IMDRF International Medical Device Regulators Forum

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Preface

The document herein was produced by the International Medical Device Regulators Forum (IMDRF), a voluntary group of medical device regulators from around the world.

1 Introduction

What is clinical evaluation?

Clinical evaluation is a set of ongoing activities that use scientifically sound methods for the assessment and analysis of clinical data to verify the safety, clinical performance and/or effectiveness of the device when used as intended by the manufacturer.

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 development of a medical device in order to identify data that need to be generated for regulatory purposes and will inform if a new device clinical investigation is necessary, together with the outcomes which need to be studied. It is then repeated periodically as new safety, clinical performance, and/or effectiveness information about the device is obtained during its use. This information is fed into the ongoing risk management process (according to ISO 14971:2007) and may result in changes to the manufacturer's risk assessment, Instructions for Use and post market activities.

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 Essential Principles of Safety and Performance of Medical Devices (the Essential Principles). 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 are minimised and acceptable when weighed against the benefits of the intended performance, and that any claims made about the device's safety, clinical performance and/or effectiveness (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 safety, clinical performance and/or effectiveness 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 Principles that require support from relevant clinical data;
- identify available clinical data relevant to the device and its intended use;
- evaluate (appraise and analyse) clinical data in terms of its suitability and contribution to demonstrating the safety, clinical performance, and/or effectiveness of the device in relation to its intended use;
- generate clinical data needed to address remaining questions of safety, clinical performance, and/or effectiveness;
- bring all the clinical data together to reach conclusions about the safety, clinical performance, and/or effectiveness 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 Principles 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 clinical performance, and/or effectiveness 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, clinical performance, and/or effectiveness of comparable 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, clinical performance, and/or effectiveness characteristics.

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

This document supersedes an earlier version produced under the Global Harmonization Task Force (GHTF) with the same title in May, 2007(GHTF/SG5/N2R8:2007).

2 Scope

The primary purpose of this document is to provide manufacturers 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 IVDDs.

3 References

IMDRF/GHTF final documents

GHTF SG1/ *N044:2008 Role of Standards in the Assessment of Medical Devices*

GHTF SG1/ N071:2012 *Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'*

GHTF SG1/ N78:2012 *Principles of Conformity Assessment for Medical Devices*

IMDRF GRRP WG/N47 FINAL: 2018 *Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices*

IMDRF SaMD WG/N41:2017 *Software as a Medical Device (SaMD): Clinical Evaluation*

IMDRF Registry WG/N33FINAL:2016 *Principles of International System of Registries Linked to Other Data Sources and Tools*

IMDRF Registry WG/N42FINAL:2017 *Methodological Principles in the Use of International Medical Device Registry Data*

IMDRF Registry WG/N46 FINAL: 2018 *Tools for Assessing the Usability of Registries in Support of Regulatory Decision-Making*

GHTF SG1/N011R20:2008 *Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED)*

IMDRF MDCE WG (PD1)/ Nx *Clinical Evidence – Key definitions and Concepts*

International standards

ISO 14155-1: 2011 *Clinical investigation of medical devices for human subjects — Good clinical practice*

ISO 14971:2007 *Medical devices - Application of risk management to medical devices*

4 Definitions

Adverse Event: Any untoward medical occurrence

Clinical Data: **S**afety, clinical performance and/or effectiveness information that is generated from the clinical use of a medical device.

Clinical Evaluation: A set of ongoing activities that use scientifically sound methods for the assessment and analysis of clinical data to verify the safety, clinical performance and/or effectiveness of the device when used as intended by the manufacturer.

Clinical Evidence: The clinical data and the clinical evaluation report pertaining to a medical device.

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

Clinical Investigation Plan: Document that states the rationale, objectives, design and pre-specified analyses, 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.

Effectiveness: The ability of a medical device to achieve clinical outcome(s) in its intended use

as claimed by the manufacturer.

Safety: Acceptable risks as weighed against benefits, when using the device according to the manufacturer's Instructions for Use.

