Klinische Daten - Herausforderungen seit der Einführung der MDR

Clinical data - challenges since the introduction of the MDR

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Clinical data - challenges since the introduction of the MDR

MDR challenges

Since May 26, 2021, the MDR is fully applicable

Many challenges of

- transitioning legacy devices to the MDR (previously certified and marketed under MDD)
- introducing new devices

Examplesfor clinical challenges

- Increased clinical data requirements under the MDR
- Increased requirements regarding presentation and analysis of clinical data (within the MDCG and MEDDEV framework)
- New clinical investigations
- Strategies for post-market clinical follow-up (PMCF) and implementation of those activities

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Relevant MDCG guidance documents

- MDCG 2019-9 Summary of safety and clinical performance
- MDCG 2020-1 Guidance on Clinical Evaluation of Medical Device software
- MDCG 2020-5 Guidance on clinical evaluation – Equivalence
- MDCG 2020-6 Guidance on sufficient clinical evidence for devices previously CE marked under Directives 93/42/EEC or 90/385/EEC
- MDCG 2020-7 Post-market clinical follow-up (PMCF) Plan Template
- MDCG 2020-8 Post-market clinical follow-up (PMCF) Evaluation Report Template
- MDCG 2020-13 Clinical evaluation assessment report template

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Clinical evaluation in the MDR

According to MDR article 61, the clinical evaluation shall be based on clinical data providing sufficient clinical evidence. It shall be performed with the aim to

- confirm conformity with relevant general safety and performance requirements (GSPR) under the normal conditions of the intended use of the device,
- evaluate the undesirable side-effects and
- demonstrate the acceptability of the benefit-risk-ratio

The clinical evaluation process is laid down in Annex XIV part A1 (clinical evaluation plan).

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Clinical evaluation in the MDR

More rigorous clinical evidence for class III and implantable medical devices

- Clinical data to be obtained from clinical investigations
- But: MDR allows for exemptions under certain conditions

No exception for active implantable medical devices

For class III devices and some class IIb devices an authority or an expert panel may be consulted (Article 61 (2))

Continuous update of data throughout the entire product life cycle

Obligation for post-market clinical follow-up (PMCF)

Clinical data - challenges since the introduction of the MDR

Clinical data sources - new devices

- Clinical investigation(s) conducted by the manufacturer with the concerned device
- Clinical investigation or other studies of a proven equivalent product reported in the literature

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Equivalence route in the MDR

- Equivalence principle via the literature route is severely restricted
- Manufacturers must have sufficient access to the data of devices with which they intend to demonstrate equivalence
- For class III products, a contract with the manufacturer of the equivalent device is required
- Considerthe conduct of a PMCFstudy if the equivalence route has been chosen

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Equivalence route in the MDR

The MDR requires **that technical, biological,** and **clinical characteristics** are considered when claiming equivalence to another device.

The manufacturer is expected to fully identify and **disclose any differences** between the two devices.

To demonstrate equivalence, it is required that

- there is **no clinically significant difference** in the safety and clinical performance of the devices
- considerations of equivalence are based on **adequate scientific justification**

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Clinical data sources – legacy devices

- Clinical investigation(s) conducted by the manufacturer with the concerned device
- Clinical investigation or other studies of a proven equivalent device reported in the literature

Legacy devices only

- Scientific literature with clinical data on the concerned device
- Clinically relevant information obtained by the manufacturer from post-market surveillance (PMS), in particular from the PMCF

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Clinical data sources – legacy devices

Rank	Type of clinical data and evidence
1	Results of high-quality clinical investigations covering all device variants, indications, etc.
2	Results of high-quality clinical investigations with some gaps
3	Outcomes of high-quality clinical data collection systems (e.g., registries)
4	Outcomes from studies with potential methodological flaws but where data can still be quantified, and acceptability justified

Clinical data - challenges since the introduction of the MDR

Clinical data sources – legacy devices

Rank	Type of clinical data and evidence
5	Equivalence data (reliable/quantifiable)
6	Evaluation of the state of the art (incl. evaluation of data from similar devices)
7	Complaints and vigilance data
8	Proactive PMS data (e.g., data from surveys)
9	Individual case reports
10	Compliance to common specifications (non-clinical elements)
11	Simulated use / animal / cadaveric testing
12	Pre-clinical and bench testing / compliance to standards

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Sufficient clinical evidence – legacy devices

- What are the clinical data required to provide sufficient clinical evidence necessary to demonstrate conformity with the relevant GSPR?
- The MDR requires that the level of clinical evidence is to be defined by the manufacturer (MDCG 2020-6)
- Data that have been sufficient for a conformity assessment under the MDD might not be sufficient to provide sufficient clinical evidence for the purpose of MDR requirements.

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Sufficient clinical evidence – legacy devices

- Class III legacy devices and implantable legacy devices which are not well-established technologies should have sufficient clinical data as a minimum at level 4.
- For well-established devices conformity with the relevant GSPRs might be confirmed by “cumulative evidence” from different sources including level 1-3 (e.g., equivalence data, state of the art, PMS data).
- MDCG 2020-6 does not provide an explicit definition of “sufficient clinical data” but points out that in the end this is the result of a qualified evaluation which allows the conclusion that the medical devices under consideration are safe and fulfil the intended medical benefit.

