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GUIDELINES ON MEDICAL DEVICES

**CLINICAL EVALUATION:
A GUIDE FOR MANUFACTURERS AND NOTIFIED
BODIES**

The present guidelines are part of a set of guidelines relating to questions of application of EU-Directives on MEDICAL DEVICES. They are legally not binding. The guidelines have been carefully drafted through a process of intensive consultation of the various interested parties (competent authorities, Commission services, industries, other interested parties) during which intermediate drafts were circulated and comments were taken up in the document. Therefore, this document reflects positions taken by representatives of interested parties in the MEDICAL DEVICES sector.

These guidelines incorporate changes introduced by Directive 2007/47/EC amending Council Directive 90/385/EEC and Council Directive 93/42/EEC and will be applicable as of 21st March 2010. The transitional period allowing a gradual implementation of the guidelines will therefore end on 20 March 2010.

Note:

This document is a revision of an earlier document published in April 2003 as MEDDEV 2.7.1

This document has been drafted on the basis of GHTF Guideline SG5/N2R8:2007 Clinical Evaluation of 29 June 2007 published at www.gh tf.org

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Preface

These guidelines on Clinical Evaluation are part of a set of Medical Device Guidelines that promote a common approach by Manufacturers and Notified Bodies involved in clinical evaluation procedures according to the relevant annexes of the Medical Devices Directives and by the National Competent Authorities charged with safeguarding public health.

They have been carefully drafted through a process of consultation with various interested parties during which comments were taken up in the documents. Therefore, it reflects positions taken in particular by representatives of National Competent Authorities and Commission Services, Notified Bodies, industry and other interested parties in the MEDICAL DEVICES sector.

The guidelines are regularly updated accordingly with regulatory developments. The latest version of the guidelines should always be used. This revision of these guidelines has:

- amended the document according to the most recent amendment to the Medical Device Directives (Directive 2007/47/EC) and in the light of experience
- and has carefully considered and transposed into the European context the Global Harmonisation Task Force (GHTF) international regulatory guidance document on clinical evaluation (SG5/N2R8:2007).

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

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

However, only the text of the Directives is authentic in law. On certain issues not addressed in the Directives, national legislation may be different from these guidelines.

1. Introduction

What is clinical evaluation?

Clinical evaluation is the assessment and analysis of clinical data pertaining to a medical device in order to verify the clinical safety and performance of the device.

When is clinical evaluation undertaken?

Clinical evaluation is an ongoing process conducted throughout the life cycle of a medical device. It is first performed during the conformity assessment process leading to the marketing of a medical device and then repeated periodically as new clinical safety and performance information about the device is obtained during its use. This information is fed into the ongoing risk analysis and may result in changes to the Instructions for Use.

Why is clinical evaluation important?

When placing a medical device on the market the manufacturer must have demonstrated through the use of appropriate conformity assessment procedures that the device complies with the relevant Essential Requirements covering safety and performance. Generally, from a clinical perspective, it is expected that the manufacturer has demonstrated the device achieves its intended performance during normal conditions of use and that the known and foreseeable risks, and any adverse events, are minimised and acceptable when weighed against the benefits of the intended performance, and that any claims made about the device's performance and safety (e.g. product labelling and instructions for use) are supported by suitable evidence.

With regard to post market activities, manufacturers are expected to implement and maintain surveillance programs that routinely monitor the clinical performance and safety of the device as part of their Quality Management System. The scope and nature of such post market surveillance should be appropriate to the device and its intended use. Using data generated from such programs (e.g. safety reports, including adverse event reports; results from published literature, any further clinical investigations and formal post market surveillance studies; etc), a manufacturer should periodically review performance, safety and the benefit-risk assessment for the device through a clinical evaluation, and update the clinical evidence accordingly. This ongoing clinical evaluation process should allow manufacturers to communicate with conformity assessment bodies and Regulatory Authorities in accordance with local reporting requirements, any information that has an important bearing on the benefit-risk assessment of the device or that would indicate a need for labelling changes regarding contraindications, warnings, precautions or instructions for use etc.

What is the process?

To conduct a clinical evaluation, a manufacturer needs to:

- identify the Essential Requirements that require support from relevant clinical data;
- identify available clinical data relevant to the device and its intended use;
- evaluate data in terms of its suitability for establishing the safety and performance of the device;
- generate any clinical data needed to address outstanding issues;

- bring all the clinical data together to reach conclusions about the clinical safety and performance of the device.

The results of this process are documented in a clinical evaluation report. The clinical evaluation report and the clinical data on which it is based serve as the clinical evidence that supports the marketing of the device.

The clinical evidence, along with other design verification and validation documentation, device description, labelling, risk analysis and manufacturing information, is needed to allow a manufacturer to demonstrate conformity with the Essential Requirements and is part of the technical documentation of a medical device.

How detailed should the clinical evaluation be?

A clinical evaluation should be thorough and objective (i.e. it should consider both favourable and unfavourable data), with the intention of demonstrating valid clinical evidence of the safety and performance of the device. However, 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 incremental innovation, so they are not completely novel. Thus, it is often possible to draw on the clinical experience and literature reports of the safety and performance of equivalent devices to establish the clinical evidence, thereby reducing the need for clinical data generated through clinical investigation of the device in question. Similarly, it may be possible to use compliance with recognised standards to satisfy the clinical evidence requirements for devices based on technologies with well established safety and performance characteristics.

The depth and extent of clinical evaluations should be flexible, not unduly burdensome, and appropriate to the nature, classification, intended use, manufacturer's claims and risks of the device in question. Therefore, this guidance is not intended to impose specific requirements.

2. Scope

The primary purpose of this document is to provide manufacturers and notified bodies with guidance on how to conduct and document the clinical evaluation of a medical device as part of the conformity assessment procedure prior to placing a medical device on the market as well as to support its ongoing marketing. It is also intended to provide guidance to regulators and other stakeholders when assessing clinical evidence provided by manufacturers.

This document provides the following guidance:

- general principles of clinical evaluation;
- how to identify relevant clinical data to be used in a clinical evaluation;
- how to appraise and integrate clinical data into a summary; and
- how to document a clinical evaluation in a clinical evaluation report.

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

3. References

European Legislation

Council Directive 90/385/EEC of 20 June 1990 concerning active implantable medical devices

Council Directive 93/42/EEC of 14 June 1993 concerning medical devices

GHTF final documents

SG1/N011:2008	<i>Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED)</i>
SG1-N44:2008	<i>Role of Standards in the Assessment of Medical Devices</i>
SG1/N029:2005	<i>Information Document Concerning the Definition of the Term “Medical Device”</i>
SG1/N040:2006	<i>Principles of Conformity Assessment for Medical Devices</i>
SG1-N41R9:2005	<i>Essential Principles of Safety and Performance of Medical Devices</i>
SG5/N1R8:2007	<i>Clinical Evidence – Key definitions and Concepts</i>
SG5/N2R8:2007	<i>Clinical Evaluation</i>

International standards

<i>ISO 14155-1: 2003</i>	<i>Clinical investigation of medical devices for human subjects – Part 1 General requirements</i>
<i>ISO 14155-2: 2003</i>	<i>Clinical investigation of medical devices for human subjects – Part 2 Clinical investigation plan</i>
<i>ISO14971: 2007</i>	<i>Medical devices – application of risk management to medical devices.</i>

European guidance documents

MEDDEV 2.10/2	Designation and monitoring of Notified Bodies within the framework of EC Directives on medical devices
MEDDEV 2.12/2	Guidelines on post-market clinical follow up
NBOG BPG 2009-1	Guidance on design dossier examination and report content http://www.nbog.eu/resources/NBOG_BPG_2009_1.pdf
NBOG BPG 2009-4	Guidance on NB’s Tasks of Technical Documentation Assessment on a Representative Basis http://www.nbog.eu/resources/NBOG_BPG_2009_4_EN.pdf

4. Definitions

Adverse Event: Any untoward medical occurrence in a subject.
Note: For the purposes of this document, this is intended to include any adverse event whether device related or not

Clinical Data: Safety and/or performance information that are generated from the use of a medical device. *(This term is further explained in GHTF document SG5/N1R8:2007)*

Clinical Evaluation: The assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer. *(This term is further explained in GHTF document SG5/N1R8:2007)*

Clinical Evidence: The clinical data and the clinical evaluation report pertaining to a medical device. *(This term is further explained in GHTF document SG5/N1R8:2007)*

Clinical Investigation: Any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety and/or performance of a medical device. *(This term is further explained in GHTF document SG5/N1R8:2007)*

Clinical Investigation Plan: Document that states the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation.

