Clinical Evaluation Procedure

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1. Purpose

The purpose of this procedure is to have a controlled process to plan, obtain, assess and analyse CLINICAL DATA that apply to a MEDICAL DEVICE, with the goal to evaluate the CLINICAL SAFETY and CLINICAL PERFORMANCE of the MEDICAL DEVICE when used as intended by the manufacturer.

2. Scope

This procedure applies to CLINICAL EVALUATION of all MEDICAL DEVICES developed and maintained by the organization that are CE marked or that need to be CE marked in order to legally market the product. A clinical evaluation report is completed to demonstrate conformity to *Annex I Essential Requirements* and conducted in accordance with *Annex X* CLINICAL EVALUATION of the EU Medical Device Directive (MDD).

3. Operational Responsibilities

SL#	Role	Responsibilities
1.	Clinical Application Specialist	Responsible for the execution of this procedure, and: • Has overall responsibility for the CLINICAL EVALUATION outputs • Author of the Clinical Evaluation Report • Review the Post Market Surveillance Plan (PMSP) The Clinical Application Specialist can alternatively be referred to as the clinical evaluator.
2.	Clinical representative/expert/peer	• Reviewer and Approver of the Clinical Evaluation Report, • The person shall have sufficient clinical experience to assess the accuracy of the Clinical Evaluation Report. Both the Clinical Application Specialist and the clinical representative shall meet the requirements as in Appendix 1.
3.	Q & R	• Reviewer of the Clinical Evaluation Report • Reviewer of the Post Market Surveillance Plan
4.	Safety Officer	• Communicate inputs from/to Risk management from/to Clinical evaluation process • Communicate inputs from/to PMS from/to Clinical evaluation process • Reviewer of the PMSP
5.	Product Manager	• Author of the PMSP

4. Procedure

4.1. General Requirements

The CLINICAL EVALUATION is an ongoing process, conducted throughout the product life cycle, in which CLINICAL DATA pertaining to MEDICAL DEVICE, of any class, is gathered, appraised and analyzed to determine whether there is SUFFICIENT CLINICAL EVIDENCE to demonstrate product compliance with the relevant essential requirements for safety and performance, when using the device according to its Instructions for Use (IFU).

Conformity to the Essential Requirements is assumed when the product information materials, CLINICAL EVALUATION, and available CLINICAL DATA are in alignment. As part of compliance to the essential requirements, the CLINICAL EVALUATION addresses the clinical risk/benefit profile for the product in accordance with its intended use based on CLINICAL DATA.

The CLINICAL EVALUATION shall assess the residual risks with the clinical benefits to demonstrate acceptability of that profile.

The CLINICAL EVALUATION can cover a single device or a product family. If a product family is covered, all devices must be listed in the clinical evaluation report (CER), and device equivalence addressed.

4.1.1. Clinical Evaluation for new product (non-CE marked):

The CLINICAL EVALUATION of a new product is integral part of the Design and Development planning activities. The evaluation of CLINICAL DATA conformity assessment is completed by identifying the essential requirements that require support from CLINICAL DATA; obtain CLINICAL DATA to support INTENDED PURPOSE, and evaluate the available CLINICAL DATA for suitability for establishing CLINICAL SAFETY and CLINICAL PERFORMANCE.

CLINICAL EVALUATION is mandatory for conformity assessment process as part of the initial CE marking and the clinical evaluation report must be updated thereafter.

4.1.2. Clinical Evaluation for CE marked product:

For released products, when developing new versions the results of the previous CLINICAL EVALUATION shall be used as input for the CLINICAL EVALUATION scoping, to identify if additional CLINICAL DATA is needed these activities are included as part of project planning. The CLINICAL EVALUATION scoping shall be updated, reviewed and approved prior to the PPC or program increment where the version/ feature is planned to be implemented. If after PPC a new feature is added to the project which poses new risk or hazards, CLINICAL EVALUATION scope shall be updated accordingly to address these new inputs.

Before release of a product the clinical evaluation report is updated with the CLINICAL DATA gathered during development to conclude and evaluate if CLINICAL SAFETY and CLINICAL PERFORMANCE is established.

If there is an adverse event or field change order (FCO) reportable to regulatory agencies, the CER shall be updated with this information, and assessed if further updates are required to support the product risk/benefit profile.

4.1.3. Interfaces with other QMS processes

The evaluation of CLINICAL DATA as part of conformity assessment is linked to:

- Design and Development planning
  The Project Planning, Monitoring and Control Procedure [0334-01-P] handles the planning of the CLINICAL EVALUATION activities during PRP projects. Once a product has been released to the market, ongoing changes are managed through the Product Change Control Procedure [0339-02-P] which may trigger a new PRP project according to the Product Realization Process [0330-01-P] or a Product

Revision Procedure [0339-03-P]. In addition to this, new information rising from the Clinical Evaluation process (regarding product performance, new features) may trigger Product Change Control [0339-02-P] for products that already on the market, or maybe used as design input as part of the Product Realization process [0330-01-P]

- Product Safety Risk Management
  CLINICAL EVALUATION will provide clinical information as input for (initial) product safety risk analysis in accordance with Product Safety Risk Management [0336-01-P]. The evaluation of CLINICAL DATA can discover new risks which will result in safety related product requirements. Product safety requirements are managed in accordance with Design Input Management [0332-01-P].

  CLINICAL EVALUATION may therefore result in changes to the risk management documents, instructions for use (IFU) and PMS activities; as well as to product design via risk mitigations and/or Product Change Control Procedure [0339-02-P]

  Additionally, risk management outputs affect the CLINICAL EVALUATION scoping:
  - Any residual risks that remain after design mitigation, for which the CLINICAL EVALUATION is expected to address their significance and impact
  - Overall product risks, to address the risk/benefit profile for the product under evaluation

- Post Market Surveillance
  The evaluation of CLINICAL DATA regarding products that are on the market for which no new ENHANCEMENTS are planned anymore, is initiated by planned Post Market Surveillance (PMS) activities in accordance with the Post Market Surveillance Procedure [0301-13-P]. PMS data shall be evaluated for information that has a potential to change the evaluation of the risk/benefit profile, and the CLINICAL PERFORMANCE and CLINICAL SAFETY of the device. Those data are required to be processed as inputs for the CLINICAL EVALUATION process in a timely manner. The Clinical Evaluation Report can also be used as an input for the post market surveillance plan (PMSP), to identify aspects that need to be addressed systematically during Post Market Surveillance (PMS) of such as estimation of residual risks and uncertainties or unanswered questions.

