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GUIDELINES ON MEDICAL DEVICES

CLINICAL EVALUATION: A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES 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

CLINICAL EVALUATION: A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES UNDER DIRECTIVES 93/42/EEC and 90/385/EEC

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1. Introduction

Pursuant to

- section 6a of Annex I to Directive 93/42/EEC (amended by Directive 2007/47/EC) and to
- section 5a of Annex 1 to Directive 90/385/EEC (amended by Directive 2007/47/EC),

the demonstration of conformity with Essential Requirements for a medical device must include a clinical evaluation, which is conducted in accordance with Annex X to Directive 93/42/EEC or with Annex 7 to Directive 90/385/EEC.

This document promotes a common approach to clinical evaluation for medical devices regulated by directives 90/385/EEC and 93/42/EEC. It does not concern in vitro diagnostic devices.

The depth and extent of clinical evaluations should be flexible and appropriate to the nature, intended purpose, and risks of the device in question. Therefore, this guidance is not intended to impose device-specific requirements.

This document uses the terms "must", "shall", "have to" where these terms are used in the Directives. "Should" is used in other instances.

2. Scope

This guide is not legally binding; only the text of the Directives is authentic in law. 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 interested parties and of experts from national Competent Authorities, it is anticipated that this guide will be followed within the Member States, thereby supporting uniform application of relevant provisions of EU Directives and common practices.

On certain issues not addressed in the Directives, national legislation may be different from this guide.

This guide is regularly updated according to regulatory developments. The latest version of the guide should always be used. This version is a complete revision of the previous texts.

The medical device legislation in Europe is currently being significantly revised. A new Regulation of the European Parliament and of the Council on medical devices will be published, which may result in changes to important concepts or definitions relating to clinical evaluation. Parts or all of this document are likely to be revised. Some contents (such as contents about notified bodies) are likely to be removed and integrated in other series of documents.

3. References

European Legislation:

- Council Directive 90/385/EEC of 20 June 1990 relating to active implantable medical devices
- Council Directive 93/42/EEC of 14 June 1993 concerning medical devices
- Commission Regulation 722/2012 of 8 August 2012 concerning active implantable medical devices and medical devices manufactured utilising tissues of animal origin

- Commission Implementing Regulation 920/2013 of 24 September 2013 on the designation and the supervision of notified bodies under Council Directive 90/385/EEC on active implantable medical devices and Council Directive 93/42/EEC on medical devices

Harmonised and International standards:

- EN ISO 14155:2011 Clinical investigation of medical devices for human subjects – Good clinical practice
- EN ISO 14971:2012 Medical devices – application of risk management to medical devices

European guidance documents:

- MEDDEV 2.12/1 Guidelines on a medical devices vigilance system
- MEDDEV 2.12/2 Guidelines on post market clinical follow-up studies: a guide for manufacturer and notified body
- MEDDEV 2.4/1 Classification of medical devices
- MEDDEV 2.7/2 Guidelines for competent authorities for making a validation/assessment of a clinical investigation application under directives 90/385/EEC and 93/42/EC
- Manual on borderline and classification in the Community regulatory framework for medical devices
- NBOG BPG 2006-1 Change of notified body
- NBOG BPG 2009-1 Guidance on design-dossier examination and report content
- NBOG BPG 2009-4 Guidance on notified body‘s tasks of technical documentation assessment on a representative basis
- NBOG BPG 2010-2 Guidance on audit report content
- NBOG BPG 2014-1 Renewal of EC design-examination and type-examination certificates: Conformity assessment procedures and general rules
- NBOG BPG 2014-2 Guidance on the information required for notified body medical device personnel involved in conformity assessment activities
- NBOG BPG 2014-3 Guidance for manufacturers and notified bodies on reporting of design changes and changes of the quality system

Other guidance documents:

- GHTF SG5 N1R7:2007: Clinical evidence - Key definitions and concepts
- GHTF SG5 N2R8:2007: Clinical evaluation
- GHTF SG5 N41R9:2005: Essential principles of safety and performance

This list contains documents available at the time this MEDDEV document was published. In general, the most recent versions of standards and legal texts should be used.

4. Definitions

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

NOTE 1: This includes events related to the investigational device or the comparator.

NOTE 2: This includes events related to the procedures involved.

NOTE 3: For users or other persons this is restricted to events related to the investigational medical device.

[EN ISO 14155:2011]

Bias: bias is a systematic deviation of an outcome measure from its true value, leading to either an overestimation or underestimation of a treatment's effect. It can originate from, for example, the way patients are allocated to treatment, the way treatment outcomes are measured and interpreted, and the way data are recorded and reported. [Adapted from GHTF SG5/N2R8:2007]

Clinical data: the safety and/or performance information that is generated from the clinical use of a device. Clinical data are sourced from:

- clinical investigation(s) of the device concerned; or
- clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated; or
- published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated.

[derived from Article 1.2.k MDD and Art. 1.2.k AIMDD]

Clinical evaluation: a methodologically sound ongoing procedure to collect, appraise and analyse clinical data pertaining to a medical device and to evaluate whether there is sufficient clinical evidence to confirm compliance with relevant essential requirements for safety and performance when using the device according to the manufacturer's Instructions for Use.

Note: In exceptional cases where an instruction for use is not required, the collection, analysis and assessment are conducted taking into account generally recognised modalities of use.

Clinical evidence: the clinical data and the clinical evaluation report pertaining to a medical device. [GHTF SG5/N2R8:2007]

Clinical investigation: systematic investigation in 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'.
[EN ISO 14155:2011]

Clinical investigation plan: document that states the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation. [EN ISO 14155:2011]

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). [EN ISO 14155:2011]

Device registry: an organised system that uses observational study methods to collect defined clinical data under normal conditions of use relating to one or more devices to evaluate specified

outcomes for a population defined by a particular disease, condition, or exposure and that serves predetermined scientific, clinical or policy purpose(s).

Note: The term “device registry” should not be confused with the concept of device registration and listing.
[MEDDEV 2.12/2 rev2]

Clinical safety: freedom from unacceptable clinical risks, when using the device according to the manufacturer’s Instructions for Use. [MEDDEV 2.7/2 revision 2]

Note: In exceptional cases where an instruction for use is not required, the collection, analysis and assessment are conducted taking into account generally recognised modalities of use.

Clinical use: use of a medical device in or on living human subjects.

Note: Includes use of a medical device that does not have direct patient contact.

Equivalent device: a device for which equivalence to the device in question can be demonstrated. [Derived from Art. 1.2.k MDD]

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. [MEDDEV 2.7/2 revision 2]

Harmonised standards: standards whose references have been published in the Official Journal of the European Communities. [Derived from article 5 of Directive 90/385/EEC and article 5 of Directive 93/42/EEC]

Hazard: potential source of harm. [EN ISO 14971:2012]

Hazard due to substances and technologies: for the purpose of this MEDDEV document, a hazard that is seen with products that share specific characteristics.
Note: This includes products that contain the same materials and substances, material combinations, use the same technologies, produce similar abrasion, are used with the same type of surgical approach, share the same manufacturing procedures or impurities, or share other characteristics.

Incident: any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health. [MEDDEV 2.12/rev 8]

Information materials supplied by the manufacturer: for the purpose of this document, this refers to the labelling, instructions for use and the manufacturer's promotional materials for the device under evaluation.

[Derived from MDD Art. 1.2.g, MDD Annex I section 13, AIMDD Art. 1.2.f, AIMDD Annex I sections 14 and 15]

Intended purpose: the use for which the device is intended according to the data supplied by the manufacturer on the labelling, in the instructions and/or in promotional materials. [MDD Art. 1.2.g, AIMDD Art. 1.2.f]

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. [EN ISO 14155:2011]

PMCF plan: the documented, proactive, organised methods and procedures set up by the manufacturer to collect clinical data based on the use of a CE-marked device corresponding to a particular design dossier or on the use of a group of medical devices belonging to the same subcategory or generic device group as defined in Directive 93/42/EEC. The objective is to confirm clinical performance and safety throughout the expected lifetime of the medical device, the acceptability of identified risks and to detect emerging risks on the basis of factual evidence. [MEDDEV 2.12/2 rev.2]

PMCF study: a study carried out following the CE marking of a device and intended to answer specific questions relating to clinical safety or performance (i.e. residual risks) of a device when used in accordance with its approved labelling. [MEDDEV 2.12/2 rev.2]

Risk: combination of the probability of occurrence of harm and the severity of that harm. [EN ISO 14971:2012]

Risk management: systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk. [EN ISO 14971:2012]

Serious adverse event: adverse event that

a) led to death,

b) led to serious deterioration in the health of the subject, that either resulted in

1) a life-threatening illness or injury, or
2) a permanent impairment of a body structure or a body function, or
3) in-patient or prolonged hospitalization, or
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 [Clinical Investigation Plan], without serious deterioration in health, is not considered a serious adverse event.
[EN ISO 14155:2011]

Sufficient clinical evidence: an amount and quality of clinical evidence to guarantee the scientific validity of the conclusions.

5. Abbreviations

AIMDD: Active implantable medical device directive (Council Directive 90/385/EEC amended by Directive 2007/47/EC)

CEAR: Clinical Evaluation Assessment Report

CER: Clinical Evaluation Report

ER: Essential Requirement

IFU: Instructions For Use

MDD: Medical Device Directive (Council Directive 93/42/EEC amended by Directive 2007/47/EC)

PMS: Post Market Surveillance

PMCF: Post Market Clinical Follow-Up

6. General principles of clinical evaluation

6.1. What is clinical evaluation?

Clinical evaluation is a methodologically sound ongoing procedure to collect, appraise and analyse clinical data pertaining to a medical device and to analyse whether there is sufficient clinical evidence to confirm compliance with relevant essential requirements for safety and performance when using the device according to the manufacturer's instructions for use.

In exceptional cases where an instruction for use is not required, the collection, appraisal, and analysis are conducted taking into account generally recognised modalities of use.

The requirements for clinical evaluation apply to all classes of medical devices. The evaluation should be appropriate to the device under evaluation, its specific properties, and its intended purpose.

Benefits and risks should be specified, e.g. as to their nature, probability, extent, duration and frequency. Core issues are the proper determination of the benefit/risk profile in the intended target groups and medical indications, and demonstration of acceptability of that profile based on current knowledge/ the state of the art in the medical fields concerned.

Clinical evaluation is a responsibility of the manufacturer and the clinical evaluation report is an element of the technical documentation of a medical device.

For compliance with European medical device directives,

- the clinical evaluation addresses the following Essential Requirements:
  - Annex 1 sections 1, 2, 5 of AIMDD (for active implantable medical devices), or
  - Annex I sections 1, 3, 6 of MDD (for medical devices);

  see Appendix A7 (Analysis of the clinical data - compliance to specific Essential Requirements);

- the evaluation must follow defined and methodologically sound procedures as described in:
  - Annex 7 of AIMDD (for active implantable medical devices), or
  - Annex X of MDD (for medical devices);

- where demonstration of conformity with essential requirements based on clinical data is not deemed appropriate, an adequate justification has to be given. The justification is included in the clinical evaluation report with contents according to:
  - Annex 7 section 1.5 of AIMDD (for active implantable medical devices), or
  - Annex X section 1.1d of MDD (for medical devices).

Conformity to the Essential Requirements can only be assumed when the following items are aligned with each other:

- the information materials supplied by the manufacturer (the labelling, instructions for use, available promotional materials, including accompanying documents foreseen by the manufacturer)
- the clinical evaluation (the device description used for the clinical evaluation, other contents of the clinical evaluation report)
- the available clinical data (such as results of Clinical Investigations, publications, PMS studies, etc.).

Particularly, evaluators should address if the following points are adequately supported by sufficient clinical evidence:

- the intended purpose described in the information materials supplied by the manufacturer (including for all medical indications);
- the clinical performance and benefits described in the information materials supplied by the manufacturer (including, for example, any claims on product performance and safety);
- measures for risk avoidance and risk mitigation described in the information materials supplied by the manufacturer (including, for example the declaration of the residual risks, contraindications, precautions, warnings, instructions for managing foreseeable unwanted situations);
- the usability of the device for the intended users and the suitability of the information materials supplied by the manufacturer for the intended users (including, if applicable, for lay or disabled persons);
- instructions for target population groups (including, for example, pregnant women, paediatric populations).

6.2. When is clinical evaluation undertaken and why is it important?

Clinical evaluation is conducted throughout the life cycle of a medical device, as an ongoing process.

Usually, it is first performed during the development of a medical device in order to identify data that need to be generated for market access. Clinical evaluation is mandatory for initial CE-marking and it must be actively updated thereafter.

Clinical evaluation is necessary and important because it ensures that the evaluation of safety and performance of the device is based on sufficient clinical evidence throughout the lifetime that the medical device is on the market. This ongoing process enables manufacturers to provide notified bodies and competent authorities with sufficient clinical evidence for demonstration of conformity of the device with the Essential Requirements throughout its lifetime (for example for CE marking, fulfilment of post-market surveillance and reporting requirements, or during surveillance procedures).

6.2.1. Clinical evaluation undertaken for the development of a medical device

Premarket research and development are guided by clinical evaluation and risk management. Typically, manufacturers carry out clinical evaluations to

- define needs regarding clinical safety and clinical performance of the device;
- in case of possible equivalence to an existing device, evaluate if there are clinical data available and determine equivalence; for additional information, see Appendix A1 (Demonstration of equivalence);
- carry out a gap analysis and define which data still need to be generated with the device under evaluation, whether clinical investigations are necessary and if so, to define the study design; for additional information, see Section 10 (Analysis of the clinical data) and Appendix A2 (When should additional clinical investigations be carried out?).

As the initial clinical evaluation identifies the questions to be answered by a clinical investigation, the clinical evaluation process should generally commence in advance of any clinical investigation[1].

6.2.2. Clinical evaluation for initial CE-marking

Clinical evaluation is required to be carried out for the conformity assessment process leading to the CE-marking and placing on the market of a medical device. The purpose is to:

- document that there is sufficient clinical evidence to demonstrate conformity with the Essential Requirements covering clinical performance and clinical safety;
- identify aspects that need to be addressed systematically during post-market surveillance (PMS), e.g. in post market clinical follow-up studies (PMCF Studies) required under the medical device directives. Typically, these aspects include estimation of residual risks and uncertainties or unanswered questions (such as rare complications, uncertainties regarding long-term performance, safety under wide-spread use).

6.2.3. Updating the clinical evaluation

a. <u>Frequency of updates</u>

The manufacturer should define and justify the frequency at which the clinical evaluation needs to be actively updated.

When doing so, the manufacturer should typically consider:

- whether the device carries significant risks

  (e.g. based on design, materials, components, invasiveness, clinical procedures, high-risk anatomical locations, high-risk target populations (e.g. paediatrics, elderly), severity of disease/ treatment challenges).
- whether the device is well established, taking into consideration:
  - innovation;

[1] Including for the planning of clinical investigations and production of documents described in standard EN ISO 14155

- relevant changes in clinical sciences, materials sciences or other sciences related to the device under evaluation;
- the current level of confidence in the evaluation of clinical performance and clinical safety of the device; the manufacturer should consider
  - the data available from clinical investigations, PMCF studies, registries or other systematic studies (including the number of devices used, if that usage was representative of the usage in the market, the results to date);
  - the total number of devices used so far in the market, and expected reporting rates under the vigilance system.

- whether there are risks and uncertainties or unanswered questions, in the medium or long-term, that would influence the frequency of updates.
- design changes or changes to manufacturing procedures (if any).

The clinical evaluation is actively updated:

- when the manufacturer receives new information from PMS that has the potential to change the current evaluation;
- if no such information is received, then
  - at least annually if the device carries significant risks or is not yet well established; or
  - every 2 to 5 years if the device is not expected to carry significant risks and is well established, a justification should be provided.