Clinical Investigator: The individual responsible for the conduct of a clinical investigation who takes the clinical responsibility for the well-being of the subjects involved.

Clinical Performance: The ability of a medical device to achieve its intended purpose as claimed by the manufacturer.

Clinical Safety: The absence of unacceptable clinical risks, when using the device according to the manufacturer's Instructions for Use.

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

Serious Adverse Event: An adverse event that

- 1 led to a death;
- 2 led to a serious deterioration in health of a patient, user, or others that:
 - (a) results in a life threatening illness or injury;
 - (b) results in a permanent impairment of a body structure or body function;
 - (c) requires in patient hospitalisation or prolongation of existing hospitalisation
 - (d) results in medical or surgical intervention to prevent permanent impairment to body structure or a body function;
 - (e) led to foetal distress, foetal death or a congenital abnormality/birth defect.

Harmonised Standards: Standards deemed to offer the presumption of conformity to the Essential Requirements of the Directives.

Technical Documentation: The documented evidence, normally an output of the quality management system that demonstrates compliance of a device to the Essential Requirements.

5. General principles of clinical evaluation

5.1 What is the scope of a clinical evaluation?

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. This includes data specific to the device in question as well as any data relating to devices claimed as equivalent by the manufacturer.

The evaluation must also address any clinical claims made about the device, the adequacy of product labelling and product information (particularly claims, contraindications, precautions/warnings), and the suitability of instructions for use.

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. Considerations should include:

(a) whether there are any design features of the device or target treatment 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 and method of application) and the specific claims made by the manufacturer about the clinical performance and safety of the device. 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;

(b) whether data from equivalent devices can be used to support the safety and/or performance of the device in question.

The devices should have the same intended use and will need to be compared with respect to their technical and biological characteristics. These characteristics should be similar to such an extent that there would be no clinically significant difference in the performance and safety of the device. The *intended use* relates to the clinical condition being treated, the severity and stage of disease, the site of application to/in the body and the patient population; the *technical characteristics* relate to the design, specifications, physiochemical properties including energy intensity, deployment methods, critical performance requirements, principles of operation and conditions of use; and *biological characteristics* relate to biocompatibility of materials in contact with the same body fluids/tissues. In such cases the manufacturer is expected to include the supporting non clinical information within the technical documentation for the device and cite its location within the clinical evaluation report. (Note: the clinical evaluation is not intended to assess the technical and biological characteristics *per se*); and

(c) the data source(s) and type(s) of data to be used in the clinical evaluation.

Manufacturers are able to draw on any one or combination of data sources set out in Section 6.0. Factors that should be considered when choosing the type of data to be used in the clinical evaluation include the design, intended use and risks of the device; the developmental context of the technology on which the device is based (new vs. established technology); and, for established technology, the proposed clinical application of that technology. Clinical evaluation of medical devices that are based on existing, well established technologies and intended for an established use of the technology is most likely to rely on compliance with recognised standards and/or literature review and/or clinical experience of equivalent devices.

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. Therefore for implantable or class III devices, clinical investigations are required unless it can be duly justified to rely on existing clinical data alone, as stated in the annex X of Directives 93/42/EEC and annex 7 of 90/385/EEC as amended. The manufacturer will need to give consideration to the advantages and limitations of each data type.

5.2 How is a clinical evaluation performed?

Once the scope has been defined, there are three distinct stages in performing a clinical evaluation (Figure 1):

- identification of pertinent standards and clinical data;
- appraisal of each individual data set, in terms of its relevance, applicability, quality and clinical significance; and
- analysis of the individual data sets, whereby conclusions are reached about the performance, safety and presentational aspects (labelling, patient information and instructions for use) of the device.

Each of these stages is covered in separate sections later in this document.

At the end of the clinical evaluation a report is prepared and combined with the relevant clinical data to form the clinical evidence for the device. If the manufacturer concludes there is insufficient clinical evidence to be able to declare conformity with the Essential Requirements, the manufacturer will need to generate additional data (e.g. conduct a clinical investigation, broaden the scope of literature searching) to address the deficiency. In this respect clinical evaluation can be an iterative process.

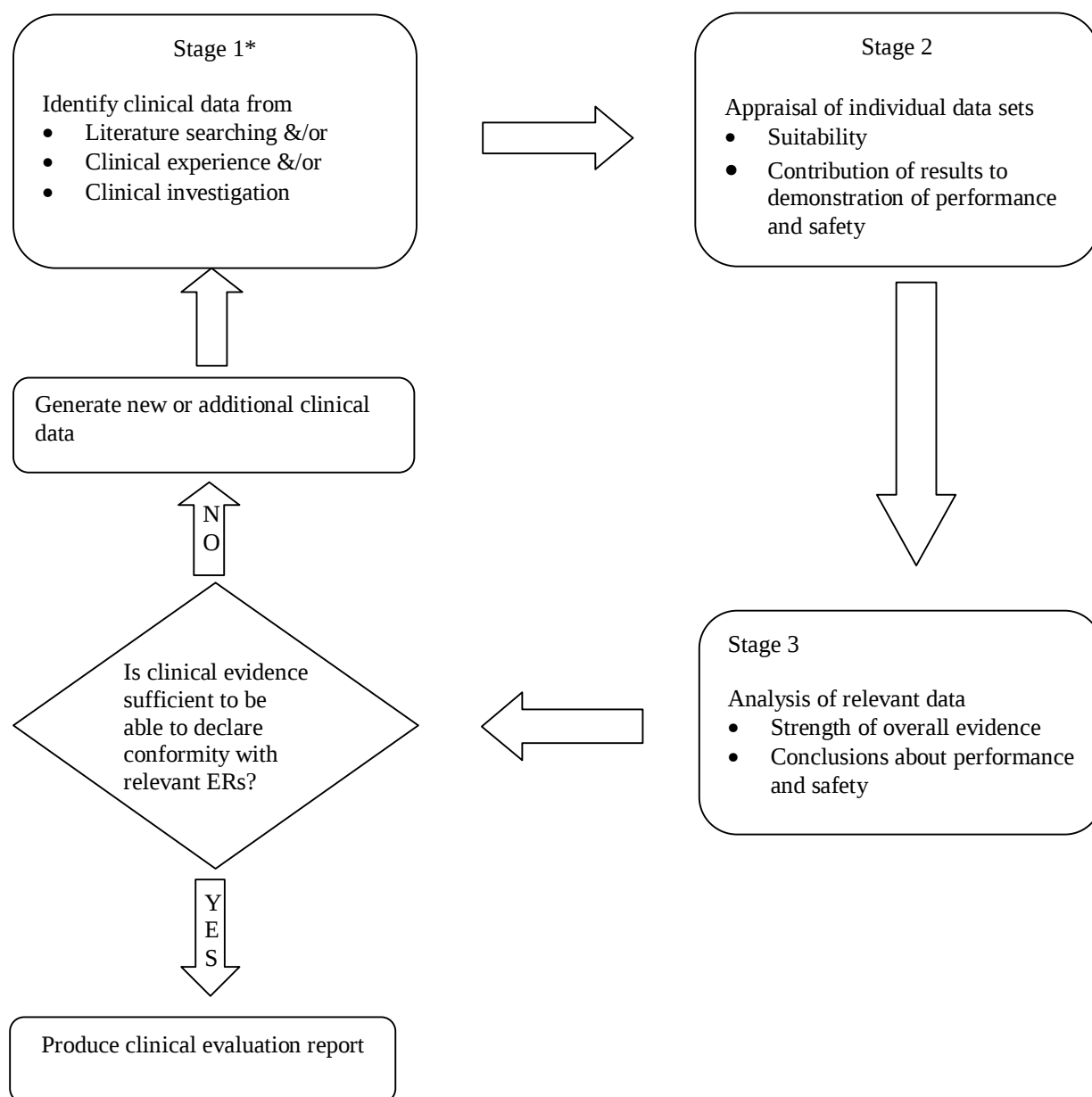
5.3 Who should perform the clinical evaluation?

The clinical evaluation should be conducted by a suitably qualified individual or individuals. A manufacturer must be able to justify the choice of the evaluator(s) through reference to qualifications and documented experience.

As a general principle, evaluators should possess knowledge of the following:

- the device technology and its application;
- research methodology (clinical investigation design and biostatistics); and
- diagnosis and management of the conditions intended to be treated or diagnosed by the device.

