Asian Harmonization Working Party
WORKING TOWARDS MEDICAL DEVICE HARMONIZATION IN ASIA

PROPOSED FINAL DOCUMENT

Title: Clinical Evaluation

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This document has been adopted from Final Document of GHTF/SG5/N2R8:2007.

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Preface

The document herein was produced by the Asian Harmonization Working Party (AHWP), a group of experts from medical device regulatory authorities and medical device industry. The document is intended to provide non-binding guidance for use in the regulation of medical devices, and has been subject to consultation throughout its development.

The Global Harmonization Task Force (GHTF) document GHTF SG5/N2R8:2007 was used as a basis for the development of this AHWP document.

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 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, 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 labeling 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 Principles 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 demonstration of the conformity of the device to the relevant Essential Principles.
The clinical evidence, along with other design verification and validation documentation, device description, labeling, risk analysis and manufacturing information, is needed to allow a manufacturer to demonstrate conformity with the relevant 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 favorable and unfavorable data), with the intention of demonstrating valid clinical evidence of the safety and performance of the device as intended by the manufacturer. However, it is important to recognize 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 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 recognized standards to satisfy the clinical evidence requirements for devices based on technologies with well established safety and performance characteristics.

The depth and extent of the clinical evaluation should, therefore, be flexible and not unduly burdensome, and appropriate to the nature, intended use and risks of the device in question.

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.

2 Scope

The Scope of this document is an ongoing Clinical Evaluation process conducted throughout the life cycle of a medical device.

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 IVDs.

3 References

GHTF & AHWP final documents

SG1/N029:2005 *Information Document Concerning the Definition of the Term "Medical Device"*

SG1/N041:2005 *Essential Principles of Safety and Performance of Medical Devices*

SG1/N68:2012 *Essential Principles of Safety and Performance of Medical Device*

SG2/N021:2000 *Adverse Event Reporting Guidance for the Medical Device Manufacturer or its Authorized Representative*

SG5/N1R8:2007 *Clinical Evidence – Key Definitions and Concepts*

SG5/N2R8:2007 *Clinical Evaluation*

International standards

ISO 14155: 2011 *Clinical investigation of medical devices for human subjects – Good Clinical Practice*

4 Definitions

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

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

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

NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

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

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.

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

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

NOTE "Clinical trial" or "clinical study" are synonymous with "clinical investigation".

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

NOTE: The term "protocol" is synonymous with "CIP". However, protocol has many different meanings, some not related to clinical investigation, and these can differ from country to country.

Clinical Performance: The ability of a medical device to achieve its intended use 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 Principles of Safety and Performance for Medical Devices (SG1/N041:2005 and AHWP).*

Investigation site: Institution or site where the clinical investigation is carried out.

NOTE: For the purpose of this International Standard, "investigation site" is synonymous with "investigation centre".

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

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

Serious Adverse Event: Adverse event that

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

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

Recognised Standards: Standards deemed to offer the presumption of conformity to specific essential principles of safety and performance (*GHTF SG1/N012 and AHWP*).

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 (GHTF SG1/N041:2005 and AHWP).*

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 labeling 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 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;

- whether data from comparable 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 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

- 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 evaluations of medical devices that are based on existing, well-established technologies and intended for an established use of those technologies are 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 performance, safety and presentational aspects (labeling, 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 relevant 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.