Comparable Device: A medical device with related function chosen by the manufacturer to inform the clinical evaluation of the device in question.

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 Principles of Safety and Performance for Medical Devices and IVD Medical Device* (IMDRF GRRP WG/N47 FINAL: 2018).

Intended Use / Purpose: The objective intent of the manufacturer regarding the use of a product, process or service as reflected in the specifications, instructions and information provided by the manufacturer.

Serious Adverse Event: An adverse event that

1. led to a death;
2. led to a serious deterioration in health 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 inpatient 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.

Recognised Standards: Standards deemed to offer the presumption of conformity to specific essential principles of safety and performance. (SG1/ N044:2008)

Technical Documentation: The documented evidence, normally an output of the quality management system, that demonstrates compliance of a device to the *Essential Principles of Safety and Performance of Medical Devices* (IMDRF/GRRP WG/N47 FINAL: 2018).

5 General principles of clinical evaluation

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 comparable by the manufacturer.

The evaluation must also address any clinical claims made about the device, the adequacy of product labelling and product information (particularly 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 Principles that need to be addressed from a clinical perspective. Considerations should include:

- 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 safety, clinical performance and/or effectiveness 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;

- whether data from comparable devices can be used to support the safety, clinical performance and/or effectiveness of the device in question.

  Comparable devices should be considered with respect to relevant aspects including intended use, technical and/or biological characteristics to inform the clinical evaluation of the device. These characteristics should be broadly similar, but consideration must be given to how differences may affect the safety, clinical performance and/or effectiveness of the device. In some circumstances, these characteristics are similar to such an extent that there would be no clinically significant difference in the safety, clinical performance and/or effectiveness of the device. For example, *intended use* includes 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* include the design, specifications, physiochemical properties including energy intensity, deployment methods, critical performance requirements, and principles of operation; and *biological characteristics* include biocompatibility of materials in contact with body fluids/tissues. Some additional considerations for comparability are given in Appendix A. The manufacturer is also 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

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

  Manufacturers may be able to leverage existing information drawn from 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 comparable 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. The manufacturer will need to give consideration to the advantages and limitations of each data type.

How is a clinical evaluation performed?

Once the scope has been defined, there are three discrete 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 safety, clinical performance and/or effectiveness 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 Principles, 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.

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.

