Regulatory, quality and clinical affairs

NX-451 – What to know when working with medical devices

Session 9

Kim Rochat

last update 2025-04-17

Kim Rochat

Medical Device regulation – Compliance need

Compliance to GSPR

Medical Devices manufactured shall comply with the applicable requirements of the Medical Device Regulation (MDR) or the In Vitro Diagnostic Regulation (IVDR) while their product shall comply with the General Safety and Performance Requirements as defined in Annex I of these regulations

Implement a QMS

Manufacturer shall implement a Quality Management System that define company processes.

COMPLETED

Prepare a Technical File

For each device, manufacturer shall assemble a technical documentation that provides evidences of compliance with the requirements

COMPLETED

Clinical evaluation

Manufacturer shall collect and evaluate clinical data to demonstrate clinical relevance of the devices (risk / benefit ratio)

Conformity assessment / Notification

Depending on the situation, a conformity assessment with a notified body is to be done, or an authorization for a clinical investigation is to be requested or a notification shall be performed

COMPLETED

Medical Device regulation – Manufacturer obligations

Kim Rochat

Article 10

General obligations of manufacturers

1. When placing their devices on the market or putting them into service, manufacturers shall ensure that they have been designed and manufactured in accordance with the requirements of this Regulation.

3. Manufacturers shall conduct a clinical evaluation in accordance with the requirements set out in Article 61 and Annex XIV, including a PMCF.

Article 5

Placing on the market and putting into service

3. Demonstration of conformity with the general safety and performance requirements shall include a clinical evaluation in accordance with Article 61.

Medical Device regulation – Art 61

Kim Rochat

GSPR 1 & 8

Level of clinical evidence

Defined method & sound procedure

Clinical Evaluation Report

Article 61

Clinical evaluation

1. Confirmation of conformity with relevant general safety and performance requirements set out in Annex I under the normal conditions of the intended use of the device, and the evaluation of the undesirable side-effects and of the acceptability of the benefit-risk- ratio referred to in Sections 1 and 8 of Annex I, shall be based on clinical data providing sufficient clinical evidence, including where applicable relevant data as referred to in Annex III.

The manufacturer shall specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. That level of clinical evidence shall be appropriate in view of the characteristics of the device and its intended purpose.

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 currently available relating to the safety, performance, design characteristics and intended purpose of the device, where the following conditions are satisfied:

— it is demonstrated that the device subject to clinical evaluation for the intended purpose is equivalent to the device to which the data relate, in accordance with Section 3 of Annex XIV, and

— the data adequately demonstrate compliance with the relevant general safety and performance requirements;

(b) a critical evaluation of the results of all available clinical investigations, taking duly into consideration whether the investigations were performed under Articles 62 to 80, any acts adopted pursuant to Article 81, and Annex XV; and

(c) a consideration of currently available alternative treatment options for that purpose, if any.

12. The clinical evaluation, its results and the clinical evidence derived from it shall be documented in a clinical evaluation report as referred to in Section 4 of Annex XIV, which, except for custom-made devices, shall be part of the technical documentation referred to in Annex II relating to the device concerned.

Medical Device regulation – GSPR 1 & 8

GENERAL SAFETY AND PERFORMANCE REQUIREMENTS

1. Devices shall achieve the performance intended by their manufacturer and shall be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose. They shall be safe and effective and shall not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art.

- Devices shall be designed to be suitable for their **intended purpose**.
- They shall be safe and effective and shall not compromise the safety of patients or users.
- Associated risks are acceptable when weighed against the benefits to the patient, accounting for the generally acknowledged state of the art

8. All known and foreseeable risks, and any undesirable side-effects, shall be minimised and be acceptable when weighed against the evaluated benefits to the patient and/or user arising from the achieved performance of the device during normal conditions of use.

- All known risks shall be minimized/acceptable **when weighed against the evaluated benefits to the patient/user** during normal conditions of use.

