HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

# GUIDANCE FOR CONSULTATION

GN-20: Guidance on Clinical Evaluation

# CONTENTS

## PREFACE

This document is intended to provide general guidance. Although we have tried to ensure that the information contained here is accurate, we do not, however, warrant its accuracy or completeness. The Health Sciences Authority (HSA) accepts no liability for any errors or omissions in this document, or for any action/decision taken or not taken as a result of using this document. The information contained in this document should not be a substitute for professional advice from your own professional and healthcare advisors.



## REVISION HISTORY

| Guidance Version (Effective Date) *[3 latest revisions]* | Revision |
|---|---|
| GN-20: Revision 1 (01 December 2017) | R1 |
| R2 ►GN-20: Revision 2 (01 November 2022) | R2 |
| R3 ►GN-20: Revision 3 (-------) | R3 |

**Where applicable, changes and updates made in each document revision are annotated with or within the arrow symbol "►". Deletions may not be shown.*

# 1. INTRODUCTION

## 1.1. Purpose

R3 ► For medical devices to be supplied in Singapore, they must be supported by clinical evidence that aligns with their intended purpose and classification, and must conform to the relevant Essential Principles of Safety and Performance (EP), as outlined in GN-16: Guidance on Essential Principles for Safety and Performance of Medical Devices.

EP 9 Clinical evaluation provides that every medical device requires clinical evidence demonstrating compliance with the applicable provisions of the essential principles, and a clinical evaluation should be conducted based on the device's intended purpose use and classification.

The clinical evaluation should evaluate relevant clinical data to determine whether the medical device has a favourable benefit-risk profile, which can be established through clinical investigation reports, published literature reviews, and clinical experience, including real-world data.

This document provides general guidance the considerations and steps on preparing and presenting clinical evidence for demonstrating a medical device's conformance to the EP for regulatory submission purposes. ◄

## 1.2. Background

R3 ► Clinical evaluation is a set of ongoing activities that use scientifically sound methods for the assessment and analysis of clinical data pertaining to a medical device in order to verify the safety and performance of the medical device. 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 and performance information about the medical device is obtained during its use. This information is fed into the ongoing risk management process (according to ISO 14971) and may result in changes to the product owner's risk assessment, clinical investigation documents, Instructions for Use and post-market activities.

When placing a medical device on the market, product owners must have demonstrated through the use of appropriate conformity assessment procedures that the medical device complies with the EP. Generally, it is expected that the product owner has demonstrated the medical device achieves its intended performance during use according to its labelling (i.e. information supplied by the product owner) and that the known and foreseeable risks are minimised and acceptable when weighed against the benefits. Any claims made about the medical device's safety and performance should be supported by suitable evidence.

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

To conduct a clinical evaluation, a product owner needs to:

- identify the Essential Principles that require support from relevant clinical data;
- identify available clinical data relevant to the medical device and its intended purpose;
- evaluate (appraise and analyses) clinical data in terms of its suitability and contribution to demonstrating the safety and performance of the medical device in relation to its intended purpose;
- generate clinical data needed to address remaining questions of safety and performance;
- bring all the clinical data together to reach conclusions about the safety and performance of the medical 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 medical 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 product owner to demonstrate conformity with the EP and is part of the technical documentation of a medical device. ◄

### 1.3. Scope

The scope of this document is to provide product owners 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.

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.

A clinical evaluation should be thorough and objective (i.e it should consider both favourable and unfavourable data), with the intention of demonstrating valid clinical evidence of the safety and performance of the medical 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 medical 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 medical devices to establish the clinical evidence, thereby reducing the need for clinical data generated through clinical investigation of the medical device in question. Similarly, it may be possible to use compliance with recognised standards to satisfy the clinical evidence requirements for medical devices based on technologies with well-established safety and performance characteristics.

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

R3 ► This guidance should be read together with the other relevant regulatory guidance documents and regulatory guidelines including but not restricted to:

- GN-16: Guidance on Essential Principles for Safety and Performance of Medical Devices
- GN-17: Guidance on Preparation of a Product Registration Submission for General Medical Devices using the ASEAN CSDT
- GN-18: Guidance on Preparation of a Product Registration Submission for *In Vitro* Diagnostic (IVD) Medical Devices using the ASEAN CSDT
- GN-21: Guidance on Change Notification for Registered Medical Devices
- GN-34: Guidance Document for IVD Analysers

- TR-02: Contents of a Product Registration Submission for In Vitro Diagnostic Medical Devices using the ASEAN CSDT
- Other Product Specific Regulatory guidelines

Applicants are strongly encouraged to familiarise themselves with the criteria and requirements outlined in the guidance and guideline documents when preparing their submission. ◄

## 1.4. Definitions

Definitions that do not indicate they are set out in the Health Products Act 2007 (*Act*) and Health Products (Medical Devices) Regulations 2010 (*Regulations*) are intended as guidance in this document. These definitions are not taken verbatim from the above legislation and should not be used in any legal context. These definitions are meant to provide guidance in layman terms.