411 **Figure 1 Stages of a Clinical Evaluation**

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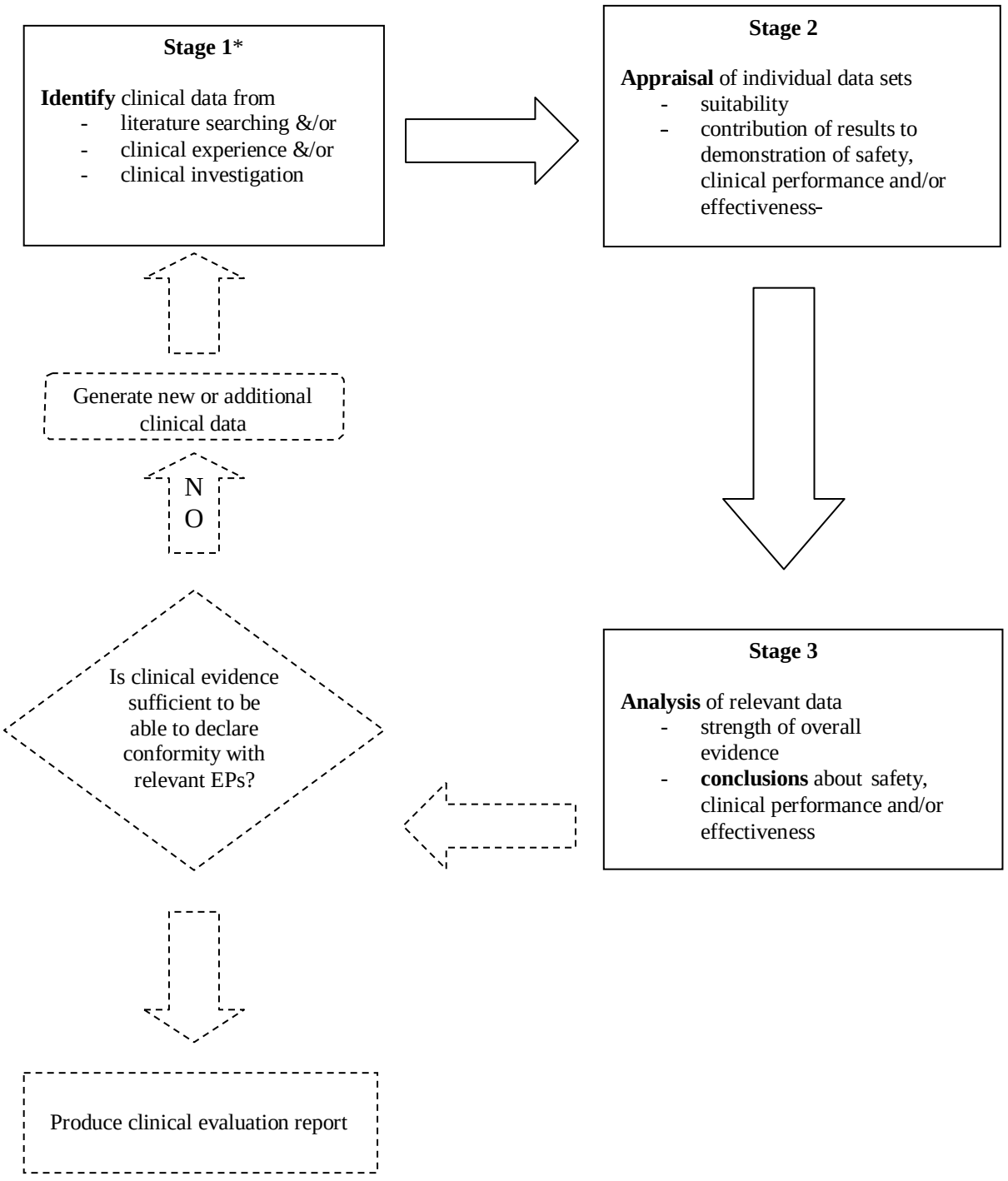

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427 EPs = Essential Principles of safety and performance of medical devices
428 * - Conformance to performance standards may be sufficient to demonstrate compliance to relevant Essential Principles
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What about in vitro diagnostic devices (IVDDs)?

Clinical evaluation should be performed for in vitro diagnostic devices as part of conformity assessment to the Essential Principles in a manner similar to other devices. The basic principles of objective review of clinical data will apply as described in this guidance document. However, IVDDs offer some unique definitions and concepts, which have been defined in the GHTF/SG5/N6:2012: Clinical Evidence for IVD medical devices – Key Definitions and Concepts, as well as challenges in demonstrating clinical evidence and delineating when the elements of clinical evidence are appropriate for the IVDDs, which have been addressed in the GHTF/SG5/N7:2012: Clinical Evidence for IVD medical devices – Scientific Validity Determination and Performance Evaluation.

What about Software as a Medical Device (SaMD)?

An SaMD can best be described as software that utilizes an algorithm (logic, set of rules, or model) that operates on data input (digitized content) to produce an output that is intended for medical purposes as defined by the SaMD manufacturer. Like other medical device, SaMD clinical evaluation shall be consistent with this document. Moreover, IMDRF developed a specific guidance "Software as a Medical Device (SaMD): Clinical Evaluation SaMD WG/N41:2017" to address more detailed instructions on SaMD clinical evaluation.

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 comparable 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 searching

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 safety, clinical performance and/or effectiveness 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 comparable 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 searching

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 B.

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 C.