- Release for market introduction
  To provide evidence of conformance to applicable Essential Requirements as part of the conformity assessment procedure required for affixing the CE mark as described in EU MDD Product Compliance Procedure [0338-12-P].

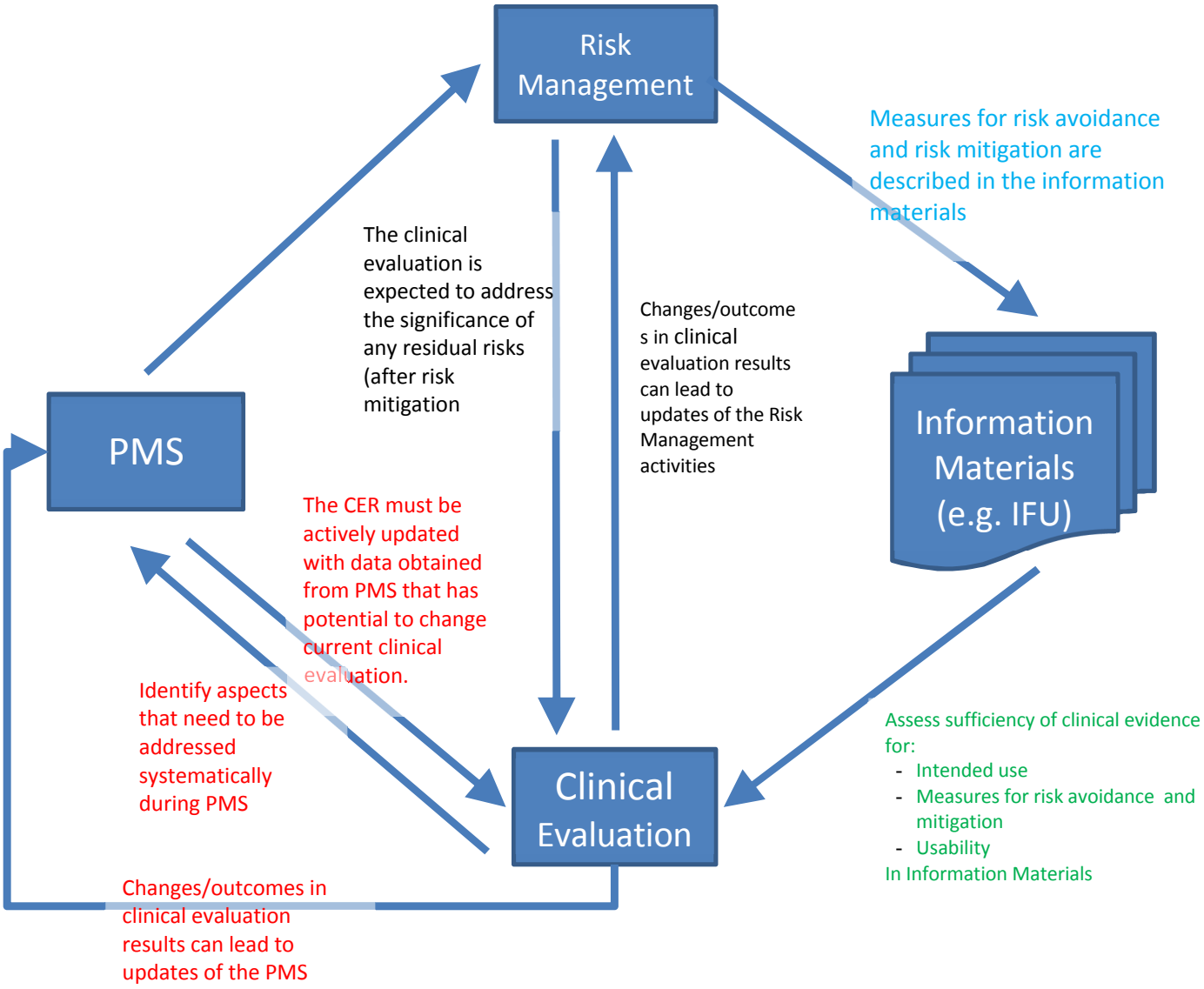

Figure 1: Clinical Evaluation interfaces with Risk Management, Post Market surveillance and Information materials (*Red*: Clinical Evaluation and PMS interface; *Green*: Clinical Evaluation and Information materials interface; *Black*: Clinical Evaluation and RMM interface; *Blue*: RMM and Information Materials interface)

4.2. Process Description

The CLINICAL EVALUATION is based on a comprehensive analysis of available pre- and post- market CLINICAL DATA that is relevant to the intended purpose of the device in question, including CLINICAL PERFORMANCE data and CLINICAL SAFETY data.
The CLINICAL EVALUATION is cyclic process which is performed in the following stages

- Stage 0: Define the scope of the CLINICAL EVALUATION; and identify EQUIVALENT DEVICES.
- Stage 1: Identify and collect pertinent CLINICAL DATA.
- Stage 2: Appraise each individual data set, in terms of its scientific validity relevance and weighing to the CLINICAL EVALUATION.
- Stage 3: Analyse the data, to verify whether the following can be determined:
  Compliance with Essential Requirements (including but not limited to: ER1, ER3, ER6) on performance and safety of the device, including its benefit/risk profile. The contents of labeling is aligned with the current available CLINICAL DATA. Residual risks and uncertainties or unanswered questions, are acceptable for CE-marking, and whether they are required to be addressed during PMS.
- Stage 4: Document the results in the clinical evaluation report

Each of these stages is detailed in this procedure (see Figure 2).

Note: These stages of the CLINICAL EVALUATION process, are often iterative, as any new information uncovered during the appraisal and analysis stages, which raises new questions, should lead to (or consider) a change to the scope of the CLINICAL EVALUATION, which would lead to a new cycle of retrieving, appraising and analyzing additional data.

