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GUIDELINES ON MEDICAL DEVICES

CLINICAL EVALUATION:
A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES

The present Guide is part of a set of Guidelines relating to questions of application of EC-Directives on medical Devices. They are not legally binding. The Guidelines have been carefully drafted through a process of intensive consultation of the various interest parties (competent authorities, Commission services, industries, other interested parties). Therefore, this document reflects positions taken by representatives of interest parties in the medical devices sector.

1. Contents

2. 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, not unduly burdensome, and appropriate to the nature, intended use, and risks of the device in question. Therefore, this guidance is not intended to impose device-specific requirements.

3. 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 the aforementioned 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 which may result in changes to important concepts or definitions relating to clinical evaluation.

4. 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
- Manual on borderline and classification in the Community regulatory framework for medical devices

Other guidance documents:

- GHTF SG5 N2R8:2007: Clinical evaluation

5. 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]

Class effect: for the purpose of this MEDDEV document, a class effect is an effect 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, or share other characteristics.

Clinical Data: the safety and/or performance information that is generated from the 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.

[Art. 1.2.k AIMDD]

Clinical Evaluation: a methodologically sound ongoing procedure to collect and analyse clinical data pertaining to a medical device and to assess whether there is sufficient clinical evidence to confirm compliance with relevant essential requirements for safety and performance when using the device according to the manufacturer's Instructions for 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 state(s) 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]

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]

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

Equivalent device: a similar 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]

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

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

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, without serious deterioration in health, is not considered a serious adverse event.
[EN ISO 14155:2011]

Sufficient clinical evidence: clinical data of an amount and quality to guarantee the scientific validity of the conclusions. [Derived from section 2.3.1 of Annex X of MDD and Annex 7 of AIMD]

6. Abbreviations

AIMDD: Active implantable medical device directive (Council Directive 90/385/CEE amended by Directive 2007/47/EC)
CEAR: Clinical Evaluation Assessment Report
ER: Essential Requirement
IFU: Instructions for use
MDD: Medical device directive (Council Directive 93/42/CEE amended by Directive 2007/47/EC)
PMS: Post**-**market surveillance
PMCF: Post-market clinical follow-up

7. General principles of clinical evaluation

7.1. What is clinical evaluation?

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

The requirements for clinical evaluation apply to all classes of medical devices. 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 Directive 90/385/EEC relating to active implantable medical devices, or
  - Annex I sections 1, 3, 6 of Directive 93/42/EEC concerning medical devices;

- the evaluation must follow defined and methodologically sound procedures as described in:
  - Annex 7 of Directive 90/385/EEC relating to active implantable medical devices,
  - Annex X of Directive 93/42/EEC concerning medical devices;

- where demonstration of conformity with essential requirements based on clinical data is not deemed appropriate, a 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 Directive 90/385/EEC relating to active implantable medical devices,
  - Annex X section 1.1d of Directive 93/42/EEC concerning medical devices.

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

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

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

Clinical evaluation is 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 reporting requirements, or during surveillance procedures).

The product information is an integral part of the product. It reflects under which conditions and for what purposes the device is intended to be used. When evaluating a device the evaluators shall address whether the contents of the product information (including label, instructions for use, accompanying documents possibly foreseen by the manufacturer) are aligned with the relevant aspects of the clinical evaluation and supported by the clinical evidence. Particularly, the evaluators should address

- if the description of the intended use is fully supported by the clinical evidence (including, for example, the medical indications);
- if descriptions of the clinical performance, benefits, and risk mitigation measures are fully supported by the clinical evidence (including for example any claims, the declaration of residual risks, contraindications, precautions, warnings, risk mitigation measures, instructions for managing foreseeable unwanted situations).
- the suitability of the product information for the intended users and the usability aspects.

7.2.1. 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 performance of the device.

- in case of possible equivalence to an existing device, assess if there is scientific literature available on a CE-marked medical device, 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 11 (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 commence in advance of any clinical investigation.

7.2.2. Clinical evaluation for initial CE-marking

Clinical evaluation must be carried out for the conformity assessment process leading to the CE-marking and marketing 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 safety;
- identify aspects that need to be addressed systematically during post-market surveillance (PMS), e.g. in post-market clinical follow-up (PMCF) studies required for the device under the medical device directives. Typically, these aspects include residual risks and uncertainties (such as rare complications, uncertainties regarding medium- and long-term performance, safety under wide-spread use).

7.2.3. Updating the clinical evaluation

a. General considerations on updating the clinical evaluation

With regard to post-market activities, manufacturers are required to implement and maintain surveillance programs that routinely monitor the clinical performance and safety of the device as part of their Quality Management System[1]. The scope and nature of such post-market surveillance should be appropriate to the device and its intended use.

Post-market surveillance regularly generates new data. These include safety reports, results from published literature, registries, post-market clinical follow-up studies, and other data about device usage. Those data need to be assessed for unexpected information and information that has a potential to change the assessment of the clinical performance and safety of the device. That data need 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*.

When updating the clinical evaluation, the evaluators should verify if:

- the benefit/risk profile, side-effects (whether previously known or newly emerged) and risk mitigation measures are still
  - compatible with a *high level of protection of health and safety* and acceptable according to current knowledge;
  - correctly addressed in the product information of the device;
  - correctly addressed by the manufacturers current PMS-plan;
- claims are still justified.

While clinical evaluation is informed by post-market surveillance, it also generates new information that needs to be fed into the post-market surveillance and risk management process. Clinical evaluation can therefore result in changes to the manufacturer's risk management documents and post-market surveillance 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.

b. Frequency of updates

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

When doing so, the manufacturer should typically take into account:

- whether the device carries significant risks (e.g. whether serious adverse events are expected, either due to side-effects or in case of failure to deliver the performance intended by the manufacturer).
- whether the device is well established, taking into consideration:
  - innovation;

[1] Annexes 2, 4, and 5 to Council Directive 90/385/EEC relating to active implantable medical devices
Annexes II, IV, V, VI, and VII to Council Directive 93/42/EEC concerning medical devices

- the current level of confidence in the assessment of clinical performance and safety of the device; the manufacturer should take into account
  - the number of devices used in the setting of clinical investigations, PMCF studies, registries or other systematic studies, and if that usage was representative of the usage in the market;
  - the total number of devices used so far, and expected reporting rates under the spontaneous user reporting scheme;
  - whether there are risks and uncertainties in the medium or long-term, and if the amount and duration of current data cover that period;
- design changes or changes to manufacturing procedures.