When involvement of notified bodies is required, updates are usually coordinated with the notified body. Typically, they are aligned with the timetable for surveillance audits and the renewal of the certificates.

b. <u>General considerations on updating the clinical evaluation</u>

Manufacturers are required to implement and maintain a PMS system that routinely monitors the clinical performance and clinical safety of the device as part of their quality management system[2]. The scope and nature of such PMS should be appropriate to the device and its intended purpose.

PMS regularly generates new data (e.g. safety reports, results from published literature, registries, PMCF studies, and other data about device usage). Those data need to be evaluated for information that has a potential to change the evaluation of the risk/benefit profile, and the clinical performance and clinical safety of the device. Those data are required to be fed into the clinical evaluation process in a timely manner.

In accordance with the Directives, the clinical evaluation and the clinical evaluation report *must be actively updated with data obtained from post-market surveillance*[3].

When updating the clinical evaluation, the evaluators should verify:

- if the benefit/risk profile, undesirable side-effects (whether previously known or newly emerged) and risk mitigation measures are still

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[2] AIMDD Annexes 2, 4, and 5
MDD Annexes II, IV, V, VI, and VII

[3] MDD Annex X letter 1.1.c

- compatible with a high level of protection of health and safety and acceptable according to current knowledge/ the state of the art;
- correctly addressed in the information materials supplied by the manufacturer of the device;
- correctly addressed by the manufacturer's current PMS plan;

- if existing claims are still justified;
- if new claims the manufacturer intends to use are justified.

While clinical evaluation requires data from PMS activities, it also generates new information that have to be fed into the PMS and risk management process. Clinical evaluation can therefore result in changes to the manufacturer's risk management documents, instructions for use (IFU) and PMS activities.

If the manufacturer concludes there is not sufficient clinical evidence to be able to declare conformity with the Essential Requirements, the manufacturer will need to :

- stop placing the devices on the market until conformity is restored, and
- take necessary corrective and preventive action.

6.3. How is a clinical evaluation performed?

The clinical evaluation is based on a comprehensive analysis of available pre- and post-market clinical data relevant to the intended purpose of the device in question, including clinical performance data and clinical safety data.

There are discrete stages in performing a clinical evaluation:

- Stage 0: Define the scope, plan the clinical evaluation (also referred to as scoping and the clinical evaluation plan).
- Stage 1: Identify pertinent data.
- Stage 2: Appraise each individual data set, in terms of its scientific validity, relevance and weighting.
- Stage 3: Analyse the data, whereby conclusions are reached about
  - compliance with Essential Requirements (including ER1, ER3, ER6) on performance and safety of the device, including its benefit/risk profile,
  - the contents of information materials supplied by the manufacturer (including the label, IFU of the device, available promotional materials, including accompanying documents possibly foreseen by the manufacturer),
  - residual risks and uncertainties or unanswered questions (including on rare complications, long term performance, safety under wide-spread use), whether these are acceptable for CE-marking, and whether they are required to be addressed during PMS.
- Stage 4: Finalise the clinical evaluation report

  The clinical evaluation report summarises and draws together the evaluation of all the relevant clinical data documented or referenced in other parts of the technical documentation. The clinical evaluation report and the relevant clinical data constitute the clinical evidence for conformity assessment.

Each of these stages is covered in separate sections later in this document (see the figure below). During the course of a clinical evaluation the stages are often iterative. Indeed, the appraisal and analysis stage may uncover new information and raise new questions, with a need to widen the

scope of the evaluation, refine the clinical evaluation plan, and to retrieve, appraise and analyse additional data.

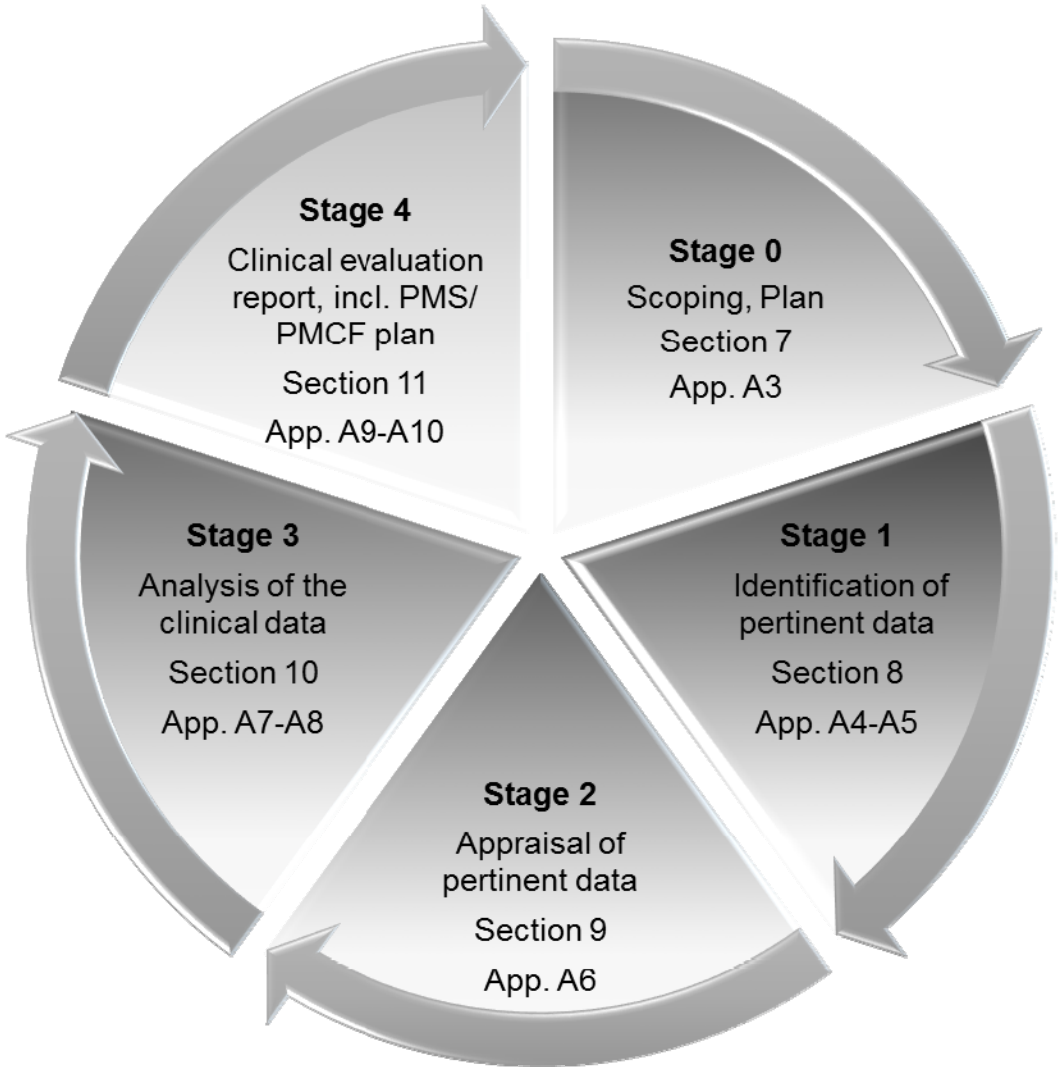

Figure: Stages of a clinical evaluation and references to sections and appendices of this document.

6.4. Who should perform the clinical evaluation?

The clinical evaluation should be conducted by a suitably qualified individual or a team.

The manufacturer should take the following aspects into consideration:

- The manufacturer defines requirements for the evaluators that are in line with the nature of the device under evaluation and its clinical performance and risks.
- The manufacturer should be able to justify the choice of the evaluators through reference to their qualifications and documented experience, and to present a declaration of interest for each evaluator.
- As a general principle, the evaluators should possess knowledge of the following:
  - research methodology (including clinical investigation design and biostatistics);

- information management (e.g. scientific background or librarianship qualification; experience with relevant databases such as Embase and Medline);
- regulatory requirements; and
- medical writing (e.g. post-graduate experience in a relevant science or in medicine; training and experience in medical writing, systematic review and clinical data appraisal).

- With respect to the particular device under evaluation, the evaluators should in addition have knowledge of:
  - the device technology and its application;
  - diagnosis and management of the conditions intended to be diagnosed or managed by the device, knowledge of medical alternatives, treatment standards and technology (e.g. specialist clinical expertise in the relevant medical specialty).
- The evaluators should have at least the following training and experience in the relevant field:
  - a degree from higher education in the respective field and 5 years of documented professional experience; or
  - 10 years of documented professional experience if a degree is not a prerequisite for a given task.

There may be circumstances where the level of evaluator expertise may be less or different; this should be documented and duly justified.

7. Definition of the scope of the clinical evaluation (Stage 0)

Before a clinical evaluation is undertaken the manufacturer should define its scope, based on the Essential Requirements that need to be addressed from a clinical perspective and the nature and history of the device. This is also referred to as scoping.

The scope serves as a basis for further steps, including the identification of pertinent data. The manufacturer sets up a description of the device under evaluation, and a clinical evaluation plan.

A clinical evaluation is required to be critical[4]. Therefore, it needs to identify, appraise and analyse both favourable and unfavourable data.

Depending on the stage in the lifecycle of the product, considerations for setting up a clinical evaluation plan should include different aspects. Typical examples are listed below.

Aspects (not an exhaustive list)	**Before CE-marking**	**For CE marked devices**
• The device description. For additional information, see Appendix A3 (Device description - typical contents)	X	X
• Whether there are any design features of the device, or any indications or target populations, that require specific attention. The clinical evaluation should cover any design features that pose special performance or safety	X	X

[4] Sections 1.1.1., 1.1.2, 1.1.3 MDD and AIMDD.

concerns (e.g. presence of medicinal, human or animal components), the intended purpose and application of the device (e.g. target treatment group and disease, proposed warnings, contraindications, precautions, and method of application) and the specific claims made by the manufacturer about the clinical performance and clinical safety of the device.		
• Information needed for evaluation of equivalence, if equivalence may possibly be claimed.	X	
• The risk management documents of the device, e.g. the hazard identification list, clinical risks identified from the risk analysis. The scope of the clinical evaluation will need data from and cross references to the manufacturer's risk management documents. The risk management documents are expected to identify the risks associated with the device and how such risks have been addressed. The clinical evaluation is expected to address the significance of any clinical risks that remain after design risk mitigation strategies have been employed by the manufacturer.	X	X
• The current knowledge/ state of the art in the corresponding medical field, such as applicable standards and guidance documents, information relating to the medical condition managed with the device and its natural course, benchmark devices, other devices and medical alternatives available to the target population.	X	X
• Data source(s) and type(s) of data to be used in the clinical evaluation. Data relevant to the clinical evaluation may be generated and held by the manufacturer or available from scientific literature. For additional information, see Section 8.1 (Data generated and held by the manufacturer), and Appendix A4 (Sources of literature).	X	X
• Whether the manufacturer has introduced/ intends to introduce any relevant[5] changes, including - design changes, - changes to materials and manufacturing procedures, - changes to the information materials supplied by the manufacturer (label, IFU, available promotional materials including accompanying documents possibly foreseen by the manufacturer) or other claims, - and whether the claim of equivalence to an existing device is still appropriate.		X
• Whether there are any specific clinical concerns that have newly emerged and need to be addressed.		X
• PMS aspects that need[6] regularly updating in the clinical evaluation report:		X

[5] Many changes are not clinically relevant (such as administrative changes to the labelling) and need not be considered for setting up a Clinical Evaluation plan.

- new clinical data[7] available for the device under evaluation;
- new clinical data available for the equivalent device (if equivalence is claimed);
- new knowledge about known and potential hazards, risks[8], performance, benefits[9] and claims[10], including
  - data on clinical hazards seen in other products (hazard due to substances and technologies);
  - changes concerning current knowledge/ the state of the art, such as changes to applicable standards and guidance documents, new information relating to the medical condition managed with the device and its natural course, medical alternatives available to the target population;
  - other aspects identified during PMS.		

• Needs for planning PMS activities.		X

It is important to recognise that there is considerable diversity in the types and history of technologies used in medical devices and the risks posed by them. Many devices are developed or modified by increments, so they are not completely novel. It may be possible to draw on the clinical experience and literature reports of the safety and performance of an equivalent device to establish the clinical evidence, thereby reducing the need for clinical data generated through clinical investigation of the device under evaluation. Similarly, it may be possible to use compliance with harmonised standards to satisfy the clinical evidence requirements for devices based on technologies with well established safety and performance characteristics.

8. Identification of pertinent data (Stage 1)

8.1. Data generated and held by the manufacturer

Data generated and held by the manufacturer typically include the following items (not a complete list):

- All pre market clinical investigations
- All clinical data generated from risk management activities and the PMS programmes which the manufacturer has implemented in Europe and in other countries, including the following items (not a complete list):
  - PMCF studies, such as post market clinical investigations and any device registries sponsored by the manufacturer

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[6] Requirement according to letter 1.1.c of Annex X MDD, and section 1.4 AIMDD: "The Clinical Evaluation and its documentation must be actively updated with data obtained from the post-market surveillance…."

[7] References: Annex 1, Essential Requirements 1, 2, 5, 5a, and Annex 7 AIMDD; and Annex I, Essential Requirements 1, 3, 6, 6a, and Annex X MDD.

[8] For further detail, refer to standard EN ISO 14971 and other harmonised standards.

[9] For further detail, refer to standard EN ISO 14971 and other harmonised standards.

[10] Claims made by the manufacturer on the clinical performance and clinical safety of the device under evaluation.

- PMS reports, including vigilance reports and trend reports
- the literature search and evaluation reports for PMS
- incident reports sent to the manufacturer (including the manufacturer's own evaluation and report)
- complaints regarding performance and safety sent to the manufacturer, including the manufacturer's own evaluation and report
- analysis of explanted devices (as far as available)
- details of all field safety corrective actions
- use as a custom made device
- use under compassionate use/ humanitarian exemption programs
- other user reports

- Relevant pre-clinical studies (e.g. bench test reports including verification and validation data)

With regard to those data:

- All data generated and held by the manufacturer need to be identified.
- Complete data need to be entirely disclosed and made available to the evaluators; this includes data from Europe and other countries; it includes clinical studies as well as use data.
- All data sets should be documented (adequately summarised[11], appraised, analysed and referenced) in the clinical evaluation report.

8.2. Data retrieved from literature

Literature searching is used to identify data not held by the manufacturer that are needed for the clinical evaluation.

Literature searching identifies potential sources of clinical data for establishing:

- Clinical data relevant to the device under evaluation, which are data that relate either to the device under evaluation or to the equivalent device (if equivalence is claimed).
- Current knowledge/ the state of the art.

  Includes applicable standards and guidance documents, data that relate to benchmark devices, other devices, critical components and medical alternatives or to the specific medical conditions and patient populations intended to be managed with the device. The data are typically needed in order to

  - describe the clinical background and identify the current knowledge/ state of the art in the corresponding medical field,
  - identify potential clinical hazards (including hazards due to substances and technologies, manufacturing procedures and impurity profiles),
  - justify the validity of criteria used for the demonstration of equivalence (if equivalence is claimed),
  - justify the validity of surrogate endpoints (if surrogate endpoints are used).

The following aspects should be considered for literature searching:

[11] to the extent that it can be critically reviewed by others

- The searching strategy should be thorough and objective, i.e. it should identify all relevant favourable and unfavourable data.

  For some devices, clinical data generated through literature searching will represent the greater part (if not all) of the clinical evidence. Thus, when conducting a literature review a comprehensive search should be conducted. If a comprehensive search is not deemed necessary, reasons should be documented.
- Several searches with different search criteria or focus are usually necessary to obtain the necessary data. For additional information, see Appendix A4 (Sources of literature).
- A literature search and other retrieval of data are carried out based on a search protocol. The search protocol documents the planning of the search before execution. For additional information, see Appendix A5 (Literature search and literature review protocol, key elements) and Appendix A6 (Appraisal of clinical data - examples of studies that lack scientific validity for demonstration of adequate clinical performance and/or clinical safety).
- Once the searches have been executed, the adequacy of the searches should be verified and a literature search report should be compiled to present details of the execution, any deviations from the literature search protocol, and the results of the search.
- It is important that the literature search is documented to such degree that the methods can be appraised critically, the results can be verified, and the search reproduced if necessary.