Kim Rochat

Risk benefit assessment

The clinical evaluation of a medical device shall demonstrate that its **intended clinical benefits**

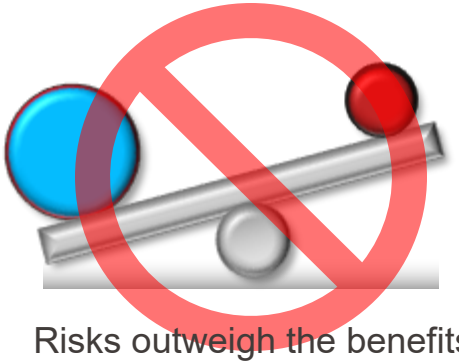
- improved patient outcomes
- enhanced safety,
- increased quality of life

outweigh the potential risks, including

- device malfunctions,
- user errors,
- adverse effects,

It is supported by the outcome of the risk assessment (see slide 23 of session 6)

Benefits outweigh the risks



Risks outweigh the benefits

Benefits for patient

Residual risk of device or risk of procedure

Kim Rochat

Risk benefit assessment - Example

Deep Brain Stimulator (DBS)

DBS is a neurosurgical implant that delivers electrical impulses to specific areas of the brain through implanted electrodes. It's used to modulate abnormal brain activity (indicated for Parkinson's disease, Obsessive-Compulsive Disorder (OCD), Epilepsy and more)

Risks

- **Surgical risks** - Bleeding in the brain, Infection, Seizures
- **Hardware-related risks** - Lead migration or breakage, Battery failure or Skin erosion over the device
- **Stimulation-related effects** - Speech difficulties, balance problems, tingling, mood changes, apathy, or hypomania
- **Cognitive effects** - may affect memory or executive function in some patients
- **Psychiatric side effects -** depression, suicidality, impulsivity

Kim Rochat

Risk benefit assessment - Example

Deep Brain Stimulator (DBS)

Benefits

- **Significant symptom relief -** Patients with Parkinson's may experience 50–80% improvement in tremor and motor symptoms**.**
- **Improved quality of life** - Patients can regain independence and mobility.
- **Reduction in medication** - Fewer side effects from long-term dopaminergic drugs (like dyskinesia or hallucinations).

Risk benefit evaluation

- The patients considered for DBS typically suffer from severe, disabling symptoms that haven't responded to medication

  ⇒ Only remaining option

- The magnitude of benefit (especially for tremor and motor control) is often high to very high.

  ⇒ "game changer" for the patient

- Most of the risk are manageable

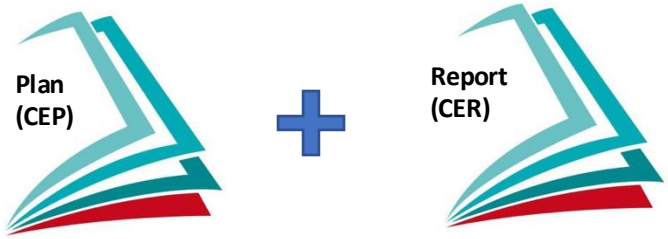
  ⇒ Adequate and know risk controls

DBS on and off https://www.youtube.com/shorts/wZZ4Vf3HinA

Clinical Evaluation – Definitions

Clinical Evaluation - Article 2(44) of the MDR

"a systematic and planned process to **continuously** generate, collect, analyze and assess the **clinical data** pertaining to a device in order to **verify the safety and performance**, including **clinical benefits**, of the device when used **as intended by** the manufacturer"



Clinical Evaluation is composed of the Clinical Evaluation Plan (CEP) and the Clinical Evaluation Report (CER)

Clinical Evaluation – Definitions

Clinical Data (as per 2017/745 MDR, Art. 2 (48):

Information concerning safety and/or performance that is generated from the clinical use of a medical device and is sourced from:

- clinical investigation(s) of the device concerned,
- clinical investigation(s) or other studies reported in scientific literature, of a device for which equivalence to the device in question can be demonstrated,
- reports published in peer reviewed scientific literature on other clinical experience of either the device in question or a device for which equivalence to the device in question can be demonstrated,
- clinically relevant information coming from post-market surveillance, in particular the post-market clinical follow-up;

Clinical Evidence (as per 2017/745 MDR, Art. 2 (51):

The clinical data and the clinical evaluation results pertaining to a medical device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer.

