Clinical Evaluation of Medical Device Software

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Clinical TTM, AIMD and SaMD

14 May 2025

Agenda

A word on Perspective and Expertise.

Defining and Describing the Device and Intended Purpose

Analysis

Definitions

The Clinical Evaluation Plan & State of the Art

PMCF

The Clinical Evaluation Process

Levels of Clinical Data & When it is not appropriate

POLL 1

When **SHOULD** a software manufacturer perform their first Clinical Evaluation?

01 During initial development

02 Prior to submission

03 During submission

04 After Certification

POLL 2

When **DOES** a software manufacturer perform their first Clinical Evaluation?

01 During initial development

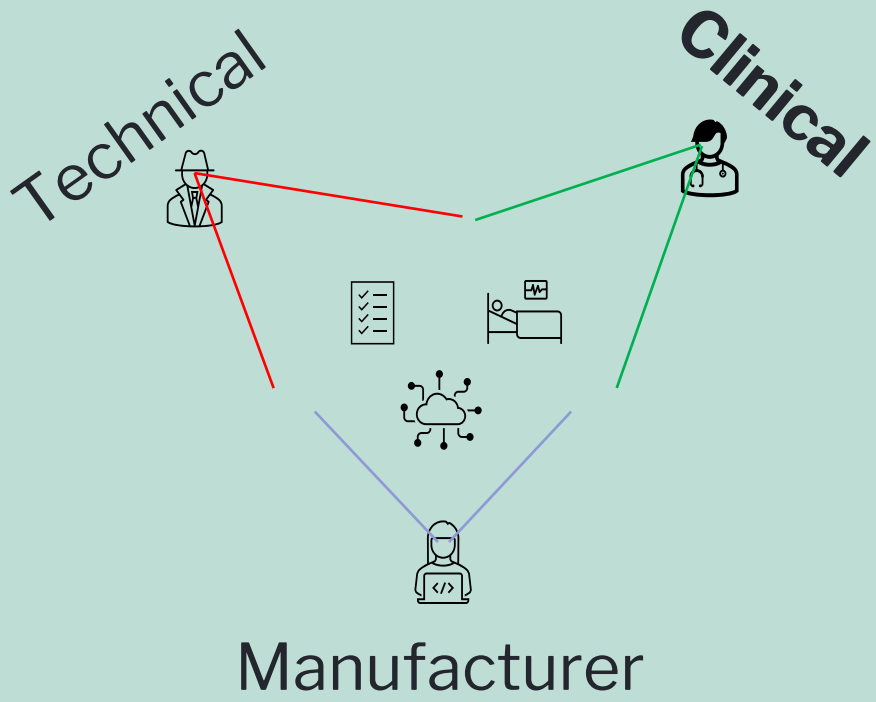
02 Prior to submission

03 During submission

04 After Certification

Perspective and Expertise

Perspective: When writing the Clinical Evaluation, consider the perspective of the Clinical Assessor.



Expertise: Consider whether additional expertise is required to perform the Clinical Evaluation. How will you justify appropriate expertise has been involved? The NB will require records of experience and conflicts of interest.

Generally, a range of experience is needed to write a good CER, including in:

-research methodology, information management, regulatory requirements, medical writing, specific clinical expertise.

-The device and its application, the condition and its diagnosis/management, medical alternatives, treatment standards and technology

Meddev 2.7.1 Rev 4 : 6.4 Who should perform the clinical evaluation?

What is a Clinical Evaluation?

MDR Article 61(1)

- Confirmation of conformity with GSPRs (including evaluation of the undesirable side-effects and of the acceptability of the benefit-risk- ratio per **GSPR 1 and 8)**
- under the **Normal Conditions of the Intended Use**
- Shall be based on **Clinical Data** providing **Sufficient Clinical Evidence**
- **Manufacturer shall specify and justify** the level of clinical evidence necessary
- **Evidence shall be appropriate** in view of the characteristics and intended purpose of the device.
- This shall be achieved via the **Clinical Evaluation**

GSPR 1:

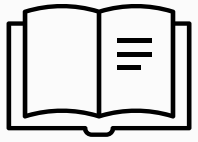
Achieving Performance, and being **safe and effective**, in **Normal Conditions of Use**

Benefit / Risk must be acceptable, when considering the **State Of the Art**.