Abstracts lack sufficient detail to allow issues to be evaluated thoroughly and independently, but may be sufficient to allow a first evaluation of the relevance of a paper. Copies of the full text papers and documents should be obtained for the appraisal stage.

The literature search protocol(s), the literature search report(s), and full text copies of relevant documents, become part of the clinical evidence and, in turn, the technical documentation for the medical device.

9. Appraisal of pertinent data (Stage 2)

9.1. General considerations

In order to determine the value of the data identified in stage 1, the evaluators should appraise each individual document in terms of its contribution to the evaluation of the clinical performance and clinical safety of the device.

Uncertainty arises from two sources: the methodological quality of the data, and the relevance of the data to the evaluation of the device in relation to the different aspects[12] of its intended purpose. Both sources of uncertainty should be analysed to determine a weighting for each data set.

The evaluators should therefore:

- identify information contained in each document,
- evaluate the methodological quality of work done by the authors and from that, the scientific validity of the information,
- determine the relevance of the information to the clinical evaluation, and
- systematically weight the contribution of each data set to the clinical evaluation.

[12] For example different medical indications, target populations, intended users.

9.2. The appraisal plan

To ensure systematic and unbiased appraisal of the data, the evaluators should set up an appraisal plan that describes the procedure and the criteria to be used for the appraisal.

- The appraisal plan typically includes:
  - criteria for determining the methodological quality and the scientific validity of each data set.
  - criteria for determining the relevance to the clinical evaluation (relevance to the device and to the different aspects of its intended purpose).
  - criteria for weighting the contribution of each data set to the overall clinical evaluation.
- The appraisal should be thorough and objective, i.e. it should identify and attribute adequate weighting both to favourable and unfavourable contents of each document.
- The criteria adopted for the appraisal should reflect the nature, history and intended clinical use of the device. They should be documented and justified on the basis of current knowledge / the state of the art, applying accepted scientific standards.
- There are many acceptable ways, both qualitative and quantitative, by which the appraisal can be carried out[13]. For many well established devices and lower-risk devices, qualitative data may be adequate to fulfil the requirements of the MDD and AIMDD. The evaluation criteria should be adjusted accordingly.
- The appraisal plan should be documented in the clinical evaluation report.

9.3. Conduct of the appraisal

The evaluators should

- follow the pre-defined appraisal plan strictly and apply its criteria consistently throughout the appraisal;
- base their appraisal on the full text of publications and of other documents (not abstracts or summaries), so as to review all of the contents, the methodology employed, the reporting of results, the validity of conclusions drawn from the investigation or report, and evaluate any limitations and potential sources of error in the data;
- document the appraisal in the clinical evaluation report to the extent that it can be critically reviewed by others.

9.3.1. How to evaluate methodological quality and scientific validity

The evaluators should examine the methods used to generate/ collect the data and evaluate the extent to which the observed effect (performance or safety outcomes) can be considered to be due to intervention with the device or due to

- confounding influences (e.g. the natural course of the underlying medical condition / regression to the mean, concomitant treatments)

[13] For an example, refer to Appendix D of the GHTF SG5 document N2R8:2007 on Clinical Evaluation (Appendix D: A Possible Method of Appraisal)

- bias
- random error
- inadequate disclosure of information
- misinterpretation

Some papers considered unsuitable for demonstration of adequate performance because of poor elements of the study design or inadequate analysis may still contain data suitable for safety analysis or vice versa.

Examples of aspects that can be taken into consideration for evaluating the methodological quality and the scientific validity of the evidence are detailed below.

a. Study design of pre-market and post-market clinical investigations

Considerations may need to include:

- adequacy of the sample size and power calculation
- adequacy and relevance of endpoints (including validity of surrogate endpoints, if used)
- adequacy of applied controls (including choice of the study type and of comparators, if applicable)
- prospective randomisation of patients (in case of multiple treatment arms)
- adequacy of inclusion and exclusion criteria, and of stratification of patients (e.g. in respect to age, medical indication, severity of the condition, gender, other prognostic factors)
- distribution of prognostic factors (in case of multiple groups, were the groups comparable for these factors?)
- blinding of patients (may include use of sham devices or sham surgery), professional users, outcome assessors (blinded endpoints)
- adequacy of the follow-up period, including if follow-up was long enough for outcomes to occur, and if follow-up was frequent enough to detect temporary side effects and complications (such as prolonged wound healing)
- reliability of the methods used for quantifying symptoms and outcomes (including validation of the methods)
- adequate recording and reporting of serious adverse events and device deficiencies
- adequate handling of medications and concomitant interventions
- adequacy of procedures for retrieving complete information (e.g. procedures to be applied when contacts with patients are lost, disclosure of reasons for patients leaving the study, conduct of sensitivity analysis for determining if missing data affect conclusions)

The evaluators should verify whether clinical investigations have been defined in such a way as to confirm or refute the manufacturer's claims for the device; and whether these investigations include an adequate number of observations to guarantee the scientific validity of the conclusions.

b. Additional aspects for appraisal of the quality of clinical investigations generated and held by the manufacturer

Where a clinical investigation has been carried out by or on behalf of a manufacturer, it is expected that documentation relating to the design, ethical and regulatory approvals, conduct, results and conclusions of the investigation needed for the clinical evaluation will be available for consideration, as appropriate. These may include:

- the clinical investigation plan;
- clinical investigation plan amendments and the rationale for these changes;
- case report form templates, monitoring and audit records;
- the relevant ethics committee documentation;
- regulatory authority approvals as required by applicable regulations;
- the signed and dated clinical investigation report (for investigations that are terminated);
- the latest intermediate report available and the latest collation on serious adverse events (for investigations that are ongoing);
- when a clinical investigation is conducted outside of the EU, an analysis whether the results are transferable to the European population;
- a gap analysis, when a clinical investigation is conducted to standards different from EN ISO 14155; the gap analysis should contain sufficient information to be read and understood by an independent party.

The clinical investigation plan sets out how the study was intended to be conducted. It contains important information about the study design such as the selection and assignment of participants to treatment, masking (blinding of participants and investigators) and measurement of responses to treatment, which may be important sources of bias that can be assessed and possibly discounted when trying to determine the actual performance of the device. In addition the clinical investigation plan sets out the intended participant follow-up, approaches to statistical analyses and methods for recording outcomes, which may impact on the quality, completeness and validity of results obtained for performance and safety outcomes.

Also, by having the clinical investigation plan, its amendments and the clinical investigation report available, the evaluators will be able to assess the extent to which the investigation was conducted as planned and, where deviations from the original plan have occurred, the impact those deviations had on the veracity of the data generated and the conclusions that can be drawn from the investigation about the performance and safety of the device.

The clinical investigation report should be signed by the sponsor and the coordinating or principal investigator to provide assurance that the report is an accurate reflection of the conduct and results of the clinical investigation.

Another important consideration of the evaluation will be to assess whether the conduct of the investigation was in accordance with applicable regulations, and in accordance with the current applicable ethical standards that have their origin in the Declaration of Helsinki. Clinical investigations not in compliance with applicable ethical standards, medical device standards (for example EN ISO 14155 or comparable standards) or regulations should not be used for demonstration of performance and/or safety of the device. The reasons should be noted in the report.

c. <u>Information derived from vigilance data, device registry data, case series, patient dossiers, and other use data</u>

Evaluators need to consider significant differences between sources of information in respect to:

- procedures used for retrieving information about outcomes
- quality aspects of registers and patient dossiers

In case of information based on vigilance reporting, evaluators should consider that expected undesirable side-effects and complications of devices are not reportable under the vigilance reporting system. Under-reporting or lack of reporting of expected side effects or complications by users is common. Therefore, the vigilance system does not typically deliver adequate information about the true frequency of expected undesirable side-effects and complications. Systematic scientific data are needed for such purposes. Vigilance data, including trend analysis, should be used for identification of unexpected risks.

In case of information based on device registries, case series, retrospective analyses of patient dossiers, and other use data, the retrieval of information about outcomes may be incomplete and unreliable (have all the patients been considered? are the patients representative of the use of the device? did the register/ professional lose contact with patients if they moved on to different professionals? was there a passive or active follow-up of patients by the professionals involved? for how long?). Significant differences may exist between device registries. For instance, they may offer an important or limited coverage of a country. The evaluators should take into account the possibility of patients leaving the coverage of a registry or the follow-up of a professional when experiencing serious adverse outcomes. In routine practice, there are also significant differences in the duration of the follow-up of patients by surgeons and other professionals, and in the quality of patient dossiers and data retrieval.

For clinical experience data it is important that any reports or collations of data (e.g. the manufacturer's PMS reports) contain sufficient information for the evaluators to be able to undertake a rational and objective evaluation of the information and make a conclusion about its significance with respect to the performance and safety of the device in question.

Reports of clinical experience that are not adequately supported by data, such as anecdotal reports or opinions, may contribute to the evaluation, e.g. for the identification of unexpected risks, but should not be used as proof of adequate clinical performance and clinical safety of the device.

d. Data processing and statistics

Aspects to consider may include:

- suitability of methods for data processing (transforming data that are suitable for analysis), converting data to a consistent format, reconstructing missing statistics from other statistics, dealing with missing data;
- exclusions from the analysis and their implications (including disclosure and adequacy of the intention-to-treat and per-protocol populations, disclosure of results from both the intention-to-treat and the per-protocol populations);
- adequacy of statistical methods.

e. Quality assurance

- compliance with Good clinical practice (GCP), such as EN ISO 14155 or equivalent standards;
- compliance with the clinical investigation plan, independent monitoring and auditing;
- compliance with legal requirements.

While a publication in a renowned peer reviewed scientific journal is generally accepted as an indicator of scientific quality, such publication is not considered an acceptable reason for bypassing or reducing appraisal activities.

f. Report quality

Evaluators should consider:

- adequacy of disclosure of methods used
- adequacy of disclosure of data, including
  - completeness of the reporting of adverse events and outcomes
  - sufficient description about the distribution of prognostic factors in the study population and in different study arms
  - disclosure of all the results the study was originally designed to generate
- validity of conclusions drawn by the authors (example: conclusions not in line with the results section of the document)

Possible conflicts of interest of the authors of the publications should also be taken into consideration.

It is recognised that, where manufacturers source clinical investigation data reported in the scientific literature, the documentation readily available to the manufacturer for inclusion in the clinical evaluation is likely to be no more than the published paper itself. In case of missing information, the rating of the methodological quality of a publication may need to be downscaled.

For additional information see Appendix A6 (Appraisal of clinical data - examples of studies that lack scientific validity for demonstration of adequate clinical performance and/or clinical safety).

9.3.2. How to determine the relevance of a data set for the clinical evaluation

When evaluating the relevance of collected data it is important to consider whether the data are intended to directly demonstrate adequate clinical performance and clinical safety of the device (often referred to as pivotal data), or whether the data serves an indirect supportive role.

a. Pivotal data

- Pivotal data must have the data quality necessary for demonstration of adequate clinical performance and clinical safety of the device under evaluation (see Appendix A6, Appraisal of clinical data - examples of studies that lack scientific validity for demonstration of adequate clinical performance and/or clinical safety);
- be generated either with the device under evaluation or with an equivalent device used in its intended purpose (for an equivalent device, equivalence must be demonstrated; see Appendix A1, Demonstration of equivalence).

b. Other data

Data that are not pivotal are generally appraised and weighted for their contribution for purposes such as:

- identifying and defining the current knowledge/ state of the art in the corresponding medical field, so as to define acceptability criteria for the evaluation of the benefit/risk profile and of specific side-effects of the device under evaluation;
- identifying hazards (including hazards due to substances and technologies), individual case reports may be used for identification of new and previously unknown hazards that are associated with the device;
- justifying the validity of criteria used for the demonstration of equivalence (if equivalence is claimed);
- justifying the validity of surrogate endpoints (if surrogate endpoints are used).
- providing input for the planning of pivotal studies.

The corresponding information is, in general, summarised in a literature review section of the clinical evaluation report.

c. Aspects to consider when determining relevance

The table below shows examples of aspects that could be used for determining if and in what respect data are relevant to the clinical evaluation.

Description	Examples
To what extent are the data generated representative of the device under evaluation?	- device under evaluation - equivalent device - benchmark device - other devices and medical alternatives - data concerning the medical conditions that are managed with the device
What aspects are covered?	- pivotal performance data - pivotal safety data - claims - identification of hazards - estimation and management of risks - establishment of current knowledge/ the state of the art - determination and justification of criteria for the evaluation of the risk/benefit relationship - determination and justification of criteria for the evaluation of acceptability of undesirable side-effects - determination of equivalence - justification of the validity of surrogate endpoints
Are the data relevant to the intended purpose of the device or to claims about the device?	- representative of the entire intended purpose with all patient populations and all claims foreseen for the device under evaluation - concerns specific models/ sizes/ settings, or concerns specific aspects of the intended purpose or of claims - does not concern the intended purpose or claims
If the data are relevant to specific aspects of the intended purpose or claims, are they relevant to a specific - model, size, or setting of the device?	- smallest / intermediate / largest size - lowest / intermediate / highest dose - etc.
- user group?	- specialists - general practitioners - nurses

	- adult healthy lay persons - disabled persons - children - etc.
- medical indication (if applicable)?	- migraine prophylaxis - treatment of acute migraine - rehabilitation after stroke - etc.
- age group?	- pre-term infants / neonates / children / adolescents / adults / old age
- gender?	- female/ male
- type and severity of the medical condition?	- early / late stage - mild / intermediate / serious form - acute / chronic phase - etc.
- range of time?	- duration of application or use - number of repeat exposures - duration of follow-up

9.3.3. How to weight the contribution of each data set

Based on their scientific validity and relevance, the data should be weighted according to their relative contributions.

Due to the diversity of medical devices, there is no single, well established method for weighting clinical data:

- the evaluators should identify appropriate criteria to be applied for a specific evaluation;
- these pre-defined criteria should be followed strictly by the evaluators.

Typically, clinical data should receive the highest weighting, when generated through a well designed and monitored randomized controlled clinical investigation (also called randomised controlled trial), conducted with the device under evaluation in its intended purpose, with patients and users that are representative of the target population.

Note: It is acknowledged that randomized clinical investigations may not always be feasible and/or appropriate and the use of alternative study designs may provide relevant clinical information of adequate weighting.

When rejecting evidence, the evaluators should document the reasons (both for studies and reports that have been generated and are held by the manufacturer, and for other documents identified during Stage 1).

10. Analysis of the clinical data (Stage 3)

10.1. General considerations

The goal of the analysis stage is to determine if the appraised data sets available for a medical device collectively demonstrate compliance with each of the Essential Requirements pertaining to the clinical performance and clinical safety of the device, when the device is used according to its intended purpose.

In order to demonstrate compliance, the evaluators should

- use sound methods;
- make a comprehensive analysis;
- determine if additional clinical investigations or other measures are necessary;
- determine PMCF needs.

10.2. Specific considerations

a. Use sound methods

A literature review that describes current knowledge/ the state of the art should be prepared with relevant literature identified during Stage 1 and appraised during Stage 2.

Weighting criteria developed and assigned during the appraisal stage can be used to identify those sets of data, which may be considered to be pivotal.

The methods available for analysing clinical data generally are either qualitative or quantitative. Depending on the nature of the medical device and the circumstances, it is likely that qualitative (i.e. descriptive) methods will need to be used for some devices. Reliance on qualitative methods should be justified. Generally, available clinical data such as numbers of incidents in the post market phase should be assessed quantitatively in relation to current knowledge/ the state of the art.