Clinical Evaluation – Definitions

Clinical Performance:

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;

Clinical Safety:

The absence of unacceptable clinical risks, when using the device according to the manufacturer's Instructions for Use.

as per 2017/745 MDR, Art. 2 (52)

Clinical Benefit :

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.

as per 2017/745 MDR, Art. 2 (53)

Kim Rochat

Clinical Evaluation – Definitions

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.

Also known as clinical trial or clinical study.

Clinical evaluation ≠ Clinical investigation

Clinical Evaluation – Objectives and process

- The objectives of the clinical evaluation are:
  - Demonstration of conformity to GSPRs #1 and 8
  - Demonstration of a positive Benefit/Risk ratio
  - Substantiation of Safety and Performance Claims and intended clinical benefits (in accordance with product information materials)
  - Identification of aspects that need to be addressed systematically during post-market surveillance and clinical follow-up (PMS and PMCF)

- The clinical evaluation is the outcome of a **process** that starts with the definition of a Clinical Evaluation Plan (CEP) and which is concluded by the completion of a Clinical Evaluation Report (CER).

- 'The clinical evaluation shall be thorough and objective and take into account **both favourable** and **unfavourable data**. Its depth and extent shall be **proportionate and appropriate** to the nature, classification, intended purpose and risks of the device in question, as well as to the manufacturer's claims in respect of the device.' – Annex XIV MDR

Kim Rochat

Clinical Evaluation – Objectives and process

Phase	Input to CER	Output from CER
R&D	• Marketing claims • Market positioning • GSPR + Applicable Std's	• Risk analysis • V&V activities • Indications (IFU) • PMS plan + Clinical Design Plan
Pre-clinical	• Test results (Mechanical testing/ Biocomp) • Risk analysis • Pre-clinical - Animal testing	• Design of pre-clinical investigation protocol
Clinical	• Clinical Investigation Report (CIR) findings	• Design of clinical investigation protocol (CIP) • Risk analysis • IFU
Post marketing	• PMS/ PMCF • Risk analysis	• Design of PMCF protocol • IFU • Risk analysis

Kim Rochat

Clinical Evaluation – Objectives and process

Clinical Evaluation Plan (CEP)

- **Defines the scope:** Describes the device, its intended purpose, target population, and clinical claims to be evaluated.
- **Specifies data sources:** Details how clinical data will be gathered - literature, clinical investigations, post-market data, etc.
- **Outlines evaluation methodology**: Sets criteria for appraising relevance, validity, and weighting of clinical evidence.
- **Definition of Safety and Performance parameters**: Identify and justify measurable objectives that the device must achieve to be considered safe and performing as intended.
- **Plans for updates**: Includes frequency and triggers for re-evaluation throughout the device lifecycle (linked to PMS & PMCF plans).