Typically the clinical evaluation is updated:

- when the manufacturer receives new information from post-market surveillance that has the potential to change the current evaluation;
- if no such information is received, at least
  - annually if the device carries significant risks and/or is not yet well established;
  - every 5 years if the device is not expected to carry significant risks and is well established;
  - every 2 to 3 years in all other cases.

When involvement of notified bodies is required, the exact timing is usually coordinated with the notified body's surveillance audits and with the timetable for renewal of the certificates.

7.3. 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 use of the device in question, including clinical performance data and safety data.

There are discrete stages in performing a clinical evaluation:

- Stage 0: Definition of the scope (planning the clinical evaluation, also referred to as scoping or the clinical evaluation plan).
- Stage 1: Identification of pertinent data.
- Stage 2: Appraisal of each individual data set, in terms of its scientific validity, relevance and weighting.
- Stage 3: Analysis of the data, whereby conclusions are reached about the performance, safety and the product information (including the label, instructions for use of the device, accompanying documents possibly foreseen by the manufacturer), and conclusions are reached about compliance with Essential Requirements, and about residual risks and uncertainties that are acceptable for CE-marking and that need to be addressed during post-market surveillance (such as rare complications, uncertainties regarding medium- and long term performance, safety under wide-spread use).

Each of these stages is covered in separate sections later in this document. During the course of a clinical evaluation the stages are often iterative. Indeed, the appraisal and analysis stage may uncover unexpected data and raise new questions, with a need to widen the scope of the evaluation and to retrieve, appraise and analyse additional data.

The clinical evaluation report draws together the evaluation of the relevant clinical data documented or referenced in other parts of the Technical File. The clinical evaluation report and the relevant clinical data constitute the clinical evidence for conformity assessment.

7.4. Who should perform the clinical evaluation?

The clinical evaluation should be conducted by a suitably qualified individual or individuals. 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 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:
  - the device technology and its application;
  - research methodology (including clinical investigation design and biostatistics);
  - diagnosis and management of the conditions intended to be managed or diagnosed by the device, knowledge of alternative treatments, treatment standards and technology (e.g. specialist clinical expertise in the relevant medical specialty);
  - 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);
- The evaluators should have at least the following experience in the relevant field:
  - a higher degree and 5 years of documented professional experience; or
  - 10 years of documented professional experience if a higher degree is not a prerequisite for a given task.

8. Define 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, or the clinical evaluation plan.

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

A clinical evaluation must be critical. Therefore, it needs to identify and consider 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 aspects 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 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 safety of the device.	X	
• Information needed for assessment of equivalence, if equivalence is 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 to be informed by and cross referenced 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 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 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 - Appendix A4 (Data that is generated and held by the manufacturer), - and Appendix A5 (Literature searches - Sources of literature)	X	X
• Whether the manufacturer has introduced/ intends to introduce any		X

changes, including changes to the product information (label, instructions for use, accompanying documents possibly foreseen by the manufacturer) or claims.		
• Whether there are any specific clinical concerns that have newly emerged and need to be addressed.		X
• PMS aspects that need regularly updating in the clinical evaluation report: - new clinical data available for the device under evaluation; - new clinical data available for the equivalent device (if equivalence is claimed)[2]; - new knowledge about known and potential hazards, risks, performance benefits[3] and claims, including - data on possible adverse class effects seen in other products; - changes concerning current knowledge/ the state of the art, such as 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 post-market surveillance.		X
• Whether there is emerging off-label usage that the manufacturer intends to evaluate.		X

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[2] References: Annex 1, Essential Requirements 1, 2, 5, 5a, and Annex 7 of Directive 90/385/EEC for active implantable medical devices. For other medical devices Annex I, Essential Requirements 1, 3, 6, 6a, and Annex X of Directive 93/42/EEC.

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

9. Identification of pertinent data (Stage 1)

9.1. Data generated and held by the manufacturer

With regard to those data:

- All clinical data generated and held by the manufacture need to be identified.
- Complete data should be made available to the evaluators; this includes data from Europe and other countries; it includes clinical studies as well as use data (such as vigilance reporting, complaints, PMS reports, PMCF and registry data, other data held by the manufacturer).
- The data shall be entirely disclosed and adequately summarised in the clinical evaluation report.

9.2. Data retrieved from literature

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

Literature searching delivers the evidence for establishing:

- Current knowledge/ the state of the art.
  References that relate to benchmark devices, other devices and alternative therapies or to the specific medical conditions intended to be managed with the device are typically needed in order to
  - identify and define the current knowledge/ state of the art in the corresponding medical field,
  - identify hazards (including adverse class effects),
  - 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).
- Clinical data relevant to the device under evaluation.
  - References that relate either to the device under evaluation or to the equivalent device (if equivalence is claimed) are needed for the demonstration of adequate clinical performance and safety of the device.
  - 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.

The following aspects should be considered for literature searching:

- The searching strategy should be thorough and objective, i.e. it should identify both 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 reasonable efforts should be made to conduct a comprehensive search.
- Several searches with different search strategies are usually necessary to obtain the necessary references. For additional information, see Appendix A5 (Literature searches - Sources of literature).
- Typically, 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 A6 (Literature searches - Literature search protocol, key elements).
- 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 assessment of the relevance of the paper. Copies of the full text papers and references shall be obtained for the appraisal stage.

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

10. Appraisal of clinical data (Stage 2)

Each reference / piece of data identified in stage 1 (whether generated and held by the manufacturer, published, or from other sources) needs to undergo the appraisal procedure. The purpose of the appraisal of a reference is to estimate the value of its contribution to the assessment of the clinical performance and safety of the device.

Uncertainty about the value of the data arises from two sources:

- the relevance of the data to the intended clinical use.
- the methodological quality of the data.

Both sources of uncertainty shall be analysed to determine a weighting for each piece of evidence. The evaluators should therefore

- identify evidence contained in each reference,
- evaluate the methodological quality of work done by the authors and from that, the scientific validity of the evidence, and
- determine the relevance of the evidence for the clinical evaluation,
- systematically weight the contribution of each piece of evidence.