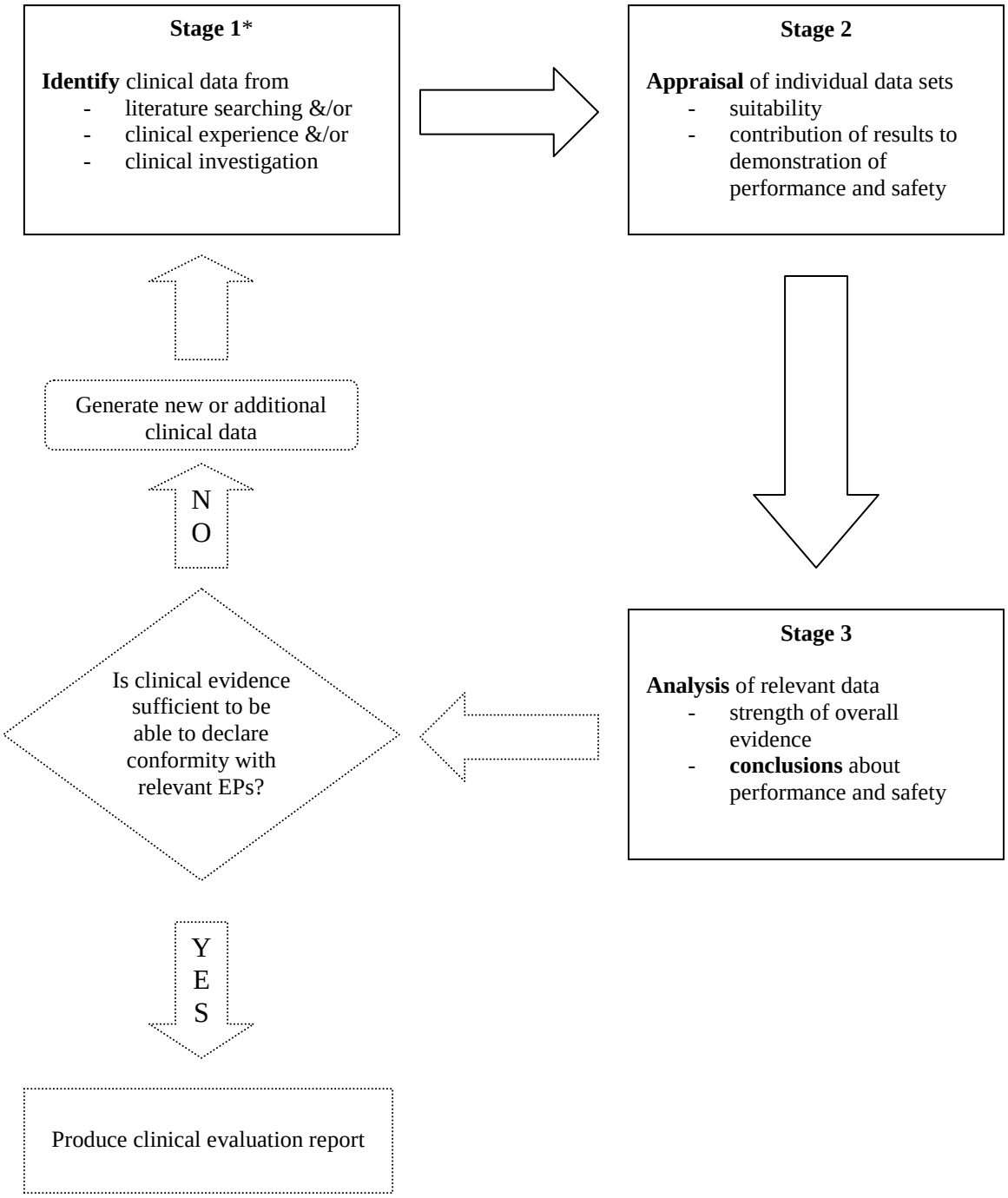
Who should perform the clinical evaluation?

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.

Figure 1 Stages of a Clinical Evaluation



EPs = Essential Principles of safety and performance of medical devices
* - Conformance to performance standards may be sufficient to demonstrate compliance to relevant Essential Principles

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 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 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 methodology 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 mayhelp to maximize data retrieval.

The literature search methodology 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 methodology 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.

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

The literature search methodology, 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.

Example of evidence table.

Study details	Population and setting	Intervention (Method of allocation to Intervention /Control	Outcomes /results	Comments
Author's: Years : Citation:	Source of population/s : Report the following Sample characteristics	Method of allocation: Example: Intervention/s description: Describe intervention in detail including :	Include relevant detail on outcome Limitation	

	including population demographics (report age,sex, sexual and etc.	• what was delivered • by whom • how delivered • when /where • how often • how long for etc		

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 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); 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 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 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?

[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.

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 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).

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, or to a comparable standard, and in compliance with local regulations.

It is recognized 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 expected that all 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; and
- the signed and dated final clinical investigation 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 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.

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 conformity to the relevant Essential Principles for the device. **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 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 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 D.