Kim Rochat

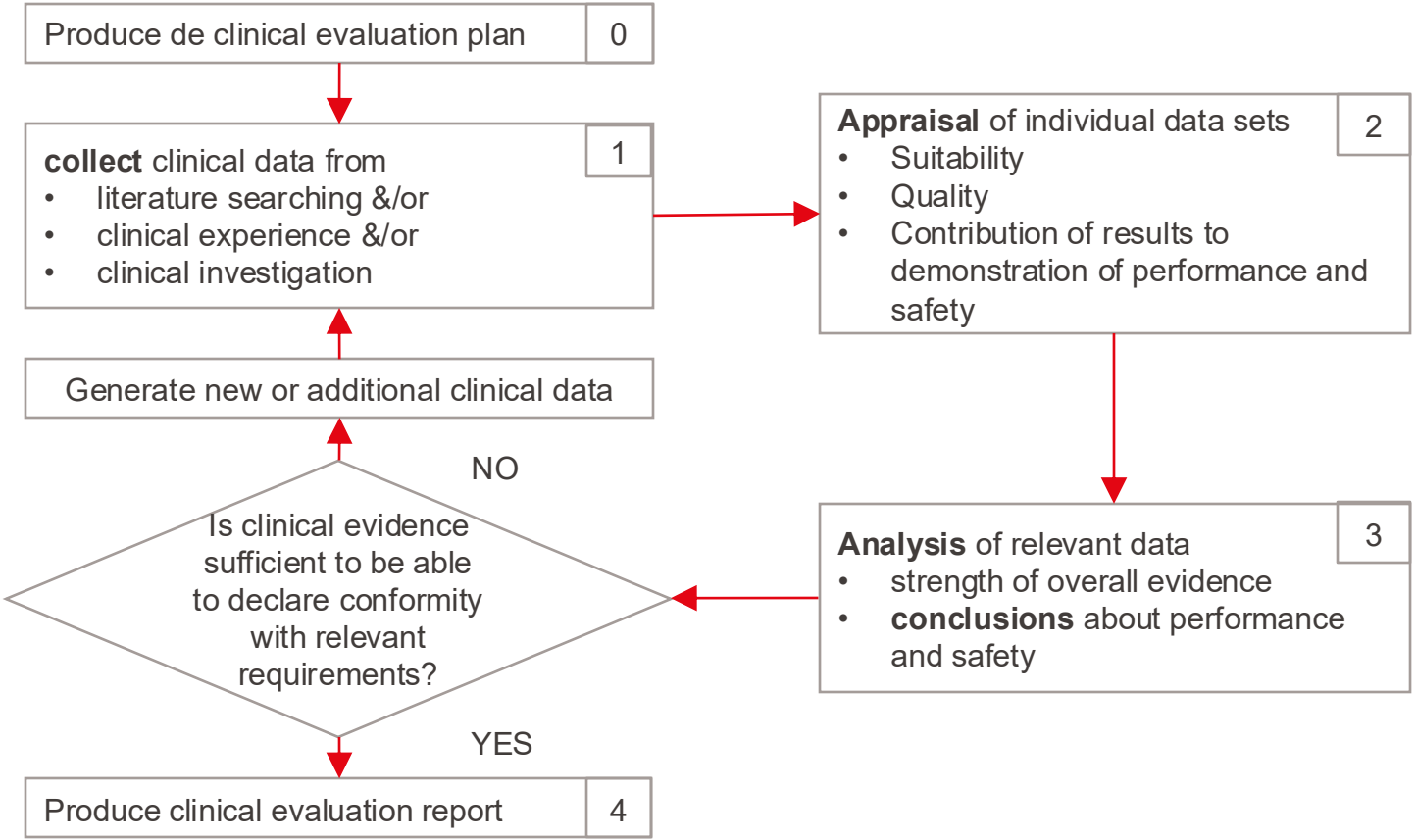
Clinical Evaluation – Objectives and process

Clinical Evaluation Report (CER)

- **Summarizes clinical data:** Integrates data from literature, clinical studies, and post-market surveillance.
- **Demonstrates conformity:** Shows the device meets MDR safety and performance requirements (Annex I).
- **Assesses benefit-risk:** Includes a thorough analysis of benefits versus risks based on evidence.
- **Justifies clinical evidence sufficiency:** Supports that the device has an acceptable risk-benefit profile and performs as intended.
- **Specifies / justifies PMCF needs**: Identified what residuals risks must be monitored during Post Market clinical follow-up (PMCF) if any.