Figure 1: Stages of clinical evaluation



*Conformity to harmonized performance standards may be sufficient to demonstrate compliance to relevant Essential Requirements (ERs)

6. Sources of data/documentation used in a clinical evaluation (Stage 1)

Data relevant to the clinical evaluation may be held by the manufacturer (e.g. manufacturer sponsored pre and post market investigation reports and adverse event reports for the device in question) or in the scientific literature (e.g. published articles of clinical investigations and adverse event reports for the device in question or for equivalent devices).

The manufacturer is responsible for identifying data relevant to the device and determining the types and amount of data needed for the clinical evaluation.

Where data are used from a combination of sources, the principles applicable to each source apply to that data component within the clinical evaluation.

6.1 Data generated through literature search

Literature searching can be used to identify published clinical data that is not in the possession of the manufacturer that may assist the manufacturer to establish acceptable performance and safety of a medical device. The data generated through literature searching 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) or to equivalent devices.

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.

Published data will need to be assessed with respect to its possible contribution and weighting in establishing both the performance of the device in question and its safety. Papers considered unsuitable for demonstration of performance because of poor study design or inadequate analysis may still contain data suitable for assessing the safety of the device.

The key elements of literature search

The search strategy should be based on carefully constructed review questions. A protocol should be developed to identify, select and collate relevant publications to address these questions. This should be developed and executed by persons with expertise in information retrieval, having due regard to the scope of the clinical evaluation set out by the manufacturer.

The involvement of information retrieval experts will help to maximise data 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 to be applied to published literature and justification for their choice; and
- strategies for addressing the potential for duplication of data across multiple publications;

Once the literature search has been executed, a report should be compiled to present the results of the search. A copy of the protocol should be included and any deviations noted. A possible format for the literature search report is located at Appendix A.

It is important that the literature search is documented to such a degree that the methods can be appraised critically, the results can be verified, and the search reproduced if necessary. A possible methodology is presented in Appendix B.

Which data/documentation from the literature search should be included in the clinical evaluation?

The following documentation should be used in the clinical evaluation by the clinical evaluator:

- the literature search protocol;
- the literature search report; and
- published articles and other references identified as being relevant to the device in question and suitable for evaluation.

The literature search protocol, the literature search report and copies of relevant references become part of the clinical evidence and, in turn, the technical documentation for the medical device. With respect to the clinical evaluation, it is important that the clinical evaluator be able to assess the degree to which the selected papers reflect the intended application/use of the device, etc.

Copies of the actual papers and references are necessary to allow the evaluator to review the methodology employed (potential sources of bias in the data), the reporting of results and the validity of conclusions drawn from the investigation or report. Abstracts may lack sufficient detail to allow these issues to be assessed thoroughly and independently.

6.2 Data generated through clinical experience

These types of clinical data are generated through clinical use that is outside the conduct of clinical investigations and may relate to either the device in question or equivalent devices.

Such types of data may include:

- manufacturer-generated post market surveillance reports, registries or cohort studies (which may contain unpublished long term safety and performance data);
- adverse events databases (held by either the manufacturer or Regulatory Authorities);
- data for the device in question generated from individual patients under compassionate usage programs prior to marketing of the device;
- details of clinically relevant field corrective actions (e.g. recalls, notifications, hazard alerts)

The value of clinical experience data is that it provides real world experience obtained in larger, heterogeneous and more complex populations, with a broader (and potentially less experienced) range of end-users than is usually the case with clinical investigations¹.

The data are most useful for identifying less common but serious device-related adverse events; providing long term information about safety and performance, including durability data and information about failure modes and elucidating the end-user “learning curve”. It is also a particularly useful source of clinical data for low risk devices that are based on long

¹In contrast, clinical investigations involve the use of specific inclusion criteria to create a homogenous population to reduce sources of variation and, therefore, increase confidence that the outcomes observed in the investigation are due to intervention with the device in question. Also, investigators participating in the investigation are chosen on the basis of their expertise and competence and often undergo training over and above that available to other end-users of the device.

standing, well-characterised technology and, therefore, unlikely to be the subject of either reporting in the scientific literature or clinical investigation.

How may clinical experience data/documentation be used in the clinical evaluation?

If a manufacturer chooses to use clinical experience data it is important that any reports or collations of data contain sufficient information 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 opinion, should not be used.

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 reporting may vary considerably between countries. The analyses of data within these reports may, for some devices, provide reasonable assurance of both clinical safety and performance.

It may be helpful to provide a table summarising device-related 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. Manufacturers should 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 literature such as inclusion of contraindications etc).

6.3 Data from clinical investigations

The guidance included within this section applies to clinical investigations carried out by or on behalf of a manufacturer specifically for the purposes of conformity assessment in accordance with applicable regulations. Such clinical investigations are generally expected to be designed, conducted and reported in accordance with EN ISO 14155, Parts 1 and 2, *Clinical Investigations of Medical Devices for Human Subjects*, or to a comparable standard, and in compliance with local regulations.

It is recognised that where manufacturers source clinical investigation data reported in the scientific literature (i.e. investigations of either the device in question or equivalent devices that are undertaken by a third party), the documentation readily available to the manufacturer for inclusion in the clinical evaluation is likely to be no more than the published paper itself.

What clinical investigation documentation/data should be used in the clinical evaluation?

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;
- the relevant Ethics Committee(s)' documentation, opinion(s) and comments for each;
- investigation site, including a copy of the approved informed consent form(s) and patient information documents;
- case report forms, monitoring and audit records;
- Regulatory Authority approvals and associated correspondence as required by applicable regulations; and
- the signed and dated final report.

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 significance of results obtained for performance and safety outcomes.

Also, by having the clinical investigation plan, its amendments and the final report available, the evaluator will be able to assess the extent to which the investigation was conducted as planned and, where deviations of 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 or regulations should be rejected. The reasons for rejection of the investigation should be noted in the report.

7. Appraisal of clinical data (Stage 2)

The purpose of undertaking appraisal of the data is to understand the merits and limitations of the clinical data. Each piece of data is appraised to determine its suitability to address questions about the device, and its contribution to demonstrating the safety and performance of the device (including any specific claims about safety or performance).

What should be covered by the appraisal?

The data needs to be suitable for appraisal. It should be assessed for its quality and for its relevance to the device in question (i.e. the data must be either generated for the device in question or for an equivalent device) and its intended use. In addition, any reports or collations of data should contain sufficient information for the evaluator 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/or safety of the device in question.

Further appraisal needs to be undertaken to determine the contribution of each data subset to establishing the safety and performance of the device. The evaluator should examine the methods used to generate/collect the data and assess the extent to which the observed effect (performance or safety outcome(s)) 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, concomitant treatment(s)) or bias.²

There is no single, well established method for appraising clinical data. Therefore, the evaluator should identify, in advance, the appropriate criteria to be applied for a specific circumstance

These criteria should be applied consistently. Some examples to assist with the formulation of criteria are given in Appendix C.

For many lower risk devices and devices based on long standing technology, the available data may be qualitative rather than quantitative in nature, so the evaluation criteria should be adjusted accordingly. The criteria adopted for the appraisal should be justified by the evaluator.

Although there will be some overlap of safety and performance data, the data should be categorised to allow for separate analysis. Additional categories may also be needed, depending on the nature and intended use of the device to address additional claims. The data should also be weighted according to its relative contribution. An example of a method of data appraisal is shown in Appendix D.

² 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 recording and reporting of data.

8. Analysis of the clinical data (Stage 3)

The goal of the analysis stage is to determine if the appraised data sets available for a medical device collectively demonstrate the clinical performance and safety of the device in relation to its intended use.

The methods available for analysis of clinical data generally are either quantitative or qualitative. Given the context within which most medical devices are developed (i.e. limited need for clinical investigations because of incremental changes in device design and therefore high use of literature and experience data), often qualitative (i.e. descriptive) methods will need to be used primarily to address such incremental changes, if justified.

Any 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 the performance and safety of the device, respectively. It may be useful to explore the results of the pivotal datasets, 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 included.

As a final step the evaluator should consider the basis on which it can be demonstrated that the combined data show:

- the device performs as intended by the manufacturer;
- the device does not pose any undue safety concerns to either the recipient or end-user; and
- any risks associated with the use of the device are acceptable when weighed against the benefits to the patient.

Such considerations should take into account 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 of alternative diagnostic modalities or treatments and current standard of care should also be taken into consideration.

The product literature and instructions for use should be reviewed to ensure they are consistent with the data and that all the hazards and other clinically relevant information have been identified appropriately.