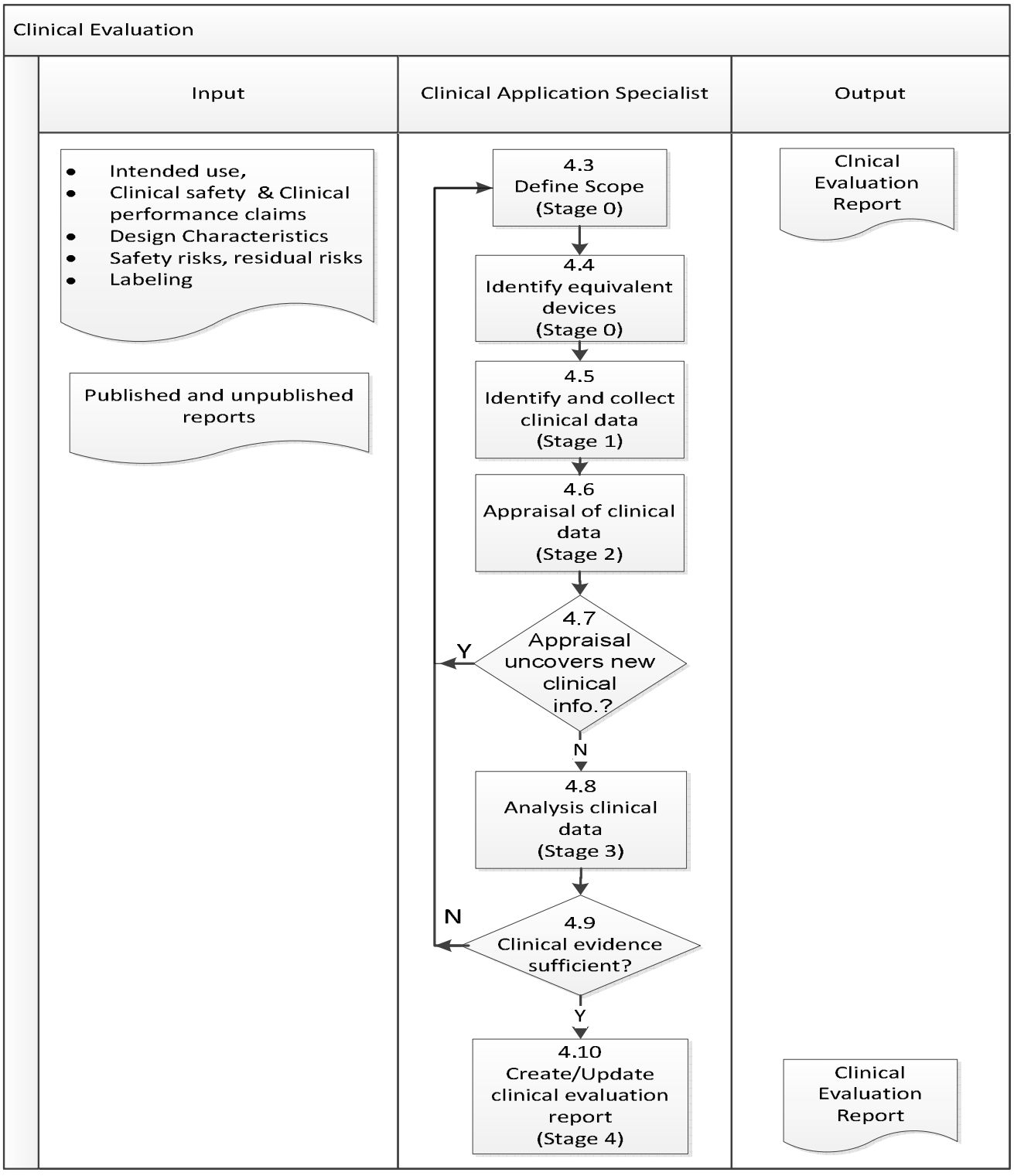

Figure 2: Clinical Evaluation Stages

4.3. Define Scope (Stage 0)

The scoping stage of the CLINICAL EVALUATION acts as the plan which forms the basis for the ensuring that CLINICAL EVALUATION activities. The scope is based on the Essential Requirements that are applicable to CLINICAL SAFETY and CLINICAL PERFORMANCE of MEDICAL DEVICEs.
The scope shall include the following items:

- Device Description
- EU product classification
- Intended use/Indications for use of the device, with consideration of knowledge, experience, education and training of intended users
- **Specific claims made about the CLINICAL SAFETY and CLINICAL PERFORMANCE of the MEDICAL DEVICE/application**
- **Product information (contraindications, precautions / warnings) and the instructions of use.**
- Any design features that pose special CLINICAL PERFORMANCE or CLINICAL SAFETY concerns. This also includes indications or target populations that require special attention.
- Device Risk Management file, including the device's hazard identification list, and clinical risks identified during risk analysis, as well as the significance of any risk that remains after design risk mitigations.
- The current knowledge/ state of the art in the corresponding medical field, such as applicable standards and guidance documents, information relating to the medical condition managed with the device, benchmark devices, other devices and medical alternatives available.
- Internal data to support the CLINICAL EVALUATION. For example, previous Clinical Evaluation reports, PMS records (complaints, FCOs, MDRs/MDVs, Trip reports), product validation and verification reports, Usability test reports, Risk Management File and Clinical feasibility reports
- There will be differences in scope based on whether the product under development is preparing for an initial CE marking, or is a CE marked device undergoing a design change. In addition to the aforementioned bullet points, the below items shall be considered based the product CE mark status.

Before initial CE Marking	**CE Marked Devices**

• If the device is not yet on the market, identify EQUIVALENT DEVICEs. See section 4.4 for information on EQUIVALENT DEVICEs.
• For items in **bold text** above, limited information may be available at the scoping stage. At a minimum, the following information shall be available:
  o Claims
  o Contraindications, Warnings, Precautions
	• Device changes including changes to: design, claims, contraindications, warnings, precautions
	• Whether the equivalency claims to existing device is still valid
	• New specific clinical concerns
	• Post market surveillance information including adverse events and reportable field change orders.

4.4. Identify Equivalent Devices (Stage 0)

It may be possible to draw on the clinical experience and literature reports of the safety and performance of an EQUIVALENT DEVICE to establish the clinical evidence, thereby reducing the need for CLINICAL DATA collection for the device under evaluation.
Comparison of the MEDICAL DEVICE under CLINICAL EVALUATION to an EQUIVALENT DEVICE can be done for a device prior to initial CE marking, or when a CE marked device has a significant change that would necessitate additional CLINICAL EVALUATION. An EQUIVALENT DEVICE must be legally CE marked, and be objectively compared to the MEDICAL DEVICE under CLINICAL EVALUATION with respect to clinical and technical characteristics, illustrating similarities and differences in the CER.