There are many acceptable ways, both qualitative and semi-quantitative, by which the appraisal can be carried out. The evaluators should set up an appraisal plan that identifies, in advance, the appropriate criteria to be applied for a specific circumstance:

- The appraisal shall be thorough and objective, i.e. it shall identify and attribute adequate weighting both to favourable and unfavourable contents of each reference.
- The full text of publications and of other references need to be used for the appraisal, so as to allow the evaluators to review all of the contents, the methodology employed, the reporting of results and the validity of conclusions drawn from the investigation or report, and evaluate any limitations and potential sources of error in the data.
- The appraisal plan typically includes:
  - criteria for determining the methodological quality and the scientific validity of each piece of evidence.
  - criteria for determining the relevance to the clinical evaluation.
  - criteria on how to weight the contribution of the evidence to the assessment of the device under evaluation.

The criteria adopted for the appraisal are chosen in relation to the nature, history and intended clinical application of the device. They shall be documented and justified on the basis of current knowledge / the state of the art, applying accepted scientific standards. For many lower-risk devices and devices based on long-standing technology, qualitative data may be adequate, so the evaluation criteria should be adjusted accordingly.

- Criteria defined in the appraisal plan shall be applied consistently during the conduct of the appraisal.
- The appraisal plan and the results of the appraisal shall be documented either in the Clinical Evaluation Report, or in a separate document.

10.1. How to evaluate the methodological quality and the scientific validity of the evidence

For the determination of the methodological quality of publications and reports, the evaluators should examine the methods used to generate/collect the data and assess 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. natural course of the underlying medical condition / regression to the mean, concomitant treatments)
- bias
- random error
- inadequate disclosure of information
- misinterpretation

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

a. <u>Study design</u>

- adequacy of the sample size
- 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)
- 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, 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)
- blinding of professional users
- blinding of outcome assessors
- 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 quantification methods for symptoms and outcomes (including validation of the methods)
- 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 assess whether clinical investigations have been defined in such a way as to confirm or refute the manufacturer's claims for the device; these investigations shall include an adequate number of observations to guarantee the scientific validity of the conclusions.

When evaluating procedures for retrieving information about outcomes, evaluators need to take into account if there are significant differences between reporting systems.

In case of vigilance reporting, the evaluators should take into account that expected side-effects and complications of devices are not reportable under the vigilance reporting system. Under-reporting or lack of reporting is therefore common. Therefore, the vigilance system does not typically deliver adequate information about the frequency of expected side-effects and complications. Reliance on reactive reporting systems is inappropriate when proactive studies are required. The data can be used appropriately, i.e. for identification of unexpected risks.

In case of other use data (registers, retrospective analysis of patient dossiers, etc.) quality aspects need to be apprised. The evaluators should take into account that:

- significant differences exist between registers; for instance, they may offer an important or limited coverage of a country;
- 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;
- The retrieval of information about outcomes may be incomplete and unreliable; the evaluators should, for example, take into account the possibility of patients escaping the coverage of a register or the follow-up of a professional when experiencing an adverse outcome.

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 assessment 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, should not be used as proof of adequate clinical performance and safety of the device.

b. <u>Data processing methods</u>

- 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

c. <u>Quality assurance</u>

- compliance with Good clinical practices (GCP), EN ISO 14155, or equivalent standards
- compliance with the clinical investigation plan, independent monitoring and auditing
- peer review

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

d. <u>Report quality</u>

- 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: Contents of the conclusions sections not in line with the results section of the reference)

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. While detail of information may be missing in a publication, it shall be verified to the extent it is available to a third party. In case of missing information, the rating of the methodological quality of a publication may need to be downscaled.

For additional information:

- see Appendix A8 (Appraisal of clinical data - Examples of studies that lack scientific validity for demonstration of adequate clinical performance and/or safety)
- see Appendix A9 (Appraisal of clinical data - Additional aspects for appraisal of the quality of clinical investigations generated and held by the manufacturer Appraisal of clinical data)

10.2. How to determine the relevance of the evidence for the clinical evaluation

10.2.1. Pivotal data

For clinical data supposed to demonstrate adequate clinical performance and safety of the device under evaluation (often referred to as pivotal data), the data must be either generated:

- for the device under evaluation or
- for an equivalent device in its intended use. For equivalent devices, equivalence must be demonstrated. For additional information, see Appendix A1 (Demonstration of equivalence).

10.2.2. Other data

References that are not pivotal are generally appraised and weighted for their contribution in activities 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 assessment of the benefit/risk profile and of specific side-effects of the device under evaluation;
- identifying hazards, including adverse class effects, 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).

10.2.3. Examples

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 assessment of the risk/benefit relationship - determination and justification of criteria for the assessment of acceptability of side-effects - determination of equivalence - justification of the validity of surrogate endpoints
Is the data relevant to the intended use of the device or to claims on the device?	- is representative of the entire intended use with all patient populations and all claims foreseen for the device under evaluation - concerns specific models/ sizes/ settings, or concerns sepcific aspects of the intended use or of claims - does not concern the intended use or claims
If the data are relevant to specific aspects of the intended use 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?	- migraine prophylaxis - treatment of acute migraine - rehabilitation after stroke - etc.
- age group?	- pre-term infants / neonates / children / adolescents / adults / old age
- 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

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10.3. How to weight the contribution of each piece of evidence

Based on its scientific validity and its relevance, the data should be weighted according to its relative contribution. There is no single, well established method for weighting clinical data. The evaluators should identify, in advance, the appropriate criteria to be applied for a specific circumstance. These criteria should be applied consistently.

Typically, evidence generated through a well designed and monitored randomized controlled trial conducted with the device under evaluation in its intended use with patients and users that are representative of the target population should receive the highest weighting.

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

11. Analysis of the clinical data (Stage 3)

11.1. General considerations

The methods available for analysing clinical data generally are either qualitative or quantitative. Given the context within which most medical devices are developed it is most likely that qualitative (i.e. descriptive) methods will need to be used.

Evaluation criteria developed and assigned during the appraisal stage can be used to identify those sets of data which may be considered to be “pivotal” to the demonstration of adequate clinical performance and safety of the device. 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, certainty about the performance 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. Where relevant, a rationale should be given for their lack of value to the evaluation.