The results of the pivotal datasets should be explored, looking for consistency of results across particular device performance characteristics and identified risks. If the different datasets report similar outcomes, confidence in the robustness increases. If different results are observed across the datasets, it will be helpful to determine the reason for such differences. Regardless, all data sets should be considered and included. The reviewers should take into account the weighting attributed to data sets during Stage 2 when addressing conflicting information. Where relevant, a rationale should be given for the lack of value of a data set to the evaluation.

In general, data that are not methodologically sound (such as single patient reports) should not be used for demonstration of adequate clinical performance and clinical safety of a device.

For additional information, see Appendix A6 (Appraisal of clinical data - examples of studies that lack scientific validity for demonstration of adequate clinical performance and/or clinical safety).

In exceptional situations, when an evaluation is based on limited data, this shall be described and justified in the clinical evaluation report. See additional information and specific considerations in Appendix A8 (Devices for unmet medical needs - aspects to consider).

b. Make a comprehensive analysis

The evaluators should:

- Determine compliance with each of the Essential Requirements pertaining to the clinical performance and clinical safety of the device. For detailed information concerning specific Essential Requirements, see Appendix A7 (Analysis of the clinical data - compliance to specific Essential Requirements).
- The evaluation includes
  - the adequacy of pre-clinical testing (e.g. bench testing, animal testing) to verify safety
  - risks to patients, users or other persons associated with the intended purpose of the device
  - benefits to patients
  - confirmation that the device achieves the performance(s) intended by the manufacturer, including all claims made by the manufacturer
  - confirmation of usability, that the design adequately reduces the risk of use error as far as possible, and that the design is adequate for the intended users (lay, professional, disabled or other users, if applicable)
  - adequacy of the information materials supplied by the manufacturer, including if risk mitigation measures are correctly addressed in the IFU (handling instructions, description of risks, warnings, precautions, contraindications, instructions for managing foreseeable unwanted situations)
- Take into consideration all products covered by the clinical evaluation and all aspects of their intended purpose. Any gaps in evidence need to be identified, including in respect to information relevant to:
  - understanding the interaction between the device and the body;
  - the comprehensiveness of the available data, taking into account:
    - the entire range of products/ models/ sizes/ settings covered by the evaluation
    - the entire range of conditions of use and of the intended purpose
    - the estimated number of patients exposed to the device
  - the type and adequacy of patient monitoring
  - the number and severity of adverse events
  - the adequacy of the estimation of associated risk for each identified hazard
  - the severity and natural history of the condition being diagnosed or treated
  - current standards of care, including the availability and the benefit/risk profiles of other devices and medical alternatives
- Assess if there is consistency and alignment between the clinical evaluation, the information materials supplied by the manufacturer, and the risk management documentation for the device under evaluation; any discrepancies should be identified in order to ensure that all the hazards and other clinically relevant information have been identified and analysed appropriately.
- Assess if there is consistency between the documents mentioned above and current knowledge/ the state of the art.

c. <u>Determine if additional clinical investigations or other measures are necessary</u>

The evaluators should identify additional clinical investigations or other measures that are necessary in order to generate any missing data and eliminate compliance issues.

Data needed to address the identified gaps should be determined so that conclusions can be drawn with confidence in relation to conformity with the essential requirements, including:

- evaluation of the safety, performance and the benefit/risk profile
- compatibility with a high level of protection of health and safety (that can be determined by considering current knowledge/ the state of the art, with reference to standards and available alternatives, risk minimisation, patient needs and preferences)
- the acceptability of any undesirable side-effects

- the risk of use error and the adequacy of the IFU to the intended users,
- consistency between available information

See Appendix A2 for detailed information on when additional clinical investigations should be carried out.

d. Determine PMCF needs

In order to determine needs, the evaluators should describe residual risks and any uncertainties or unanswered questions. The evaluators should also include aspects such as rare complications, uncertainties regarding medium- and long-term performance, or safety under wide-spread use.

10.3. Where demonstration of conformity based on clinical data is not deemed appropriate

Where demonstration of conformity with Essential Requirements based on clinical data is not deemed appropriate, adequate justification for any such exclusion has to be given:

- The justification must be based on the output of the risk management process. This should include an evaluation of background clinical data identified from the literature, and an appraisal of their relevance to the device under evaluation.
- The device/body interaction, the clinical performances intended and the claims of the manufacturer have to be specifically considered.
- Adequacy of demonstration of conformity with the Essential Requirements based on performance evaluation, bench testing and pre-clinical evaluation in the absence of clinical data has to be duly substantiated.
- A clinical evaluation is still required and the above information and evidence-based justification should be presented in the clinical evaluation report.

11. The clinical evaluation report (CER, Stage 4)

A clinical evaluation report shall be compiled to document the clinical evaluation and its output.

The clinical evaluation report should contain sufficient information to be read and understood by an independent party (e.g. regulatory authority or notified body). Therefore, it should provide sufficient detail for understanding the search criteria adopted by the evaluators, data that are available, all assumptions made and all conclusions reached.

The contents of the clinical evaluation report shall be cross-referenced to the relevant documents that support them. It should be clear which statements are substantiated by which data, and which reflect the conclusions or opinions of the evaluators. The report should include references to literature-based data and the titles and investigational codes (if relevant and available) of any clinical investigation reports, with cross-references to the location in the manufacturer's technical documentation.

The amount of information may differ according to the history of the device or technology. Where a new device or technology has been developed, the report would need to include an overview of the developmental process and the points in the development cycle at which all clinical data have been generated.

It is important that the report outlines the different stages of the clinical evaluation:

- Stage 0, scope of the clinical evaluation:
  - explains the scope and context of the evaluation, including which products/ models/ sizes/ settings are covered by the clinical evaluation report, the technology on which the medical device is based, the conditions of use and the intended purpose of the device;
  - documents any claims made about the device's clinical performance or clinical safety.
- Stage 1, identification of pertinent data:
  - explains the literature search strategy;
  - presents the nature and extent of the clinical data and relevant pre-clinical data that have been identified.
- Stage 2, appraisal of pertinent data:
  - explains the criteria used by the evaluators for appraising data sets;
  - summarises the pertinent data sets (methods, results, conclusions of the authors);
  - evaluates their methodological quality, scientific validity, the relevance for the evaluation, the weighting attributed to the evidence, and any limitations;
  - presents justifications for rejecting certain data or documents.
- Stage 3, analysis of the clinical data:
  - explains if and how the referenced information, such as confirmation of compliance with clinical data requirement from applicable harmonised standards and the clinical data, constitute sufficient clinical evidence for demonstration of the clinical performance and clinical safety of the device under evaluation;
  - explains whether there are adequate data for all aspects of the intended purpose and for all products/ models/ sizes/ settings covered by the clinical evaluation.
  - describes the benefits and risks of the device (their nature, probability, extent, duration and frequency);
  - explains the acceptability of the benefit/risk profile according to current knowledge/ the state of the art in the medical fields concerned, with reference to applicable standards and guidance documents, available medical alternatives, and the analysis and conclusions of the evaluators on fulfilment of all Essential Requirements pertaining to clinical properties of the device (MDD ER1, ER3, ER6; AIMDD ER1, ER2, ER5);
  - analyses if there is consistency between the clinical data, the information materials supplied by the manufacturer, the risk management documentation for the device under evaluation;
  - whether there is consistency between these documents and the current knowledge/ the state of the art;
  - identifies any gaps and discrepancies;
  - identifies residual risks and uncertainties or unanswered questions (such as rare complications, uncertainties regarding medium- and long term performance, safety under wide-spread use) that should be further evaluated during PMS, including in PMCF studies.

The evaluators should check the clinical evaluation report, provide verification that it includes an accurate statement of their analysis and opinions, and sign the report. They should provide their CV and their declaration of interests to the manufacturer.

The clinical evaluation report should be dated and version controlled.

A suggested format for the clinical evaluation report is located at Appendix A9 (Clinical evaluation report - proposed table of contents, examples of contents).

Suggestions for aspects that should be checked for the release of a clinical evaluation report are summarised in Appendix A10 (Proposed checklist for the release of the clinical evaluation report).

Information on declaration of interests can be found in Appendix A11 (Information on declarations of interests).

12. The role of the notified body in the assessment of clinical evaluation reports

The notified body plays a key role in the assessment and verification of clinical evaluation reports and supporting documentation provided by medical device manufacturers to support demonstration of conformity of a device with the Essential Requirements of the relevant Directive.

Detailed recommendations for notified bodies are given in Appendix A12 (Activities of notified bodies). These include:

- guidance for notified bodies on the assessment of clinical evaluation reports provided by medical device manufacturers as part of technical documentation (including design dossiers) and
- guidance for notified body in development of their internal procedures for assessment of clinical aspects relating to medical devices.

In addition, documents of the Notified Bodies Operations Group (NBOG) should also be consulted. NBOG documents include best practice guides, checklists and forms.

Pursuant to section 6a of Annex I MDD and to section 5a of Annex 1 AIMDD, the demonstration of conformity with the Essential Requirements must include a clinical evaluation conducted in accordance with Annex X of Directive 93/42/EEC or with Annex 7 AIMDD. This is applicable for all classes of medical device.

Where demonstration of conformity with Essential Requirements based on clinical data is not deemed appropriate this must be adequately justified by the manufacturer and based on the output of the risk management process. The device-body interaction, the intended purpose and the claims of the manufacturer have to be specifically considered. The adequacy of demonstration of conformity based on performance evaluation, bench testing and pre-clinical evaluation in the absence of clinical data must be duly substantiated. The notified body must review the manufacturer’s justification, the adequacy of data presented and whether or not conformity is demonstrated. Nevertheless a clinical evaluation is still required and the above information and an evidenced justification should be presented as the clinical evaluation for the device in question.

Appendices

A1. Demonstration of equivalence

Pursuant to Annex X of Directive MDD and Annex 7 AIMDD, the evaluation of clinical data (i.e. the clinical evaluation), where appropriate taking account of any relevant harmonised standards, must follow a defined and methodologically sound procedure based on:

1. either a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device, where:
   - there is demonstration of equivalence of the device to the device to which the data relates, and
   - the data adequately demonstrate compliance with the relevant Essential Requirements.
2. or a critical evaluation of the results of all clinical investigations made.
3. or a critical evaluation of the combined clinical data provided from 1 and 2.

Clinical, technical and biological characteristics shall be taken into consideration for the demonstration of equivalence:

- Clinical:
  - used for the same clinical condition (including when applicable similar severity and stage of disease, same medical indication), and
  - used for the same intended purpose, and
  - used at the same site in the body, and
  - used in a similar population (this may relate to age, gender, anatomy, physiology, possibly other aspects), and
  - not foreseen to deliver significantly different performances (in the relevant critical performances such as the expected clinical effect, the specific intended purpose, the duration of use, etc.).
- Technical:
  - be of similar design, and
  - used under the same conditions of use, and
  - have similar specifications and properties (e.g. physicochemical properties such as type and intensity of energy, tensile strength, viscosity, surface characteristics, wavelength, surface texture, porosity, particle size, nanotechnology, specific mass, atomic inclusions such as nitrocarburising, oxidability), and
  - use similar deployment methods (if relevant), and
  - have similar principles of operation and critical performance requirements.
- Biological: Use the same materials or substances in contact with the same human tissues or body fluids.

  Exceptions can be foreseen for devices in contact with intact skin and minor components of devices; in these cases risk analysis results may allow the use of similar materials taking into account the role and nature of the similar material. Different aspects of equivalence and compliance to different Essential Requirements can be affected by materials. Evaluators should consider biological safety (e.g. in compliance to ISO 10993) as well as other aspects necessary for a comprehensive demonstration of equivalence. A justification explaining the situation should be provided for any difference.

For assuming equivalence,

- equivalence can only be based on a single device[14];
- all three characteristics (clinical, technical, biological) need to be fulfilled;
- similar means that no clinically significant difference in the performance and safety of the device would be triggered by the differences between the device under evaluation and the device presumed to be equivalent;
- the differences between the device under evaluation and the device presumed to be equivalent need to be identified, fully disclosed, and evaluated; explanations should be given why the differences are not expected to significantly affect the clinical performance and clinical safety of the device under evaluation;
- the manufacturer should investigate if the medical device presumed to be equivalent has been manufactured via a special treatment (e.g. a surface modification, a process that modifies material characteristics); if this is the case, the treatment could cause differences in respect to technical and biological characteristics; this should be taken into account for the demonstration of equivalence and documented in the CER;
- if measurements are possible, clinically relevant specifications and properties should be measured both in the device under evaluation and the device presumed to be equivalent, and presented in comparative tabulations;
- comparative drawings or pictures should be included in order to compare shapes and sizes of elements that are in contact with the body;
- the manufacturer is expected to:
  - include the supporting non-clinical information (e.g. pre-clinical study reports) in the technical documentation of the device, and
  - in the clinical evaluation report, summarise the information and cite its location in the technical documentation;
- for the evaluation of the technical characteristics, devices that achieve the same therapeutic result by different means cannot be considered equivalent;
- for the evaluation of the biological characteristics:
  - when a detailed chemical characterisation of materials in contact with the body is needed, ISO 10993-18 Annex C can be used to show toxicological equivalence but this is just a part of the evaluation of the biological criteria;
  - sourcing and manufacturing procedures may adversely affect impurity profiles; analytical methods chosen to characterise medical devices should appropriately take into consideration knowledge concerning expected impurity profiles (tests may have to be repeated when production methods or sourcing are changed);
  - it may be necessary to show from histopathological studies that the same host response is achieved in vivo in the intended application and the intended duration of contact;
  - for animal tests, differences between species may limit the predictive value of the test; the choice of the test and its predictive value should be justified;
  - abrasion, if relevant, and host response to particles may also need to be considered.
- the only clinical data that are considered as relevant are the data obtained when the equivalent device is a CE-marked medical device used in accordance with its intended purpose as documented in the IFU.

[14] Evaluators may wish to refer to several devices that are equivalent. In such a situation, equivalence of every single device to the device under evaluation should be fully investigated, demonstrated, and described in the clinical evaluation report.

Note: Exceptions can be considered. When the equivalent device is not a CE-marked device, information concerning the regulatory status of the equivalent device and a justification for the use of its data should be included in the clinical evaluation report. The justification should explain if the clinical data is transferrable to the European population, and an analysis of any gaps to good clinical practices (such as ISO 14155) and relevant harmonised standards.

A2. When should additional clinical investigations be carried out?

a. How should manufacturers and evaluators decide if there is sufficient clinical evidence?

When clinical data are required in order to draw conclusions as to the conformity of a device to the Essential Requirements, the data need to be in line with current knowledge/ the state of the art, be scientifically sound, cover all aspects of the intended purpose, and all products/ models/ sizes/ settings foreseen by the manufacturer.

If gaps are present that cannot be addressed by other means, clinical investigations should be planned and carried out.

b. Considerations

Implants and high-risk devices, those based on technologies where there is little or no experience, and those that extend the intended purpose of an existing technology (i.e. a new clinical use) are most likely to require clinical investigation data.

For compliance with Annex X section 1.1.a MDD and Annex 7 AIMDD, clinical investigations with the device under evaluation are required for implantable and class III devices unless it can be duly justified to rely on existing clinical data alone.

The need for clinical investigations depends on the ability of the existing data to adequately address the benefit/risk profile, claims, and side-effects in order to comply with the applicable Essential Requirements. Clinical investigations may therefore also be required for other devices, including for devices in class I and class IIa, and for class IIb devices that are not implantable.

When deciding if additional clinical investigations need to be carried out, the manufacturer should perform a detailed gap analysis. The gap analysis should determine whether the existing data are sufficient to verify that the device is in conformity with all the Essential Requirements pertaining to clinical performance and clinical safety.