Device equivalence can apply to the complete device(s) or to part of the device, e.g. to an individual clinical application or feature or to a particular algorithm used or a combination thereof, as long as all device aspects as mentioned are covered. One or multiple devices can be utilized for equivalence, however if multiple EQUIVALENT DEVICEs are referenced, then equivalence of every single device should be fully investigated, demonstrated and described in the CER.

The selected EQUIVALENT DEVICE(s) should preferably be a predecessor CE-marked MEDICAL DEVICE (e.g. a previous release). If a Philips device is not available, a CE-marked MEDICAL DEVICE from other manufacturers (i.e. non-Philips branded devices) can be utilized if technical data for the device is made available or is generated.

For the demonstration of equivalence, the device's clinical and technical characteristics shall be taken into consideration as follows:

- Clinical characteristics:
  - used for the same clinical condition (similar severity, same medical indication), and
  - used for the same INTENDED PURPOSE, and
  - used in a similar population (age, gender, anatomy, physiology, etc.), and
  - not foreseen to deliver significantly different performances.
- Technical Characteristics:
  - be of similar design, and
  - used under the same conditions of use, and
  - have similar specifications and properties (e.g. SW modules, SW interfaces), and
  - use similar deployment methods, and
  - have similar principles of operation and critical performance requirements.

While MEDDEV 2.7/1 also discusses biological characteristics, this characteristic is not applicable to stand alone software which does not come into direct/indirect contact with the patient or user.
At this stage, it should also be identified if compliance with harmonized standards could satisfy the clinical evidence requirements for devices based on technologies with well-established safety and performance characteristics.
The output of this comparison is the basis to which equivalence is demonstrated between the MEDICAL DEVICE under evaluation and EQUIVALENT DEVICE(s). In subsequent stages, CLINICAL DATA from the EQUIVALENT DEVICE(s) will be utilized to demonstrate compliance to the relevant Essential Requirements.

The CLINICAL EVALUATION scope and EQUIVALENT DEVICE identification is to be conducted during the Design and Development phase, and completed by the PPC milestone of the PRP process. The CLINICAL EVALUATION scope shall be reviewed with the reviewers/approvers of CLINICAL EVALUATION deliverables as identified in Mandatory Roles for Document Creation, Review and Approval [0730-02-W1] for their consensus.

4.5. Identify and Collect CLINICAL DATA (Stage 1)

Identify and collect available pre - and post - market CLINICAL DATA relevant for the device/application, which can be published or unpublished information. The section is divided into two subcategories:

- Data generated and held within Philips Healthcare
- Data obtained from published literature of the MEDICAL DEVICE under CLINICAL EVALUATION and/or EQUIVALENT DEVICE

4.5.1. Clinical Data generated and held within Philips organization

The following data will be acquired from the relevant stakeholders:

- CLINICAL DATA generated from risk management activities
- CLINICAL DATA generated from PMS activities:
  - Product Safety Risk Management Reports, vigilance reports, and trend reports
  - Post Market Surveillance information search including: adverse event reports, complaints regarding performance or safety, and Field Change Order (FCO) details/information
- Reports related to the device/application under development. This includes, as applicable: verification and validation reports, bench test reports, clinical feasibility reports, etc.

The following information, if applicable to the collected data, shall be documented in the CER:

- Search strategy for adverse events and recall database (search period, identify devices)
- Investigated database(s)
- Date of the search
- Search results: all data identified and utilized to support the clinical evaluation report shall be referenced (including document numbers) in the CER.

4.5.2. Clinical Data obtained from published reports and literature

Conduct a literature search of the MEDICAL DEVICE under CLINICAL EVALUATION and/or EQUIVALENT DEVICE to identify CLINICAL DATA not held by the organization to:

- Collect relevant CLINICAL DATA and
- Establish current knowledge and state of the art practices.
  This portion draws on the current practices used in the relevant medical field, current standards/guidance documents, data related to benchmark devices, and medical alternatives.

The literature search is intended to use a comprehensive and objective search strategy to identify all data, documented to the extent that the methods are transparent, and reproducible if necessary; see Appendix 2 for possible sources of data.

The literature search protocol shall include:

- Identified sources of data
- Establish inclusion and exclusion criteria
- Selection criteria and a justification of their choice by analysis of primary operating functions of the device (POFs)
- Address potential duplication of data

The following information, if applicable to the collected data, shall be documented in the Clinical Evaluation Report:

- Search strategy
- Date of the search
- Search results
- The literature search protocol(s), the literature search report(s), and full text copies of relevant documents, will become part of the clinical evidence.

4.6. Appraisal of Clinical Data (Stage 2)

To determine the value of the data identified, each individual piece of CLINICAL DATA is appraised to determine its contribution to the evaluation of the CLINICAL PERFORMANCE and CLINICAL SAFETY of the device, by assessment of both data quality and relevance.
For this purpose, the appraisal process should be as follows:

- Identify the information in each article
- Evaluate the methodology and assess the scientific validity of the information (see appendices 4 and 5)
- Determine relevance of the information for the CLINICAL EVALUATION
- Weigh the contribution of each data set to the overall CLINICAL EVALUATION

The goal of the appraisal is to determine if the device performs as intended by the manufacturer, it does not pose undue safety concerns, and any risks associated with the use of the device are acceptable.

4.6.1. Appraisal Plan

To ensure systematic and unbiased appraisal of the data, an appraisal plan is to be documented in the CER.
The appraisal plan should include criteria for the following:

- Criteria determining the methodological quality and scientific validity of data
- Criteria to determine relevance to the device/INTENDED PURPOSE
- Criteria for weighing the contribution of each data set to the overall CLINICAL EVALUATION

Note: that for well-established devices and lower risk devices, qualitative data may be adequate to fulfil the requirements of the MDD. Adjust the evaluation criteria accordingly.
The appraisal should be conducted on full text copies of the CLINICAL DATA, while appraisal criteria are consistently followed during the appraisal stage.

4.6.2. Appraisal Plan Execution

4.6.2.1. Evaluation of data quality and scientific validity
The clinical information should be evaluated in a consistent manner, to verify whether the observed effect (performance/safety outcome) is contributed by the device under investigation and not due to confounding influences, BIAS, random error, inadequate disclosure of information and misinterpretation.