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 safety of the device in relation to its intended use. For detailed information on the assessment of the specific Essential Requirements, see Appendix A11.

Any gaps in evidence need to be identified, including 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 use
  - the 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
  - the availability and the benefit/risk profiles of other devices and medical alternatives
  - current standards of care
  - etc.
- the assessment of the specific Essential Requirements, including on
  - safety and the adequacy of pre-clinical testing (e.g. bench testing, animal testing)
  - risks to patients, users or other persons associated with the intended use of the device
  - benefits to patients
  - confirmation that the device achieves the performance(s) intended by the manufacturer
  - confirmation of all claims made by the manufacturer
  - adequacy of the manufacturer's product information, including if risk mitigation measures are correctly addressed in the instructions for use (handling instructions, description of risks, warnings, precautions, contraindications, instructions for managing foreseeable unwanted situations)
- consistency and alignment between the clinical data, the manufacturer's product information, 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;
- consistency between the documents mentioned above and current knowledge/ the state of the art.

Data requirements for addressing the above gaps should be determined so that conclusions can be drawn with confidence in relation to:

- assessment of the safety and the benefit/risk ratio
- compatibility with a high level of protection of health and safety that is currently applicable to the device (as derived from the current knowledge/ the state of the art, and risk minimisation)
- the acceptability of any undesirable side-effects
- the risk of use error and the adequacy of the instructions for use to the intended users,
- consistency between available information

The evaluators should:

- determine compliance with each of the Essential Requirements pertaining to the clinical performance and safety of the device
- determine if additional clinical investigations and other measures are necessary in order to generate any missing data. For additional information, see Appendix A2 (When should additional clinical investigations be carried out?)describe residual risks and uncertainties (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

11.2. Demonstration of adequate clinical performance and safety of a device based on limited clinical data

In general, data that are not methodologically sound (such as single patient reports) should not be used for demonstration of adequate clinical performance and safety of a device.
For additional information, see Appendix A8 (Appraisal of clinical data - Examples of studies that lack scientific validity for demonstration of adequate clinical performance and/or 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 A10 (Devices for unmet medical needs – Aspects to consider).

11.3. 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.
- 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 evidenced justification should be presented in the clinical evaluation report.

12. The Clinical Evaluation Report (CER)

A clinical evaluation report shall be compiled that documents 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).

The contents of the clinical evaluation report shall be cross-referenced to the relevant documents that support them. It shall be clear what contents are substantiated by which evidence, what assumptions have been made, what contents reflect opinions of the evaluators. The report should Include full citations for literature-based data and the titles and investigation codes (if relevant) of any clinical investigation reports, with cross-references to the location in the manufacturer's technical documentation.

The amount of information will differ according to the history of the technology. Where a completely new technology has been developed, the report would need to give an overview of the developmental process and the points in the development cycle at which clinical data have been generated. For long standing technology, a shorter description of the history of the technology could be used.

The clinical evaluation report should explain the criteria and strategies adopted by the evaluators, describe the assumptions made, summarise relevant information in a comprehensive way. 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 use of the device;
  - documents any claims made about the device's clinical performance or safety.
- Stage 1, identification of pertinent data:
  - explains the literature search strategy;
  - presents the nature and extent of the clinical data that have been identified.
- Stage 2, appraisal of pertinent data:
  - explains the criteria used by the evaluators for identifying evidence;
  - summarises the pertinent references/ pieces of data (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 references.
- Stage 3, analysis of the clinical data:
  - explains if and how the referenced information, such as harmonised standards and/or clinical data, constitute sufficient clinical evidence for demonstration of the clinical performance and safety of the device under evaluation;
  - explains whether there is adequate data for all aspects of the intended use and for all products/ models/ sizes/ settings covered by the clinical evaluation.
  - explains 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);
  - discloses any gaps;
  - analyses if there is consistency between the clinical data, the manufacturer's product information, the risk management documentation for the device under evaluation, and whether there is consistency between these documents and the current knowledge/ the state of the art;
  - identifies any discrepancies;

- identifies residual risks and uncertainties (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 shall 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.

The CER should be dated and version controlled.

A suggested format for the clinical evaluation report is located at Appendix A12 (Clinical evaluation reports - 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 A13 (Proposed checklist for the release of the clinical evaluation report).

Information on declaration of interests can be found in Appendix A14 (Information on declarations of interests).

13. The role of the Notified Body in the assessment of clinical evaluations

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.

This section of the document is intended

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

Pursuant to section 6a of Annex I to Directive 93/42/EEC and to section 5a of Annex 1 to Directive 90/385/EEC, 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 of Directive 90/385/EEC. 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 use 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.

13.1. 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 classification of the device 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, post market surveillance plan and post-market clinical follow up.
  - As part of the representative sampling of devices[4] for review of their technical documentation the notified body assesses the clinical evaluation report presented for class IIa[5] and IIb devices and assesses the validity of the conclusions drawn by the manufacturer.
- 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,
  - verifies the manufacturer's assessment of that data and
  - assesses the validity of the conclusions drawn by the manufacturer.

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,
  - verifies the manufacturer's assessment of that data and
  - assesses the validity of the clinical evaluation report and the conclusions drawn by the manufacturer.

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. This arises from the obligation placed on the manufacturer to actively update the clinical evaluation with data obtained from post-market surveillance e.g. post-market clinical follow-up 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 guideline. Any such checklists are intended only as an aide memoir for assessment and should not replace the Clinical Evaluation Assessment Report (CEAR) outlined below.

[4] In accordance with NBOG BPG 2009-4

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

13.2. 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), verifies 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.

13.2.1. 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 is 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, 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;
- if a critical evaluation of relevant scientific literature is provided as the only source of clinical data, the notified body verifies that the device under assessment is demonstrated as equivalent to the device to which the data relates in all necessary areas (i.e. clinical, technical, biological) and that the data adequately addresses each of the relevant essential requirements;
- 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[6];
- 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 post-market surveillance plan in place for the particular device and justified the appropriateness and adequacy of this plan;

[6] Note: A clinical evaluation is required for all classes of medical devices, the relevance of the data or the need for clinical investigation data should always be assessed and documented by the notified body;

- 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 post-market clinical follow up;
- justified the appropriateness of the planned post-market clinical follow up;
- justified and documented if post-market clinical follow-up is not planned as part of the post-market surveillance plan for the device;
- identified the sources of clinical data which will be gathered from the manufacturer's post-market surveillance system and in particular post-market clinical follow up;
- concluded that the contents of the instructions for use are supported by clinical evidence (description of the intended use, 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 benefits and are compatible with a high level of protection of health and safety,

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;
- complete and adequate documentation (according to previous sections);
- adequate procedures (according to previous sections)
- the validity of any justification given;
- the listing, characterisation and 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;
- the use of the list of identified hazards to be addressed through analysis of clinical data as described in section 11;
- 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 EMEA's scientific opinion is unfavourable.