Special attention should be given to aspects such as:

- new design features, including new materials,
- new intended purposes, including new medical indications, new target populations (age, gender, etc.),
- new claims the manufacturer intends to use,
- new types of users (e.g. lay persons),
- seriousness of direct and/or indirect risks,
- contact with mucosal membranes or invasiveness,
- increasing duration of use or numbers of re-applications,
- incorporation of medicinal substances,
- use of animal tissues (other than in contact with intact skin),

- issues raised when medical alternatives with lower risks or more extensive benefits to patients are available or have become newly available[15],
- issues raised when new risks are recognised (including due to progress in medicine, science and technology)
- whether the data of concern are amenable to evaluation through a clinical investigation,
- etc.

Data on the safety and performance of other devices and alternative therapies, including benchmark devices and equivalent devices, should be used to define the state of the art or identify hazards due to substances and technologies. This will allow the clinical data requirements to be established more precisely in relation to the intended purpose of a device. Precision in this analysis and the choice of selected medical indications and target populations may reduce the amount of clinical data needed from additional clinical investigations.

A3. Device description - typical contents

The description should be detailed enough to allow for a valid evaluation of the state of compliance with Essential Requirements, the retrieval of meaningful literature data and, if applicable, the assessment of equivalence to other devices described in the scientific literature:

- name, models, sizes, components of the device, including software and accessories
- device group to which the device belongs (e.g. biological artificial aortic valve)
- whether the device is being developed/ undergoing initial CE-marking/ is CE-marked
- whether the device is currently on the market in Europe or in other countries, since when, number of devices placed on the market
- intended purpose of the device
  - exact medical indications (if applicable)
  - name of disease or condition/ clinical form, stage, severity/ symptoms or aspects to be treated, managed or diagnosed
  - patient populations (adults / children / infants, other aspects)
  - intended user (use by health care professional / lay person)
  - organs / parts of the body / tissues or body fluids contacted by the device
  - duration of use or contact with the body
  - repeat applications, including any restrictions as to the number or duration of re-applications
  - contact with mucosal membranes/ invasiveness/ implantation
  - contraindications
  - precautions required by the manufacturer
  - single use / reusable
  - other aspects
- general description of the medical device including
  - a concise physical and chemical description
  - the technical specifications, mechanical characteristics
  - sterility
  - radioactivity

[15] See Appendix A7.2 (Conformity assessment with requirement on acceptable benefit/risk profile)

- how the device achieves its intended purpose
- principles of operation
- materials used in the device with focus on materials coming in contact (directly or indirectly) with the patient/ user, description of body parts concerned
- whether it incorporates a medicinal substance (already on the market or new), animal tissues, or blood components, the purpose of the component
- other aspects

- whether the device is intended to cover medical needs that are otherwise unmet/ if there are medical alternatives to the device / if the device is equivalent to an existing device, with a description of the situation and any new features
- if the device is intended to enter the market based on equivalence:
  - name, models, sizes, settings components of the device presumed to be equivalent, including software and accessories
  - whether equivalence has already been demonstrated
- Intended performance, including the technical performance of the device intended by the manufacturer, the intended clinical benefits, claims regarding clinical performance and clinical safety that the manufacturer intends to use
- For devices based on predecessor devices: Name, models, sizes of the predecessor device, whether the predecessor device is still on the market, description of the modifications, date of the modifications.
- The current version number or date of the information materials supplied by the manufacturer (label, IFU, available promotional materials and accompanying documents possibly foreseen by the manufacturer).

A4. Sources of literature

There are different sources of clinical literature that can be searched for clinical evaluation. A comprehensive search strategy is required, normally involving multiple databases. The search strategy should be documented and justified. Important sources include the following:

- Scientific literature databases
  - MEDLINE or Pubmed can provide a good starting point for a search. However, with possibly incomplete coverage of European Journals and reduced search features, comprehensiveness may not necessarily be guaranteed.
  - Additional databases may need to be used to ensure adequate coverage of devices and therapies in use in Europe, to identify relevant clinical trials and publications of user experience[16], and to facilitate searches by device name and manufacturer (e.g. EMBASE/Excerpta Medica, the Cochrane CENTRAL trials register, etc.).
  - Information coverage and search features available in scientific databases can change with time. Criteria for selecting adequate databases therefore need to be defined and re-evaluated on a regular basis.
- Internet searches

[16] Studies yielding negative results or user experience (such as publications about risks that are based on a case or a case series) may not qualify for publication in high impact medical journals. Low impact journals available to European users and other sources may therefore need to be searched.

Searches provide important data, examples include information on:

- harmonised standards and other standards applicable to the device in question and containing information on clinical performance and clinical safety.
- Field safety corrective actions for the equivalent and/or other devices. These can be found on manufacturer's web sites, internet sites of European Competent authorities, the U.S. Food and Drug Administration (FDA), possibly other sites.
- Implant registry reports.
- Documents available in systematic review databases (e.g. the Cochrane Database of Systematic Reviews, Prospero international prospective register of systematic reviews).
- Expert documents produced by professional medical associations that are important for assessment of current knowledge/ the state of the art, including clinical practice guidelines and consensus statements.
- Meta-analyses and reviews of health technology assessment (HTA) institutes and networks.
- Identification of studies via the WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov.

- Non-published data

  Non published data are important for many devices and retrieval of such data should be considered, including for monitoring of any changes, e.g.

  - The label and IFU of the equivalent device (if equivalence is claimed by the manufacturer) and/or of benchmark devices and other devices.
  - Data provided to manufacturers from implant registries.
  - Data presented at congresses.

- Citations referenced in scientific literature can be important and should be screened. Literature found to be relevant is likely to cite other literature that is of direct interest to the manufacturer. Additionally, it may be necessary to retrieve some of the referenced literature in order to appraise the scientific quality of a document.

A5. Literature search and literature review protocol, key elements

The output of the literature search and literature review are:

- Literature on the device in question and the equivalent device.

  Note: If the manufacturer holds own clinical data for the device in question (e.g. own pre-market clinical investigations, PMCF Studies, other PMS data), the literature is considered together with those data for consistent appraisal and overall analysis.
- A review of the current knowledge/ the state of the art needed for the proper conduct of the appraisal and analysis of the clinical data of the device under evaluation and the equivalent device (i.e. applicable standards and guidance documents, information on the medical conditions that are relevant to the clinical evaluation, therapeutic/ management/ diagnostic options available for the intended patient population, etc.).

The literature collected may relate directly to the device in question (e.g. publications of clinical investigations of the device in question that have been performed by third parties, its side effects or complications, incidence reports) and/or to equivalent device, benchmark devices, other devices and medical alternatives available to the intended patient population.

The literature search and literature review protocol should address the background to and the objective of the review, specifying the literature review questions and the methods for identification, selection, collection and appraisal of the relevant publications needed to address them. It should include the literature search methodology (literature search protocol).

The selection of literature should be objective and justified, i.e. include all relevant data, both favourable and unfavourable. With respect to the clinical evaluation, it is important that the clinical evaluators are able to assess the degree to which the selected papers reflect the intended application/ use of the device.

Objective, non-biased, systematic search and review methods should be used. Examples are:

- PICO (patient characteristics, type of intervention[17], control, and outcome queries)
- Cochrane Handbook for Systematic Reviews of Interventions
- PRISMA (The Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement
- MOOSE Proposal (Meta-analysis Of Observational Studies in Epidemiology)

The protocol should specify the elements described below, addressing the background, objective, and methods for identification, selection, and collection of the relevant publications to address the literature review questions.

A5.1. Background to the literature search and the literature review

This section documents the importance of and rationale for the literature review and includes, but is not limited to:

- Device name/model
- Importance of literature review to risk management process. The literature review will provide data on current interventions[18] for the intended patient population (state of the art) in order to give input to the assessments of acceptable benefit/risk profiles, what is currently considered as providing a high level of protection of health and safety and what are considered acceptable side-effects.
- Previous literature reviews
- Importance of review to risk management process
- Previous literature searches conducted by the manufacturer
- If including equivalent or benchmark devices, name and model of the devices.
- The CER will need to establish equivalence to the device under evaluation or the relevance of benchmark devices to the clinical evaluation.

A5.2. Objective

This section documents the research question(s), which should be consistent with the scope of the clinical evaluation and carefully constructed using a process (e.g. PICO):

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[17] The term Intervention includes therapies, diagnostic measures, measures for the management of diseases or medical conditions.

[18] Includes therapies, diagnostic measures, measures for the management of diseases or medical conditions.

- Population(s)/disease(s) or condition(s)
- Intervention(s)
- Comparator group(s)/control(s)
- Outcome(s)/endpoint(s)

The inputs for the review question(s) (e.g. PICO) are the device description and the intended performance of the device including any claims on clinical performance and clinical safety which the manufacturer wants to use. Also information from the risk management process is needed as an input.

A5.3. Methods

The methods section of the protocol documents the plans for literature search, study selection, data collection, and analysis methods. It defines the literature search strategy and the inclusion/exclusion criteria for the documents found.

The protocol should include:

- the literature search methodology

  The purpose of a literature search protocol is to plan the search before execution. It should be developed and executed by persons with expertise in information retrieval, having due regard to the scope of the clinical evaluation set out by the manufacturer. The involvement of information retrieval experts will help to optimize literature retrieval to identify all relevant published literature.

  The importance of a literature search protocol is for critical appraisal of the methods. The search strategy should be based on carefully constructed review questions.
- the sources of data that will be used and a justification for their choice (see Appendix A4, Sources of literature)
- the extent of any searches of scientific literature databases (the database search strategy);
- attempts to identify all published literature
- which electronic databases are to be searched, with justification
- the extent of any Internet searching and searching non-published information, including the search strategy and justification
- exact search terms and any limits
- limits for start and end dates of each search
- the selection/criteria (such as inclusion/exclusion criteria) to be applied to published literature and justification for their choice
- strategies for addressing the potential for duplication of data across multiple publications;
- strategies for avoiding retrieving publications of data generated and already held by the manufacturer
- the data collection plan that defines data management practices to ensure data integrity during extraction (e.g. quality control/second review of extracted data by additional reviewer)
- the appraisal plan, which defines the methods for appraising each publication, including the relevance of the data to the intended clinical use and the methodological quality of the data
- the analysis plan, which defines the methods for analysing the data including data processing and transformation

Any deviations from the literature search protocol should be noted in the literature search report.

A6. Appraisal of clinical data - examples of studies that lack scientific validity for demonstration of adequate clinical performance and/or clinical safety

a. Lack of information on elementary aspects:

This includes reports and publications that omit disclosure of

- the methods used
- the identity of products used
- numbers of patients exposed
- what the clinical outcomes were
- all the results the clinical study or investigation planned to investigate
- undesirable side-effects that have been observed
- confidence intervals/ calculation of statistical significance
- if there are intent-to-treat and per protocol populations: definitions and results for the two populations

b. Numbers too small for statistical significance

Includes publications and reports with inconclusive preliminary data, inconclusive data from feasibility studies, anecdotal experience, hypothesis papers and unsubstantiated opinions.

c. Improper statistical methods

This includes

- results obtained after multiple subgroup testing, when no corrections have been applied for multiple comparisons.
- calculations and tests based on a certain type of distribution of data (e.g. Gaussian distribution with its calculations of mean values, standard deviations, confidence intervals, t-tests, others tests), while the type of distribution is not tested, the type of distribution is not plausible, or the data have not been transformed. Data such as survival curves, e.g. implant survival, patient survival, symptom-free survival, are generally unlikely to follow a Gaussian distribution.

d. Lack of adequate controls

In the following situations, bias or confounding are probable in single arm-studies and in other studies that do not include appropriate controls:

- when results are based on subjective endpoint assessments (e.g. pain assessment).
- when the endpoints or symptoms assessed are subject to natural fluctuations (e.g. regression to the mean when observing patients with chronic diseases and fluctuating symptoms, when natural improvement occurs, when the natural course of the disease in a patient is not clearly predictable).
- when effectiveness studies are conducted with subjects that are likely to take or are foreseen to receive effective co-interventions (including over-the-counter medication and other therapies).
- when there may be other influencing factors (e.g. outcomes that are affected by variability of the patient population, of the disease, of user skills, of infrastructure available for planning/ intervention/ aftercare, use of prophylactic medication, other factors).

- when there are significant differences between the results of existing publications, pointing to variable and ill controlled influencing factors.

In the situations described above, it is generally not adequate to draw conclusions based on direct comparisons with external or historic data (such as drawing conclusions by comparing data from a clinical investigation with device registry data or with data from published literature).

Different study designs may allow direct comparisons and conclusions to be drawn in these situations, such as randomised controlled design, cross-over design, or split-body design.

e. Improper collection of mortality and serious adverse events data

Demonstration of adequate benefits and safety is sometimes based on mortality data or occurrence of other serious outcomes that limit a subject's ability to live in his home and be available for follow-up contacts. In this type of study,

- consent of the subjects for contacting reference persons/ institutions for retrieval of medical information should be obtained during recruitment; when subjects can no longer be found, outcomes should be investigated with the reference persons/ institutions;
- the consequences of missing data on the results should be analysed (e.g. with a sensitivity analysis); alternatively, when patients can no longer be found and their outcomes cannot be identified, they should be considered to meet the SAE endpoint under investigation (e.g. the mortality endpoint of a study).

In mortality studies (and other studies addressing serious outcomes) procedures for investigating serious patient outcomes, numbers of subjects lost to follow-up, reasons why subjects leave the study, and the results of sensitivity analysis should be fully disclosed in reports and publications.

f. Misinterpretation by the authors

Includes conclusions that are not in line with the results section of the report or publication, such as

- reports and publications not correctly addressing lack of statistical significance/ confidence intervals that encompass the null hypothesis.
- effects too small for clinical relevance.

g. Illegal activities

Includes clinical investigations not conducted in compliance with local regulations. Clinical investigations are generally expected to be designed, conducted and reported in accordance with EN ISO 14155 or to a comparable standard, and in compliance with local regulations and the Declaration of Helsinki.

A7. Analysis of the clinical data - compliance to specific Essential Requirements

While this appendix describes the needs for the clinical evaluation (MDD ER1, ER3, ER6; AIMDD ER1, ER2, ER5), there may be additional essential requirement(s) that need support of sufficient clinical evidence for the conformity assessment.

A7.1. Conformity assessment with requirement on safety

(MDD ER1 / AIMDD ER1)

The information materials supplied by the manufacturer (including label, IFU, available promotional materials including accompanying documents possibly foreseen by the manufacturer), should be reviewed to ensure they are consistent with the relevant clinical data appraised in stage 2 and that all the hazards, information on risk mitigation and other clinically relevant information have been identified appropriately.

Input from the risk management and the use of standards:

- Risk management documents should determine if all identified hazards are fully covered by harmonised standards or other relevant standards or if there are gaps needed to be covered by clinical data.
- Risk management documents should determine if all identified risks relating to patient treatment, method of operation of the device or risks relating to usability have been minimised or if there are question regarding clinical risks that need to be solved.
- Harmonised standards are generally expected to be applied in full in order to confer a presumption of conformity.
- If technical developments provide a higher level of safety than current harmonised standards, then the higher level of safety should be prioritised in order to meet the Essential Requirements on reducing the risks as far as possible, that risks must be compatible with a high level of protection of health and safety, and that side effects must be acceptable (MDD ER2 and ER3 and ER6; AIMDD ER1 and ER5).

Examples:

- Electrical hazards should be covered by compliance to EN 60601-1 and applicable collateral standards regarding medical electrical equipment, so that the device will not compromise the safety and health of patients or users. Under these circumstances, residual risks regarding electrical hazards are acceptable and additional clinical data are not needed unless negative issues are detected during PMS activities.
- Harmonised standards on usability (EN 62366 and if applicable EN 60601-1-6) are expected to be applied to ensure that usability aspects are taken into consideration during the device development. However, they do not give guidance on a detailed level of design, while usability aspects are known to cause or contribute to a large portion of incidents. Therefore, clinical data may be needed to prove that the risk of use error, due to the ergonomic features of the device and the environment in which the device is intended to be used, has been reduced as far as possible.