Considerations to be taken in order to evaluate the scientific validity of the CLINICAL DATA:

- Study design (when evaluating clinical investigation published in an article):
  Evaluate the sample size, adequacy of applied controls, randomization, blinding, method reliability, adequacy of reporting.
- Sources of information should be considered:
  Data derived from reports of clinical experience that are not adequately supported by data; of from the Vigilance system; or trend analysis will be used to identify unexpected risks, whereas scientific data is required to identify risks or hazards related to the device, if applicable.
- Statistical methods and data processing considerations
  - Suitability of the methods used for data processing
  - Exclusions from analysis and implications
  - Adequacy of statistical methods
- Quality assurance: Compliance with standards and legal requirements
- Overall report quality:
  - Adequacy of disclosure of data and methods used
  - Validity of conclusions drawn by the authors
  - Possible conflict of interests

4.6.2.2. Determination of data set relevance for CLINICAL EVALUATION
The clinical evaluator should distinguish between two types of data: (1) PIVOTAL DATA which are intended directly to demonstrate adequate CLINICAL SAFETY and performance of the device, and (2) other data that indirectly support the CLINICAL SAFETY and performance.

PIVOTAL DATA must have the necessary data quality to demonstrate adequate CLINICAL PERFORMANCE and safety of the device under evaluation, and must be generated either by the device itself or its equivalent. The other data is appraised for its contribution for:

- Identifying the state of the art/current knowledge to define the acceptability criteria for the evaluation of benefit/risk profile
- Identifying hazards
- Justifying the validity of criteria used for the demonstration of Equivalence
- Providing input for the planning of pivotal studies

4.6.2.3. How to weigh the contribution of each data set:
Appropriate criteria should be applied for a specific evaluation, and should be followed strictly by all evaluators. The highest score will be given to CLINICAL DATA that is generated through well designed, monitored randomized controlled CLINICAL INVESTIGATION, conducted with the device/EQUIVALENT DEVICE
Rejecting of any CLINICAL DATA should be documented with the appropriate rationale in the Clinical Evaluation report [0301-01-T1].

4.7. Appraisal of the data uncovers new clinical information?

If new information is discovered during the appraisal process, raising new questions (such as risks, hazards) which necessitate refinement of the CLINICAL EVALUATION scope, the evaluators should consider the need to revisit and update the CLINICAL EVALUATION strategy. It could lead to redefining scope, and to retrieve, appraise and analyse additional data. Additionally, these data should be communicated to Risk management process leaders and stakeholders as part of the Product Safety Risk Management procedure [0336-01-P].

4.8. Analysis of the Clinical Data (Stage 3)

The appraised CLINICAL DATA are evaluated to determine if it demonstrates compliance with each of the Essential Requirements pertaining to the CLINICAL PERFORMANCE and CLINICAL SAFETY of the device, when the device is used according to its INTENDED PURPOSE.
As the clinical evaluation is performed current industry knowledge and practices are taken into account and documented in the Clinical Evaluation report [0301-01-T1].

4.8.1. Specific considerations to be made during data analysis

The following aspects should be considered when conducting the analysis for the CLINICAL DATA:

- Identify PIVOTAL DATA and give additional weight to these findings.
- Results from pivotal data should be consistent across the entire data for the particular device performance and identified risks. Any difference that is observed will be provided with reason and where relevant rationale should be provided.
- Use quantitative methods to analyse the CLINICAL DATA when possible. If quantitative methods are unavailable, use qualitative methods for the analysis of CLINICAL DATA.
- All CLINICAL DATA should be considered and included, taking into account the weighing when addressing conflicting information

Based on the CLINICAL DATA, determine compliance with each Essential Requirement pertaining to the CLINICAL PERFORMANCE and CLINICAL SAFETY of the device.

The evaluation of compliance to the Essential Requirement should take into account the following:

- Internal data (V&V reports, etc.) to verify safety risks to patients and users
- Benefits to patients
- Confirmation that the device achieves its intended performance, including claims made by the manufacturer
- Confirmation of usability, that the design adequately reduces the risk of use error as far as possible, and that the design is adequate for the intended users
- Product label and instructions for use (IFU)
- When the clinical evaluation report is written for a product family, all products shall be covered by the CLINICAL EVALUATION and all aspects of their INTENDED PURPOSE should be considered. Any gaps in evidence need to be identified, **when** relevant to:
    - the comprehensiveness of the available data, such as range of products, INTENDED PURPOSE, number of patients exposed to the device
    - the type and adequacy of patient monitoring (if applicable)
    - 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
    - current standards of care, including the availability and the benefit/risk profiles of other devices and medical alternatives
- Assess if there is consistency and alignment between the CLINICAL EVALUATION, the information materials supplied with the device, and available clinical data for the device under evaluation; any discrepancies should be identified in order to ensure that all the hazards and other clinically relevant information have been identified and analysed appropriately.
- Assess if there is consistency between the documents mentioned above and current knowledge/ the state of the art.

4.9. Clinical Evidence sufficient?

Yes, clinical evidence is sufficient
If the amount and quality of clinical data are sufficient to conclude that the CLINICAL SAFETY and CLINICAL PERFORMANCE of the MEDICAL DEVICE/application and conformity to essential requirements can be declared, continue with documenting the results and conclusion in the Clinical Evaluation Report [0301-01-T1].

No, there is no SUFFICIENT CLINICAL EVIDENCE
If the available CLINICAL DATA are insufficient to confirm CLINICAL SAFETY and/or CLINICAL PERFORMANCE of the MEDICAL DEVICE/application; and/or new clinical information is uncovered during the analysis process in which new questions rise, the scope of the clinical evaluation shall be revisited and updated, to collect new or additional CLINICAL DATA. The iterative search results are to be documented in the Clinical Evaluation report.

If new information is discovered during the analysis or the appraisal (section 4.7) stages, raising new product risks or hazards the evaluators should consider the need to revisit and update the CLINICAL EVALUATION strategy. This may lead to redefining the scope of the Clinical Evaluation, and to retrieve, appraise and analyse additional data. Additionally, these data should be communicated to Risk management process leaders and stakeholders who will process these inputs as part of the Product Safety Risk Management procedure [0336-01-P].Any other information such as data on product performance, new technologies, other technical capabilities from equivalent product on the market, may be used as inputs for design and development activities as part of the PRP process [0330-01-P] for new products; or may trigger the Product Design Change Process [0339-02-P] and Product Revision procedure [0339-03-P] for products that are already on the market. These data should be considered by the design team as part of the iterative development cycles, and may lead to development of new product features, or modification of planned design features.