GSPR 8:

- **Risks and side effects** shall be acceptable when evaluating against the **benefits**,

- From the **achieved performance** during **Normal Conditions of Use**

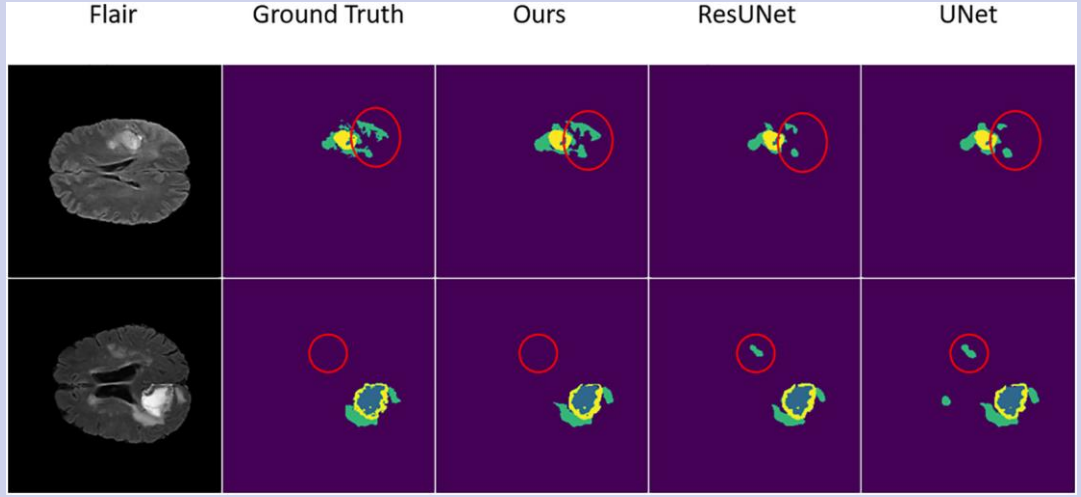


Meddev 2.7.1 Rev 4 : CLINICAL EVALUATION: A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES UNDER DIRECTIVES 93/42/EEC and 90/385/EEC

Poll 3

Is this Clinical Data?

A test of device segmentation performance against a ground truth based on retrospectively collected clinical data …



A. Yes

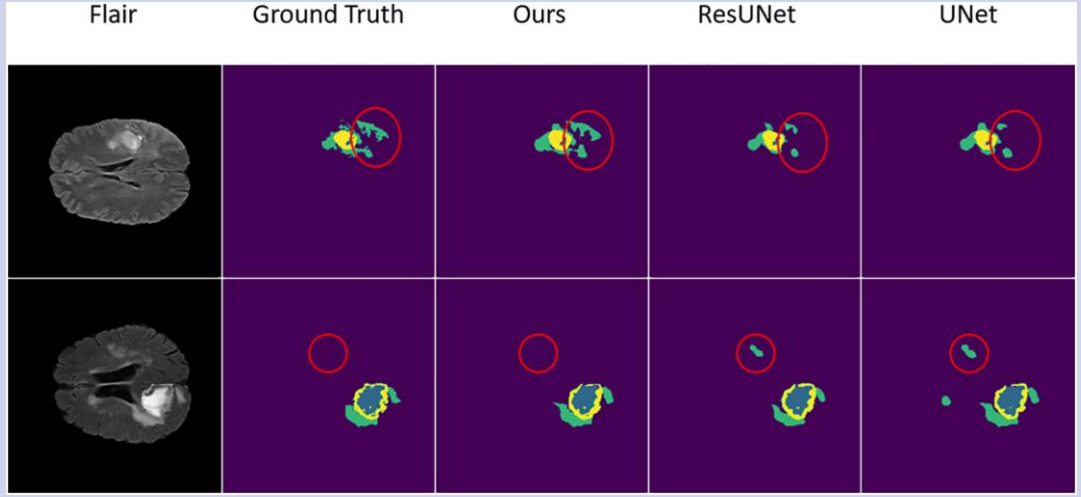
B. No

C. It Depends …

Poll 3

Is this Clinical Data?

A test of device segmentation performance against a ground truth based on retrospectively collected clinical data …



B. No

It does not examine use. *

* Unless it does…

What is Clinical Data?

Article 2(48) “Clinical Data”:

- Clinical data is data collected from USE of the device, and therefore can directly assess performance and safety related to **Normal Conditions of Intended Use**
- From clinical investigations, studies, surveys, registries, and other **clinical experience**, including PMS and PMCF, i.e. from when the device has been **used** and therefore **data related to use** has been collected
- Different activities can collect different types of data, e.g. Clinical Studies are better for collecting data in “ideal” conditions of use. PMCF for “real” conditions of use. (more on this later)

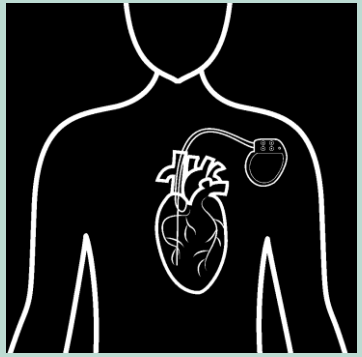
What *isn’t* (likely to be) clinical data:

- The output of running retrospectively collected data through an algorithm on a bench, e.g. “**Retrospective Analysis**” (MDCG 2020-1), used to measure **algorithmic performance**.
- This does not create clinical data on the device. This is because the device in question was not USED.
- **Other data and analysis will be required** to demonstrate device safety and performance in “**normal conditions of the intended use**”

What is Performance and Benefit?