A7.2. Conformity assessment with requirement on acceptable benefit/risk profile (MDD ER1 / AIMDD ER1)

It is expected,

- that the clinical evaluation demonstrates that any risks which may be associated with the intended purpose are minimised and acceptable when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety; and
- that the IFU correctly describe the intended purpose of the device as supported by sufficient clinical evidence; and
- that the IFU contain correct information to reduce the risk of use error, information on residual risks and their management as supported by sufficient clinical evidence (e.g.

handling instructions, description of risks, warnings, precautions, contraindications, instructions for managing foreseeable unwanted situations).

a. Evaluation of the description of the intended purpose of the device

The information materials supplied by the manufacturer (including label, IFU, available promotional materials including accompanying documents possibly foreseen by the manufacturer) should be reviewed. The evaluators should evaluate if the description provided by the manufacturer correctly identifies those medical conditions and target groups for which conformity with the relevant Essential Requirements has been demonstrated through sufficient clinical evidence. When reading the IFU, there should be no uncertainty for users as to when a given medical condition or medical indication or target population is covered by the CE marking or when it falls entirely under the user's own responsibility (off label use).

b. Evaluation of the device's benefits to the patient

Positive impacts of a device on the health of an individual should be meaningful (relevant for the patient) and measurable. The nature, extent, probability and duration of benefits should be considered. Benefits may include:

- positive impact on clinical outcome (such as reduced probability of adverse outcomes, e.g. mortality, morbidity; or improvement of impaired body function),
- the patient's quality of life (significant improvements, including by simplifying care or improving the clinical management of patients, improving body functions, providing relief from symptoms),
- outcomes related to diagnosis (such as allowing a correct diagnosis to be made, provide earlier diagnosis of diseases or specifics of diseases, or identify patients more likely to respond to a given therapy),
- positive impact from diagnostic devices on clinical outcomes, or
- public health impact (such as to the ability of a diagnostic medical device to identify a specific disease and therefore prevent its spread, to identify phases, stages, location, severity or variants of disease, predict future disease onset).

c. Quantification of benefit(s) to the patients

Defining specified *endpoints* is indispensable for setting up clinical investigations and properly performing the identification, appraisal, and analysis of the clinical data.

- Benefit(s) are often evaluated along a scale or according to specific endpoints or criteria (types of benefits), or by evaluating whether a pre-identified health threshold was achieved. The change in subjects' condition or clinical management as measured on that scale, or as determined by an improvement or worsening of the endpoint, determines the magnitude of the benefit(s) in subjects. Variation in the magnitude of the benefit across a population may also be considered.
- The clinical relevance of these changes should be discussed and justified.
- Ideally, these parameters should be directly clinically relevant.
- In certain cases benefits can be assumed when validated surrogate endpoints are met (such as obtaining certain results with laboratory tests or measurements of anatomical or physiological properties).

- Based on the current state of medical knowledge, the evaluators shall justify and document the clinical relevance of endpoints used for the clinical evaluation of a device and demonstrate the validity of all surrogate endpoints (if surrogate endpoints have been used).

The probability of the patient experiencing one or more benefit(s) is another important aspect of evaluating benefits and the clinical performance of a device.

- Based on the clinical data provided and on a sound statistical approach, a reasonable prediction of the proportion of "responders" out of the target group or subgroups should be made.
- The data may show that a benefit may be experienced only by a small proportion of patients in the target population, or, on the other hand, that a benefit may occur frequently in patients throughout the target population. It is also possible that the data will show that different patient subgroups are likely to experience different benefits or different levels of the same benefit.
- If the subgroups can be identified, the device may be indicated for those subgroups only.
- In some cases, however, the subgroups may not be identifiable. Magnitude and probability of clinical benefits will have to be put together when weighing benefits against risks.
- A large benefit experienced by a small proportion of subjects may raise different considerations than does a small benefit experienced by a large proportion of subjects. For example, a large benefit, even if experienced by a small population, may be significant enough to outweigh risks, whereas a small benefit may not, unless experienced by a large population of subjects.

The duration of effect(s) (i.e. how long the benefit can be expected to last for the patient, if applicable to the device)

- The duration should be characterised (for example as a statistical distribution) on the basis of sound clinical data and appropriate statistical approaches.
- PMCF will be decisive to refine and corroborate reasonable predictions over time.
- The mode of action may play an important role: Some treatments are curative, whereas, some may need to be repeated frequently over the patient's lifetime.
- To the extent that it is known, the duration of a treatment's effect may directly influence how its benefit is defined. Treatments that must be repeated over time may introduce greater risk, or the benefit experienced may diminish each time the treatment is repeated.
- The evaluation of the duration of effect should take into consideration current knowledge/ the state of the art and available alternatives.

d. <u>Evaluation of the clinical risks of devices</u>

The risk management documents are expected to identify the risks associated with the device and how such risks have been addressed. The clinical evaluation is expected to address the significance of any risks that remain after design risk mitigation strategies have been employed by the manufacturer.

PMS reports are compiled by the manufacturer and often include details of the device's regulatory status (countries in which the device is marketed and date of commencement of supply), regulatory actions undertaken during the reporting period (e.g. recalls, notifications), a tabulation of incidents (particularly serious adverse events/ incidents, including deaths, stratified into whether the manufacturer considers them to be device-related or not) and estimates of the incidence of incidents.

Post-marketing data about incidents are generally more meaningful when related to usage but caution is needed. The extent of user reporting in the medical devices vigilance system may vary considerably between countries, users, and type of incident. Considerable under-reporting by users is expected. However, the analyses of data within these reports may, for some devices, provide reasonable assurance of both clinical safety and performance.

It may be helpful to provide a table summarising device-related incidents, paying particular attention to serious adverse events/ incidents, with comments on whether observed device-related incidents are predictable on the basis of the mode of action of the device.

To demonstrate the extent of the probable risk(s)/ harm(s), the following factors - individually and in the aggregate - should be addressed:

- Nature severity, number and rates of harmful events associated with the use of the device:
  - Device-related serious adverse events/ incidents: Those events that may have been or were attributed to the use of the device and produce an injury or illness that is life-threatening, results in permanent impairment or damage to the body, or requires medical or surgical intervention to prevent permanent harm to the body.
  - Device-related non-serious/ non-reportable harmful events: Those events that may have been or were attributed to the use of the device and that do not meet the criteria for classification as a device-related serious adverse events/ incidents.
  - Procedure-related incidents: Harm to the patient that results from use of the device but is not caused by the device itself. For example, anaesthetic-related complications associated with the implantation of a device.
- Probability of a harmful event: The proportion of the intended population that would be expected to experience a harmful event; whether an event occurs once or repeatedly may be factored into the measurement of probability.
- Duration of harmful events (i.e., how long the adverse consequences last): Some devices can cause temporary, minor harm; some devices can cause repeated but reversible harm; and other devices can cause permanent, debilitating injury. The severity of the harm should be considered along with its duration.
- Risk from false-positive or false-negative results for diagnostic medical devices :
  - if a diagnostic device gives a false-positive result, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease;
  - if a diagnostic device gives a false-negative result, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition;
  - other risks associated with false-positives and false-negatives.
- It is also important to look at the totality of the harmful events associated with the device. The number of different types of harmful events that can potentially result from using the device and the severity of their aggregate effect has to be considered. When multiple harmful events occur at once, they have a greater aggregate effect.
- Comment specifically on any clinical data that identifies hazards not previously considered in the risk management documentation, outlining any additional mitigation required (e.g. design modification, amendment of information materials supplied by the manufacturer such as inclusion of contraindications in the IFU).

e. <u>Evaluation of acceptability of the benefit/risk profile</u>

- Evaluate if the clinical data on benefits and risks are acceptable for all medical conditions and target populations covered by the intended purpose when compared with the current

state of the art in the corresponding medical field and whether limitations need to be considered for some populations and/or medical conditions.

- The current knowledge/ state of the art therefore needs to be identified and defined, possibly also relevant benchmark devices and medical alternatives available to the target population. Typically, documentation of the clinical background shall include the following information:
  - clinical background
    - information on the clinical condition(s) to be treated, managed, or diagnosed
    - prevalence of the condition(s)
    - natural course of the condition(s)
  - other devices, medical alternatives available to the target population, including evidence of clinical performance and safety
    - historical treatments
    - medical options available to the target population (including conservative, surgical and medicinal)
    - existing devices, benchmark devices
- Sufficient detail of the clinical background is needed so that the state of the art can be accurately characterised in terms of clinical performance, and clinical safety profile. The selection of clinical data that characterises the state of the art should be objective and not selective of data on the basis of being favourable for the device under evaluation. Information should be provided on alternative approaches that have been used or considered and their benefits and drawbacks. Deficiencies in current therapies should be identified from a critical and comprehensive review of relevant published literature. The literature review should demonstrate if the device addresses a significant gap in healthcare provision. Where there is no such clinical need, the design solution needs to show an improved or at least equivalent benefit/risk profile compared to existing products or therapies.
- If or when treatment comparability versus accepted therapy is not available at the time of placing on the market, this should be clearly described in the device IFU.
- Even if a device cannot compete with an agreed first-line treatment or the best in class, it may add to the portfolio of acceptable treatments, as even a first-line treatment will likely have contraindications or non-responders.
- Devices, that might not be best-in-class, might provide sufficient clinical evidence for an acceptable benefit/risk-profile for specific, defined subgroups or even superior clinical performance under specific conditions (e.g. emergency outdoor conditions).
- The position within the treatment portfolio has to be specified properly in the clinical evaluation report and other relevant documentation.

  Example: A system for deep brain stimulation has a proven effectiveness for the treatment of depression. However, the implantation of electrodes in the brain is associated with major risks. Less invasive treatment options are available to patients suffering from depression. Taking into account the available treatment portfolio, the manufacturer has limited the medical indication of the device to "therapy resistant depression", which is reflected in the IFU and in other relevant documentation.

A7.3. Conformity assessment with requirement on performance (MDD ER3 / AIMDD ER2)

The devices must achieve the performances intended by the manufacturer. The ability of a medical device to achieve its intended purpose as claimed by the manufacturer needs to be demonstrated, including any direct or indirect medical effects on humans as well as the clinical benefit on patients resulting from the technical or functional, including diagnostic characteristics of a device, when used as intended by the manufacturer.

Clinical performance includes any claims about clinical properties and safety of the device that the manufacturer intends to use. It is expected:

- that the devices achieve their intended performances during normal conditions of use, and
- that the intended performances are supported by sufficient clinical evidence.

Evaluation of clinical performance can vary widely between device groups, especially between therapeutic and diagnostic devices. The following list gives examples of performance data relevant particularly to diagnostic devices:

- Reproducibility of independent acquisition of images (same patient, same machine, different operator and interpreter).
- Reproducibility of independent reporting of images (same patient, same machine, same images, different interpreter/analyser).
- Diagnostic sensitivity and specificity of the test for major clinical indications; positive and negative predictive values according to varying pre-test probabilities.
- Comparisons of performance of new iterations of diagnostic software against previous software versions.
- Normal values by age and gender, covering all groups in which the diagnostic system may be used.

A7.4. Conformity assessment with requirement on acceptability of undesirable side-effects (MDD ER6 / AIMDD ER5)

Any undesirable side-effect must constitute an acceptable risk when weighed against the performances intended.

In order to evaluate the acceptability of the side-effects of a device:

- there needs to be clinical data for the evaluation of the nature, severity and frequency of potential undesirable side-effects;
- the clinical data should contain an adequate number of observations (e.g. from clinical investigations or PMS) to guarantee the scientific validity of the conclusions relating to undesirable side-effects and the performance of the device;
- in order to evaluate if undesirable side-effects are acceptable, consideration has to be given to the state of the art, including properties of benchmark devices and medical alternatives that are currently available to the patients, and reference to objective performance criteria from applicable standards and guidance documents.

If there is lack of clinical data or an insufficient number of observations, conformity with the requirement on acceptability of undesirable side-effects is not fulfilled.

Example:

A reasonable probability (80%) of observing at least one event of an undesirable side-effect when 15 subjects are studied requires a side-effect with an actual probability of 10%. If only 15 patients have been studied, from a statistical point of view, there could be serious side-effects with an actual probability of 10% that have not had a reasonable chance to be detected. The device would only be acceptable (for any type and severity of undesirable side-effects), if that magnitude is acceptable when weighted against the performance of the device and the current state of the art.

The table below shows corresponding numbers for undesirable side-effects with an actual probability of 10%, 5% and 1%.

	Case 1	Case 2	Case 3
Chance of observing at least 1 event (P)	80%	80%	80%
Actual probability of event	10%	5%	1%
Number of subjects studied (n)	15	32	161

The threshold proposed as acceptable for any new device will depend on the severity and detectability of side effects concerned.

A8. Devices for unmet medical needs - aspects to consider

Like all medical devices, medical devices for unmet medical needs must fully comply with the Essential Requirements in order to be CE-marked. The evaluators should assess whether devices deliver clinical benefits to patients for

- medical conditions that are life threatening, or cause permanent impairment of a body function, and
- for which current medical alternatives are insufficient or carry significant risks.

Corresponding devices are referred to as "breakthrough products" in this Appendix.

a. Breakthrough products

In exceptional cases, major benefits may justify relatively high levels of uncertainty, and access to the market may be granted on the basis of limited clinical evidence such as

- experience available from compassionate use/ humanitarian exemption programs, use of custom-made devices, results of feasibility studies;
- limited long-term data.

In addition to general aspects described in this MEDDEV document, the evaluators should fully disclose the situation and address the following items in the clinical evaluation report:

- the exact intended purpose, including the medical indication (if applicable to the device), the product was developed for and whether residual risks and uncertainties or unanswered questions are considered acceptable in this indication (often a niche indication);
- explanations of why current medical alternatives are considered to be insufficient or to carry significant risks;
- explanations of the benefits delivered by the device under evaluation;

- whether the IFU clearly describe
  - the exact intended purpose (including medical indications) and any limitations,
  - the limited clinical experience,
  - uncertainties or unanswered questions about residual risks and benefits to patients[19];
- the need to set up a stringent PMCF plan with information on
  - the type and quality of data that needs to be generated in the post-market phase in order to further evaluate the clinical performance and clinical safety of the device;
  - how to generate data in a timely manner and aspects thereof, including projections on the numbers of patients that will be managed with the device per year;
  - in the following cases, the manufacturer should aim at including all patients in PMCF studies:
    - a device that carries significant risks (i.e. expected to cause serious adverse events), or
    - a device for rare diseases.
- the need to actively update the clinical evaluation report when new significant information become available, and in accordance with Section 6.2.3 b of the present document.

In these exceptional cases, notified bodies should perform annual assessments of the updated clinical evaluation reports and the results of PMCF studies.

b. Subsequent products

Devices that enter the market subsequent to a therapeutic/ diagnostic breakthrough can not be judged by the same criteria as listed above for breakthrough devices. When performing a clinical evaluation for these devices, the following considerations should be taken into account:

- when a device enters the market subsequent to a therapeutic/diagnostic breakthrough, clinical evidence is likely to have evolved rapidly since the first breakthrough device became available
- with the evolving body of evidence, entering the market with large uncertainty may no longer be legitimate
- if PMCF data are required, PMCF Studies should also be foreseen for devices that enter the market subsequent to a therapeutic/ therapeutic breakthrough

A9. Clinical evaluation report - proposed table of contents, examples of contents

Examples of contents that are shown in the table are for illustration. The contents of the clinical evaluation report will vary according to the nature and history of the device under evaluation.

[19] Example: *"No serious long-term adverse effects have been reported to date".* This would be an inadequate description of limited experience and of uncertainties as to residual risks.