If after re-scoping, due to reasons such as a lack of available literature, a demonstration of conformity based on the CLINICAL DATA is deemed inappropriate then justification must be given:

- Based on the output of the risk management process, including an evaluation of CLINICAL DATA, and appraisal of their relevance to the device under evaluation
- Considering the specific CLINICAL PERFORMANCEs intended, and the product clinical claims
- Demonstration of conformity with the Essential Requirements based on performance evaluation, bench testing, other available data and evaluation in the absence of clinical data has to be duly substantiated

4.10. Create/Update Clinical Evaluation Report

All gathered information as indicated in the sections above, together with the results and conclusion from the CLINICAL EVALUATION shall be documented in the Clinical Evaluation Report [0301-01-T1]. The conclusion of the CER shall include information on:

- The remaining risks associated with the 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 benefit of device use outweighs undesirable risk
- The intended CLINICAL PERFORMANCEs described by the manufacturer are achieved by the device

The Clinical Evaluation Report should be a standalone document that could be read and understood by independent party. Therefore, the report should provide sufficient detail for understanding the search criteria adopted by the evaluators, data that are available, all assumptions made and all conclusions reached.

The contents of the clinical evaluation report shall be cross-referenced to the relevant documents that support them, up to the level that it is clear which statements are substantiated by which data, and which reflect the conclusions or opinions of the evaluators. The report should include references to literature-based data as well as references to the location in the manufacturer's technical documentation.
If individual clinical applications or clinical features become part of a MEDICAL DEVICE, their respective evaluation reports shall become part of the overall CLINICAL EVALUATION of the MEDICAL DEVICE.
This report shall be reviewed, and approved in accordance with General Document Control [0730-02-P]. The clinical evaluation report shall be completed at the RfD milestone in PRP projects.

4.10.1. Clinical Evaluation report maintenance

For products that undergo PRP activities, Clinical Evaluation report updates are planned as part of the Project Planning, Monitoring and Control Procedure [0334-01-P] and following this procedure. Assess the extent of updates required for the project, and at a minimum update the market experience and updated internal documentation references. A complete update shall take place **at least every 5 years.**

For products that are on the market for which no new ENHANCEMENTS are planned anymore (no new PRP activities) the Clinical Evaluation report [0301-01-T1] will be actively updated with following frequency that shall be defined and justified in the post market surveillance plan as follows:

- when the manufacturer receives new information from PMS (adverse events or recall) that has the potential to change the current CLINICAL EVALUATION
- if no such information is received, then every 5 years if the device is not expected to carry significant risks and is well established

Ensure the clinical evaluation report is actively updated with the activities specified in accordance with the PMSP.
Any deviation from these update intervals shall be supported with a justification that will be provided in the Clinical Evaluation Report based on the following considerations:

- Whether the device carries significant risks e.g. based on design, components, related clinical procedures, high-risk target populations).

- Whether there are risks and uncertainties or unanswered questions, in the medium or long- term, that would influence the frequency of updates.
- Product design changes
- Whether the device is well established, taking into consideration:
  - Device innovation;
  - relevant changes in clinical sciences or other sciences related to the device under evaluation;
  - the current level of confidence in the evaluation of CLINICAL PERFORMANCE and CLINICAL SAFETY of the device; considering:
    - the data available from CLINICAL INVESTIGATIONS, registries or other systematic studies including the number of devices used, if that usage was representative of the usage in the market, the results to date
    - the total number of devices used so far in the market, and expected reporting rates under the vigilance system.

5. Definitions & Acronyms

5.1. Definitions

Term	Definition
BIAS	A systematic deviation of an outcome measure from its true value, leading to either an overestimation or underestimation of a treatment's effect.
CLINICAL DATA	The CLINICAL SAFETY and/or CLINICAL PERFORMANCE information that is generated from the use of a device, sourced from either: - CLINICAL INVESTIGATION(s) of the device concerned; - CLINICAL INVESTIGATION(s) or other studies reported in the scientific literature of a similar device for which equivalence to the device in question can be demonstrated; - published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated.
CLINICAL EVALUATION	An ongoing procedure to collect, appraise and analyze CLINICAL DATA pertaining to a MEDICAL DEVICE, throughout its entire lifecycle; and to evaluate whether there is SUFFICIENT CLINICAL EVIDENCE to confirm compliance with relevant essential requirements for safety and performance when using the device according to the manufacturer's Instructions for Use.
CLINICAL INVESTIGATION	A designed and planned systematic study in or on human subjects undertaken to verify the safety and/or performance of a specific MEDICAL DEVICE.
CLINICAL PERFORMANCE	The ability of a MEDICAL DEVICE to achieve its INTENDED PURPOSE as intended by the manufacturer.
CLINICAL SAFETY	The absence of unacceptable clinical risks, when using the device according to the manufacturer's instructions for use.
ENHANCEMENT	An improvement to something that is already adequate and impacts DESIGN INPUT. It can be the addition of something new or a better way of doing something that has already been done.
EQUIVALENT DEVICE	A device for which equivalence to the device in question can be demonstrated
INTENDED PURPOSE	the use for which the device is intended according to the data supplied by the manufacturer on the labelling, in the instructions and/or in promotional materials.
MEDICAL DEVICE	Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be specifically for diagnostic and/or therapeutic purposes and necessary for proper application, intended by the manufactures to be used for human beings for the

Term	Definition
	purpose of: • diagnosis, prevention, monitoring, treatment or alleviation of disease, • diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap, • investigation, replacement or modification of the anatomy or of a physiological process, • control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.
PIVOTAL DATA	Information/data which are intended to directly demonstrate adequate CLINICAL PERFORMANCE and CLINICAL SAFETY of the device
SUFFICIENT CLINICAL EVIDENCE	An amount and quality of clinical evidence to guarantee the scientific validity of the conclusions.