ADVERSE EFFECT *(as set out in the Act)*: means any debilitating, harmful, toxic or detrimental effect that the medical device has been found to have or to be likely to have on the body or health of humans when such a medical device is used by or administered to humans.

ADVERSE EVENT: any event or other occurrence, that reveals any defect in any medical device or that concerns any adverse effect arising from the use thereof.

R3 ►

CLINICAL DATA: Safety and/or performance information that is generated from the clinical use of a medical device.

Explanation: Sources of clinical data may include:

- results of pre- and post-market clinical investigations of the medical device concerned;

- results of pre- and post-market clinical investigations or other studies reported in the scientific literature of a comparable medical device;
- published and/or unpublished reports on other clinical experience of either the medical device in question or a comparable medical device;
- other sources of clinical experience such as real-world data including data from registries, adverse event databases and medical records.

CLINICAL EVALUATION: The assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the medical device when used as intended by the product owner.

Explanation: This is a process undertaken by product owners of medical devices to help establish compliance with the relevant Essential Principles for Safety and Performance. The result of this process is a report that can be reviewed by the Authority and which details the extent of available data and its quality and demonstrates how the compliance with the Essential Principles is satisfied by the clinical data.

The inputs for clinical evaluation are primarily clinical data in the form of clinical investigation reports, literature reports/reviews and clinical experience (including real-world data). The data required to establish the initial evidence of compliance with the Essential Principles may vary according to the characteristics of the medical device, its intended purpose, the claims made by the product owner, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use. A key goal of the clinical evaluation is to establish that any risks associated with the use of the medical device are acceptable when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety. The clinical evaluation will, therefore, also need to cross-reference risk management documents.

Clinical evaluation is an ongoing process. Information about clinical safety and performance (e.g. adverse event reports, results from any further clinical

investigations, published literature, etc) should be monitored routinely by the product owner once the medical device is available on the market and the benefits and risks reassessed in light of this additional information. ◄

CLINICAL EVIDENCE: The clinical data and the clinical evaluation report pertaining to a medical device.

Explanation: Clinical evidence is an important component of the technical documentation of a medical device, which along with other design verification and validation documentation, medical device description, labelling, risk analysis and manufacturing information, is needed to allow a product owner to demonstrate conformity with the Essential Principles. It should be cross-referenced to other relevant parts of the technical documentation that impact on its interpretation.

In accordance with applicable local regulations, clinical evidence, in part or in total, may be submitted to and reviewed by conformity assessment bodies and regulatory authorities. The clinical evidence is used to support the marketing of the medical device, including any claims made about the clinical safety and performance of the medical device, and the labelling of the medical device. Annex 1 shows how the need for clinical evidence drives the processes of data generation and clinical evaluation, which produce clinical data and clinical evidence, respectively.

Clinical evidence should be reviewed and updated throughout the product life cycle by the product owner as new information relating to clinical safety and performance is obtained from clinical experience during marketing (e.g. adverse event reports, results from any further clinical investigations, formal post market surveillance studies) of the medical device in question and/or comparable medical devices.

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

Explanation: This term is synonymous with 'clinical trial' and 'clinical study'. Clinical investigations include feasibility studies and those conducted for the purpose of gaining market approval, as well as investigations conducted following marketing approval.

CLINICAL INVESTIGATION PLAN: Document that states the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record keeping of the clinical investigation.

CLINICAL SAFETY: The absence of unacceptable clinical risks, when using the medical device according to the product owner's Instructions for Use.

R3 ►
COMPARABLE DEVICE: A medical device with related function chosen by the product owner to inform the clinical evaluation of the device in question. ◄

CONFORMITY ASSESSMENT: The systematic examination of evidence generated and procedures undertaken by the product owner, under requirements established by the Regulatory Authority, to determine that a medical device is safe and performs as intended by the product owner and, therefore, conforms to the Essential Principles.

INTENDED PURPOSE/INTENDED USE *(as set out in the Regulations)*: in relation to a medical device or its process or service, means the objective intended use or purpose, as reflected in the specifications, instructions and information provided by the product owner of the medical device.

R3 ►

PERFORMANCE: The ability of a medical device to achieve its intended purpose as stated by the product owner. Performance may include both clinical and technical aspects. ◄

PRODUCT OWNER *(as set out in the Regulations)*: in relation to a health product, means a person who —

- supplies the health product under his own name, or under any trade mark, design, trade name or other name or mark owned or controlled by him; and
- is responsible for designing, manufacturing, assembling, processing, labelling, packaging, refurbishing or modifying the health product, or for assigning to it a purpose, whether those tasks are performed by him or on his behalf.

R3 ►

RECOGNISED STANDARDS: Standards deemed to offer the presumption of conformity to specific essential principles of safety and performance.