Table of contents	Example of contents
1. Summary	Executive summary, summary for external purposes. This section should summarise the determination of the benefit/risk profile in the intended target groups and medical indications, and the demonstration of acceptability of that profile based on the state of the art in the medical fields concerned.
2. Scope of the clinical evaluation	See Section 7 and Appendix A3. Identification of devices covered by this clinical evaluation report, products, models, sizes, software versions, accessories, their proprietary names, code names assigned during device development. Name and address of the manufacturer. Whether this clinical evaluation is submitted to the AIMDD as amended by directive 2007/47/EC, or to the MDD as amended by directive 2007/47/EC. Concise physical and chemical description, including materials. Whether the device incorporated medicinal substances (already on the market or new), tissues, or blood products. Mechanical and physicochemical characteristics; others (such as sterile vs. non-sterile, radioactivity etc.); picture or drawing of the device. Technologies used, whether the device is based on a new technology, a new clinical application of an existing technology, or the result of incremental change of an existing technology. Description of innovative aspects of the device. Device group the device belongs to. How the device achieves its intended purpose. Positioning in relation to available treatment/ management/ diagnostic options. Exact description of the intended purpose as described in the device's IFU[20], with exact medical indications (if applicable) and contraindications; claims made in available promotional materials. Name of disease or condition, clinical form, stage, severity, symptoms or aspects to be treated/ managed/ diagnosed, target patient population, target user group. Intended application of the device, single use/reusable, invasive/non invasive, implantable, duration of use or contact with the body, maximum number of repeat applications. Identification of organs, tissues or body fluids contacted by the device. Precautions. Claims on clinical performance and clinical safety foreseen by the manufacturer. Whether the device is already CE marked, whether it is on the market, since when, in what regions, history of the device, including date of past modifications with reasons and description, sales volumes. Changes since the last report, whether the device has been

[20] In exceptional cases where an instruction for use is not required, describe the generally recognised modalities of use

	modified, identification of new products, models, sizes, software, accessories, new intended purposes, new claims, new events related to the device with an impact on clinical evaluation. Identification of the sections of the clinical evaluation report that are concerned with the new information and have been modified. Other aspects.
3. Clinical background, current knowledge, state of the art	See Sections 8-10 and Appendices A4-A5. Identification of medical fields concerned/ relevant medical conditions. Brief summary and justification of the literature search strategy applied for retrieval of information on current knowledge/ the state of the art, including sources used, search questions, search terms, selection criteria applied to the output of the search, quality control measures, results, number and type of literature found to be pertinent. Appraisal criteria used. Applicable standards and guidance documents. Description, natural course and consequences of the medical conditions concerned. Whether there are different clinical forms, stages and severities of the conditions. Frequency in the general population, by age group, gender, ethnicity, familiar predispositions, genetic aspects. Description of available therapeutic/ management/ diagnostic options, historical context and developments, summary of advantages and disadvantages of the different options, benefit/ risk profiles and limitations in relation to the different clinical forms, stages, and severities of the medical conditions and in relation to different target populations. Description of the benefits and risks (nature, extent, probability, duration, frequency), acceptability of undesirable side-effects and other risks (including the nature, severity, probability and duration of acceptable harm). Hazards due to substances and technologies that could be relevant to the device under evaluation. The mechanisms of harm, clinical aspects of minimisation and management of side effects and other risks. Types of users. Diverging opinions of professionals as to the use of the different medical options. Unmet medical needs.
4. Device under evaluation	
4.1. Type of evaluation	Whether the clinical evaluation is based on - scientific literature currently available, and/or - clinical investigations made or - whether demonstration of conformity with essential requirements based on clinical data is not deemed appropriate. If clinical data is not deemed appropriate, include considerations according to Section 10.3.
4.2. Demonstration of	See Appendix A1.

equivalence (only when equivalence is claimed)	Identification of the equivalent device and its manufacturer. Exact name, models, sizes, software versions, accessories, etc. Name of the manufacturer. Relationship to the device under evaluation (predecessor/ successor, others). Regulatory status. If the device is not CE-marked, justification for the use of the data. Comparison of clinical, biological and technical characteristics (see Appendix A1 for details). Justification of equivalence, description of relevant clinical, biological and technical characteristics that affect clinical properties of the device, differences between the intended purpose of the device under evaluation and the equivalent device (indications, contraindications, precautions, target patient groups, target users, mode of application, duration of use/ number of re-applications, others), type of device-body interaction. Choice, justification and validity of parameters and models for non-clinical determination of characteristics. Identification of pre-clinical studies carried out and literature used, concise summaries of studies and literature (methods, results, conclusions of the authors), evaluation of the methodological quality of the study or document, the scientific validity of the information. Comparative tabulations for the device under evaluation versus the equivalent device showing parameters relevant to the evaluation of the three characteristics. Comparative drawings or pictures of the device and the equivalent device showing the elements in contact with the body. Identification of differences, evaluation if differences are expected or not to influence the clinical performance and clinical safety of the device, reasons for assumptions made. Conclusions concerning equivalence. Whether the comparison carried out covers all products/ models/ sizes/ settings/ accessories and the entire intended purpose of the device under evaluation, or only certain products/ models/ sizes/ settings/ accessories, or selected aspects of the intended purpose, which ones. Conclusions whether equivalence is demonstrated or not; if it is demonstrated, confirmation that the differences are not expected to affect the clinical performance and clinical safety of the device under evaluation; description of any limitations and gaps.
4.3. Clinical data generated and held by the manufacturer	See Section 8.1. Identification of clinical data generated and held by the manufacturer.
4.4. Clinical data from literature	See Section 8.2 and Appendices A4-A5. Brief summary and justification of the literature search strategy applied for retrieval of clinical data, including objectives, sources used, search questions, search terms, selection criteria applied to the output of the search, quality control measures, results, number and type of literature found to be pertinent.
4.5. Summary and appraisal	See Section 9 and Appendix A6.

of clinical data	- Feasibility Studies - Pivotal clinical investigations - PMCF Studies - Other use data Summaries of clinical data generated and held by the manufacturer and of scientific literature found to be pertinent. Including brief summary of the studies or references (methods, results, conclusion of the authors), evaluation of their methodological quality, scientific validity of contents, relevance to the clinical evaluation, weighting attributed to the data, contents used (performance data, safety data, both) reasons for rejecting a study or document, reasons for rejecting some of its contents.
4.6. Analysis of the clinical data	
4.6.1. Requirement on safety (MDD ER1 / AIMDD ER1)	See Section 10 and Appendix A7.1. Summary of conformity assessment with requirement on safety (MDD ER1 / AIMDD ER1). Analysis whether there are special design features that pose special safety concerns (e.g. presence of medicinal, human or animal components) that where identified in the device risk management documentation and that required evaluation from a clinical perspective, and whether these have been adequately addressed. Whether the risks identified in the risk management documentation and literature have been adequately addressed. Whether all the hazards and other clinically relevant information (e.g. clinical precautions for reduction of risks, clinical management of risks) have been identified appropriately. Whether the safety characteristics and intended purpose of the device requires training of the end-user or other precautions, if users foreseen are adequate, if training requirements and other precautions are described in the IFU. Whether there is full consistency between current knowledge/ the state of the art, the available clinical data, the information materials supplied by the manufacturer, and the risk management documentation for the device.
4.6.2. Requirement on acceptable benefit/risk profile (MDD ER1 / AIMDD ER1)	See Section 10 and Appendix A7.2. Summary of conformity assessment with requirement on acceptable benefit/risk profile (MDD ER1 / AIMDD ER1). Summary of the total experience with the device, including estimated numbers and characteristics of patients exposed to the device in clinical investigations, PMCF, from other user experience, and in the market; duration of follow-up. Nature, extent/severity, probability/frequency, duration of benefits to the patients and of undesirable side-effects and other risks. For each aspect of the intended purpose, whether the benefit/risk profile including its uncertainties or unanswered questions is compatible with a high level of protection of health and safety, corresponding justifications.

4.6.3. Requirement on performance (MDD ER3 / AIMDD ER2)	See Section 10 and Appendix A7.3. Summary of conformity assessment with requirement on performance (MDD ER3 / AIMDD ER2). Description of clinical performance. For each intended performance, extent to which evaluation of benefits is possible based on available data, limitations of the data, description of gaps, uncertainties or unanswered questions, and assumptions. whether available data allows adequate evaluation of performance, limitations of the data, gaps, uncertainties or unanswered questions. Whether there is sufficient clinical evidence for every intended performance.
4.6.4. Requirement on acceptability of side-effects (MDD ER6 / AIMDD ER5)	See Section 10 and Appendix A7.4. Summary of conformity assessment with requirement on acceptability of undesirable side-effects (MDD ER6 / AIMDD ER5). Whether the data available is of sufficient amount and quality for the detection of undesirable side-effects and their frequency, limitations of the data, description of gaps, uncertainties or unanswered questions, and assumptions. Whether the undesirable side-effects are acceptable and corresponding justifications.
5. Conclusions	See Section 11. Clear statement concerning compliance to Essential requirements. Acceptability of the benefit/risk profile according to current knowledge/ the state of the art in the medical fields concerned and according to available medical alternatives. Adequacy of the information materials supplied by the manufacturer, whether the intended purpose and risk reduction measures are adequate; discrepancies. Suitability of the device, including its IFU, for the intended users and usability aspects; discrepancies. Adequacy of claims foreseen by the manufacturer; discrepancies. If there is consistency between the clinical data, the information materials supplied by the manufacturer, the risk management documentation for the device under evaluation; discrepancies. Whether there is consistency between these documents and the current knowledge/ the state of the art; discrepancies. Description of residual risks and uncertainties or unanswered questions, whether these are acceptable for CE-marking, how these should be followed during PMS (uncertainties regarding medium- and long term performance, safety under wide-spread use, residual risks such as undesirable side-effects and complications occurring at rates below detection possibilities of currently available clinical data, others). Whether these are already being addressed in ongoing PMS activities, e.g. in currently ongoing PMCF studies. Whether new or additional PMS activities, including PMCF studies, should be foreseen.
6. Date of the next clinical evaluation	See Section 6.2.3.

	Suggested date, justification of the date.
7. Dates and signatures	See Section 11. Date of the clinical evaluation report. Statement that the evaluators agree with the contents of the report. Dates, names and signatures of the evaluators. Final release by the manufacturer. Date, name and signature.
8. Qualification of the responsible evaluators	See Section 6.4.
9. References	See Section 11.

A10. Proposed checklist for the release of the clinical evaluation report

The following aspects should be checked for the release of a clinical evaluation report:

- Can the report be read and understood by a third party, does it provide sufficient detail for understanding the data that are available, all assumptions made and all conclusions reached?
- If clinical data have been generated and are held by the manufacturer, are all data mentioned and adequately summarised in the report?
- If equivalence is claimed,
  - is demonstration of equivalence included in the report?
  - does the report disclose all the differences between the device under evaluation and the equivalent device?
  - does it explain why the differences are not expected to affect the clinical performance and clinical safety of the device?
- If the product is already in the market in Europe or elsewhere, has the latest PMS/ PMCF data been taken into consideration and has it been summarised and referenced in the report?
- In respect to current knowledge/ the state of the art,
  - has the report been updated?
  - is current knowledge/ the state of the art summarised in the report and is it adequately substantiated by literature?
  - does the content of the report fully correspond to current knowledge/ the state of the art?
  - does the report explain why the benefit/risk profile and the undesirable side-effects are acceptable in relation to current knowledge/ the state of the art?
- If the report covers several models/ sizes/ settings and/or different clinical situations, is there sufficient clinical evidence and are the report's conclusions correct for
  - all the devices?
  - all its sizes, models and settings?
    (including the smallest/ largest size, highest/ lowest dose, etc.)
  - every medical indication?
    (as described in the IFU/ not excluded with contraindications in the IFU)
  - the entire target population?
    (from pre term infants to old age, for males and females, etc., if not restricted in the IFU)
  - every form, stage and severity of the medical condition, as applicable?

(including the most severe/ most benign forms, acute/ chronic stage, if not excluded in the IFU)
  - all intended users?
    (including lay persons, if not excluded in the IFU, and any unusual user group)
  - the whole duration of product use, including the maximal number of repeated exposure? (as allowed by the IFU)
  - if there are any discrepancies as to the above, are they identified in the report's conclusions?
- Is conformity to each of the relevant Essential Requirements (AIMDD ER1,2,5 / MDD ER1,3,6) clearly stated and are all discrepancies identified in the report's conclusions?
- Do the information materials supplied by the manufacturer correspond with the contents of the report and are all discrepancies identified in the report's conclusions?
- Do the report's conclusions identify all residual risks and uncertainties or unanswered questions that should be addressed with PMS/ PMCF studies?
- Is the report dated?
- Is the qualification of the evaluators included in the report and correct?
- Does the manufacturer hold a CV and declaration of interests of each of the evaluators and are these up-to-date?

A11. Information on declarations of interests

Declarations of interests of the evaluators should be held by the manufacturer and cover relevant financial interests outside the current work as an evaluator.

Declarations of interests should contain statements that clarify the extent of the declaration.

For example:

- the time span included (e.g. grants, sources of revenue or benefits paid or promised to be paid over the 36 months prior to the evaluation)
- whether financial interests of family members are included or not (namely spouse or partner living in the same residence as the evaluator, children and adults for whom the evaluators is legally responsible)

Typical contents:

- employment by the manufacturer
- participation as an investigator in clinical studies of the device, or in pre-clinical testing of the device
- ownership/ shareholding possibly affected by the outcome of the evaluation
- grants sponsored by the manufacturer
- benefits such as travelling or hospitality (if beyond what is reasonably necessary for the work as an employee or external evaluator)
- interests in connection with the manufacturing of the device or its constituents
- interests in connection with intellectual property, such as patents, copyrights and royalties (whether pending, issued or licensed) possibly affected by the outcome of the evaluation
- other interests or sources of revenues possibly affected by the result of the evaluation

The declaration of interests should be dated and signed by the evaluator and the manufacturer.

A12. Activities of notified bodies

A12.1. Notified body assessment of clinical evaluation by conformity assessment route

The notified body assessment of clinical Evaluation reports and the supporting data presented by manufacturers is required for all medical devices. The timing and frequency of the notified body reviews will vary according to the risk carried by the device, how well established the device is (see Section 6.2.3) and the conformity assessment procedure that is applied.

This includes for medical devices in accordance with Directive 93/42/EEC:

- An audit as part of a quality system approval procedure (Annex II, section 3):
  - the notified body assesses the manufacturer's procedure for clinical evaluation, PMS plan and PMCF plan and (if applicable) results of PMCF.
  - as part of the representative sampling of devices[21]; for review of their technical documentation the notified body assesses the clinical evaluation report presented for class IIa[22] and IIb devices as presented below for a design dossier.
- A design dossier (Annex II, section 4) or type examination dossier (Annex III) assessment:
  - the notified body assesses the data presented in the clinical evaluation report,
  - assesses the validity of the conclusions drawn by the manufacturer, and
  - the conformity of the device to relevant essential requirements.

For active implantable medical devices in accordance with Directive 90/385/EEC:

- A design dossier (Annex 2, section 4) or type examination dossier (Annex 3) assessment:
  - the notified body assesses the data presented in the clinical evaluation report,
  - assesses the validity of the clinical evaluation report and the conclusions drawn by the manufacturer, and
  - the conformity of the device to relevant essential requirements.

The notified body should also have documented procedures to address the review of updates to clinical evaluation reports during their scheduled surveillance activities and at the time of changes to or extensions of EC design-examination/EC type-examination certificates. The review should take into account aspects described in Section 6.2.3. This arises from the obligation placed on the manufacturer to actively update the clinical evaluation with data obtained from PMS e.g. PMCF and ongoing literature reviews/surveys.

In addition, notified bodies should refer to guidance, checklists and other documents available on the assessment of clinical evaluations by notified bodies from the Notified Body Operations Group (NBOG). These should be considered in addition to this guidance. Any such checklists are intended only as an aide memoire for assessment and should not replace the Clinical Evaluation Assessment Report (CEAR) outlined below.