13.2.2. 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. For devices other than class III devices the CEAR should be maintained as a separate document.

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 CER
- Clinical evaluation process
- Clinical evaluation report authors
- Clinical equivalence assessment – if data from equivalent is used
- Clinical investigation assessments and reports
- Justification if no clinical investigation performance
- Instructions for use, labelling and training
- Justification if no post-market clinical follow up is planned
- Post-market surveillance
- Post-market clinical follow up
- 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 application 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 13.2.1 above. One single "unacceptable risk/benefit ratio" leads to a negative conclusion[7];

The clinical evaluation assessment report should:

- 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,

[7] In some cases, the combination of the conditions specified in order to characterise different individual risk/benefit ratios as acceptable may be contradictory or impracticable, and so also leads to an overall negative conclusion. Positive benefit/risk ratios for specific aspects do not compel an overall positive benefit/risk ratio for the device.

- 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 use and benefits, and that side-effects and risks have been properly evaluated
- Record the notified body's assessment of the clinical safety, performance and benefit/risk ratio
- Record the notified body's assessment of the 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 13.2.1.

13.2.3. Clinical data from equivalent devices

The notified body should clearly document its review of clinical data presented from equivalent devices 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 equivalent devices should be clearly evident and assessed by the notified body.

Data from similar devices which may have an impact, or inform the benefit/risk assessment of the device under evaluation should also be considered by the notified body.

The notified body should also assess the level of access to the clinical data from equivalent devices that the applicant manufacturer has, as much will be commercially sensitive and confidential and so its critical appraisal and analysis may not be possible.

13.3. Evaluation as part of quality system related procedures (Annex II.3 of Directive 93/42/EEC)

13.3.1. 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, preclinical 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 post-market surveillance 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).

13.3.2. 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 use, 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.

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

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

13.4. 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 evaluations 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 evaluations in order to:

a. ensure that suitable resources, especially clinical competence necessary for such evaluation, are available within[8] 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 evaluation team should be able to evaluate a risk analysis, the risk management strategy performed by the manufacturer, and the scientific validity of clinical investigations and publications.

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

   Such an evaluation 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 expert should work with the external clinical expert to ensure they are appropriately aware of the relevant legislation, guidelines 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 review and considered as part of the overall certificate decision.

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

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[8] 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 evaluation of 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 post-market surveillance systems in particular post-market clinical follow up 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 evaluations which are based on incomplete, unclear or uncertain datasets should be subject to careful examination.

Clinical evaluations which are based on incomplete clinical investigations or clinical investigations which were halted or terminated earlier than their intended duration should be carefully examined. 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 13.2.2 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 post-market surveillance conducted by manufacturers, vigilance and market surveillance information from competent authorities, post-market clinical follow up 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.

Appendices

A1. Demonstration of equivalence

Pursuant to Annex X of Directive 93/42/EEC and Annex 7 of Directive 90/385/EEC 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 similar severity and stage of disease), and
  - used for the same intended purpose, and
  - used at the same site in the body, and
  - used in a similar population (including age, gender, anatomy, physiology), and
  - have no clinically significant difference in the relevant critical performances according to the expected clinical effect, for a specific intended use, in a similar duration of use.
- 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 intensity of energy, tensile strength, viscosity, surface characteristics, wavelength, surface texture, porosity), 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.

For assuming equivalence,

- all three characteristics (clinical, technical, biological) need to be fulfilled;
- similar underlies 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 safety of the device under evaluation;
- 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;
  - 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 shall be justified.
  - abrasion, if relevant, and host response to particles may also need to be considered;
  - when changing materials, demonstration of biocompatibility is not an acceptable substitute for a comprehensive demonstration of equivalence.
- The only clinical data that are considered as relevant are the data obtained when the equivalent device:
  - is a medical device that conforms to the requirements of the medical device directives and
  - is used in accordance with its intended use as documented in the instructions for use.

Example showing where equivalence could be applied:

- The manufacturer adds a new guidewire to its family of guidewires that are already CE marked, where tolerance on tip angle is tightened (nominal unchanged), and modifications are made to the packaging.

Examples where equivalence cannot be applied:

- A catheter for delivery of a stent is designed by analogy to CE marked catheters in the market, but with an integrated pressure sensor in the tip of the catheter (while the compared device does not have an integrated pressure sensor), that will measure physiological parameters in the heart and blood vessels.
- A pulmonary balloon dilatation catheter with the same materials but a significantly different shape.
- A pulmonary balloon dilation catheter, when the materials used in existing CE-marked products are unknown but presumed to meet ISO 10993.
- A medical device using ultrasound for renal denervation while the CE-marked device uses radiofrequency energy.
- A spinal device requiring anterior access while the CE-marked device requires posterior access.

A2. When should additional clinical investigations be carried out?

a. General 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(s) 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, however, depends on the ability of the existing data to adequately address the identified benefits, risks, and claims. 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 safety.

Special attention should be given to aspects such as

- new design features, including new materials,
- new intended uses (including new medical indications),
- new claims,
- 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 that in contact with intact skin),
- issues raising when medical alternatives with lower risks or more extensive benefits to patients are available or become newly available,
- whether the data of concern are amenable to evaluation through a clinical investigation.

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

When clinical data is required in order to draw conclusions as to the conformity of a device to the Essential requirements, the data needs to be in line with current knowledge/ the state of the art, be scientifically sound, cover all aspects of the intended use, 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.