STANDALONE SOFTWARE (also known as SaMD in IMDRF context): a software and/or mobile application that is intended to function by itself and are not intended for use to control or affect the operation of other hardware medical devices. ◄

TECHNICAL DOCUMENTATION: The documented evidence, normally an output of the quality management system that demonstrates compliance of a medical device to the essential principles.

# 2. GENERAL PRINCIPLES OF CLINICAL EVALUATION

## 2.1. What is the scope of a clinical evaluation?

The clinical evaluation is based on a comprehensive analysis of available pre- and post-market clinical data relevant to the intended purpose of the medical device in question, including clinical performance data and safety data. This includes data specific to the medical device in question as well as any data relating to medical devices claimed as comparable by the product owner.

The evaluation must also address any clinical claims made about the medical 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 product owner 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 medical 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 medical device (e.g. target treatment group and disease, proposed warnings, contraindications and method of application) and the specific claims made by the product owner about the performance and safety of the medical device. The scope of the clinical evaluation will need to be informed by and cross-referenced to the product owner's risk management documents. The risk management documents are expected to identify the risks associated with the medical 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 product owner

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

R3 ► Comparable devices should be considered with respect to relevant aspects including intended purpose, technical and/or biological characteristics to inform the clinical evaluation of the medical device. These characteristics should be broadly similar, but consideration must be given to how differences may affect the safety and performance of the medical device. In some circumstances, these characteristics are similar to such an extent that there would be no clinically meaningful difference in the safety and performance of the medical device. While evidence and data from comparable medical devices may support specific features or functions of the device in question in certain use cases, it may not be sufficient to demonstrate compliance with the Essential Principles. Additional clinical evidence may still be necessary from other studies to address any gaps in the clinical evaluation and ensure compliance with the Essential Principles.

Intended purpose (including indications for use) includes the clinical condition being diagnosed, monitored, treated or managed, 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. Biological characteristics includes biocompatibility of materials in contact with body fluids/tissues. Some additional considerations for comparability are given in Annex 2. As part of the clinical evaluation report, the product owner is also expected to assess the supporting non-clinical information and summarise it. (Note: the clinical evaluation is not intended to comprehensively assess the technical and biological characteristics) ◄

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

R3 ► Product owners may be able to leverage existing information drawn from any one or combination of data sources set out in Section 3. ◄ Factors that should be considered when choosing the type of data to be used in the clinical evaluation include the design, intended purpose and risks of the medical device; the developmental context of the technology on which the medical 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 medical devices. High-risk medical 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 product owner will need to give consideration to the advantages and limitations of each data type.

## 2.2. How is a clinical evaluation performed?

Once the scope has been defined, there are three discrete stages in performing a clinical evaluation (Annex 3):

- identification of pertinent standards and clinical data;
- appraisal of each individual data set, in terms of its relevance, applicability, quality and clinical significance; and
- analysis of the individual data sets, whereby conclusions are reached about the performance, safety and presentational aspects (labelling, patient information and Instructions for Use) of the medical 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 medical device. If the product owner concludes there is insufficient clinical evidence to be able to declare conformity with the Essential Principles, the product owner 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.

### 2.3. Who should perform the clinical evaluation?

The clinical evaluation should be conducted by a suitably qualified individual or individuals. A product owner must be able to justify the choice of the evaluators through reference to qualifications and documented experience.

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

- the medical 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 medical device.

### 2.4. What about *In Vitro* Diagnostic (IVD) Medical Devices?

R3 ► As with other medical devices, IVD medical devices are required to undergo clinical evaluation to demonstrate conformity to the Essential Principles. Clinical evaluation, including clinical performance studies, is a standard component of the clinical data generated for IVD medical devices. Therefore, it is important to consider good study practices, as well as factors such as the standards of the laboratories conducting these studies (e.g. accredited third-party clinical laboratories) and the adequacy of the study methodology design, which should be appropriate for the risk of the IVD (e.g. how well is the marker in question).

The principles of objective review of clinical data and considerations outlined in this document, should be applied in a similar manner together with the

requirements and considerations in GN-18: Guidance on Preparation of a Product Registration Submission for *In Vitro* Diagnostic Medical Devices using the ASEAN CSDT and TR-02: Contents of a Product Registration Submission for In Vitro Diagnostic Medical Devices using the ASEAN CSDT.

### 2.5. What about Standalone Software (Software as a Medical Device - SaMD)?

Standalone software (SaMD) generally refers to software that utilises an algorithm, logic, set of rules, or model to process digitised content as data input and generate an output intended for medical purposes as defined by the standalone software product owner. As with other medical devices, clinical evaluation of SaMD should align with the guidelines outlined in this document.