What 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 comparable devices. Such types of data may include:

- manufacturer-generated post market surveillance reports, registries or cohort studies (which may contain unpublished long term safety, clinical performance, and/or effectiveness 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); and

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 investigations[1]. The data are most useful for identifying less common but serious device-related adverse events; providing long term information about safety, clinical performance, and/or effectiveness 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 standing, well-characterized 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 safety, clinical performance and/or effectiveness 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 safety, clinical performance and/or effectiveness.

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

Registries that fit the IMDRF definition and qualifiers have potential to be used for regulatory decision making (IMDRF/REGISTRY WG/N33 FINAL: 2016 - *Principles of International System of Registries Linked to Other Data Sources and Tools*). To support regulatory purposes, the quality and robustness of registry data used must be carefully assessed. Guidance has been provided on methodological principles in the clinical evaluation across the device lifecycle using international registries (IMDRF/Registry WG/N42FINAL:2017 - *Methodological Principles in the Use of International Medical Device Registry Data*), and the use of registry-generated data in support of regulatory decisions (IMDRF/Registry WG/N46 FINAL: 2018 - *Tools for Assessing the Usability of Registries in Support of Regulatory Decision-Making*).

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 ISO 14155:2011, *Clinical investigation of medical devices for human subjects -- Good clinical practice*, 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 comparable 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

[1] In 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.

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 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;
- Documents related to financial disclosure, financial agreements or conflict of interests; 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 safety, clinical performance and/or effectiveness 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, clinical performance and/or

effectiveness of the device (including any specific claims about safety, clinical performance and/or effectiveness).

What should the appraisal cover?

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 a comparable 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 safety, clinical performance and/or effectiveness of the device in question.

Further appraisal needs to be undertaken to determine the contribution of each data subset to establishing the safety, clinical performance and/or effectiveness 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]. The evaluator should also assess whether clinical data are collected ethically and in conformance with good clinical practice (such as ISO 14155:2011), and whether clinical data are applicable to the population for which the marketing authorization is being sought. Refer to Appendix D for details regarding considerations of data from various jurisdictions.

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 E.

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, clinical performance and/or effectiveness data, the data should be categorized 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 F.

8 Analysis of the clinical data (Stage 3)

The goal of the analysis stage is to make a benefit/risk determination if the appraised data sets available for a medical device collectively demonstrate the safety, clinical performance and/or effectiveness 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), it is most likely that qualitative (i.e. descriptive) methods will need to be used.

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 safety, clinical performance and/or effectiveness 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 confirm:

- 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.
- compliance with the relevant Essential Principles;
- whether post market clinical follow up or post approval study is necessary.

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

[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

conclusions about the safety, clinical performance and/or effectiveness 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 safety, clinical performance and/or effectiveness ;
- 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 safety, clinical performance and/or effectiveness 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 G. 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 a comparable 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.

Appendices

Appendix A: Some Considerations for Comparability

The examples given below are potential aspects for consideration with respect to comparability. There should still be summary documentation provided describing how these elements support comparability. Further, there may be cases where additional testing is needed to establish a particular degree of comparability.

Intended use:

- indications for use, including the disease or condition the device will diagnose, treat, prevent, cure or mitigate
- the severity and stage of disease
- patient population (age, gender, anatomy, physiology, other aspects)
- the site of application to/in the body (organs, parts of the body, tissues or body fluids contacted by the device)
- type of contact (contact with mucosal membranes/ invasiveness/ implantation)
- duration of use or contact with the body
- environment of use (e.g. healthcare facility, home)
- intended user (use by health care professional / lay person)
- repeat applications, including any restrictions as to the number or duration of reapplications
- other aspects

Technical:

- design (e.g. dimensions and design tolerances; how the different components of the device system work together)
- material (e.g. chemical formulation, additives, processing such as forged, state such as crystalline)
- specifications and properties (e.g. physicochemical properties such as type and intensity of energy, wavelength, porosity, particle size, viscosity, nanotechnology, specific mass, atomic inclusions such as nitrocarburising, oxidability, tensile strength and degradation characteristics)
- deployment methods (if relevant)
- critical performance requirements
- principles of operation
- other aspects

Biological:

- biocompatibility of materials in contact with body fluids/tissues
- biological action (if applicable)
- degradation mechanism and profile (if applicable)
- biological response (e.g., inflammatory response, immune response, tissue integration)
- other aspects

Appendix B: 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]

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 (incl publication date and edition))

[Attach copy of downloaded, unedited search strategy]

(vi) Selection criteria used to choose articles

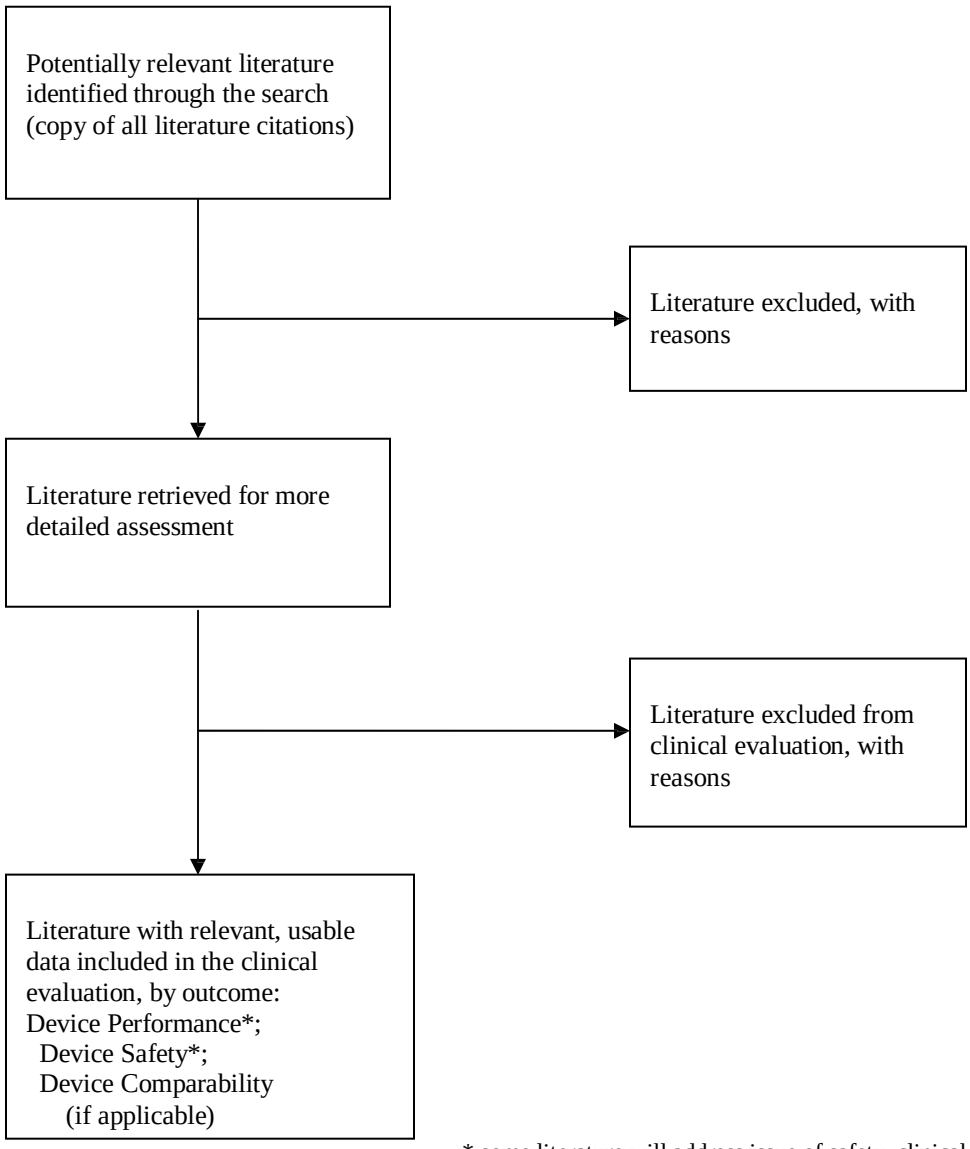
Outputs

(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 **I**ncident **R**eport **I**nvestigation **S**cheme
MAUDE	US FDA's **M**anufacturer **A**nd **U**ser Facility **D**evice **E**xperience database
MEDION	Database that indexes literature on diagnostic tests
MEDLINE	Published by US National Library of Medicine