5.2. Acronyms

Short	Long
CE	Conformité Européene
CER	Clinical Evaluation Report
FCO	Field Change Order
IFU	Instruction For Use
MDD	Medical Device Directive
MDR	Medical Device Report
MDV	Medical Device Vigilance
PMS	Post Market Surveillance
PMSP	Post Market Surveillance Plan
POF	Primary Operating Functions

6. Annexes

Document ID	Document Title
0301-01-T1	Clinical Evaluation Report
0301-01-T2	Declaration of Interest

7. References

Reference ID	Description
0301-13-P	Post Market Surveillance
0313-01-P	Product Validation
0330-01-P	Product Realization Procedure
0332-01-P	Design Input Management
0334-01-P	Project Planning, Monitoring and Control procedure
0336-01-P	Product Safety Risk Management
0338-12-P	EU MDD Product Compliance

Reference ID	Description
0338-12-T1	Essential Requirements Checklist of the EU MDD
0339-02-P	Product Change Control Procedure
0339-03-P	Product Revision Procedure
0730-02-P	General Document Control
0730-02-W1	Mandatory Roles for Document Creation, Review and Approval
93/42/EEC	European Medical Device Directive
MEDDEV 2.7/1 r.4	CLINICAL EVALUATION: A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES UNDER DIRECTIVES 93/42/EEC and 90/385/EEC

8. Records

Record Name	Description
0301-01-T1	Clinical Evaluation Report
0301-01-T2	Declaration of Interest

9. Document Control

Process	Owner(s)s
Approval	Manager Q&R Process Owner
Review	Clinical Application Specialist Q & R Mnager Project Manager
Author	Moshe Elmaliach
Approval date	See eDMS
Effective date	According to the following implementation plans: CI: EICI.0006186; EI: EICI.0006185

10. Document Change Summary

Revision	Description of changes
1.0	Initial release
2.0	Addition of clarification of the CE procedure in relation to product development and planning procedure, per product state in PRP or maintenance (section 4) Addition of reference to EU MDD Product Compliance procedure.(section 4) Addition of link to PMS procedure Addition of triggering of product design change control procedure upon new CLINICAL DATA 4.6.1 Documentation of Post Market Surveillance Plan results in CER, clarity on when updates are required (section 4.7) Minor editorial corrections
3.0	Adoption of MEDDEV 2.7.1 Rev 4

11. APPENDICES

11.1. APPENDIX 1: Qualification of the Clinical Evaluators:

The clinical application specialist/clinical representative shall be knowledgeable of the:

- device technology and its application that is evaluated
- diagnosis and management of the conditions intended to be diagnosed or managed by
- The device, knowledge of medical alternatives, the nature of the device under evaluation, and its CLINICAL PERFORMANCE and risks.

The clinical evaluators should have at least the following training and experience in the relevant field:

- a degree from higher education in a relevant field and 5 years of documented professional experience; or
- 10 years of documented professional experience if a degree is not a prerequisite for a given task.

It is helpful for the clinical evaluators or other contributors to the clinical evaluation report (CER) to have the following experience:

- research methodology (including CLINICAL INVESTIGATION design and biostatistics);
- Information management (e.g. scientific background experience with relevant databases);
- Relevant regulatory requirements;
- Medical writing (e.g. training and experience in medical writing, systematic review and CLINICAL DATA appraisal).

For the purpose of demonstration of conformity with requirements mentioned above, a resume (CV) of the evaluators will be maintained by the organization.

It is recommended to create a short biography of the clinical evaluators including their relevant qualifications, and experience in the clinical evaluation report. If the biography is not included in the CER, the clinical evaluator resume must be filed with the CER. Any deviation of the requirements mentioned above should be justified in the Clinical Evaluation report.

When for a certain clinical evaluator, there is a significant personal financial gain and/or any other conflict of interests with regards to the clinical evaluation process that the clinical evaluator may be involved with, a declaration of Interest [0301-01-T2] will be required by this Clinical Evaluator, which will be maintained as part of the project documentation.

11.2. APPENDIX 2: Sources of Literature for Clinical Evaluation

For stage 1, identification and collection of clinical data, a comprehensive search strategy is required, normally involving multiple databases.

Below are few examples of CLINICAL DATA sources and the quality of data that may be found as well as other considerations to be made when using the data acquired for the CLINICAL EVALUATION

11.2.1. Scientific literature databases

- MEDLINE or PubMed – These may not be complete with respect to coverage of European Journals, search is not elaborate and hence cannot guarantee a comprehensive output
- EMBASE/Excerpta Medica, the Cochrane CENTRAL trials register – These may help to to identify relevant clinical trials and publications of user experience, and to facilitate searches by device name and manufacturer. These searched will also enable adequate coverage of the devices and therapies in Europe. Studies yielding negative results or user experience (such as publications about risks that are based on a case or a case series) may not qualify for publication in high impact medical journals. Low impact journals available to European users and other sources may therefore need to be searched

Note: Information coverage and search features available in scientific databases may change with time. Therefore the criteria for selecting adequate databases need to be defined and revaluated on whenever conducting new/update to the CLINICAL EVALUATION.

11.2.2. Internet searches

Internet Searches provide important data, examples include information on:

- Harmonized standards and other standards applicable to the device in question and containing information on Clinical Performance and Clinical Safety.
- Field safety corrective actions for the equivalent and/or other devices. These can be found on manufacturer's web sites, internet sites of European Competent authorities, the U.S. Food and Drug Administration (FDA), possibly other sites.
- Documents available in systematic review databases (e.g. the Cochrane Database of Systematic Reviews, Prospero international prospective register of systematic reviews).
- Expert documents produced by professional medical associations that are important for assessment of current knowledge/ the state of the art, including clinical practice guidelines and consensus statements.

11.2.3. Citations referenced in scientific literature

Literature found to be relevant is likely to cite other literature that can be used as Pivotal Data. Additionally, in some review articles which are based on others, it may be necessary to retrieve some of the referenced literature in order to appraise the scientific quality of a document.

11.3. APPENDIX 3: Key elements of Literature search and Literature Review Protocol

The output of the literature search and literature review are:

- Literature on the device in question and/or the EQUIVALENT DEVICE, including PMS data
- A review of the current knowledge/ the state of the art needed for the proper conduct of the
- appraisal and analysis of the CLINICAL DATA of the device under evaluation and the equivalent
- Device (i.e. applicable standards and guidance documents, which are relevant to the CLINICAL EVALUATION, diagnostic options available for the intended patient population, etc.)

The search protocol should specify the elements described below, addressing the background, objective, and methods for identification, selection, and collection of the relevant publications to address the literature review.

11.3.1. Background to the literature search and the literature review

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

- Device name/model
- Importance of literature review to risk management process. The literature review will provide data on current used technologies in order to give input to the assessments of acceptable benefit/risk profiles, what is currently considered as providing a high level of protection of health and safety and what are considered acceptable risks
- Previous literature searches/reviews conducted for the EI/CI products
- Name and model of the equivalent and Benchmark devices.
- Equivalence to the device, or the relevance of benchmark devices to the Clinical Evaluation.