Kim Rochat

Clinical Evaluation – Objectives and process



Kim Rochat

Clinical Evaluation – Objectives and process

Two main categories of data that can be used for the clinical evaluation

1) Data generated and held by the manufacturer:

- All pre-market clinical investigations
  - Initial pilot studies
  - Studies on different version of the device
- Relevant pre-clinical studies
  - Animal testing studies
  - Bench tests (i.e. biocompatibility testing, Electrical safety testing, Usability studies, etc.
  - Software verifications, functional verifications, etc.
- Post Market Surveillance data
  - PMCF studies, device registries
  - Feedbacks and complaints, incident reports, field safety corrective actions, safety database, search etc.)
  - Surveys

Clinical Evaluation – Objectives and process

2) **Data retrieved from literature:**

- Clinical Literature:
  - Clinical data relevant to the device under evaluation, which are data that relate either to the device under evaluation or to the equivalent device
  - Reports published in peer reviewed scientific literature on other clinical experience of either the device in question or a device for which equivalence to the device in question can be demonstrated

- Current knowledge / State of the art
  - Technical standard relevant to the device
  - Professional / scientific / Medical guideline and publications
  - Regulatory guidance and requirements

Kim Rochat

Clinical Evaluation – Literature review

For the literature, to be included in the clinical evaluation, it first must be appraised to ensure it is suitable for use

Usually, we consider the appraisal in successive phases where the defined criteria are evaluated:

- L1 – Title
- L2 – Abstract
- L3 – Full text of the article

Where:

L1 appraisal: Titles of the identified articles were appraised according to the defined inclusion and exclusion criteria,

Rule of thumb: Exclusion of around 40-50%

L2 appraisal: Abstracts of the articles qualified at previous level, were appraised according to the defined inclusion and exclusion criteria,

Rule of thumb: Exclusion of around 20-30%

L3 appraisal: Full text of articles that were qualified at previous levels, appraised according to the defined suitability and contribution to the state of the art**.**

Rule of thumb: Exclusion of around 10-20%

The final L3 appraisals included in the SOTA should be around 20-50

Clinical Evaluation – Literature review

Kim Rochat

Example of appraisal criteria

Inclusion Criteria

- Articles in English (depends on linguisitic competences of evaluator)
- Human data – clinical evidence
- Devices with similar intended use and indication for use
- Review articles describing the current standard of care
- Articles reporting the current knowledge on safety or performance of a device type.