9. The Clinical Evaluation Report

At the completion of the clinical evaluation process a report should be compiled that outlines the scope and context of the evaluation; the inputs (clinical data); the appraisal and analysis stages; and conclusions about the safety and performance of the device in question.

The clinical evaluation report should contain sufficient information to be read as a stand alone document by an independent party (e.g. Regulatory Authority or Notified Body). It is important that the report outline:

- the technology on which the medical device is based, the intended use of the device and any claims made about the device's clinical performance or safety;
- the nature and extent of the clinical data that has been evaluated; and
- how the referenced information (recognised standards and/or clinical data) demonstrate the clinical performance and safety of the device in question.

The clinical evaluation report should be signed and dated by the evaluator(s) and accompanied by the manufacturer's justification of the choice of evaluator.

A suggested format for the clinical evaluation report is located at Appendix E. Again, it should be noted that the level of detail in the report content can vary according to the scope of the clinical evaluation. For example, where a manufacturer relies on clinical data for an equivalent device which has been the subject of an earlier clinical evaluation (for which the manufacturer holds the evaluation report), it may be possible to cross-reference the data summary and analysis sections to the earlier clinical evaluation report, which also becomes part of the clinical evidence for the device in question.

10. The role of the Notified Body in the assessment of clinical evaluation data

The Notified Body plays a key role in the assessment and verification of clinical evaluations 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 evaluations provided by medical device manufacturers as part of technical documentation/design dossiers and as a part of their procedures for medical devices. It might also be useful as best practice guidance for national Competent Authorities in their market surveillance activities.

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 Essential Requirements must include a clinical evaluation conducted in accordance with Annex X to Directive 93/42/EEC or with Annex 7 to Directive 90/385/EEC. This is applicable for all classes of medical devices.

Demonstration of conformity without clinical data in accordance with section 1.5 of Annex 7 to Directive 90/385/EEC and section 1.1d of Annex X to Directive 93/42/EEC must be adequately justified 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. Adequacy of demonstration of conformity based on performance evaluation, bench testing and pre-clinical evaluation in the absence of clinical evaluation 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.

Notified Body Assessment of Clinical Evaluation by Conformity Assessment Route

With regard to the review of clinical evaluations the Notified Body has different roles depending on the classification of the device and the conformity assessment procedure followed.

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
 - As part of the representative sampling of devices for review of their technical documentation the notified body verifies the clinical evaluation data presented for class IIa and IIb devices in accordance with the criteria outlined in this section.
- 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 cover review of updates to clinical evaluation data 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.

10.1. 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 sections 5 to 9 of this MEDDEV), verifies the manufacturer's identification, appraisal, analysis and assessment 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 section 10.3 of this document.

In Appendix F of this document a checklist is provided for use by a Notified Body during the assessment of clinical evaluation data. This checklist should be used as a supplementary tool but should not replace the Notified Body Report outlined below.

10.1.1 Decision-making by the Notified Body

In reviewing the evaluation of clinical data submitted by the manufacturer, the Notified Body verifies and decides whether or not the manufacturer has adequately:

- supplied clinical evaluation documentation (as referenced in sections 5 to 9);
- followed relevant procedures (as addressed by sections 5 to 9);
- described and verified the intended characteristics and performances related to clinical aspects;
- performed an appropriate risk analysis and estimated the undesirable side effects;
- involved appropriate clinical expertise in the compilation of the risk analysis to ensure risks and benefits associated with real clinical use are adequately defined;
- justified the chosen route(s) of clinical data retrieval (according to sections 5 and 6);
- identified, appraised, analysed and assessed the clinical data (according to sections 5 to 9) 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;
- provided sufficient clinical data relating to the safety, performance, design characteristics and intended purpose of the device in order to demonstrate conformity with each of the relevant essential requirements;
- if a critical evaluation of relevant scientific literature is provided, the notified body verifies that this data relates to the safety, performance, design characteristics and intended purpose of the device;
- if a critical evaluation of relevant scientific literature is provided 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, design, biological etc.);

- if a critical evaluation of relevant scientific literature is provided the notified body verifies that the data presented for equivalent devices adequately addresses each of the relevant essential requirements;
- provided specific justification if a specific clinical investigation was not performed for class III or implantable devices.

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;

- provided evidence that clinical investigations presented are in compliance with applicable regulatory and ethical requirements e.g. ethics committee approval, competent authority approval;
- 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;
- concluded on the basis of documented justification that the risks are acceptable when weighed against the intended benefits and the relevant Essential Requirements are met.

The assessment carried out by the Notified Body will typically cover 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 section 7;
- complete and adequate documentation (according to sections 5 to 9);
- adequate procedures (according to sections 5 to 9)
- 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 use of harmonised standards
- the use of the list of identified hazards to be addressed through evaluation of clinical data as described in section 8;
- the adequate estimation of the associated risks for each identified hazard by:
 - a) characterising the severity of the hazard;
 - b) estimating and characterising the probability of occurrence of harm, health impairment or loss of benefit of the treatment (document with rationale).

The decision on the acceptability of risks³ in relation to each identified hazard, and characterisation of the corresponding risk/benefit ratio as:

- unacceptable; or
- broadly acceptable; or
- acceptable under specified conditions.

For drug-device combination products where a scientific opinion from a medicinal competent authority or from the EMEA 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

³ Valid decision making criteria from applicable guidance and standards may be employed e.g. ISO 14971.

may not deliver a positive decision to issue a certificate if the EMEA's scientific opinion is unfavourable.

10.1.2 The report of the Notified Body

The Notified Body writes a report on its assessment of the submitted clinical evaluation documentation.

If a design dossier report is applicable the clinical report should be incorporated into this report. The report should clearly identify the Notified Body's assessment, verification on each of the critical elements and overall conclusions.

NBOG BPG 2009-1 defines the minimum content for a design dossier review report in the following sections:

- Manufacturer details
- Details relating to the application and NB review (including staff and experts involved in the review and the aspects assessed by each, signatures of responsible reviewers etc.)
- Device description and product specification
- Classification
- Requirements regarding manufacturing
- Requirements regarding design and construction
- Pre-clinical evaluation
- Clinical evaluation/performance evaluation
- Other applicable Directives
- Risk analysis and risk management
- Review of declaration of conformity
- Post-market surveillance
- Summary of review

The Notified Body should justify and document each step of the decision making process referred in 10.1.1.above. One single “unacceptable risk/benefit ratio” leads to a negative conclusion⁴;

The clinical evaluation assessment report should:

- Record whether the clinical evaluation documentation was complete and adequate
- Record the Notified Bodies verification of each step of the clinical evaluation process, from scoping, choice of route(s), identification, appraisal, analysis and overall assessment of the clinical data, to concluding and reporting
- Record the completeness of the clinical evaluation conducted and its accordance with this document
- 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 side-effects and risks have been properly evaluated

⁴ 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 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 10.1.1.

10.2. EVALUATION AS PART OF QUALITY SYSTEM RELATED PROCEDURES (Annex II.3 of Directive 1993/42/EEC)

10.2.1. 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), clinical investigator(s)];
- (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 of scoping, identification of clinical data (section 5), literature searching (section 6.1), collection of clinical experience (section 6.2), clinical investigation (section 6.3 and EN ISO 14155), appraisal of clinical data (section 7), analysis of clinical data (section 8), concluding, reporting (section 9) and update of clinical evaluation, including PMCF (MEDDEV 2.12/2);
- (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).

10.2.2. 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. Clinical evaluation data 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 clinical evaluation data according to the criteria outlined in this document rather than solely confirming that the manufacturer has a clinical evaluation procedure in place.

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 section 10.1 of this document.

The Notified Body, when reviewing samples of the manufacturer's clinical data evaluation, should pay special attention to the following:

- (a) whether or not the data is relevant to the device, its intended use(s) or medical procedure(s) involved and adequately cover the related clinical performance, safety and benefit/risk relation
- (b) where the manufacturer, in the selected sample, has chosen the "literature route", whether the criteria defined in section 6.1 have been applied;
- (c) where the manufacturer, in the selected sample, has selected the "clinical investigations route", whether the criteria defined in section 6.3 have been applied.

10.3. 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 clinical evaluation data 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 relevant regulatory knowledge and clinical competence necessary for such evaluation, are available within⁵ the Notified Body and by contracting external clinical experts if required.

Such expertise should be sufficient to identify and estimate the risks and benefits associated with the use of the medical devices. The evaluation team should be able to evaluate a risk analysis and the risk management strategy performed by the manufacturer.

The evaluation team should understand the device technology as well as the medical procedure.