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Clinical evaluation without clinical data

- **Article 61(10)** of the MDR allows for the use of non-clinical data only
- **But:** only possible for absolutely non-critical devices (e.g., aspiration canulas in dentistry)
- Not possible for Class III or implantable devices
- Adequate **justification** why demonstration of conformity with general safety and performance requirements (GSPRs) based on clinical data is not deemed appropriate
- Justification is to be **based on risk management**, taking into account the specific interactions between the device and the human body, and the intended clinical performance

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Clinical investigations

There are three types of medical device clinical trials that are subject to the requirements of the EU MDR:

- **Type A** Medical device clinical trials for the **assessment of conformity** according to Art. 62 are **subject to approval** Art. 62 to 81 and the requirements of Annex XV apply.
- **Type C** Medical device clinical trials as **PMCF investigation** according to Art. 74(1) are **not subject to approval but notification**. The requirements of Art. 74(1) apply.
- **Type B Other** medical device clinical trials according to Art. 82 are **neither subject to approval nor notification**

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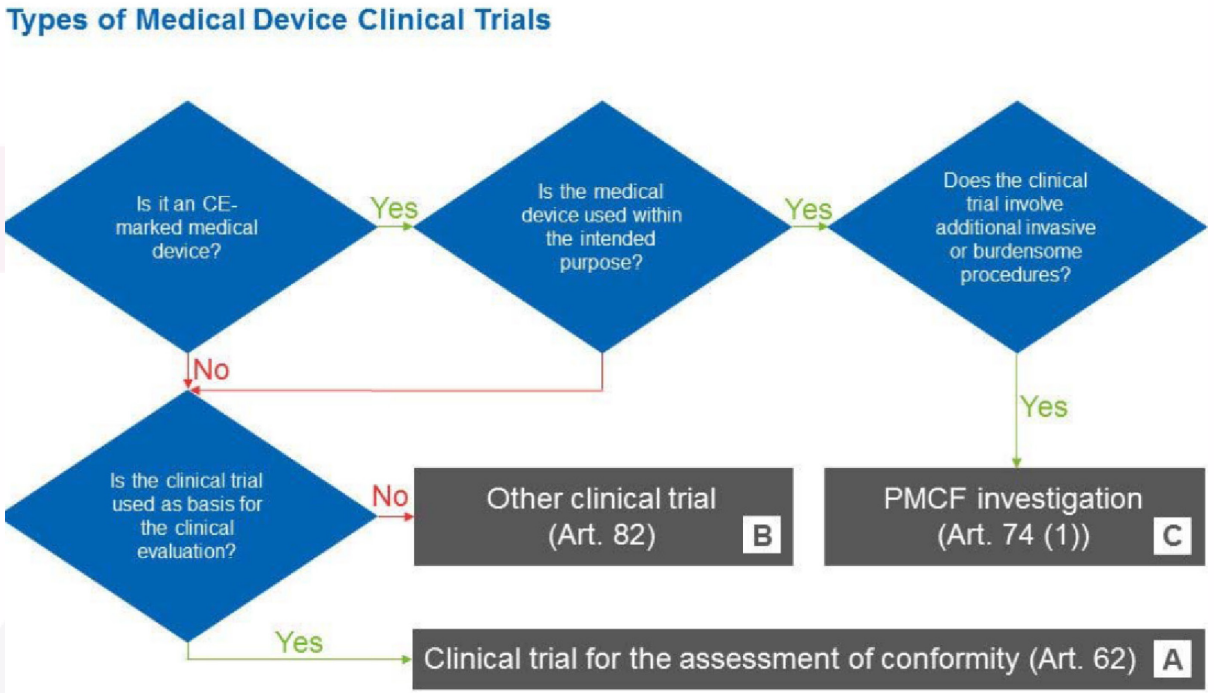
Clinical investigations

- Is the device to be used CE marked?
- Will the device be used within its intended purpose?
- Are additional invasive or patient burdensome procedures used in the clinical investigation?



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Clinical investigations

- MDD requirement to **notify** the Regulatory Authorities of an intention to perform a clinical investigation, is being replaced with
- MDR requirement to **submit an application** to conduct a clinical investigation.
- However, for lower risk devices the sponsor can still proceed to start the investigation if the application is **not refused**.
- So, in practice, at least for developers of lower risk devices, the new application procedure is unlikely to result in any new delays to starting clinical investigations in the EU.
- Issue: Medical Device manufacturers need to consider the resources and timelines for the preparation and submission of clinical investigation applications

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PMCF activities

Different types of activities related to PMCF are possible, namely:

- Searchof
  - scientific literature
  - other sources of clinical data
    - clinical registries
    - case reports (mainly to reveal potential misuse or off-label use)
- Post-market clinical studies (prospective/retrospective)
- Real-world evidence studies (non-interventional/observational studies)
- Survey of healthcare professionals

The type of required PMCF activities for a Medical Device is based on the clinical safety and performance outcome of the clinical evaluation process

Identified gaps need to be addressed by PMCF activities, such as surveys or PMCF studies

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PMCF activities

Aspect	PMCF survey	PMCF study
Data collection	Clinical application, safety and performance, possible off-label use, user experience	Clinical application, safety and performance, long-term safety data, addition of intended use
Approval Ethic committee & competent authority (GCP and ISO 14155 compliance)	Not required	Required
Cost	Cost efficient, fracture of a budget of a clinical study	High costs
Duration	Duration efficient compared to PMCF Clinical Study	Significant duration

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Examples of feedback received by the NBs

- Critical feedback from NB frequently related to formal issues related to the presentation of clinical data (e.g., inadequate predefinition of clinical outcome parameters/ endpoints, clinical benefit and sufficient clinical evidence in the CEP and adequate analysis in the CER)
    - It is highly recommended to follow the recommendations of the MDCG guidance documents!
- Parts of the intended use or product claims not sufficiently supported by clinical data
- For simple devices (e.g., spatula, aspiration cannulas for dental use) NBs agree with the approach of clinical evaluation without clinical data (MDR Article 61(10)) if adequately justified
- Strategies for PMCF and implementation of those activities not sufficiently well justified and presented

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Thank you!