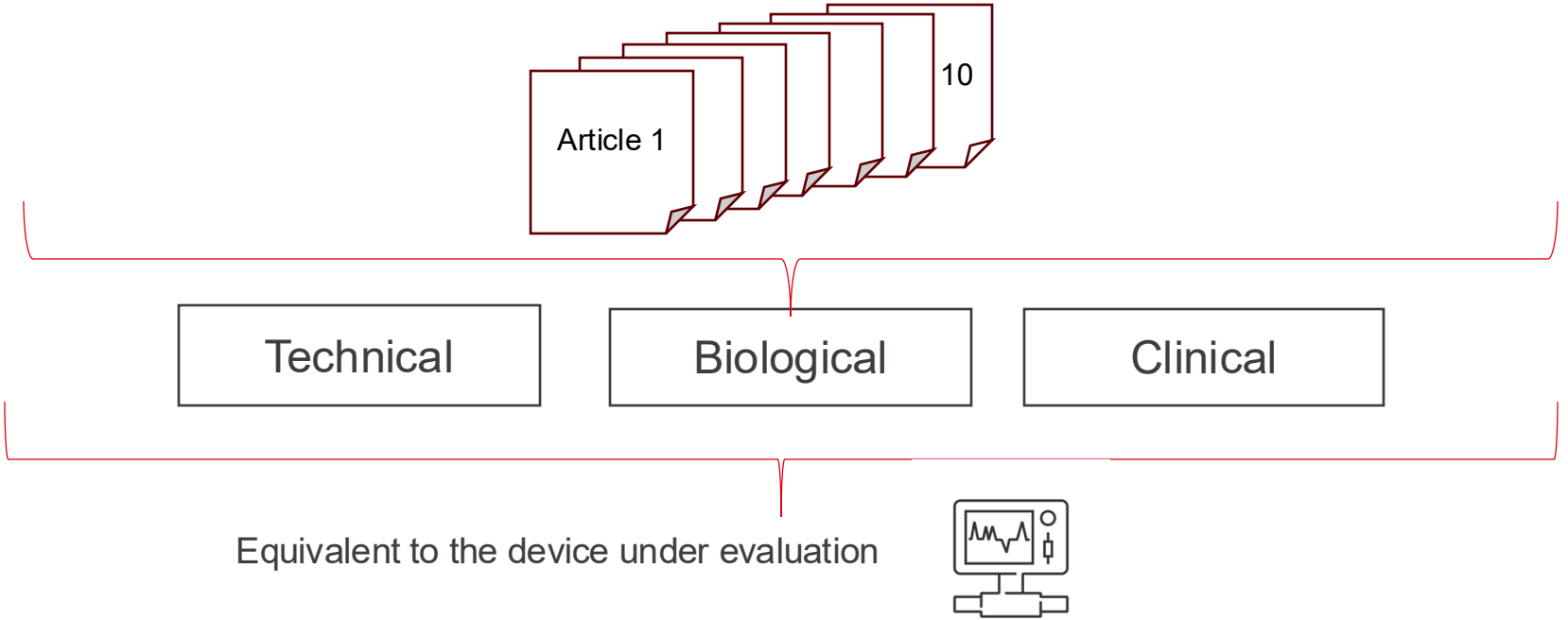
Exclusion Criteria examples

- Animal study or non-clinical study
- Conference abstract/ poster
- No access to full text of the article
- Studies focusing on invasive techniques
- Articles published before 2016
- Clinical trials that have been suspended, terminated, or withdrawn
- Technical papers
- Case studies, letters, editorials, or opinion pieces
- Duplicates

Clinical Evaluation – Literature review

Kim Rochat

When literature is used, equivalence of the device in the literature with the device under evaluation must be demonstrated as per Annex XIV MDR : ““A clinical evaluation may be based on clinical data relating to a device for which equivalence to the device in question can be demonstrated.”



Clinical Evaluation – Literature review

Kim Rochat

Technical equivalence

- similar design
- Similar mode of operation
- similar conditions of use
- similar specifications and properties, for example:
  - tensile strength
  - viscosity
  - surface characteristics,
  - software algorithms,
  - Etc.
- similar deployment methods
- similar principles of operation and critical performance requirements

Biological Equivalence

- same materials or substances
- in contact with the same human tissues or body fluids
- similar contact duration
- similar release characteristics of substances

Clinical Equivalence

- same clinical condition/purpose
- similar severity and stage of disease
- same site in the body
- similar patient population, i.e. age, anatomy, and physiology
- same user profile
- similar clinical effect regarding the specific intended purpose

Kim Rochat

Clinical Evaluation – Level of evidence

The data provided for the clinical evaluation shall have a sufficient level of evidence as stated in MDR Article 61:

"The manufacturer shall **specify** and **justify** the level of clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. That level of clinical evidence shall be **appropriate in view of the characteristics of the device and its intended purpose**."

The notion of "sufficient clinical evidence" is based on:

- Device risk class
- Clinical benefit/risk
- Novelty of the device
- History of safe use

⇒ Clinical evaluation for a class I or IIa medical device may rely on literature and bench testing while implantable or class III device will require more robust clinical data.