While software verification and validation ensure that specified software system requirements and users' needs are met, clinical evaluation SaMD is conducted to support their safety and performance when used in the intended clinical environment. The clinical evaluation process establishes a valid clinical association[1] between the software output and the specified clinical condition based on its intended purpose.

Clinical evaluation is an ongoing process throughout the software's life cycle. Continuously monitoring and data collection after the software medical device's deployment in the market ensures new or evolving risks arising from the use of the software can be detected in a timely manner in its real-world clinical environment.



[1] Clinical association refers to the extent to which the software's output, such as concepts, conclusions, and measurements, is clinically accepted or well-founded and corresponds accurately to the healthcare situation and condition referred to in the software's defined intended purpose.

Guidelines on the regulatory requirements for SaMD, including considerations for clinical evaluation may be found in - Regulatory Guidelines for Software Medical Devices - A Life Cycle Approach. ◄

# 3. SOURCES OF DATA / DOCUMENTATION USED IN A CLINICAL EVALUATION (STAGE 1)

R3 ► Data relevant to the clinical evaluation may be held by the product owner or third party, or be available in the scientific literature for the medical device in question or for comparable medical devices.

The product owner is responsible for identifying data relevant to the medical device and determining the types and amount of data needed for the clinical evaluation. ◄

## 3.1. Data generated through literature searching

Literature searching can be used to identify published clinical data that is not in the possession of the product owner that may assist the product owner to establish acceptable performance and safety of a medical device. The data generated through literature searching may relate directly to the medical device in question (e.g. reports of clinical investigations of the medical device in question that have been performed by third parties, adverse event reports) or to comparable medical devices.

For some medical 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 medical 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 medical device.

## 3.2. 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 product owner. 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;
- 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 Annex 4.

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 Annex 5.

### 3.2.1. 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 medical device in question.

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/purpose of the medical 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.

### 3.3. Data generated through clinical experience

R3 ► These types of clinical data are generated through clinical use that is outside the conduct of clinical investigations and may relate to either the medical device in question or comparable medical devices. These clinical experience data also often referred as real-world data are routinely collected from the use of the medical device.

Such types of data may include:

- post market surveillance reports, registries (product, disease, genetic testing, etc) or medical records or electronic health records (EHR), registries (which may contain unpublished long-term safety and performance data);
- adverse events databases (held by either the product owner or regulatory authorities);
- details of clinically relevant field corrective actions (e.g. recalls, notifications, hazard alerts);

- other real-world data routinely collected and related to use of medical devices, such as medical claims, pharmacy data, feedback from wearables and mobile technology, etc. ◄

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[2]. The data is most useful for identifying less common but serious medical 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 medical devices that are based on long-standing, well-characterised technology and, therefore, unlikely to be the subject of either reporting in the scientific literature or clinical investigation.

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

If a product owner 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 medical device in question. Reports of clinical experience that are not adequately supported by data, such as anecdotal reports or opinion, should not be used.



[2] 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 medical 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 medical device.

Post-market surveillance reports are compiled by the product owner and often include details of the medical device's regulatory status (countries in which the medical 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 product owner considers them to be medical device-related or not) and estimates of the incidence of adverse events. Post-market 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 medical devices, provide reasonable assurance of both clinical safety and performance.

R3 ► It may be helpful to provide a table summarising medical device-related adverse events, paying particular attention to serious adverse events, with comments on whether observed medical device-related adverse events are predictable on the basis of the mode of action of the medical device. Identified hazards not previously considered in the risk management documentation must be addressed, describing additional mitigation required (e.g. design modification, labelling changes, etc).

Registries can be used to support regulatory decision making. However, the quality and robustness of the registry data used for regulatory purposes must be carefully evaluated. Guidelines on the methodological principles for clinical evaluation throughout the device lifecycle using international registries and the use of registry-generated data to support regulatory may be found from IMDRF's published technical documents. ◄

### 3.4. Data from clinical investigations

The guidance included within this section applies to clinical investigations carried out by or on behalf of a product owner 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 R2 ► ISO 14155 - *Clinical Investigation of Medical Devices for Human Subjects* ◄, or to a comparable standard, and in compliance with local regulations.

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

### 3.4.1. 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 product owner, it is expected that documentation relating to the design, ethical and regulatory approvals, conduct, results and conclusions of the investigation needed for the clinical evaluation will be available for consideration, as appropriate. These may include:

- the clinical investigation plan;
- clinical investigation plan amendments and the rationale for these changes;
- the relevant Ethics Committee 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;
- R3 ► Documents related to financial disclosure, financial agreements or conflict of interests; 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 medical 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 clinical investigation report available, the evaluator will be able to assess the extent to which the investigation was conducted as planned and, where deviations of from the original plan have occurred, the impact those deviations had on the veracity of the data generated and the inferences that can be drawn about the performance and safety of the medical device from the investigation.

The final clinical investigation 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.

# 4. 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 medical device, and its contribution to demonstrating the safety and performance of the medical device (including any specific claims about safety or performance).