Such an evaluation may require input from a qualified medical practitioner (for example physician, dentist, nurse etc.), as appropriate for the particular device, who

⁵ 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.

has clinical experience in the pathology of the condition being treated, the usual treatment, the therapeutic alternatives etc.

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.

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;
- (c) document the opinion with rationale of all experts involved;
- (d) ensure that any external experts involved are impartial and independent from any parties involved, having due regard to any conflict of interest which may compromise impartiality (see also MEDDEV 2.10/1);
- (e) document the result of their assessment. This is achieved through a specific report which may be part of, or may be referenced, in the overall audit report, design / type examination report (as per 10.1.2 of this document) or the report on the assessment of representative samples' documentation;
- (f) preserve confidentiality of the information and data received from the manufacturer, especially within the terms for contracting external experts.

APPENDICES

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APPENDIX A

A POSSIBLE FORMAT FOR THE LITERATURE SEARCH REPORT

1. Device name/model

2. Scope of the literature search [should be consistent with scope of clinical evaluation]

3. Methods

- (i) Date of search
- (ii) Name of person(s) undertaking the literature search
- (iii) Period covered by search
- (iv) Literature sources used to identify data:
 - scientific databases – bibliographic (e.g. MEDLINE, EMBASE), specialised databases (e.g. MEDION)
 - systematic review databases (e.g. Cochrane Collaboration)
 - clinical trial registers (e.g. CENTRAL),
 - adverse event report databases (e.g. MAUDE, IRIS)
 - reference texts

Include justification for choice of sources and describe any supplemental strategies (e.g. checking bibliography of articles retrieved, hand searching of literature) used to enhance the sensitivity of the search.

- (v) Database search details:
 - search terms (key words, indexing headings) and their relationships (Boolean logic)
 - medium used (e.g. online, CD-ROM (including publication date and edition))

Attach copy of downloaded, unedited search strategy.

- (vi) Selection criteria used to choose articles

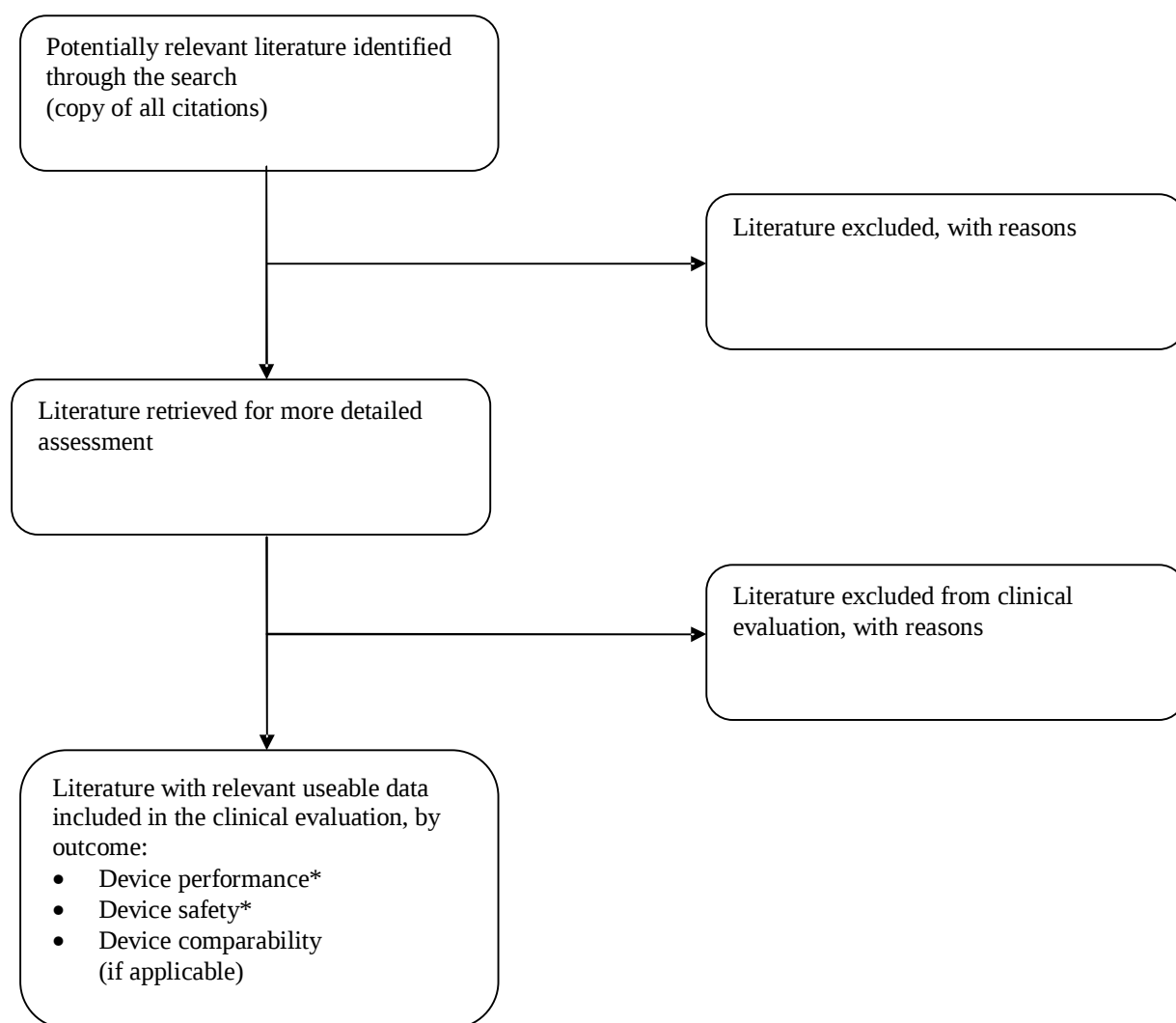
4. Outputs

- (i) Attach copy of literature citations retrieved from each database search
- (ii) Data selection process
Attach flow chart and associated tables showing how all citations were assessed for suitability for inclusion in the clinical evaluation (see Appendix B).

Notes:

EMBASE	Excerpta Medica published by Elsevier
CENTRAL	The Cochrane Central Register of Controlled Trials
IRIS	The TGA's medical device Incident Report Investigation Scheme
MAUDE	US FDA's Manufacturer And User Facility Device Experience database
MEDION	Database that indexes literature on diagnostic tests
MEDLINE	Published by US National Library of Medicine

APPENDIX B:
**A POSSIBLE METHODOLOGY FOR DOCUMENTING THE SCREENING AND SELECTION OF
LITERATURE WITHIN A LITERATURE SEARCH REPORT⁶**



*some literature will address issue of both performance and safety

⁶ Adapted from Moher D, Cook DJ, Eastwood S, Olkin I, Rennie, D & Stroup DF . Improving the quality of reports and meta-analyses of randomised controlled trials: the QUORUM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999; 354:1896-1900

APPENDIX C: SOME EXAMPLES TO ASSIST WITH THE FORMULATION OF CRITERIA⁷

The following are examples of questions to ask to assist with the formulation of criteria for data appraisal for different type of data sets. These examples are not meant to be comprehensive with regards to study types or all potential questions.

Randomised controlled trial

Clinical investigation where subjects are randomised to receive either a test or reference device or intervention and outcomes and event rates are compared for the treatment groups.

- Were the inclusion and exclusion criteria specified?
- Was the assignment to the treatment groups really random?
- Was the treatment allocation concealed from those responsible for recruiting subjects?
- Was there sufficient description about the distribution of prognostic factors for the treatment groups?
- Were the groups comparable at baseline for these factors?
- Were outcome assessors blinded to the treatment allocation?
- Were the care providers blinded?
- Were the subjects blinded?
- Were all randomised participants included in the analysis?
- Was a point estimate and measure of variability reported for the primary outcome?

Cohort study

Data are obtained from groups who have and have not been exposed to the device (e.g. historical control) and outcomes compared.

- Were subjects selected prospectively or retrospectively?
- Was an explicit description of the intervention provided?
- Was there sufficient description about how the subjects were selected for the new intervention and comparison groups?
- Was there sufficient description about the distribution of prognostic factors for the new intervention and comparison groups?
- Were the groups comparable for these factors?
- Did the study adequately control for potential confounding factors in the design or analysis?
- Was the measurement of outcomes unbiased (i.e. blinded to treatment group and comparable across groups)?
- Was follow-up long enough for outcomes to occur?
- What proportion of the cohort was followed up and were there exclusions from the analysis?
- Were drop-out rates and reasons for drop-out similar across intervention and unexposed groups?