Clinical Evaluation – Level of evidence

Annex III of MDCG 2020-6 “Clinical evidence need for medical device previously CE Marked under Directive 93/42/EEC or 90/385/EEC provide the following scale for level of evidence

LoE	Type of Data and Evidence
Rank 1	Results of high-quality clinical investigations covering all device variants, indications, patient populations, duration of treatment effect
Rank 2	Results of high-quality clinical investigations with some gaps
Rank 3	Outcomes from high quality clinical data collection systems such as registries
Rank 4	Outcomes from studies with potential methodological flaws but where data can still be quantified, and acceptability justified
Rank 5	Equivalence data (reliable / quantifiable)
Rank 6	Evaluation of state of the art, including evaluation of clinical data from similar devices
Rank 7	Complaints and vigilance data; curated data
Rank 8	Proactive PMS data, such as that derived from surveys
Rank 9	Individual case reports on the subject device
Rank 10	Compliance to non-clinical elements of common specifications considered relevant to device safety and performance
Rank 11	Simulated use / animal / cadaveric testing involving healthcare professionals or other end users
Rank 12	Pre-clinical and bench testing / compliance to standards

Clinical Evaluation – S&P Parameters

As mentioned previously the Clinical evaluation aims at providing an objective evaluation of the intended clinical benefits outweigh the potential risks (risk / benefit ratio).

Clinical benefit

CEP: detailed description of intended clinical benefits to patients with relevant and **specified clinical outcome parameters**

SOTA assessment

Definition of S&P Parameters

Define relevant clinical outputs
Set acceptance criteria

CEP: an indicative list and specification of parameters to be used to determine, based on the state of the art in medicine, the acceptability of the benefit-risk ratio for the various indications and for the intended purpose or purposes of the device

CER: Risk benefit assessment, assessment of Side-effects

Clinical evidence: available (clinical) data

Achievement of S&P Parameters

Clinical Evaluation – S&P Parameters

- Setting safety and performance parameters relevant to the device technology enable to assess the acceptability of the safety and performance of the device under evaluation when compared against standard care devices.
- The S&P Parameters are established based on the literature review (SOTA) and usually their acceptance criteria are backed by (decreasing priority):
  - society guidelines
  - meta-analysis using similar devices
  - clinical studies on similar devices
  - registries
  - applicable standards
- Parameters must be:
  - Quantifiable or qualitatively justified
  - Consistent with the device's risk class and clinical claims
  - Used to define endpoints in clinical investigations or literature review

⇒ Safety and Performance parameters are the foundation or 'ground truth' for assessing a device's risk-benefit profile under MDR.

Clinical Evaluation – S&P Parameters

Kim Rochat

Example of safety parameters for an infusion pump

	Qualitative	Quantitative
Safety	**Alarm Systems** • If the infusion rate drops below or exceeds the safe threshold, the software should immediately alert the healthcare provider, allowing for timely intervention. **Data Integrity and Security** • Data Privacy: The software must ensure that patient information (e.g., medication history, dosage logs) is securely encrypted to prevent unauthorized access, ensuring compliance with HIPAA or GDPR. • Encryption Standard: AES-256 bit encryption for data at rest and TLS 1.2 or higher for data in transit to prevent unauthorized access.	**Dosage Accuracy** • Tolerance Limit: ±1% of the programmed infusion rate for standard medications (e.g., if 10 mL/hr is programmed, the actual delivered rate should be between 9.9 and 10.1 mL/hr) **Occlusion detection time** • Detects blockage within <10 seconds **Failure Rate** • Software Failure Rate: Less than 0.001% (1 in 100,000 operations) over a 12-month period of use. **Data Security (Integrity and Privacy)** • Data Loss: Ensure zero loss of patient data, even during power outages or software updates (i.e., 100% data integrity).