Appendix C: A possible methodology for documenting the screening and selection of literature within a literature search report[3]



* some literature will address issue of safety, clinical performance and/or effectiveness

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

Appendix D: Considerations for the Application of Clinical Investigation Data Generated from Different Jurisdiction(s)

When clinical investigations are conducted ethically in accordance with applicable good clinical practice, the clinical data should be accepted for consideration in any jurisdiction. However, the applicability of the clinical data may be dependent on differences in regulatory requirements, intrinsic and extrinsic factors.

1. Considerations for differences in regulatory requirements

The clinical investigation should be conducted in compliance with both regulations required in the jurisdictions where the investigation is performed as well as where the investigational device is going to be reviewed for the market approval. Aspects of the investigation that do not meet the requirements for study conduct in each jurisdiction should be explained and justified.

2. Considerations for intrinsic and extrinsic factors

The intrinsic and extrinsic factors related to applicability may include:

1) Intrinsic factors: human genetic characteristics or demographic factors, such as race, age, gender, *etc.*;

2) Extrinsic factors: clinical practice, social environment, natural environment, cultural factors, life behavioral factors, rare or regional diseases, *etc*.

The clinical practice may include method for utilization by users, clinical facilities, levels of clinical skill, standards of care, criteria of diagnosis and concepts of treatment, *etc*. For instance, differences in clinical facilities and levels of clinical skill can affect the extrapolation of the data to intended clinical practice and the differences can impact the safety, clinical performance, and/or effectiveness of the devices which require complex operation skills. Different standards of care can affect the analysis of the benefits and risks of the studied device relative to standard practice. In addition, different diagnosis criteria and treatment concepts can also impact the compliance with relevant local guidelines for clinical practice.

The above considerations should be justified according to specific circumstances such as development status, the use experience in clinical practice, and the understanding on related diseases and their diagnosis and treatment methods. Where it is determined that some factors could have significant influence on the clinical investigation data, appropriate methods should be adopted to reduce or eliminate the influences. In those cases, additional clinical investigation may be required. Where it is determined that some factors have no significant influence, a brief explanation may be required.

Appendix E: Some Examples to Assist with the Formulation of Criteria

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 randomized 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?

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?

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

Appendix F: 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 F1 and F2. 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 F1), 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 F2). 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 safety, clinical performance and/or effectiveness 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 F1 Sample Appraisal Criteria for

Suitability Criteria	Description	Grading System	
Appropriate device	Were the data generated from the device in question?	D1 D2 D3	Actual device Comparable device Other device
Appropriate device application	Was the device used for the same intended use (e.g., methods of deployment, application, etc.)?	A1 A2 A3	Same use Minor deviation Major deviation
Appropriate patient group	Were 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 P2 P3	Applicable Limited 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 R2 R3	High quality Minor deficiencies Insufficient information

Table F2 Sample Appraisal Criteria for Data Contribution

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

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Appendix G: 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, clinical performance and/or effectiveness 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 a comparable

device. Identify the comparable device(s) and provide a justification of the comparability, cross-referenced to the relevant non-clinical documentation that supports the claim.

State the Essential Principles 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, categorized according to whether the data address the safety, clinical performance and/or effectiveness of the device in question. (Note: many individual data sets will address safety, clinical performance and/or effectiveness.) Within each category, order the data according to the importance of their contribution to establishing the safety, clinical performance and/or effectiveness of the device and in relation to any specific claims about safety, clinical performance and/or effectiveness. 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, clinical performance and/or effectiveness 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 Principles;
- the safety, clinical performance and/or effectiveness 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