⁷ Adapted from: Guidelines for the assessment of diagnostic technologies. Medical Services Advisory Committee; Commonwealth of Australia 2005.

Case-control study

Patients with a defined outcome and controls without the outcome are selected and information is obtained about whether the subjects were exposed to the device.

- Was there sufficient description about how subjects were defined and selected for the case and control groups?
- Was the disease state of the cases reliably assessed and validated?
- Were the controls randomly selected from the source of population of the cases?
- Was there sufficient description about the distribution of prognostic factors for the case and control groups?
- Were the groups comparable for these factors?
- Did the study adequately control for potential confounding factors in the design or analysis?
- Was the new intervention and other exposures assessed in the same way for cases and controls and kept blinded to case/control status?
- How was the response rate defined?
- Were the non-response rates and reasons for non-response the same in both groups?
- Was an appropriate statistical analysis used?
- If matching was used, is it possible that cases and controls were matched on factors related to the intervention that would compromise the analysis due to over-matching?

Case series

The device has been used in a series of patients and the results reported, with no control group for comparison.

- Was the series based on a representative sample selected from a relevant population?
- Were the criteria for inclusion and exclusion explicit?
- Did all subjects enter the survey at a similar point in their disease progression?
- Was follow-up long enough for important events to occur?
- Were the techniques used adequately described?
- Were outcomes assessed using objective criteria or was blinding used?
- If comparisons of sub-series were made, was there sufficient description of the series and the distribution of prognostic factors?

APPENDIX D: A POSSIBLE METHOD OF APPRAISAL

There are many methods that can be used to appraise and weight clinical data. An example of possible appraisal criteria is given in Tables D1 and D2. The criteria may be worked through in sequence and a weighting assigned for each dataset. The data suitability criteria can be considered generic to all medical devices (Table D1), however the actual method used will vary according to the device considered.

To assess the data contribution criteria of the suitable data, the evaluator should sort the data sets according to source type and then systematically consider those aspects that are most likely to impact on the interpretation of the results (Table D2). There is scope for the evaluator to determine what types of issues are most important in relation to the nature, history and intended clinical application of the device. The criteria used in the example below are based around the sorts of issues that could be considered for devices of higher risk, such as characteristics of the sample, methods of assessing the outcomes, the completeness and duration of follow-up, as well as the statistical and clinical significance of any results.

In this example, the weightings would be used to assess the strength of the datasets' contribution to demonstrating overall performance and safety of the device (Stage 3, see section 8). As a general guide in using this example, the more level 1 grades, the greater the weight of evidence provided by that particular dataset in comparison to other datasets, however, it is not intended that the relative weightings from each category be added into a total score.

Table D1 Sample Appraisal Criteria for Suitability

Sutability Criteria	Description	Grading System	
Appropriate device	Were the data generated from the device in question?	D1	Actual device
		D2	Equivalent device
		D3	Other device
Appropriate device application	Was the device used for the same intended use (e.g., methods of deployment, application, etc.)?	A1	Same use
		A2	Minor deviation
		A3	Major deviation
Appropriate patient group	Where the data generated from a patient group that is representative of the intended treatment population e.g., age, sex, etc.) and clinical condition (i.e., disease, including state and severity)?	P1	Applicable
		P2	Limited
		P3	Different population
Acceptable report/data collation	Do the reports or collations of data contain sufficient information to be able to undertake a rational and objective assessment?	R1	High quality
		R2	Minor deficiencies
		R3	Insufficient information

Table D2 Sample Appraisal Criteria for Data Contribution

Data Contribution Criteria	Description	Grading System	
Data source type	Was the design of the study appropriate?	T1	Yes
		T2	No
Outcome measures	Do the outcome measures reported reflect the intended performance of the device?	O1	Yes
		O2	No
Follow up	Is the duration of follow-up long enough to assess whether duration of treatment effects and identify complications?	F1	Yes
		F2	No
Statistical significance	Has a statistical analysis of the data been provided and is it appropriate?	S1	Yes
		S2	No
Clinical significance	Was the magnitude of the treatment effect observed clinically significant?	C1	Yes
		C2	No

APPENDIX E:
A POSSIBLE FORMAT FOR A CLINICAL EVALUATION REPORT

1. General details

State the proprietary name of the device and any code names assigned during device development.

Identify the manufacturer(s) of the device.

2. Description of the device and its intended application

Provide a concise physical description of the device, cross referencing to relevant sections of the manufacturer's technical information as appropriate. The description should cover information such as:

- materials, including whether it incorporates a medicinal substance (already on the market or new), tissues, or blood products;
- the device components, including software and accessories;
- mechanical characteristics; and
- others, such as sterile vs. non-sterile, radioactivity etc.

State the intended application of the device – single use/reusable; invasive/non invasive; implantable; duration of use or contact with the body; organs, tissues or body fluids contacted by the device.

Describe how the device achieves its intended purpose.

3. Intended therapeutic and/or diagnostic indications and claims

State the medical conditions to be treated, including target treatment group and diseases.

Outline any specific safety or performance claims made for the device

4. Context of the evaluation and choice of clinical data types

Outline the developmental context for the device. The information should include 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. The amount of information will differ according to the history of the technology. Where a completely new technology has been developed, this section 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 (with appropriate references) could be used. Clearly state if the clinical data used in the evaluation are for an equivalent device. Identify the equivalent device(s) and provide a justification of the equivalency, cross-referenced to the relevant non-clinical documentation that supports the claim.

State the Essential Requirements relevant to the device in question, in particular, any special design features that pose special performance or safety concerns (e.g. presence of medicinal,

human or animal components) that were identified in the device risk management documentation and that required assessment from a clinical perspective.

Outline how these considerations were used to choose the types of clinical data used for the evaluation. Where published scientific literature has been used, provide a brief outline of the searching/retrieval process, cross-referenced to the literature search protocol and reports.

5. Summary of the clinical data and appraisal

Provide a tabulation of the clinical data used in the evaluation, categorised according to whether the data address the performance or the safety of the device in question. (Note: many individual data sets will address both safety and performance.) Within each category, order the data according to the importance of their contribution to establishing the safety and performance of the device and in relation to any specific claims about performance or safety. Additionally, provide a brief outline of the data appraisal methods used in the evaluation, including any weighting criteria, and a summary of the key results.

Include full citations for literature-based data and the titles and investigation codes (if relevant) of any clinical investigation reports.

Cross-reference the entry for each piece of data to its location in the manufacturer's technical documentation.

6. Data analysis

6.1 Performance

Provide a description of the analysis used to assess performance.

Identify the datasets that are considered to be the most important in contributing to the demonstration of the overall performance of the device and, where useful, particular performance characteristics. Outline why they are considered to be "pivotal" and how they demonstrate the performance of the device collectively (e.g. consistency of results, statistical significance, clinically significance of effects).

6.2 Safety

Describe the total experience with the device, including numbers and characteristics of patients exposed to the device; and duration of follow-up of device recipients.

Provide a summary of device-related adverse events, paying particular attention to serious adverse events.

Provide specific comment on whether the safety characteristics and intended purpose of the device requires training of the end-user.

6.3 Product Literature and Instructions for Use

State whether the manufacturer's proposed product literature and Instructions for Use are consistent with the clinical data and cover all the hazards and other clinically relevant information that may impact on the use of the device.

7. Conclusions

Outline clearly the conclusions reached about the safety and performance of the device from the evaluation, with respect to the intended use of the device. State whether the risks identified in the risk management documentation have been addressed by the clinical data.