## 4.1. What should the appraisal cover?

The data needs to be assessed for its quality and its relevance to the medical device in question including its intended purpose (i.e. the data must be either generated for the medical device in question or for a comparable medical device). 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 medical 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 medical 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 medical device or due to confounding influences (e.g. natural course of the underlying medical condition, concomitant treatment(s)) or bias[3]. R3 ► The evaluator should also assess whether clinical data are collected in conformance with the applicable regulatory requirements or other relevant standards (e.g. ISO 14155) and whether clinical data is applicable to the population for which the marketing authorisation is being sought. Annex 6 provides considerations of clinical data from other jurisdictions. ◄

[3] 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.

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 Annex 7.

For many lower risk medical devices and medical devices based on long standing technology, the available data may be qualitative rather than quantitative in nature, so the evaluation criteria should be adjusted accordingly. The criteria adopted for the appraisal should be justified by the evaluator. Although there will be some overlap of safety and performance data, the data should be categorised to allow for separate analysis. Additional categories may also be needed, depending on the nature and intended purpose of the medical 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 Annex 8.

## 5. ANALYSIS OF THE CLINICAL DATA (STAGE 3)

R3 ► 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 clinical performance and safety of the medical device in relation to its intended purpose. ◄

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 medical 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 medical device, respectively. It may be useful to explore the results of the pivotal datasets, looking for consistency of results across particular medical 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 shows:

- the medical device performs as intended by the product owner;
- the medical device does not pose any undue safety concerns to either the recipient or end-user;
- any risks associated with the use of the medical device are acceptable when weighed against the benefits to the patient;
- R3 ► compliance with the relevant Essential Principles; and
- 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 medical 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 labelling 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.

## 6. THE CLINICAL EVALUATION REPORT

R3 ► 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 including relevant real-world data); the appraisal and analysis stages; and conclusions about the safety and performance of the medical device in question. ◄

The clinical evaluation report should contain sufficient information to be read as a standalone document by HSA. It is important that the report outline:

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

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

A suggested format for the clinical evaluation report is located at Annex 7. 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 product owner relies on clinical data for a comparable medical device which has been the subject of an earlier clinical evaluation (for which the product owner 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 medical device in question.