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), 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 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

[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.

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 and the severity and natural history of the condition being diagnosed or treated.

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 (recognized 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 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: 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

Other databases are also applicable.

[Include justification for choice of sources and describe any supplemental strategies (eg 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

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)]

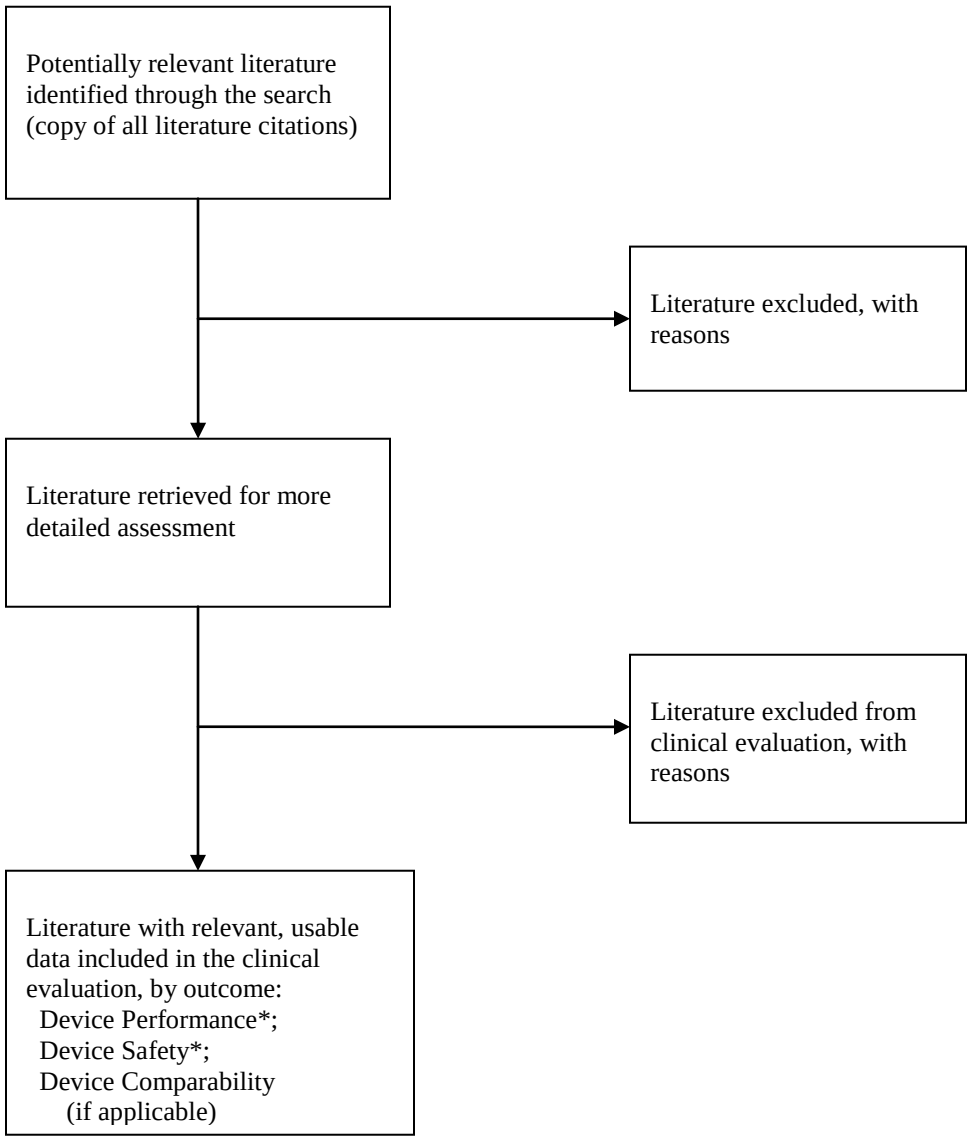
Example of Search Strategy Table :

Title	Database:	Keywords used:	Date retrieved	No of article search (hits)	No of article selected

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



* some literature will address issue of both performance and safety

[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 C: 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.

Randomized 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 (ie 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 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

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 D2 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 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 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 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 Principles;
- 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