11.3.2. Objective

The inputs for the objective are the device description and the intended performance of the device including any claims on CLINICAL PERFORMANCE and CLINICAL SAFETY which we want to use. Also information from the risk management process is needed as an input.

11.3.3. Methods

The methods section of the protocol documents the plans for literature search, study selection, data collection, and analysis methods. It defines the literature search strategy and the inclusion/exclusion criteria for the documents found. The protocol should include:

- The literature search methodology to plan the search before execution.
- 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) attempts to identify all published literature
- which electronic databases are to be searched
- the extent of any Internet searching and searching non-published information, including the search strategy and justification
- exact search terms and any limits
- limits for start and end dates of each search
- the selection/criteria (such as inclusion/exclusion criteria) to be applied to published
- literature and justification for their choice
- strategies for addressing the potential for duplication of data across multiple publications;
- strategies for avoiding retrieving publications of data generated and already held by the
- Philips Healthcare or the organization
- the appraisal plan, which defines the methods for appraising each publication, including the relevance of the data to the intended clinical use and the methodological quality of the data
- the analysis plan, which defines the methods for analysing the data including data processing

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

11.4. APPENDIX 4: Appraisal of Clinical Data – Determination of relevance for Clinical Evaluation

When evaluating the relevance of collected data set it is important to distinguish between "PIVOTAL DATA" (directly demonstrate adequate CLINICAL PERFORMANCE and CLINICAL SAFETY of the device) and "Other Data" which serves an indirect supportive role. The table below shows examples of aspects that could be used for determining if and in what respect data are relevant to the CLINICAL EVALUATION, when reviewing Clinical Data for both the device under evaluation and its equivalent.

Description	Examples
To what extent are the data generated representative of the device under evaluation?	• device under evaluation • EQUIVALENT DEVICE • benchmark device • other devices and medical alternatives • data concerning the medical conditions that are managed with the device
What aspects are covered?	• pivotal performance data • pivotal safety data • claims • identification of hazards • estimation and management of risks • establishment of current knowledge/ the state of the art • determination and justification of criteria for the evaluation of the risk/benefit relationship • determination and justification of criteria for the evaluation of acceptability of undesirable side-effects • determination of equivalence
Are the data relevant to the intended purpose of the device or to claims about the device?	• representative of the entire INTENDED PURPOSE with all patient populations and all claims foreseen for the device under evaluation • concerns specific models/settings, or concerns specific aspects of the INTENDED PURPOSE or of claims does not concern the INTENDED PURPOSE or claims
If the data are relevant to specific aspects of the INTENDED PURPOSE or claims, are they relevant to a specific - model, configuration or setting of the device?	• Specific model • Specific settings • Specific Configuration
- user group?	• specialists • General practitioners • Radiologist
- Medical indication	• rehabilitation after stroke
- age group?	• pre-term infants / neonates / children / • adolescents / adults / old age
- gender?	• female/ male

11.5. APPENDIX 5: Appraisal of Clinical Data - Examples of studies that lack scientific validity

The following sections provide few examples of studies that lack scientific validity for demonstration of adequate clinical performance and/or clinical safety.

11.5.1. Lack of information on elementary aspects:

This includes reports and publications that omit disclosure of:

- Methods used
- Identity of products used
- Numbers of patients exposed
- Clinical outcomes
- All the results the clinical study or investigation planned to investigate
- Undesirable side-effects that have been observed
- Confidence intervals/ calculation of statistical significance
- If there are intent-to-treat and per protocol populations: definitions and results for the two populations

11.5.2. Numbers too small for statistical significance

Includes publications and reports with inconclusive preliminary data, inconclusive data from feasibility studies, anecdotal experience, hypothesis papers and unsubstantiated opinions.

11.5.3. Improper statistical methods

- Results obtained after multiple subgroup testing, when no corrections have been applied for multiple comparisons.
- Calculations and tests based on a certain type of distribution of data (e.g. Gaussian distribution with its calculations of mean values, standard deviations, confidence intervals, t-tests, others tests), while the type of distribution is not tested, the type of distribution is not plausible, or the data have not been transformed. Data such as survival curves, e.g., patient survival, symptom-free survival, are generally unlikely to follow a Gaussian distribution

11.5.4. Lack of adequate controls

In the following situations, BIAS or confounding are probable in single arm-studies and in other studies that do not include appropriate controls:

- When results are based on subjective endpoint assessments (e.g. pain assessment).
- When the endpoints or symptoms assessed are subject to natural fluctuations (e.g.
- regression to the mean when observing patients with chronic diseases and fluctuating
- symptoms, when natural improvement occurs, when the natural course of the disease in
- a patient is not clearly predictable).
- When effectiveness studies are conducted with subjects that are likely to take or are
- foreseen to receive effective co-interventions (including over-the-counter medication and
- other therapies).
- When there may be other influencing factors (e.g. outcomes that are affected by
- variability of the patient population, of the disease, of user skills, of infrastructure
- available for planning/ intervention/ aftercare, use of prophylactic medication, other factors).
- When there are significant differences between the results of existing publications,
- pointing to variable and ill controlled influencing factors.

In the situations described above, it is generally not adequate to draw conclusions based on direct comparisons with external or historic data (such as drawing conclusions by comparing data from PMS with device registry data or with data from published literature).
Different study designs may allow direct comparisons and conclusions to be drawn in these situations, such as randomized controlled design, cross-over design, or split-body design

11.5.5. Improper collection of mortality and serious adverse events data

Demonstration of adequate benefits and safety is sometimes based on mortality data or occurrence of other serious outcomes that limit a subject's ability to live in his home and be available for follow-up contacts.
In mortality studies (and other studies addressing serious outcomes) procedures for investigating serious patient outcomes, numbers of subjects lost to follow-up, reasons why subjects leave the study, and the results of sensitivity analysis should be fully disclosed in reports and publications.

11.5.6. Misinterpretation by the authors

Includes conclusions that are not in line with the results section of the report or publication, such as:

- Reports and publications not correctly addressing lack of statistical significance/confidence intervals that encompass the null hypothesis.
- Effects too small for clinical relevance.

11.5.7. Illegal activities

Includes CLINICAL INVESTIGATIONS not conducted in compliance with local regulations. CLINICAL INVESTIGATIONS which are not designed, conducted and reported in accordance with EN ISO 14155 or to a comparable standard, and incompliant with local regulations and the Declaration of Helsinki.

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