A3. Device description – typical contents

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

- 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, and its sales volumes
- Intended use of the device
  - exact medical indications
  - name of disease or condition/ clinical form, stage, severity/ symptoms or aspects to be treated/ managed/ diagnosed
  - patient populations (adults / children / infants, other aspects)
  - intended user
  - hospital use / home care / other
  - 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/ optional precautions
  - single use / reusable
  - other aspects
- General description of the medical device including
  - a concise physical description
  - the techniques used, the technical specifications, mechanical characteristics
  - sterility
  - radioactivity
  - how the device achieves its intended purpose
  - 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 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 product information (label, instructions for use, accompanying documents possibly foreseen by the manufacturer)

A4. Data that are generated and held by the manufacturer

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

- All pre-and post-market clinical investigations

- all clinical data generated from risk management activities and the post-market surveillance programmes which the manufacturer runs in Europe and in other countries, including the following items (not a complete list):
  - post-market clinical follow-up studies, including registries sponsored by the manufacturer
  - post-market surveillance reports
  - the literature search and evaluation reports for post-market surveillance
  - 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)
  - details of all field safety corrective actions
  - use as a custom made device
  - use under compassionate use/ humanitarian exemption programs
  - other user reports

- Pre-clinical studies

A5. Literature searches - Sources of literature

There are different sources of clinical literature that can be searched for clinical evaluation. Important sources include the following:

- Scientific literature databases
  - Databases should be preferred that also ensure a thorough search of European journals, contain up to date information, and allow searches by device name and manufacturer (e.g. EMBASE).
  - If the literature search plan foresees other scientific databases (e.g. MEDLINE / Pubmed) with less coverage, reduced actuality and reduced search features, a justification should be presented.

- Internet searches
  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 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 Maude database held by US FDA, possibly other sites.
  - Implant registry reports.
  - Documents available in systematic review databases (e.g. the Cochrane Database 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.

- 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 instructions for use 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 are usually screened:
  - Literature found to be relevant is likely to cite other literature that is of direct interest to the manufacturer.
  - It may be necessary to retrieve some of the referenced literature in order to appraise the scientific quality of a document.

A6. Literature searches - Literature search protocol, key elements

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 importance of a literature search protocol is for critical appraisal of the methods. The search strategy should be based on carefully constructed review questions.

Established methods should be considered, such as

- PICO (patient characteristics, type of intervention, 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)

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

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

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

1. Background

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

- Importance of review to risk management process
  The literature review will provide data on current interventions/therapies for the intended patient population (state of the art) in order to give input to the assessments of acceptable benefit/risk ratios, 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
- If including equivalent devices, establish equivalence to the device in question

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

2. Objective

This section documents the research question(s), which should be carefully constructed using a process (e.g. PICO):

- Population(s)/disease(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 device performance including any claims on clinical performance and safety which the manufacturer wants to use. Also information from the risk management process is needed as an input.

3. Methods

The methods section of the protocol documents the plans for study selection, data collection, and analysis methods.

The study selection plan defines the literature search strategy and the inclusion/exclusion of documents found. The involvement of information retrieval experts will help to optimize literature retrieval. The literature search protocol should include:

- the sources of data that will be used and a justification for their choice;
- the extent of any searches of scientific literature databases (the database search strategy);
- 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; and
- strategies for avoiding retrieving publications of data generated and already held by the manufacturer;
- data collection and 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 analysis plan defines the methods for analysing the data including data processing and transformation.

A7. Literature searches - A possible template for a literature search protocol

[Three main sources: Esther's Proposal, proposal of Jeremy/Gert/Danielle, N2R7 Document]

1. Background

- Device name/model
- Importance of review to risk management process
- Previous literature searches conducted by the manufacturer
- If including equivalent devices, include name and model of the device and establish equivalence to the device under evaluation

2. Objective (should be consistent with the scope of the clinical evaluation)

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

3. Methods

- Study selection plan

i. *Define literature search for identifying studies*

- Attempts to identify all published literature
- Determining and justifying which electronic databases are to be searched
- Determining and justifying the extent of any Internet searching and searching non-published information, including the search strategy
- Defining exact search terms and any limits
- Setting limits for start and end dates of each search

ii. Define criteria for selecting relevant literature

- Inclusion criteria
- Exclusion criteria
- Justification of the inclusion and exclusion criteria, including strategies for addressing potential duplications of data
  - duplication across multiple publications/literature,
  - duplications of published data with data that was generated and is already held by the manufacturer

References

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D.G., The PRISMA Group. (2010). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. *International Journal of Surgery*, *8*: 336-341.

Higgins, J.P.T, & Green, S. (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

1 Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D., Moher, D., Becker,
2 B.J., Sipe, T.A., & Thacker, S.B.(2000). Meta-analysis of observational studies in epidemiology: a
3 proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.
4 *Journal of American Medical Association, 283(15):*2008-2012.

A8. Appraisal of clinical data - Examples of studies that lack scientific validity for demonstration of adequate clinical performance and/or 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 investigation planned to investigate
- side-effects that have been observed
- confidence intervals/ calculation of statistical significance
- if there are intent-to-treat and perprotocol populations: definitions and results for the two populations

b. Numbers too small for statistical significance

Includes reports and publications based on inconclusive, preliminary, pilot or anecdotal experience, hypothesis papers, 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 distribution of data (e.g. Gaussian distribution with its calculations of mean values, standard deviations, confidence intervals, t-tests, others tests), while the 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).
- in case of other influencing factors (e.g. in 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 comparisons with external or historic data (such as drawing conclusions by comparing data from a clinical investigation with registry data or with data from published literature).

Different types of studies allow to draw adequate conclusions in these situations, such as randomised controlled trials, cross-over trials, or trials with 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.

A9. Appraisal of clinical data - 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 final report (for investigations that are terminated);
- the latest intermediate report and the latest collation on serious adverse events (for investigations that are ongoing).

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 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 final 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 inferences that can be drawn about the performance and safety of the device from the investigation.

The final report should be signed by its author and appropriate reviewers to provide assurance that the final 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 the current applicable ethical standards that have their origin in the Declaration of Helsinki and in accordance with applicable regulations. Clinical investigations not in compliance with applicable ethical standards, medical device standards (for example EN ISO 14155 or comparable standards) or regulations should be rejected. The reasons for rejection of the investigation should be noted in the report.