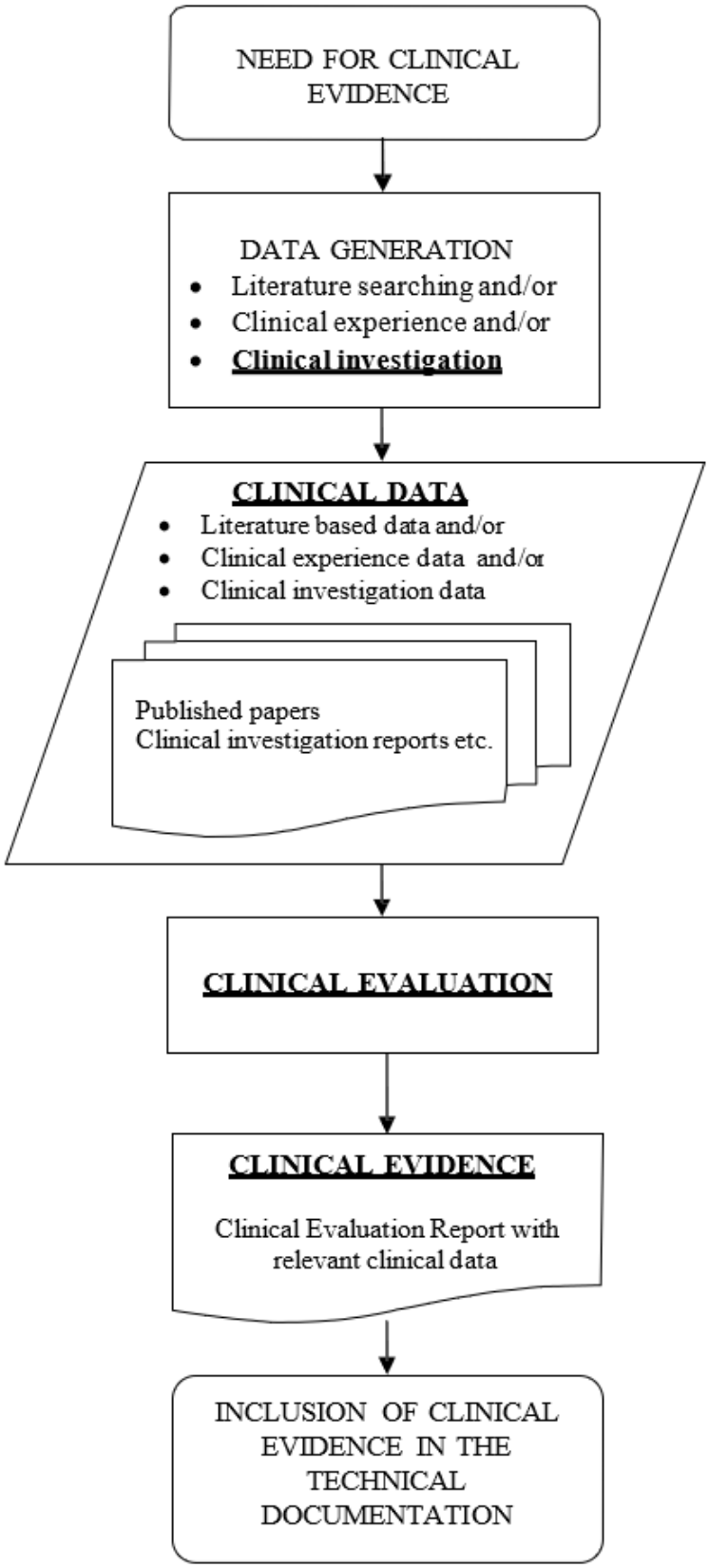
## 7. REFERENCES

I. Clinical Evidence – Key Definitions and Concepts (IMDRF MDCE WG/N55 FINAL:2019)

II. Clinical Evaluation (IMDRF MDCE WG/N56 FINAL:2019)

## ANNEX 1

## Overview of process for data generation and clinical evaluation



R3 ►

## ANNEX 2

## Some Considerations for Comparability

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

**Intended use:**

- Indications for use, including the disease or condition the medical device will diagnose, treat, prevent, cure or mitigate
- Severity and stage of disease
- Patient population (e.g. age, gender, anatomy, physiology)
- Site of application to/in the body (organs, parts of the body, tissues or body fluids contacted by the medical device)
- Type of contact (e.g. contact with mucosal membranes, invasiveness, implantation)
- Duration of use or contact with the body
- Environment of use (e.g. healthcare facility, home)
- Intended user (e.g. use by health care professional, lay person)
- Repeat applications, including any restrictions as to the number or duration of reapplications

**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
- Critical performance requirements/characteristics
- Principles of operation