Clinical Evaluation – S&P Parameters

Kim Rochat

Example of performance parameters for an infusion pump

	Qualitative	Quantitative
Performance	**Accuracy and Precision** • Measurement Accuracy: The software must ensure precise control over the flow rate. If the prescription is for 5 milliliters per hour, the software should deliver exactly that, with minimal deviation. **Reliability and Uptime** • System Stability: The infusion pump software should be highly reliable, with no unexpected crashes **User interface usability** • Supports intuitive and error-resistant programming and monitoring	**Uptime and Reliability** • System Uptime: Target at least 99.99% uptime over a year, meaning the software is operational 99.99% of the time without downtime due to crashes or maintenance. **Response Time** • Screen Update Speed: Display changes should update within 200 milliseconds to ensure smooth user interaction. **Battery life** • The pump shall be able to operate during 24h in normal conditions of use without interruption

Clinical Evaluation – Updates

- Art 2017/745 Art. 61 (11) states:

'The clinical evaluation and its documentation shall be updated throughout the life cycle of the device concerned with clinical data obtained from the implementation of the manufacturer's PMCF plan in accordance with Part B of Annex XIV and the post-market surveillance plan referred to in Article 84. For class III devices and implantable devices, the PMCF evaluation report and, if indicated, the summary of safety and clinical performance referred to in Article 32 shall be updated at least annually with such data.'

⇒ The clinical evaluation is actively updated:

- When the manufacturer receives new information from PMS that has the potential to change the current evaluation; if no such information is received, then
  - at least annually if the device carries significant risks or is not yet well established; or
  - every 2 to 5 years if the device is not expected to carry significant risks and is well established, a justification should be provided.
  - typically, aligned with the timetable for surveillance audits and the renewal of the certificates.
- Frequency must be justified in the Clinical Evaluation Plan (CEP)

Clinical Evaluation – Updates

- The clinical evaluation should be conducted by a suitably qualified individual or a team.
- Evaluators and their competencies to be documented in the CER with
  - Scientific background,
  - Expertise in research methodology, medical writing, regulatory requirements, ev. device technology and application; medical field, etc.
  - Declaration of interest

- Minimal Evaluator credentials
  - Higher degree and 5 years of professional experience – Or
  - 10 years of professional experience if a higher degree is not a prerequisite for a given task.

Clinical Evaluation – Outcome

- **Summary of the evidence with respect to the device safety and performance**
  - Substantiation of performance and safety parameters
- **Substantiation of safety and performance claims**
  - Discussion and presentation of evidence that substantiate relevant claims and identification of potential gaps in evidence
- **Substantiation of clinical benefit**
  - Similarly, discussion and presentation of evidence that substantiate clinical benefit and identification of potential gaps
- **Formal conclusion and discussion on the benefit-risk ratio**
  - Formally reviewing risks outlined by Risk analysis, show how they have been addressed by the clinical data.
  - Conclusion on whether new risks have identified, and if the risk analysis needs to be updated
  - Formally conclude on weather the risks associated with the use of the device are acceptable when weighed against the benefits to the patient.

Clinical Evaluation – In a nutshell

- Mandatory under EU MDR (2017/745) for all medical devices
  - ⇒ Ensures the device meets safety, performance, and clinical benefit requirements
- Continuous lifecycle process, not a one-time task
  - ⇒ Starts during development and is maintained through PMS & PMCF
- Based on clinical data:
  - ⇒ Includes literature, equivalent devices, clinical investigations, and real-world use
- Structured in key documents:
  - Clinical Evaluation Plan (CEP) – Defines strategy, scope, and methods
  - Clinical Evaluation Report (CER) – Presents findings, benefit-risk, and MDR conformity
- Level of required evidence depends on:
  - Risk class, novelty of the device, and clinical claims
- Must demonstrate:
  - Acceptable benefit-risk profile
  - Scientific validity of claims
  - Compliance with GSPRs (Annex I)
- Reviewed by Notified Bodies (Class IIa and above)
- Must meet expectations in Annex XIV, MDCG 2020-6, and related guidances

Q&A