A10. Devices for unmet medical needs – Aspects to consider

Like all medical devices, medical devices for unmet medical needs must fully comply to 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.

a. Breakthrough products

In exceptional cases, benefits may legitimate relatively high levels of uncertainties, and access to the market 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 shall fully disclose the situation and address the following items in the clinical evaluation report:

- the exact indication the product was developed for and where residual risks and uncertainties were considered acceptable (often a niche indication);
- explanations why current medical alternatives are considered to be insufficient or to carry significant risks;
- explanations on the benefits delivered by the device under evaluation;
- whether the instructions for use clearly describe
  - exact indications and any limitations of the intended use,
  - the limited clinical experience,
  - uncertainties about residual risks and benefits to patients;

  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.
- the need to set up a stringent post-market clinical follow-up (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 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:
    - devices that carry significant risks (i.e. expected to cause serious adverse events), or
    - devices for rare diseases;
- the clinical evaluation needs to be updated when new information become available and at least annually in the absence of new information.

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

b. Devices that enter the market subsequent to a therapeutic breakthrough

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 breakthrough, clinical evidence is likely to have evolved rapidly since the first breakthrough device became available.
- The evaluators shall not assume that a device can enter the market based on the limited evidence that was acceptable for earlier devices. With the evolving body of evidence, entering the market with large uncertainties may no longer be legitimate.
- PMCF studies should also be foreseen for devices that enter the market subsequent to a therapeutic breakthrough product.

A11. Analysis of the clinical data - Guidance to the assessment of the specific Essential Requirements

While this appendix describes 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.

1. Conformity assessment with requirement on safety (MDD ER1 / AIMDD ER1)

The manufacturer's product information (including label, instructions for use, accompanying documents possibly foreseen by the manufacturer), should be reviewed to ensure they are consistent with the relevant clinical data 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.

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. Risks regarding electrical hazards are acceptable under these circumstances and *do not need clinical data* to be evaluated and proven.
- 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. Also, 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.

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 risk 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).

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

It is expected,

- that the clinical evaluation demonstrates that any risks which may be associated with the intended use 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 instructions for use correctly describe the intended use of the device as supported by sufficient clinical evidence; and
- that the instructions for use 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).

Assessment of the description of the intended use of the device

The product literature and instructions for use should be reviewed. The evaluators should assess 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 instructions for use, there should be no uncertainties for users as to when a given medical condition or target population is covered by the CE marking or when it falls entirely under the user's own responsibility (off label use).

Assessment 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, they may include:

- clinical outcome (such as the probability of adverse outcomes, e.g. mortality, morbidity, improvement of impaired body function); for diagnostic medical devices, demonstration of impact of diagnosis on clinical outcomes,
- demonstration of impact of diagnosis on clinical outcomes (for diagnostic medical devices),
- 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), 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).

Quantification of benefit(s) to the patients:

- Defining specified endpoints is indispensable for setting up clinical investigations and properly performing the literature search, appraisal of the clinical data, and analysis of the clinical data.
- Benefit(s) are often assessed 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, is what allows determining 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 shall 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 a 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 assessing 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)

- The duration should be predictable (for example as a statistical distribution) on the basis of sound clinical data and appropriate statistical approaches.
- Post-Market Clinical Follow-up 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.

<u>Assessment 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.

Post-market surveillance 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 adverse events (particularly serious events and deaths, stratified into whether the manufacturer considers them to be device-related or not) and estimates of the incidence of adverse events.

Post-marketing data about adverse events are generally more meaningful when related to usage but caution is needed because the extent of spontaneous reporting may vary considerably between countries and between users. Considerable under-reporting must be 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 summarizing device-related adverse events, paying particular attention to serious adverse events, with comments on whether observed device-related adverse events 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 - will have to be addressed:

- Nature severity, number and rates of harmful events associated with the use of the device:
  - Device-related serious adverse events: 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 adverse 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 event.
  - Procedure-related adverse events: Harm to the patient that results from use of the device but is not caused by the device itself. For example, anesthetic-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 product information such as inclusion of contraindications in the instructions for use).

Assessment of acceptability of the benefit/risk ratio

The evaluators will assess if the clinical data on benefits and risks are acceptable

- for all medical conditions and target populations covered by the intended use when compared with the current state of the art in the corresponding medical field and whether limitations shall 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:
  - Therapeutic background
    - information on disease state(s) to be treated
    - prevalence of disease(s)
    - natural course
  - other devices, medical alternatives available to the target population, including evidence of clinical performance and safety
    - historical treatments
    - current treatments (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 safety profile. The selection of clinical data that characterises the state of the art shall be objective and not selective of data on the basis of being favourable for the device under assessment. Information shall 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 shall 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 ratio 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 instructions for use.
- 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-ratio 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 IFU, clinical evaluation report, summary of safety and clinical performance and other relevant documentation.

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.

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.

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

Aspects of assessment of clinical performance can widely vary between device groups, especially between therapeutic and diagnostic devices. The following list shows examples of aspects that are seen in 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

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

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

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

- the nature, severity and frequency of potential side-effects need to be known;
- the clinical data should contain an adequate number of observations to guarantee the scientific validity of the conclusions relating to side-effects and the performance of the device;
- in order to assess if side-effects are acceptable, consideration has to be given to the state of the art, including properties of benchmark devices and other options that are currently available to the patients.

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

Example:

A reasonable probability (80%) of observing at least one event of a side-effect when 15 subjects are studied requires a side-effect with an actual probability of 10%.I 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 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 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

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A12. Clinical evaluation reports - 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.

Table of contents	Example of contents
1. Summary	Executive summary, summary for external purposes.
2. Scope of the clinical evaluation	See 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 conforms to Council Directive 90/385/EEC as amended by directive 2007/47/EC, or to Council Directive 93/42/EEC as amended by directive 2007/47/EC. Changes since the last report, whether the device has been modified, identification of new products, models, sizes, software, accessories, new intended uses, new claims, new events with an impact on clinical evaluation. Identification of the sections of this clinical evaluation report that are concerned with the new information and have been modified. Other aspects
3. Current knowledge, state of the art	
3.1. Medical field concerned by the device	Identification of medical fields concerned/ relevant medical conditions.
3.1.1. Identification of pertinent data	See Section 9 and Appendices A4-A7. Brief summary and justification of the literature search strategy applied for retrieval of information 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.
3.1.2. Evaluation of the data	See Appendix A11. 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 nature, extent, probability and duration of benefit to the patients, of other