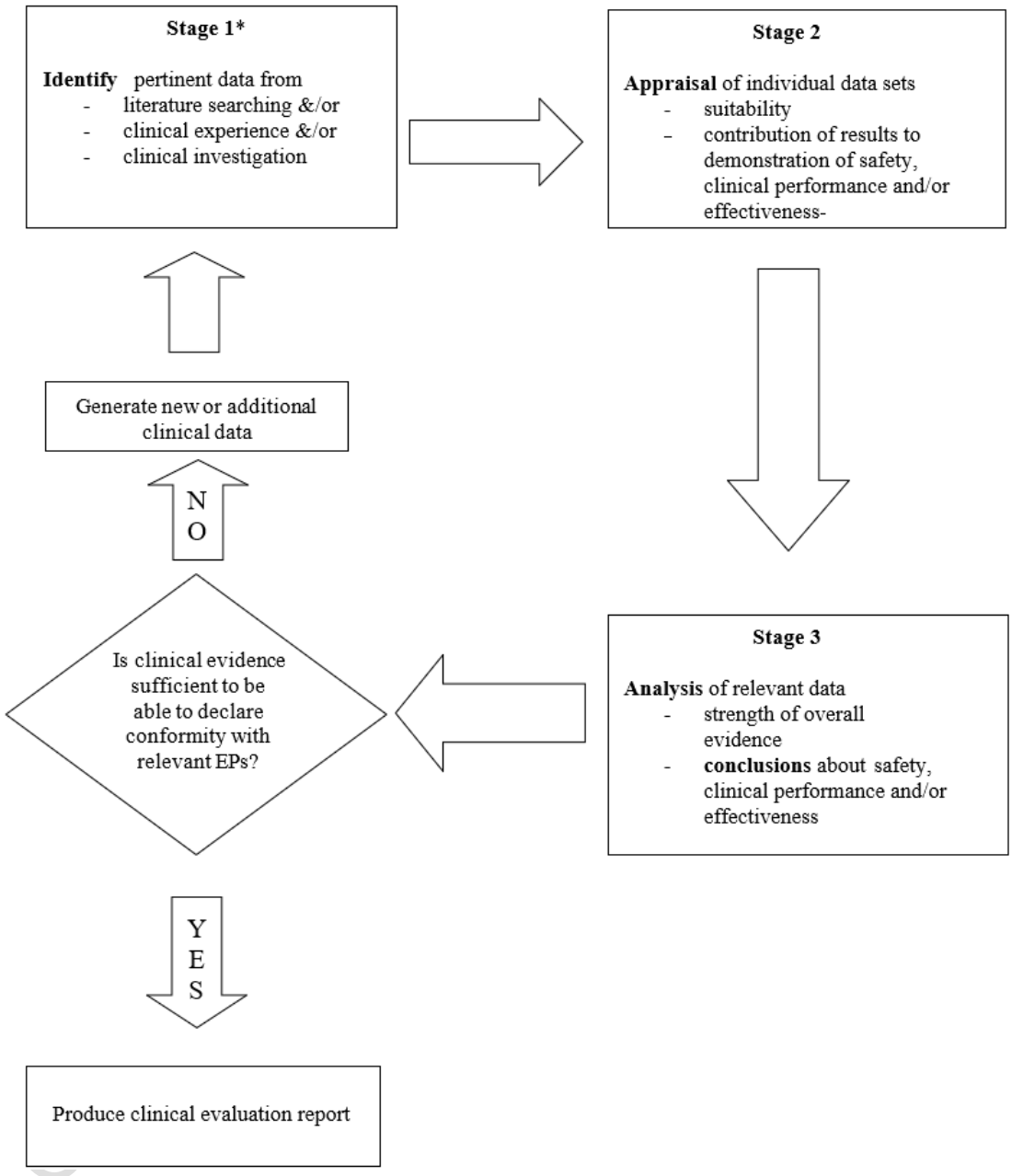
**Biological:**

- Biocompatibility of materials in contact with body fluids/tissues
- Biological action
- Degradation mechanism and profile
- Biological response (e.g., inflammatory response, immune response, tissue integration)

◄

# ANNEX 3

## 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.

## ANNEX 4

## A Possible Format for the Literature Search Report

### A. Medical device name/model

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

### C. Methods

- Date of search
- Name of person(s) undertaking the literature search
- Period covered by search
- 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 (eg checking bibliography of articles retrieved, hand searching of literature) used to enhance the sensitivity of the search]
- 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]
- Selection criteria used to choose articles

### D. Outputs

- Attach copy of literature citations retrieved from each database search
- Data selection process [Attach flow chart and associated tables showing how all citations were assessed for suitability for inclusion in the clinical

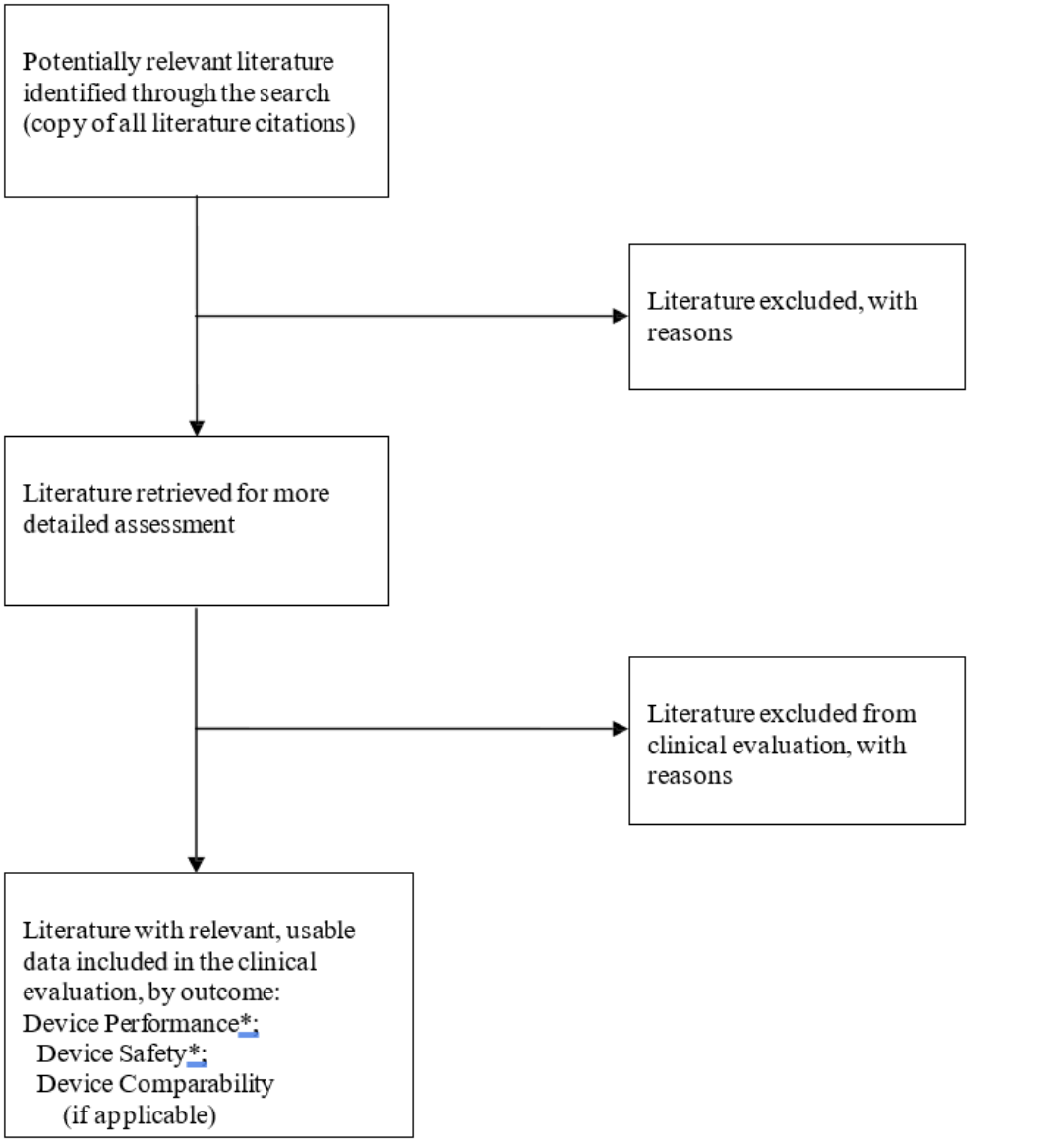
evaluation (see Annex 5)]