For each proposed clinical indication state whether:

- the clinical evidence demonstrates conformity with relevant Essential Requirements;
- the performance and safety of the device as claimed have been established; and
- the risks associated with the use of the device are acceptable when weighed against the benefits to the patient

APPENDIX F

Clinical evaluation checklist for Notified Bodies				
Ref	Requirement	Fulfilled	Comment	
0	Conformity without Clinical Data			
0.1	Any demonstration of conformity without clinical data (Annex 7.1.5 of 90/385/EEC and Annex X.1.1d of 93/42/EEC) must be adequately justified and based on - the output of the risk management process - viewed in the context of the device-body interaction - the intended clinical performance - the claims of the manufacturer. Adequacy of demonstration of conformity based on performance evaluation, bench testing and pre-clinical evaluation in the absence of clinical evaluation 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. - Is the manufacturer's justification adequate? - Is the performance evaluation, bench testing and pre-clinical evaluation adequate to demonstrate conformity to the Essential Requirements?	Yes • No • N/A. •		
1	Clinical Evaluation, General			
1.1	The manufacturer should include in the technical documentation a statement on the route(s) applied to retrieve the clinical data used to affix the "CE" marking. The statement should make clear whether that clinical data was obtained from the published literature or the results of clinical investigations or a	Yes • No • N/A. •	Clinical literature	
			<i>Published</i>	
			<i>Unpublished</i>	
			<i>Equivalence demonstrated</i>	
			Clinical investigation	
			Combination of literature and investigation data	

	combination of both and shall include an adequate justification of the route(s) selected and a demonstration of equivalency (technical, biological, clinical) and adequacy if clinical data from similar devices have been used		Comment
1.2	The Clinical Evaluation Report and the full clinical data used for CE marking should be included within the technical documentation	Yes • No • N/A. •	
1.3	The manufacturer has clearly documented the objectives and the scope of the clinical evaluation and specified the clinical ER's [e.g. clinical performance(s), safety, risks and favourable benefit/risk ratio related to intended use, target group(s) and indication(s)] to be met	Yes • No • N/A. •	
1.4	The manufacturer has clearly outlined the performed steps and procedures of clinical evaluation according to this MEDDEV (specifically sections 5 to 9), adequate justification given for deviations	Yes • No • N/A. •	
2	Clinical investigation route		
2.1	Need for clinical investigation		
2.1.1	Classification of device Is the device an implantable or class III medical device or an active implantable medical device?	Yes • No • N/A. •	
2.1.2	If a clinical investigation is not presented for an implantable or class III MD or an AIMD, has this been adequately justified by the manufacturer in his risk analysis and clinical evaluation?	Yes • No • N/A. •	
2.1.3	If clinical literature is presented for equivalent devices, is this clinical data when taken together with the available pre clinical data sufficient to demonstrate conformity with the essential requirements covering safety and performance of the device in question under normal conditions of use?	Yes • No • N/A. •	

2.1.4	If clinical literature is presented for equivalent devices, are there gaps in either the demonstration of compliance with each relevant essential requirement or in the demonstration of equivalence that needs addressing through the means of a specifically designed clinical investigation(s)?	Yes • No • N/A. •	
2.1.5	If clinical literature is presented for equivalent devices, is the data sufficient to address the clinical hazards identified in the risk analysis? If no, a clinical investigation(s) will be needed. The objectives of the clinical investigation(s) should focus on those aspects not sufficiently addressed by the available data.	Yes • No • N/A. •	
2.2	Conduct of clinical investigation		
2.2.1	Were the relevant annexes of the medical devices Directives (Annex 7 AIMD, Annex X MDD) and the relevant standards (EN ISO 14155-1, -2) taken into account?	Yes • No • N/A. •	
2.2.2	Requirements for clinical investigations		
2.2.3	Identification of relevant documentation, the following documentation should be requested and reviewed by the notified body:		
2.2.4	Copy of the Protocol submitted to the Competent Authority or other regulatory agency for which no grounds for objection were raised	Yes • No • N/A. •	
2.2.5	Copy of the letter of “no objection”/approval from Competent Authority/Authorities (if available) or other approval from the relevant regulatory agency(ies), together with any comments made arising from regulatory review	Yes • No • N/A. •	
2.2.6	Copy of the Ethics Committee opinion(s) and comments arising from their review or a summary of all Ethics Committee opinions and any comments/conditions arising from their reviews	Yes • No • N/A. •	

2.2.7	Copy of the signed and dated final report	Yes • No • N/A. •	
2.3	Information to be checked – the following information should be checked by the notified body		
2.3.1	Letter of “no objection” from the Competent Authority(ies)	Yes • No • N/A. •	
2.3.2	Clinical Investigation Plan (CIP): Is the CIP, used for the clinical investigation, the same as that submitted to the Competent Authority? ⁸	Yes • No • N/A. •	
2.3.3	If parameters are not as set out in the original CIP, the rationale for non-adherence	Yes • No • N/A. •	
2.3.4	Identification of any changes to CIP and rationale for any such changes	Yes • No • N/A. •	
2.3.5	Where the clinical investigation(s) was performed outside the EU, the manufacturer must demonstrate that the use of the device (including clinical practice and techniques) and patient population are equivalent to those for which the device will be used within the EU (if relevant).	Yes • No • N/A. •	
2.3.6	For drug-device combinations, have any issues or concerns raised as part of the clinical assessment of the medicinal substance by the medicinal competent authority or EMEA been considered and/or resolved?	Yes • No • N/A. •	
2.4	Final report of investigation The report should be reviewed and should include the following information		
2.4.1	Summary – a structured abstract should be provided,	Yes •	

⁸ Particular attention should be paid to: number of patients entered; objectives of investigation(s) (in particular which Essential Requirements are being addressed); duration of investigation(s) and patient follow up (short and long-term); end points in terms of diagnostic tools and patient assessment; inclusion and exclusion criteria

	presenting the essentials of the study ⁹	No • N/A. •	
2.4.2	Introduction – a brief statement placing the study in the context of the development of the medical device in question and an identification of guidelines followed in the development of the Protocol	Yes • No • N/A. •	
2.4.3	Materials and methods ¹⁰	Yes • No • N/A. •	
2.4.4	Summary of the clinical investigation plan ¹¹	Yes • No • N/A. •	
2.4.5	Results – this section should contain summary information with a description of the analysis and results ¹²	Yes • No • N/A. •	
2.4.6	Discussions and conclusions ¹³	Yes • No • N/A. •	
2.4.7	Signature – the final report should be signed off by the	Yes •	

⁹ Including title of investigation(s); identification of the medical device(s), including names, models as relevant for complete identification; name of sponsor; statement indicating whether the investigation(s) was performed in accordance with CEN/ISO Standards; objectives; subjects; methodology; investigation(s) initiation and completion dates, including date of early termination, if applicable; results; conclusions; authors of report; date of report.

¹⁰ Including device description; summary description of the device and its intended use, together with any modifications performed during the investigation.

¹¹ Including the clinical investigation objectives; the investigation design; type of investigation; investigation end points; ethical considerations; subject population; inclusion/exclusion criteria; sample size; treatment and treatment allocation; investigation variables; concomitant medications/treatments; duration of follow up; statistical analysis including investigation hypothesis or pass/fail criteria, sample size calculation, statistical analysis methods.

¹² Including the investigation initiation date; investigation completion/suspension date; the disposition of patients/devices; the patient demographics; clinical investigation plan compliance; the analysis to include safety report, including a summary of all adverse events and adverse device events seen in the investigation, including a discussion of the severity, treatment required, resolution and assessment by the investigator of relation to treatment; performance or efficacy analysis; any sub group analysis for special population; a description of how missing data, including patients lost to follow up or withdrawn, were dealt with in the analysis

¹³ Including the performance and safety results of the study; the relationship of risks and benefits; clinical relevance and importance of the results, particularly in the light of other existing data and discussion of comparison with “state of the art”; any specific benefits or special precautions required for individual subjects or at risk groups; any implications for the conduct of future studies.

	sponsor, the co-ordinating clinical investigator (if appointed) and principal investigator at each centre	No • N/A. •	
2.4.8	Annex to the report, containing clinical investigation plan, including amendments, list of investigators and their institutions, list of other parties involved, list of monitors, list of statisticians (if applicable), list of Ethics Committees and their approval letters.	Yes • No • N/A. •	
2.5	NB assessment of the clinical investigation(s) data presented		
2.5.1	Have any identified pass/fail criteria of the investigation(s) been met?	Yes • No • N/A. •	
2.5.2	Have the results and conclusions of the clinical investigation(s) demonstrated compliance with the identified relevant essential requirements?	Yes • No • N/A. •	
2.5.3	Are the claims made in the device labelling substantiated by clinical data when taken together with the relevant pre-clinical data?	Yes • No • N/A. •	
2.5.4	Has the risk analysis demonstrated that the risks associated with the use of the device, as set out by the manufacturer, are acceptable when balanced against the benefits to the patient?	Yes • No • N/A. •	
2.5.5	Was the assessment performed in a critical and objective manner?	Yes • No • N/A. •	
3	Clinical literature data A critical evaluation of relevant scientific literature that is currently available relating to safety, performance, design characteristics and intended purpose in the form of a written report		
3.1	Methodology		
3.1.1	A critical evaluation of relevant scientific literature has been presented	Yes • No • N/A. •	
3.1.2	A search protocol for the identification, selection, collation and review of relevant publications should be	Yes • No •	