	clinical performance, and of detrimental effects (side-effects, other risks), acceptability of side-effects and other risks (including the nature, severity, probability and duration of acceptable harm). Class effects and adverse class effects that could be relevant to the device under evaluation, their mechanisms, 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	See Appendix 3.
4.1. Status of the device and its history	Whether the device is already CE marked, whether it is on the market, since when, in what regions, history of the device, date of past modifications with reasons and description, sales volumes.
4.2. Description	Concise physical 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 use as described in the device's instructions for use, with exact medical indications and contraindications. 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. Mandatory precautions, optional precautions. Claims on clinical performance and safety foreseen by the manufacturer.
4.3. Use of clinical data	See Section 11 and Appendix A1. Whether the clinical evaluation is based on scientific literature/ clinical investigations/ a combination of both, or whether demonstration of conformity with essential requirements based on clinical data is not deemed appropriate. Where demonstration of conformity with essential requirements based on clinical data is not deemed appropriate, considerations on the output of the risk management process, the device-body interaction, the intended use and the claims of the manufacturer. Reasons why clinical data are not necessary according to these considerations. Summary of bench testing and pre-clinical evaluation, description and justification of assumptions made, of parameters and models used, justification of the adequacy of bench testing and pre-clinical evaluation in the absence of clinical data.

4.4. Equivalence	(only if equivalence is claimed). See Appendix A1.
4.4.1. 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).
4.4.2. Demonstration of equivalence - Clinical characteristics - Biological characteristics - Technical characteristics	Justification of equivalence, description of relevant clinical, biological and technical characteristics that affect clinical properties of the device, differences between the intended use 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 (methods, results, conclusions of the authors), evaluation of the methodological quality of the study or reference, the scientific validity of the evidence. 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 safety of the device, reasons for assumptions made.
4.4.3. Conclusions concerning equivalence	Whether the comparison carried out covers all products/ models/ sizes/ settings/ accessories and the entire intended use of the device under evaluation, or only certain products/ models/ sizes/ settings/ accessories, or selected aspects of the intended use, 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 safety of the device under evaluation; description of any limitations and gaps.
4.5. Clinical data	
4.5.1. Clinical data generated and held by the manufacturer	See Section 9.1 and Appendix A4. Disclosure of all clinical data generated and held by the manufacturer.
4.5.2. Identification of scientific literature	See Section 9.2 and Appendices A4-A7. 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.
4.5.3. Summary and appraisal of clinical data	See section 10 and Appendix A8-A10. Summary of clinical data generated and held by the manufacturer and of literature found to be pertinent. Including brief summary of the studies or references (methods, results, conclusion of the

- Feasibility studies - Confirmatory studies - PMCF studies - Use data	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 reference, reasons for rejecting some of its contents.
5. Analysis of clinical data	
5.1. Requirement on safety (MDD ER1 / AIMDD ER1)	See Section 11 and Appendix A11.1. Summary of conformity assessment with requirement on safety (MDD ER1 / AIMDD ER1). Analysis whether there are special design features that pose special performance or safety concerns (e.g. presence of medicinal, human or animal components) that where identified in the device risk management documentation and that required assessment from a clinical perspective, and whether these have been adequately addressed. Whether the risks identified in the risk management documentation and literature have been addressed by the clinical data. 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 manufacturer's product information, and the risk management documentation for the device.
5.2. Requirement on acceptable benefit/risk ratio (MDD ER1 / AIMDD ER1)	See Section 11 and Appendix A11.2. Summary of conformity assessment with requirement on acceptable benefit/risk ratio (MDD ER1 / AIMDD ER1). Summary of the total experience with the device, including numbers and characteristics of patients exposed to the device; and duration of follow-up. Nature, extent/severity, probability, duration of benefits to the patients and of side-effects and other risks. For each aspect of the intended use, whether the benefit/risk profile including its uncertainties is compatible with a high level of protection of health and safety, corresponding justifications.
5.3. Requirement on performance (MDD ER3 / AIMDD ER2)	See Section 11 and Appendix A11.3. Summary of conformity assessment with requirement on performance (MDD ER3 / AIMDD ER2). Description of clinical performance. For each intended performance, extent to which assessment of benefits is possible based on available data, limitations of the data, description of gaps, uncertainties, and assumptions. whether available data allows adequate assessment of performance, limitations of the data, gaps, uncertainties. Whether there is sufficient evidence for every intended performance.
5.4. Requirement on acceptability of side-	See Section 11 and Appendix A11.4.

effects (MDD ER6 / AIMDD ER5)	Summary of conformity assessment with requirement on acceptability of side-effects (MDD ER6 / AIMDD ER5). Whether the data available is of sufficient amount and quality for the detection of side-effects and their frequency, limitations of the data, description of gaps, uncertainties, and assumptions. Whether the side-effects are acceptable and corresponding justifications.
6. Conclusions	See Sections 11. Clear statement concerning compliance to Essential requirements. Adequacy of the product information, whether the intended use and risk reduction measures are adequate, its suitability for the intended users and usability aspects. Adequacy of claims foreseen by the manufacturer, identification of discrepancies and gaps. Description of residual risks and uncertainties that are acceptable for CE-marking and should be followed during PMS (uncertainties regarding medium- and long term performance, safety under wide-spread use, residual risks such as 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.
7. Date of the next clinical evaluation	See section 7.2.3. Suggested date, justification of the date.
8. Signatures of the responsible evaluators	See Section 12. Statement that the evaluators agree with the contents of the report, dates, names and signatures.
9. Qualification of the responsible evaluators	See section 7.4.
10. References	See section 12.

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A13. 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 hold by the manufacturer, are all data disclosed 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 safety of the device?
- If the product is already in the market in Europe or elsewhere, has the latest PMS/ PMCF been taken into consideration and has it been summarised and referenced in the report?
- In respect to current knowledge/ the state of the art,
  - 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 relationship and the side-effects are acceptable in relation to current knowledge/ the state of the art?
- If the reports covers several models/ sizes/ settings and/or different clinical situations, is there valid 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?
    (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 groups)
  - 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?
- Does the IFU 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 that should be addressed with PMS/ PMCF studies?
- 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?

A14. Information on declarations of interests

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

Declarations of interest 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 reviewer, children and adults for whom the reviewer 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
- grants
- 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)
- other interests or sources of revenues

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