Article 2(52): ‘Clinical performance’

Means the **ability of a device**, resulting from any direct or indirect medical effects which stem from its technical or functional characteristics, including diagnostic characteristics, **to achieve its intended purpose** as claimed by the manufacturer, thereby **leading to a clinical benefit** for patients, when used as intended by the manufacturer;



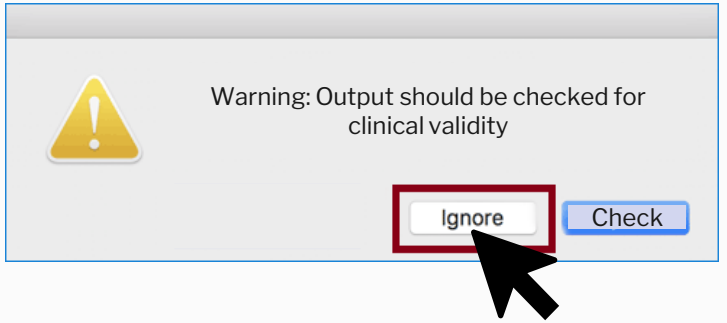
Ability of a Pacemaker to pace the heart.

Article 2(53): “Clinical benefit’

Means the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health;

Ability of a patient to walk up the stairs

Risks and Controls



You are responsible for the **impact** of your software to clinical process and decision making. Never assume your software is “risk free”. Never simply claim that the clinician is responsible for the impact of using your software.

Consider Use and Misuse

GSPR 3 States that manufacturers must identify known and foreseeable risks associated with the device and estimate and evaluate risks that exist during **Intended Use** and **Reasonably Foreseeable Misuse**.

Make Safe by Design

GSPR 4 States that **risks must be mitigated as far as possible via design**, and then take other adequate protection measures (such as alarms), before finally considering information for safety (warnings, precautions, contra-indications). Residual risks must be declared in the IFU.

Evaluate Effectiveness

How do you sufficiently demonstrate that, when the device is used:

You have identified all impacted risks?

Controls are sufficient and effective?

Residual risk is acceptable?

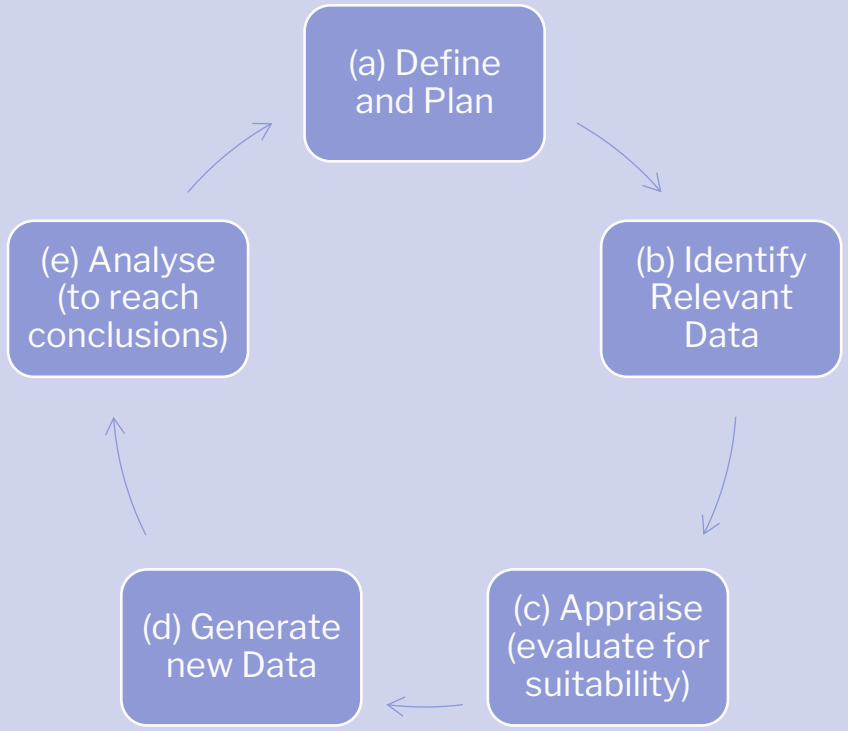
The Clinical Evaluation Process

MDR Article 61 3.A clinical evaluation shall follow a defined and methodologically sound procedure based on the following:

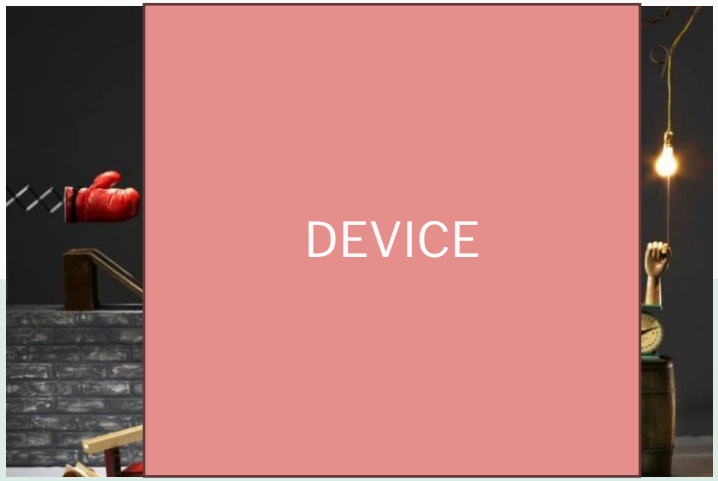
(a) a critical evaluation of the relevant scientific literature …
(b) a critical evaluation of the results of all available clinical investigations …
(c) a **consideration of currently available alternative treatment options** for that purpose …

NOTE: The Clinical Evaluation is an assessment of the Subject Device, vs the **State of the Art** (GSPR 1)

MDR Annex XIV 1. To plan, continuously conduct and document a clinical evaluation, manufacturers shall:



Defining the Device & Intended Purpose



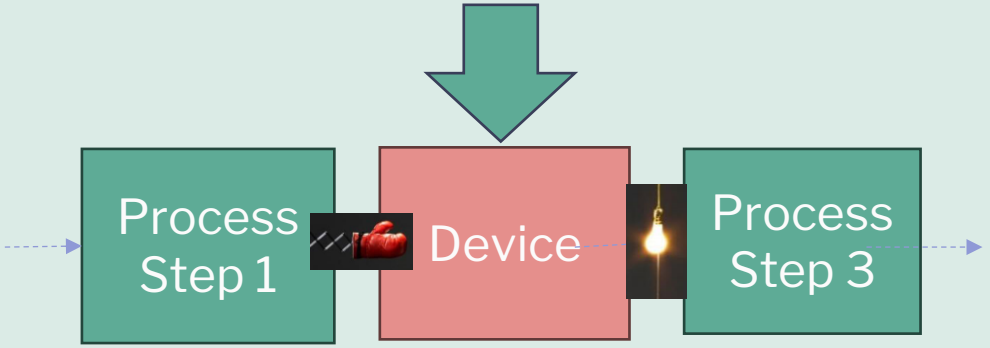
Device Description (Annex II 1,1)

Consider what is important from a clinical aspect. Focus on how the clinician and patient experiences and interacts with the device via Interfaces, inputs, workflows, etc. to achieve a desired output. Describe device inputs, workflows and outputs and how the device fits into the overall clinical process. Define characteristics impacting performance when used as intended. Less focus on internal components of the software such as software architecture, or detailed algorithm technology.

Intended Purpose (MDR Article 2 (12))

“Intended Purpose” defines the way in which the device may be used in which performances and benefit/risk is known and demonstrated. It is defined by anything stated or claimed in labelling, IFU, and marketing material. It is expected that the intended purpose is fully defined, considered, and demonstrated to be appropriate, in the clinical evaluation.

Inputs, Outputs, User Interface, Clincial workflows, processes, etc. etc.



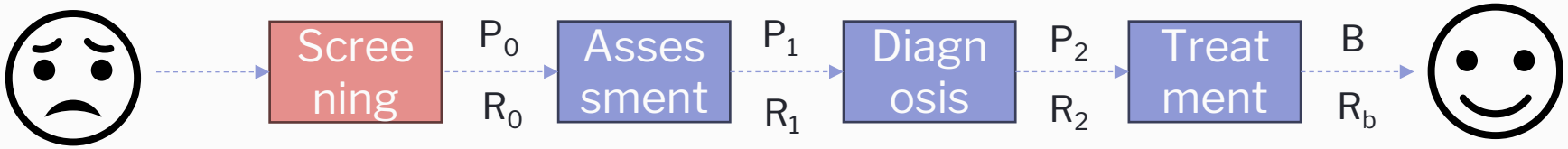
Meddev 2.7.1 Rev 4 A3

Modifying the Clinical Process

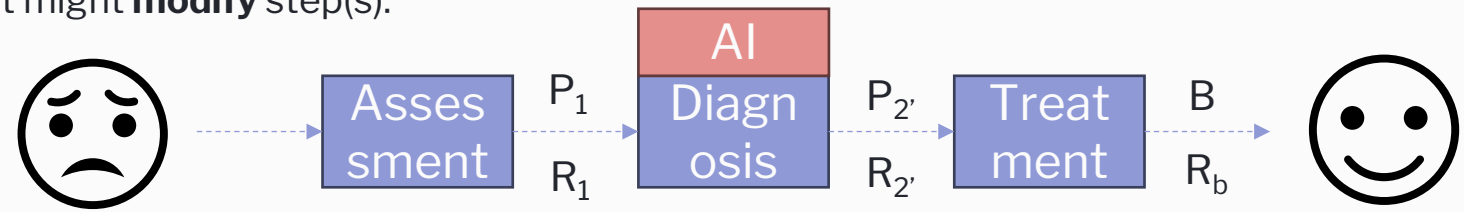
The "**State of the Art**" might look like this:

$$\frac{B_{sota}}{R_{sota}} = f(P_1, R_1, P_2, R_2, B, R_b)$$

Your device might **add** step(s):



It might **modify** step(s):



It might **completely change** the process:

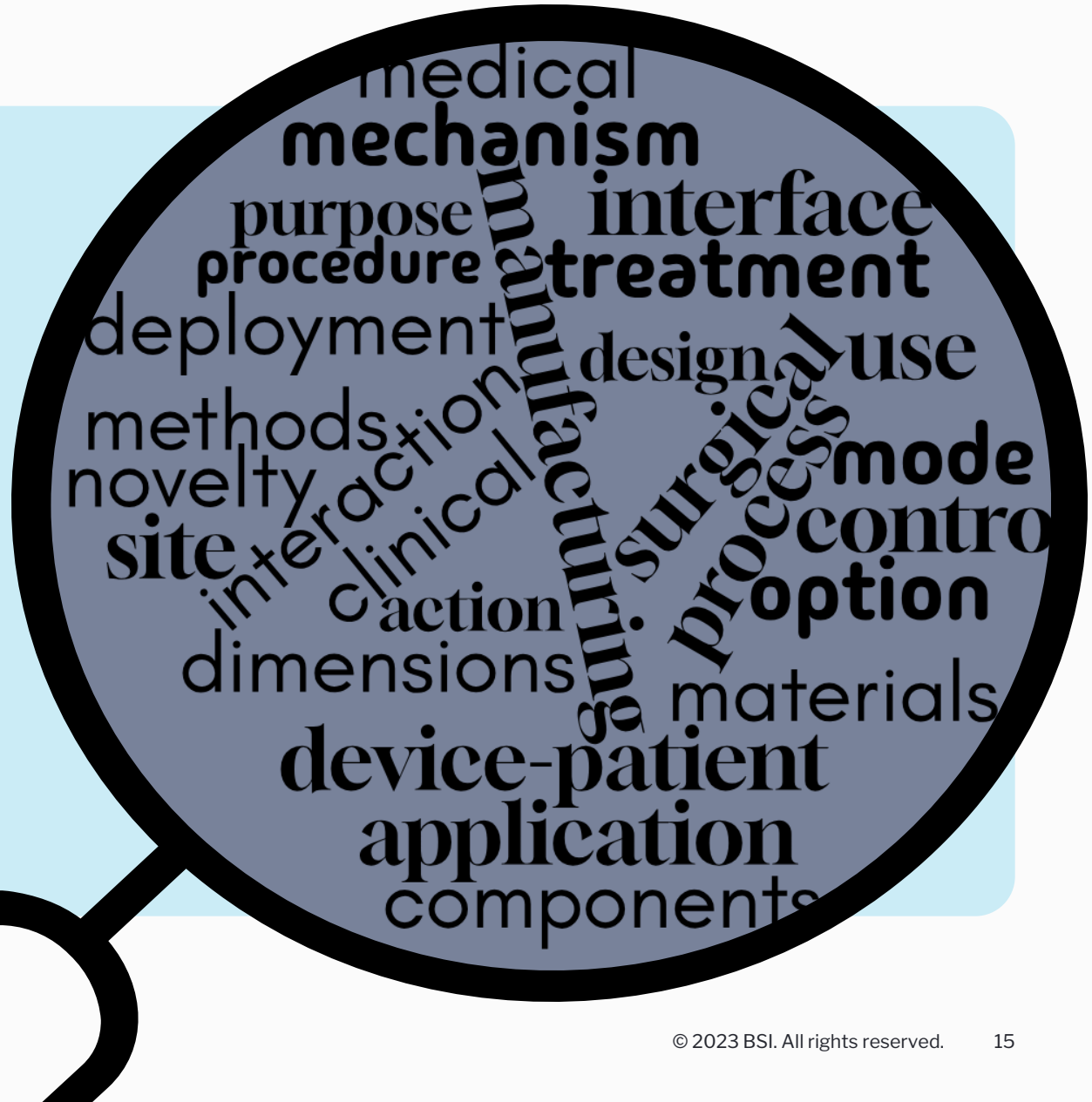
$$\frac{B_{mod}}{R_{mod}} = f(P_1'R_1', \ldots, B', R_b')$$

Q: What is the **impact** of the device to the performances and risks of the State-of-the-Art clinical process, and patient benefit?