	written.	N/A. •	
3.1.3	The objective of the literature review should be clearly defined	Yes • No • N/A. •	
3.1.4	The types of studies that are relevant to the objective of the literature review should be specified	Yes • No • N/A. •	
3.1.5	Data should be taken from recognised scientific publications. Unpublished data should also be taken into account in order to avoid publication bias.	Yes • No • N/A. •	
3.1.6	The literature review should state:		
3.1.6.1	sources of data, extent of the searches of databases or other sources of information	Yes • No • N/A. •	
3.1.6.2	rationale for the selection/ relevance of the published literature	Yes • No • N/A. •	
3.1.6.3	reasons for believing that all relevant references, both favourable and unfavourable, have been identified	Yes • No • N/A. •	
3.1.6.4	criteria for exclusion of particular references together with a justification for this exclusion.	Yes • No • N/A. •	
3.1.6.5	detailed description of the different stages of literature search (including identification, appraisal, analysis and conclusion of hits)	Yes • No • N/A. •	
3.2	Relevance of data presented		
3.2.1	A literature review should clearly establish the extent to which the literature relates to the specific characteristics and features of the device under consideration.	Yes • No • N/A. •	
3.2.2	If the published studies do not directly refer to the device in question, the manufacturer must	Yes • No •	

	demonstrate equivalence with the device, which is the subject of the published reports.	N/A. •	
3.2.3	To be equivalent, the devices should have similarity with regard to the clinical, technical and biological parameters with special attention to the performance, principles of operation and materials; or if there are differences identified, an assessment and demonstration of the significance these might have on safety and performance must be set out ¹⁴ .	Yes • No • N/A. •	
3.2.4	The manufacturer must be able to demonstrate the adequacy of the data in addressing the aspects of conformity set out in the objective	Yes • No • N/A. •	
3.3	NB Assessment of clinical data The literature review should make clear the significance that is attached to particular references based on a number of factors. These include:		
3.3.1	relevance of the author's background and expertise in relation to the particular device and/or medical procedure involved	Yes • No • N/A. •	
3.3.2	whether the author's conclusions are substantiated by the available data	Yes • No • N/A. •	
3.3.3	whether the literature reflects the current medical practice and the generally acknowledged "state of the art" technologies	Yes • No • N/A. •	
3.3.4	whether references are taken from recognised scientific publications and whether or not they have been reported	Yes • No •	

¹⁴ Equivalence means:

Clinical: used for the same clinical condition or purpose, at the same site in the body, in similar population (including age, anatomy, physiology); have similar relevant critical performance according to expected clinical effect for specific intended use.

Technical: used under similar conditions of use; have similar specifications and properties e.g. tensile strength, viscosity, surface characteristics; be of similar design; use similar deployment methods (if relevant); have similar principles of operation.

Biological: use same materials in contact with the same human tissues or body fluids.

	in peer reviewed journals	N/A. •	
3.3.5	the extent to which the published literature is the outcome of a study/studies which have followed scientific principles in relation to design ¹⁵	Yes • No • N/A. •	
3.4	Critical evaluation of the literature The literature review should contain a critical evaluation of the literature. This critical evaluation should:		
3.4.1	be written by a person suitably qualified in the relevant field, and reviewed and approved by an expert knowledgeable in the “state of the art” and able to demonstrate objectivity	Yes • No • N/A. •	
3.4.2	contain a short description of the medical device, its intended functions, description of the intended purpose and application of use	Yes • No • N/A. •	
3.4.3	contain an analysis of all the available data considered, both favourable and unfavourable	Yes • No • N/A. •	
3.4.4	establish the extent to which the literature relates to the specific characteristics and features of the device being assessed, taking due account of the extend of similarity between the device(s) covered by the literature and the device under assessment	Yes • No • N/A. •	
3.4.5	demonstrate that those aspects of the use of the device, including performance, addressed in the clinical part of the risk analysis are met as claimed by the manufacturer, and that the device fulfils its intended purpose as a medical device	Yes • No • N/A. •	
3.4.6	analyse the identified hazards, the associated risks and the appropriate safety measures of patients, medical staff and	Yes • No •	

¹⁵ For example in having demonstrable and appropriate endpoints, inclusion and exclusion criteria, an appropriate and validated number of patients submitted, carried out for an appropriate duration, providing evidence and analysis of all adverse incidents, deaths, exclusions, withdrawals and subjects lost follow-up and identifying an appropriate statistical plan of analysis. Ideally, evidence should be generated from a clinical trial (controlled if appropriate), properly designed cohort/case controlled study, well documented case histories or sequential reports conducted by appropriate experienced experts, whether in relation to the device itself or an equivalent device. If unpublished data is being included in the assessment, the literature review will need to weigh the significance that is attached to each report.

	third parties involved in the study/studies	N/A. •	
3.4.7	contain a risk analysis relevant to the device design, materials and procedures involved, taking into account any adverse events, results of post-market surveillance studies, modifications and recalls (if known)	Yes • No • N/A. •	
3.4.8	contain a description of the methods of weighting of different papers and the statistical methods of analysis employed taking into account the assessment methods, the type and duration of study and the heterogeneity of the population included within the study	Yes • No • N/A. •	
3.4.9	include an analysis of the market experience of the same or similar devices, including the results of post-marketing studies, post-market surveillance and short- and long-term adverse events	Yes • No • N/A. •	
3.4.10	contain a list of publications appropriately cross-referenced in the evaluation	Yes • No • N/A. •	
3.4.11	if the clinical data relates to an equivalent device, contain a statement that equivalence with all the relevant characteristics has been demonstrated	Yes • No • N/A. •	
3.4.12	include a conclusion ¹⁶ with a justification, including an assessment of any probable benefit to health from the use of the device as intended by the manufacturer, against probable risks of injury or illness from such use taking account of the “state of the art”. The conclusions should make clear how the objectives of the literature review have been met and identify any gaps in the evidence necessary to cover all relevant aspects of safety and performance	Yes • No • N/A. •	
3.4.13	The critical evaluation should be signed and dated by the author	Yes • No •	

¹⁶ Conclusions should consider the claimed use - indications, contra-indications and instructions for use proposed by the manufacturer.

		N/A. •	
3.5	NB Assessment of the critical evaluation of literature presented by the manufacturer		
3.5.1	Are the manufacturers' conclusions valid?	Yes • No • N/A. •	
3.5.2	Is the data, taken together with the available pre clinical data, sufficient to demonstrate compliance with the essential requirements covering safety and performance of the device in question under normal conditions of use? ¹⁷	Yes • No • N/A. •	
3.5.3	Are the claims made in the device labelling substantiated by the clinical data taken together with the pre-clinical data?	Yes • No • N/A. •	
3.5.4	Was the assessment performed in a critical and objective manner?	Yes • No • N/A. •	
4	Post-market clinical follow up – the notified body should check and review the manufacturer's post market clinical follow up plan:		
4.1	Has the manufacturer presented an appropriate plan for post-market clinical follow up in line with appropriate guidance?	Yes • No • N/A. •	
4.2	If no post-market clinical follow up plan is presented, has this been adequately justified by the manufacturer?	Yes • No • N/A. •	
4.3	Has the manufacturer an adequate post-market surveillance system in place?	Yes • No • N/A. •	
4.4	Has the manufacturer committed to inform the NB of significant updates to their clinical evaluation arising from	Yes • No •	

¹⁷ If not, identify gaps in the demonstration of compliance with the relevant essential requirements or in the demonstration of equivalence that need addressing through the means of a specifically designed clinical investigation(s).

	PMS/PMCF?	N/A. •	
5	Notified Body Decision Making		
5.1	In reviewing the evaluation of clinical data submitted by the manufacturer the NB must decide whether the manufacturer has adequately		
5.1.1	described and verified the intended characteristics and performances related to clinical aspects	Yes • No • N/A. •	
5.1.2	performed a risk analysis and estimated the undesirable side effects	Yes • No • N/A. •	
5.1.3	concluded on the basis of documented justification that the risks are acceptable when weighed against the intended benefits	Yes • No • N/A. •	
5.2	NB assessment of benefit/risk presented in the clinical evaluation data		
5.2.1	the listing and characterisation of the clinical performance of the device intended by the manufacturer and the expected benefits for the patient	Yes • No • N/A. •	
5.2.2	the use of the list of identified hazards to be addressed through evaluation of clinical data	Yes • No • N/A. •	
5.2.3	the adequate estimation of the associated risks for each identified hazard by: a) characterising the severity of the hazard; b) estimating and characterising the probability of occurrence of the harm (or health impairment or loss of benefit of the treatment) (document with rationale)	Yes • No • N/A. •	
5.2.4	the decision on the acceptability of risks in relation to	Yes •	



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