Notes:

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

968 **ANNEX 5**

969 **A possible methodology for documenting the screening and selection of**
970 **literature within a literature search report[4]**
971




972
973
974

[4] 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 Metaanalyses. *Lancet* 1999; 354: 1896-1900.

R3 ►

## ANNEX 6

## Considerations for the Application of Clinical Data Generated from Different Jurisdiction(s)

When clinical investigations are conducted ethically in accordance with applicable Good Clinical Practice (GCP), the clinical data should be accepted for consideration from 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 relevant regulations (i.e. GCP) in the jurisdictions where the investigation is performed. Consideration should be given to applicable GCP requirements in jurisdictions where the investigational device is to be reviewed for market approval. Aspects of the investigation that do not meet the applicable requirements 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.

For factors that could have significant influence on the clinical data, appropriate methods should be adopted to reduce variability. A justification should be provided for any residual variability. In some cases, additional clinical data may be required. ◄

## ANNEX 7

## 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.

R3 ►

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

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

**B. Cohort Study** - *Data are obtained from groups who have and have not been exposed to the medical 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?

**C. 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 medical 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?

**D. Case Series** - *The medical 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?

◄

## ANNEX 8

## 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 1 and 2. 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 1), 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 2). 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 5). 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 1: Sample Appraisal Criteria for Suitability

| **Suitability Criteria** | **Description** | **Grading System** |
|---|---|---|
| Appropriate device | Were the data generated from the device in question? | D1 Actual device<br>D2 Comparable device<br>D3 Other device |

| | | |
|---|---|---|
| Appropriate device application | Was the device used for the same intended purpose (e.g., methods of deployment, application, etc.)? | A1 Same purpose<br>A2 Minor deviation<br>A3 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 Applicable<br>P2 Limited<br>P3 Different population |
| Acceptable report/data collation | Do the reports or collations of data contain sufficient information to be able to undertake a rational and objective assessment? | R1 High quality<br>R2 Minor deficiencies<br>R3 Insufficient information |

1123

1124 Table 2: Sample Appraisal Criteria for Data Contribution

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

1125

1126

# ANNEX 9

## A Possible Format for a Clinical Evaluation Report

### A. General details

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

Identify the product owner(s) of the medical device.

### B. Description of the medical device and its intended application

Provide a concise physical description of the medical device, cross-referencing to relevant sections of the product owner'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 medical device components, including software and accessories;
- mechanical characteristics; and
- others, such as sterile vs. non-sterile, radioactivity etc.

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

Describe how the medical device achieves its intended purpose.

### C. Intended therapeutic and/or diagnostic indications and claims

R3 ► State the medical conditions or clinical context for treatment, diagnosis, monitoring or disease management, including target patient group and diseases. ◄

Outline any specific safety or performance claims made for the medical device.

## D. Context of the evaluation and choice of clinical data types

Outline the developmental context for the medical device. The information should include whether the medical 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 medical device. Identify the comparable medical 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 medical 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 medical 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.

## E. Summary of the clinical data and appraisal

Provide a tabulation of the clinical data used in the evaluation, categorised according to whether the data address the performance or the safety of the medical 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 medical 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 product owner's technical documentation.

## F. Data analysis

### (i) 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 medical device and, where useful, particular performance characteristics. Outline why they are considered to be "pivotal" and how they demonstrate the performance of the medical device collectively (e.g. consistency of results, statistical significance, clinically significance of effects).

### (ii) Safety

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

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

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

### (iii) Product Literature and Instructions for Use

State whether the product owner'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 medical device.

## G. Conclusions

Outline clearly the conclusions reached about the safety and performance of the medical device from the evaluation, with respect to the intended purpose of the medical 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 medical device as claimed have been established; and
- the risks associated with the use of the medical device are acceptable when weighed against the benefits to the patient.

END OF DOCUMENT