Novelty

Novelty isn't just the uniqueness of the device and its underlying technology, it's also where existing technologies are applied in different ways and for different intended purposes. It is where risks are not already well characterised within the state of the art.

The manufacturer should identify any novelty within their device, the intended purpose, established clinical processes, methods of interaction with the device, etc. and show consideration as to whether the novelty aspects introduce poorly understood risks that require specific focus to confirm safety and performance.

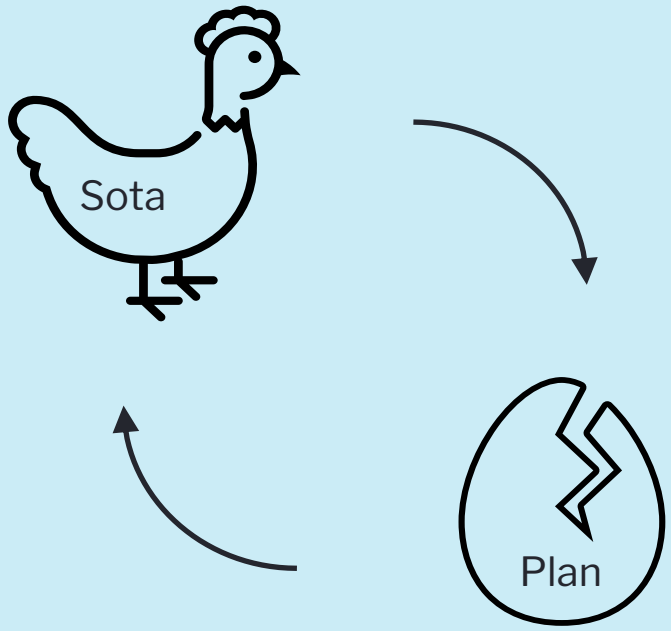


The Clinical Evaluation Plan

MDR Annex XIV 1. To plan, continuously conduct and document a clinical evaluation, manufacturers shall: (a) establish and update a clinical evaluation plan ….

A CEP should be written to evaluate the next step in your clinical evaluation. The manufacturer should define:

- Relevant GSPRs
- The device is and its “Normal Conditions of Use”
- Expected performances and benefits, and how they are measured.
- Methods to examine safety of the device
- **Indicative lists and specification of parameters to measure benefit/risk against state of the art**
- A Clinical Development Plan.



State of the Art Assessment

"State of the Art" is not defined in the MDR.

MDCG2020-1 defines it as:

The STATE-OF-THE-ART embodies what is currently and ***generally accepted as good practice in technology and medicine****. The state-of-the-art does not necessarily imply the most technologically advanced solution. The STATE-OF-THE-ART described here is sometimes referred to as the "generally acknowledged STATE-OF THE-ART"*

i.e. The state-of-the-art assessment is an assessment of current good clinical practise related to the subject device and its intended purpose.

It is NOT a discussion of being the most "technologically advanced".

In performing a state-of-the-art assessment, the manufacturer will aim to gain knowledge of:

- The disease / condition / population etc. related to the intended purpose.
- Similar Devices, that function in a clinically similar way, with a similar intended purpose.
- Devices that function in different ways, but with a similar intended purpose
- Other ways of treating the same disease / condition / population.

State-of-the-Art Outputs

Outputs

From this knowledge, the manufacture can:

Understand the **Clinical Process**

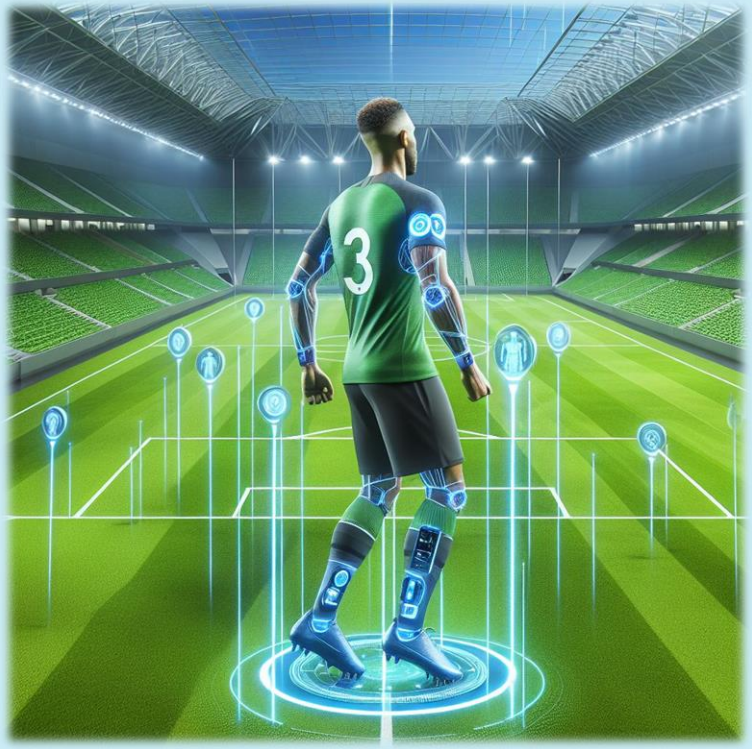
Refine **Device Design & Intended Purpose**,