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[21] In accordance with NBOG BPG 2009-4

[22] Alternatively Annex VII coupled with Annex IV, V or VI could apply rather than Annex II.3

A12.2. Examination of a design dossier (Annex II.4; Annex 2.4) or of a type examination dossier (Annex III; Annex 3)

The notified body examines the clinical evaluation documentation submitted (relevant documentation referenced in previous sections of this MEDDEV), assesses the manufacturer's identification, appraisal and analysis of that data, and validates the conclusions drawn by the manufacturer. In order to do so, the notified body should possess enough knowledge and experience in clinical evaluation as stated in previous sections of this document.

A12.2.1. Decision-making by the notified body

In reviewing the evaluation of clinical data submitted by the manufacturer, the notified body verifies and concludes whether or not the manufacturer has adequately:

- supplied clinical evaluation documentation (as referenced in previous sections);
- followed relevant procedures (as addressed by previous sections);
- described and verified the intended characteristics and performances related to clinical aspects;
- performed an appropriate risk analysis and estimated the undesirable side-effects which are aligned with the clinical evaluation;
- involved appropriate clinical expertise in the clinical evaluation and in the compilation of the risk analysis to ensure risks and benefits associated with real clinical use are adequately defined;
- provided a solid justification as the basis for their estimations of benefits, risks, undesirable side-effects, indications and contraindications of the device in question;
- justified the chosen route(s) of clinical data retrieval (according to previous sections);
- identified, appraised, analysed and assessed the clinical data (according to previous sections) and demonstrated the relevance and any limitations of the clinical data identified in demonstrating compliance with particular requirements of the Directive or cited in particular aspects of the risk analysis;
- identified all clinical data, favourable and unfavourable, that is relevant to the device and using an appropriately robust, reproducible and systematic search strategy;
- provided sufficient clinical evidence relating to the safety, including benefits to the patients, the clinical performance intended by the manufacturer (including any clinical claims for the device the manufacturer intends to use), design characteristics and intended purpose of the device, in order to demonstrate conformity with each of the relevant essential requirements;
- conducted and provided a critical evaluation of relevant scientific literature and data relating to the safety, benefits, performance, design characteristics and intended purpose of the device;
- demonstrated the equivalence of the device under evaluation to the device to which the data relates in all necessary areas, i.e. clinical, technical, biological and that the data available adequately addresses conformity to each of the relevant essential requirements (if a critical evaluation of relevant scientific literature is provided as the only source of clinical data);
- designed appropriate clinical investigations, when necessary, to address specific questions arising from the critical review of the scientific literature and address each of the relevant essential requirements;

- provided specific justification if a specific clinical investigation was not performed for class III or implantable devices;
- provided evidence that clinical investigations presented are in compliance with applicable regulatory and ethical requirements e.g. scientific validity, ethics committee approval, competent authority approval;
- provided detail of the PMS plan in place for the particular device and justified the appropriateness and adequacy of this plan;
- clearly identified which areas in the clinical evaluation and related data need to be further addressed and confirmed in the post-market phase, with specific alignment to the PMCF;
- justified the appropriateness of the planned PMCF;
- justified and documented if PMCF is not planned as part of the PMS plan for the device;
- identified the sources of clinical data which will be gathered from the manufacturer's PMS system and PMCF;
- concluded that the contents of the IFU are supported by clinical evidence (description of the intended purpose, handling instructions, type and frequency of risks, warnings, precautions, contraindications, others) and are in line with the risk analysis and clinical evaluation;
- concluded on the basis of documented evidence:

  a. that the risks are acceptable when weighed against the intended benefits and are compatible with a high level of protection of health and safety,

  b. that the intended clinical performances described by the manufacturer are achieved by the device, and

  c. that any undesirable side-effect constitutes an acceptable risk when weighed against the performances intended.

The assessment carried out by the notified body will in addition typically confirm the following aspects of the manufacturer's clinical evaluation:

- appraisal to determine suitability and any limitations of the data presented to address the essential requirements in particular relating to the safety, and performance of the device as outlined in previous sections;
- the validity of any justification given;
- characterisation and evidence-based proof of the clinical performance of the device intended by the manufacturer and the expected benefits for the defined patient group(s);
- the application of all relevant harmonised standards or appropriate justifications if not;
- identified hazards to be addressed through analysis of clinical data as described in Section 10;
- the adequate estimation of the associated risks for each identified hazard by:
  - characterising the severity of the hazard;
  - estimating and characterising the probability of occurrence of harm, impairment of health or loss of benefit of the treatment (documented and discussed based on scientifically valid clinical data);
  - the adequate description and estimation of the current state of the art in the corresponding medical field;
  - a justifiable and reasoned basis for estimation of risks and hazards.

Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product, the notified body is responsible for verifying the usefulness

of the medicinal substance as part of the device prior to the submission of an application for scientific opinion from a medicines authority.

For drug-device combination products and products incorporating stable human blood derivatives, where a scientific opinion from a medicinal competent authority or from the European Medicines Agency (EMA) has been sought, the notified body should consider any comments or considerations raised in the medicinal clinical assessment when making its final decision on the device. In the case of devices with a human blood derivative the notified body may not deliver a positive decision to issue a certificate if the EMA's scientific opinion is unfavourable.

A12.2.2. The report of the notified body

The notified body should write a Clinical Evaluation Assessment Report (CEAR) based on its assessment of the submitted clinical evaluation report and supporting documentation.

If a design dossier report is applicable to the device, the CEAR may be incorporated into this report or referenced from it. The report should clearly identify the notified body's assessment, verification on each of the critical elements and overall conclusions.

The CEAR at a minimum should address the notified body's assessment of manufacturer's application relating to the following:

- device description and product specification
- intended purpose of the device
- classification proposed for the device
- pre-clinical evaluation data presented by the manufacturer
- risk analysis and risk management and alignment with the clinical evaluation report
- clinical evaluation process
- clinical evaluation report authors
- equivalence assessment – if data from equivalent is used
- clinical investigation plans and reports
- justification if no clinical investigation has been performed
- instructions for use, labelling and, when necessary, the training plan for users
- justification if no PMCF is planned
- PMS
- PMCF
- planned frequency/ criteria for updates to the clinical evaluation
- summary of review
- conclusion on clinical benefit/risk profile
- conformance of the device to the relevant Essential Requirements

The CEAR should also provide details relating to the submission and notified body review (including staff and experts involved in the review and the aspects assessed by each, signatures of responsible reviewers, etc.)

The notified body should justify and document each step of the decision making process referred in section A12.2.1 above.

The CEAR at a minimum should include a summary of the information provided by the manufacturer relating to the following:

- Record whether the clinical evaluation documentation is complete in accordance with this document and adequate to demonstrate conformance to the Essential Requirements of the relevant Directive.
- Record the notified body's verification of each step of the clinical evaluation process, from the planning of the clinical evaluation, choice of route(s), identification, appraisal, analysis and overall assessment of the clinical data, to concluding and reporting
- Record the notified body's assessment of the clinical investigation data and/or literature review assembled, relevant procedures and compliance to relevant standards
- Verify that the device has met the claimed performance/ intended purpose and benefits, and that undesirable side-effects and risks have been properly evaluated
- Record the notified body's assessment of the clinical safety, clinical performance and benefit/risk profile
- Record the notified body's assessment of the overall conclusions drawn by the manufacturer from the clinical data presented
- Record the notified body's assessment of the validity of the clinical evaluation and its steps
- Record the notified body's conclusions on the clinical evaluation, documenting each step in the decision making process as per Section A12.2.1.

A12.2.3. Clinical data from an equivalent device and other products

a. Equivalent devices

The notified body should clearly document its assessment of clinical data presented from an equivalent device as part of a clinical evaluation. This should critically review and conclude on the equivalence or not of the device under assessment to the devices presented as equivalent in terms of their technical, biological and clinical characteristics. The relevance of each dataset from an equivalent device should be clearly evident and assessed by the notified body.

The notified body should also assess and document the level of access to the technical and clinical data from an Equivalent device that the manufacturer has. Relevant information may be commercially sensitive/ confidential and not available to the manufacturer. The notified body should challenge the ability of the manufacturer to access information that are relevant to the demonstration of equivalence. Demonstration of equivalence might be difficult or impossible in case of limited access to the technical documentation of the devices.

b. Other products

For hazard identification and when assessing the benefit/risk profile of the device, the notified body should consider current knowledge/ the state of the art.

The notified body should assess the appropriateness of the use of data from benchmark devices, other devices, and medical alternatives.

A12.3. Evaluation as part of quality system related procedures[23]

A12.3.1. Review of the manufacturer's procedures

The notified body shall, as part of the review of the manufacturer's quality system, assess the establishment, maintenance and application of the manufacturer's documented procedures for the evaluation of clinical data. This should cover:

a. the proper assignment of responsibilities to suitably qualified persons involved in the clinical evaluation (e.g. clinical evaluator(s), information retrieval expert(s), expert(s) in clinical research);

b. the integration of clinical evaluation into the quality system as a continuous process, to be specifically inter-related to, and informed by, pre clinical evaluation and risk management;

c. standard operating procedures to assure proper planning, conduct, evaluation, control and documentation planning of the clinical evaluation, identification of clinical data (previous section), literature searching (previous section), collection of clinical experience (previous section), clinical investigation (previous section and EN ISO 14155), appraisal of clinical data (previous section), analysis of clinical data (previous section), concluding, reporting (previous section) and update of clinical evaluation, procedures, reporting and updating based on data from the PMS system and from PMCF (MEDDEV 2.12/2 rev.2);

d. document control as part of overall documentation of procedures, reporting, qualifications and technical documentation/design dossier(s);

e. identification and evaluation of undesirable side-effects and of clinical performance(s). This involves identification of known or reasonably foreseeable hazards and verification of unfavourable and favourable outcome(s), qualification of their severity/magnitude and of their probability of occurrence. (It is part of the manufacturer's documented risk analysis based on both favourable and unfavourable data identified as relevant in order to give a balanced view).

A12.3.2. Review of the technical documentation of representative samples

The notified body is required to assess the technical documentation for class IIa and class IIb devices on a representative basis. The clinical evaluation report should be assessed by the notified body for at least one representative sample for each device subcategory for class IIa devices and at least one representative sample for each generic device group for class IIb devices. Further representative samples have to be assessed as part of the annual surveillance assessment cycle.

Regarding the choice of representative sample(s) the notified body will consider the novelty of the technology, similarities in design, technology, manufacturing and sterilisation methods, the intended purpose, and the results of previous relevant assessments. Assessment of representative samples includes assessment of the clinical evaluation report and available clinical data in accordance with the review procedure in this document rather than solely confirming that the manufacturer has a clinical evaluation procedure in place or that the clinical evaluation report is available.

The criteria for the technical documentation assessment on a representative basis outlined in NBOG BPG 2009-4 should be applied.

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[23] According to Article 11 MDD (Annex II.3 MDD, or Annex III MDD coupled with Annex IV, V or VI), and Article 9 AIMDD.

When performing the assessment on samples of a manufacturer's clinical evaluation, the notified body will follow the steps indicated in previous sections of this document.

A clinical evaluation assessment report should be completed and available for each device sampled and assessed.

A12.4. Notified body specific procedures and expertise

A notified body should have formal procedures in place controlled by their quality system relating to the assessment of clinical evaluation reports and associated data provided by medical device manufacturers. These procedures should also cover the review of updates to the clinical evaluation report during their scheduled surveillance activities and at the time of changes to or extensions of EC design-examination/EC type-examination certificates.

Notified bodies should establish and implement internal policies and procedures for the assessment of clinical evaluation reports and associated data in order to:

a. Ensure that suitable resources, especially clinical competence necessary for such assessment, are available within[24] the notified body to conduct and manage assessments of clinical evaluations for the notified body, normally a qualified medical doctor.

   Such expertise should be sufficient to conduct a complete review of the clinical data and clinical evaluation presented for a particular device, to identify and estimate the risks and benefits associated with the use of the medical devices and to identify what, if any, specific clinical expertise is required for the full assessment of the device.

   The assessment team should be able to assess a risk analysis, the risk management strategy performed by the manufacturer, and the scientific validity of clinical investigations and publications.

   The assessment team should have sufficient expertise in the device technology as the associated medical procedures.

   Such an assessment requires input from a qualified medical practitioner (for example physician, dentist, nurse, etc.), as appropriate for the particular device, who has clinical experience in using the device or similar devices, the pathology of the condition being treated, the usual treatment, other medical alternatives, etc.

   The notified body clinical assessor may work with external clinical experts. The notified body clinical assessor should ensure that any experts are appropriately aware of the relevant legislation, guidance and standards and to identify specific aspects of the clinical data evaluation for their specific review.

   Notified bodies should have robust procedures around the recruitment, selection, training, conflict of interest and interaction with external clinical experts including clear procedures around how the expert opinion is documented and integrated with the notified body assessment and considered as part of the overall certificate decision.

   When examining the results of clinical investigations, the assessment team shall have knowledge in planning, conduct and interpretation of clinical investigations. All assessors should be appropriately trained and qualified.

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[24] Annex XI.3 of Directive 93/42/EEC. This presupposes the availability of sufficient scientific staff within the organisation who possess experience and knowledge sufficient to assess the medical functionality and performance of devices for which it has been notified, having regard to the requirements of this Directive and, in particular, those set out in Annex I.

Particular attention should be drawn to training of external experts on the conformity assessment procedure(s), relevant guidance, standards and the context of the assessment they are providing. The notified body should be responsible for reviewing the opinion of these experts, taking account of their level of knowledge of the provisions of the Directives.

The opinion of an external clinical expert may form part of the assessment conducted by the notified body. The opinion and conclusions of the notified body, in part based on this external opinion, should be clearly documented.

The impartiality and the potential for conflict of interest of an external expert reviewer should be assessed and documented by the notified body.

b. Review the clinical evaluation report and clinical data provided by the manufacturer. The notified body should verify the validity of key statements made in the clinical evaluation report. The notified body should consider

   - statements based on published literature using the full text version of publications;
   - statements based on clinical data generated from PMS systems in particular PMCF and source verification of such data;
   - statements regarding equivalence to other devices using the original full text version of pre-market study reports assessing parameters of interest.
   - statements regarding results of own clinical investigations of the manufacturer using the original full text version of the clinical investigation plan and the clinical investigation report.

   The review of the notified body should consider the scientific validity of the clinical data set presented as part of the clinical evaluation and decide as to whether it provides evidence that the clinical benefit outweighs all associated risks.

   The data presented by the manufacturer should be scientifically robust and well presented, it should be complete and clear in its reasoning and should be of sufficient quality and validity to demonstrate the conclusions which are being drawn.

   All clinical data relevant to the device in question, both favourable and unfavourable, should be considered, appraised and assessed by the manufacturer and likewise by the notified body. An absence of unfavourable data relating to a medical device should be carefully examined.

   Clinical evaluation reports which are based on incomplete, unclear or uncertain datasets should not be accepted.

   Clinical Evaluation reports which are based on incomplete clinical investigations or clinical investigations which were halted or terminated earlier than their intended duration should be carefully examined and a robust justification for halting or termination should be sought. The original endpoints, objectives and statistical basis for the manufacturer's clinical investigation are unlikely to remain valid in circumstances when an investigation is completed prior to its original planned duration and so it is unlikely that scientific conclusions can be drawn.

c. Document the opinion with rationale of all experts involved.

d. Document the result of their assessment. This is achieved through a specific clinical evaluation assessment report which may be part of, or may be referenced, in the overall audit report, design / type examination report (as per A12.2.2 of this document) or the report on the assessment of representative samples' documentation.

e. Preserve confidentiality of the information and data received from the manufacturer, especially within the terms for contracting external experts.

f. Clearly identify how data from PMS conducted by manufacturers, vigilance and market surveillance information from competent authorities, PMCF data, and data from other relevant sources (e.g. clinical literature) is identified and reviewed by the notified body. This should clearly describe how, when and what criteria are used by the notified body to judge when a re-assessment of the benefit/risk profile of a particular device is deemed necessary.