficient inadequate/insufficient	
Description and rationale of the choice of materials and substances coming into contact with the body and body fluids, together with the evaluation of the benefit/risk ratio related to their use.	adequate/sufficient inadequate/insufficient	
Description of the innovative aspects of the investigational device and reference to previous and similar generations of the device.	adequate/sufficient inadequate/insufficient	

Description of method of cleaning, disinfection and sterilization [28]and validation	adequate/sufficient inadequate/insufficient	
Instructions of use and labels of investigational device [29]	adequate/sufficient inadequate/insufficient	
Identification and description of any medicinal substance incorporated into the investigational device, together with the justification of their use and the evaluation of the risk/benefit ratio related to their use.[30]	adequate/sufficient inadequate/insufficient N.A.	
Identification and description of any tissues of animal origin incorporated within the device, together with the justification of their use, risk mitigation and the evaluation of the risk/benefit ratio related to their use.[31]	adequate/sufficient inadequate/insufficient N.A.	
Identification and description of any human blood derivatives incorporated into the investigational device, together with the justification of their use and the evaluation of the risk/benefit ratio related to their use.[32]	adequate/sufficient inadequate/insufficient N.A	
Preclinical testing		
Preclinical evaluation based on relevant in vivo, in vitro, ex vivo, bench and performance testing and experimental data	adequate/sufficient inadequate/insufficient	
Biocompatibility evaluation following EN ISO 10993 series?	yes, in full or in part with equivalent solutions adequate/sufficient inadequate/insufficient	
Software validation	adequate/sufficient inadequate/insufficient	
Existing clinical data		
Evaluation of existing clinical data for IMD or similar devices, incl. for other indications;	adequate/sufficient inadequate/insufficient	
Analysis of ADE, history of modification or recall	adequate/sufficient inadequate/insufficient	
Risk Management		
Synthesis of risk/benefit analysis and the risk management: description of actions taken to minimize or eliminate the identified risks; identification of residual risks	adequate/sufficient inadequate/insufficient	
Anticipated risks, contraindications, warnings etc. for IMD	adequate/sufficient inadequate/insufficient	

[28] *See Appendix 3* **"***Guidance on medical devices which require sterilization"*
[29] This information could be provided as a separate document
[30] See Appendix 2 " Guidance notes on medical devices incorporating a medicinal substance or human blood derivative having ancillary action"
[31] See Appendix 6 **"**Guidance on Medical Devices incorporating tissues of animal origin"
[32] See Appendix 2 " Guidance notes on medical devices incorporating a medical substance or human blood derivate having ancillary action"

Regulatory, normative and other references		
List of applicable essential requirements of the directives and of relevant Harmonized Standards applied in full or in part and description of other solutions adopted to meet the essential requirements	adequate/sufficient inadequate/insufficient Info provided elsewhere (App. 1a and 1b)	
Statement of conformity with national/regional regulations, where appropriate; list of references	adequate/sufficient inadequate/insufficient	
Conclusions:		

Ethical Aspects[33]

Requirement	Fulfilled	Comment
Copy of the competent Ethics committee opinion	available pending favorable/positive not favorable/negative	
Justification for CI and its design	adequate/sufficient inadequate/insufficient	
Process and documents for informed consent	adequate/sufficient inadequate/insufficient	
Provisions for liability and insurance for subjects and investigator(s)	adequate/sufficient inadequate/insufficient	
Vulnerable population and individuals: possible inclusion with justification and specific protection	adequate/sufficient inadequate/insufficient	
Benefit/Risk estimation feasible and risk management acceptable against state of the art in medicine	adequate/sufficient inadequate/insufficient	
Suitability of Clinical Investigators (Principal, Coordinating or others)	adequate/sufficient inadequate/insufficient	
Suitability of Clinical Investigation Site(s)	adequate/sufficient inadequate/insufficient	
Statement on prior registration of clinical investigation in public CI registry (like WHO ICTRP or clinical	adequate/sufficient	

[33] usually depends largely on national provisions

trials.gov) (=p. 35 of DoH)	inadequate/insufficient	
Statement on publication policy (p. 36 of DoH)	adequate/sufficient inadequate/insufficient	
Conclusions:		

Abbr.:

AE	Adverse Event
ADE	Adverse Device Effect
AR	Authorized Representative
CA	Competent Authority
CI	Clinical Investigation
CIP	Clinical Investigation Plan
DD	Device Deficiency
DoH	Declaration of Helsinki
DSMB	Data Safety Monitoring Board
FIM	First-In-Man study
IB	Investigator Brochure
ICTRP	International Clinical Trial Registry Platform
IMD	Investigational Medical Device
MF	Manufacturer
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
WHO	World Health Organization