Identify **Methods** in which the SotA are measured

Identify and justify **levels of clinical evidence**

Identify appropriate measurable parameters in the form of **Safety and Performance Objectives and Endpoints**.

Identify appropriate (and required *) **Claims**



* If you can't make similar claims to the state-of-the-art , are you state-of-the-art?

Level of Clinical Evidence

Carefully consider and justify the level of clinical evidence necessary to support device intended purpose, when considering device type, risk, and evidence available on the state of the art.

Generally Clinical Evidence needs to be sufficient in quality and quantity such that:

- Claims are duly substantiated
- Risks in use are clearly understood and characterised.
- Objective comparisons can be made with the State of the Art

The higher the risk (including in foreseeable misuse), and the greater the novelty, the greater the weight of evidence required.

Also note: Different types of evidence provide different perspectives of the subject device Safety and Performance in Normal Use.

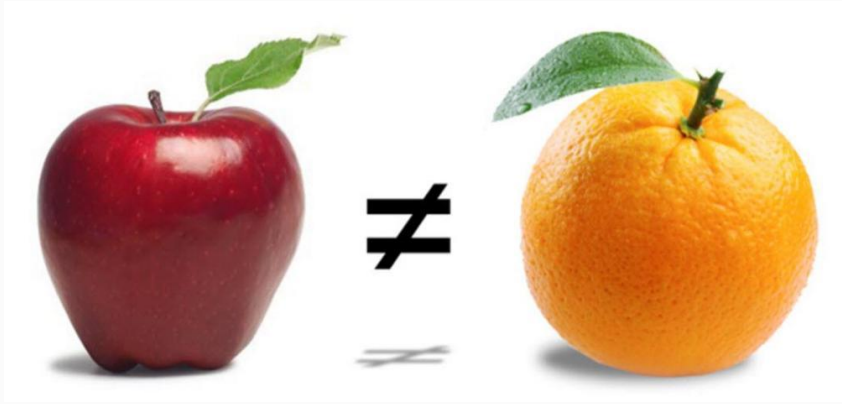
Rank	Types of clinical data and evidence	Considerations / comments
1	Results of high quality[62] clinical investigations covering all device variants, indications, patient populations, duration of treatment effect, etc	This may not feasible or necessary for certain well-established devices with broad indications (eg Class IIb legacy sutures, which could be used in every conceivable patient population)
2	Results of high quality clinical investigations with some gaps	Gaps must be justified / addressed with other evidence in line with an appropriate risk assessment, and clinical safety, performance, benefit and device claims. Assuming the gaps can be justified, there should be an appropriate PMCF plan to address residual risks. Otherwise, manufacturers shall narrow the intended purpose of the device until sufficient clinical data has also been generated.
3	Outcomes from high quality clinical data collection systems such as registries[63]	Is there sufficient evidence of the quality of the data collected by the registry[64, 65]? Are the devices adequately represented? Are the data appropriately stratified? Are the endpoints appropriate to the safety, performances and endpoints identified in the clinical evaluation plan?
4	Outcomes from studies with potential methodological flaws but where data can still be quantified and acceptability justified[66]	Many literature sources fall into this category, due to limitations such as missing information, publication bias, time lag bias, etc. This applies equally to publications in the peer-reviewed scientific literature. However, for legacy devices

MDCG 2020-6 : Appendix III

Equivalence

MDR Annex XIV 3. A clinical evaluation may be **based on clinical data relating to a device** for which equivalence to the device in question can be demonstrated…

- Technical, Biological, and Clinical equivalence needs to be established in each comparison.
- Established between the **current device** and **the device from which clinical data was collected**. Includes between different models or generations of the same device, where necessary.
- Must provide a thorough analysis identifying ANY technical, biological, or clinical differences between the devices.
- This assessment will require “sufficient levels of access to the data” on the equivalent device. This needs to be justified.
- ANY differences must have scientific justifications that they do not impact the safety and performance profile. (i.e. backed up by a scientific assessment and/or tests)
- Additional requirements for Class III or implantable devices (Article 61(4)).



MDCG 2020-5,
MDCG 2023-7

Literature Reviews and Clinical Data Appraisal

Literature Review

MDR Annex XIV 1. (b) : identify available clinical data relevant to the device and its intended purpose and any gaps in clinical evidence through a systematic scientific literature review;

Meddev 2.7.1 Rev 4 A5 : Output of the literature review are:

- Literature on the device in question
- Literature on the state of the art.

Systematic, objective literature reviews require a clearly defined protocol, with clear objectives to collect data on device and state of the art.

Clinical Data Appraisal

MDR Annex XIV 1. (c) : appraise all relevant clinical data by evaluating their suitability for establishing the safety and performance of the device;

Meddev 2.7.1 A5.3 : 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

Meddev 2.7.1. Rev 4 A6 : Appraisal of clinical data – examples of studies that lack scientific validity …

Meddev 2.7.1 Rev 4 A5

Clinical Investigations, Requirements, Benefits and Challenges

MDR Annex XV:

- Recognised Ethical Principles (e.g. ISO 14155)
- An appropriate plan, reflecting the latest scientific and technical knowledge, designed to confirm or refute the manufacturer's claims.
- Procedures appropriate to the device under investigation.
- Sufficient number of intended users, representative of normal conditions of use.
- All technical and functional features of the device involving safety and performance, and expected outcomes, shall be appropriately addressed.
- Endpoints that address benefit/performance claims and safety.
- The report shall contain a critical evaluation and include any negative findings.

Benefits:

- Minimization of variables
- Reliable collection of data
- High quality, focussed, data on population
- Well defined "Pass/Fail" endpoints.

Challenges:

- Limited to chosen endpoints.
- Narrow trial populations or insufficient definition or representation of subgroups.
- Population may be unsuitable for randomization.
- Unintentional bias caused by study design.
- "Controlled environment", vs "Real World" use.
- Ethical questions.

When Generation of Clinical Data is “not appropriate”

Article 61(10)

Specifies the following requirements:

- The device is not Class III or implantable.
- Collection of clinical data is not appropriate.
- Risks involved with interaction with the human body have been duly considered
- The GSPRs are adequately supported with non-clinical data.
- The **manufacturer has provided due justification** of the above.

Not Appropriate , isn’t “Difficult”, or “Not determined to be required”. It is not an option because clinical data has simply not been collected.

In general, where a device has a direct impact to the patient, clinical data MUST be generated (e.g. a device used within a clinical procedure, and whose use *may* impact the outcome)

If Article 61(10) is deemed to be applicable, then the manufacture must clearly demonstrate compliance to each of its requirements (left).

Carefully consider whether all risks and performances in “**Normal Conditions of Intended Use**”, have been adequately supported with pre-clinical data, and whether new data needs to be generated, including “retrospective analysis” and “simulated use” studies.

Analysis

Annex XIV (e) analyse all relevant clinical data in order to reach conclusions about the safety and clinical performance of the device including its clinical benefits.

Considering ALL collected data, an **objective** analysis against:

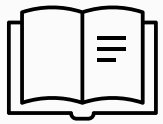
- Compliance against GSPRs
- Identified Objectives and Endpoints
- Intended Performance and Patient Benefit
- Intended and required Claims
- Acceptable levels of risk
- Other aspects related to the State of the Art

Confirmation whether collected data supports:

- GSPRs, Objectives, Endpoints, Intended Performance and benefit, claims, other aspects.
- Whether residual risks are acceptable considering performance and benefit
- Whether the subject device therefore may be considered part of the state of the art.

Identification of data weaknesses or gaps and whether:

- More data needs to be collected (and/or the Design modified) prior to release, or
- Gaps may be addressed via (specific) methods in **PMCF**



Meddev 2.7.1 Rev 4 A7

Collection of “Real-World” Clinical Data

Annex XIV Part B: PMCF

“…a **continuous process** that updates the clinical evaluation….“

Annex XIV 6. outlines the requirements and aims of PMCF, appropriately documented in a PMCF Plan, to collect data on the device in “Real-World” use, focussing on:

Performance/Safety throughout lifetime, Monitoring Side-effects, Identifying emergent risks, demonstrating continued acceptability of benefit/risk, identifying systematic misuse / off-label use.

The Manufacturer must consider what data requirements are required, and demonstrate how their methods meet each of the PMCF requirements in MDR Annex XIV 6.1

Specific Methods are likely to be needed to collect “real-world” clinical data on a device :

- To collect real-world performance data on novel aspects.
- Where equivalence has been used to bring the device to market.
- Where the manufacturer has used Article 61(10),
- To reinforce current claims, or to make new claims.

(Methods must be within currently labelled intended purpose)

NOTE: PMCF plan is part of the assessed documentation supporting device design. It is expected that the manufacturer performs PMCF as planned.

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- Levels of Clinical Data & When it is not appropriate

Questions?

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