

# Clinical evidence under the EU MDR: A notified body perspective



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This article examines clinical evaluation under the EU MDR from the perspective of clinical experts from three notified bodies. They anticipate new guidance on clinical evaluation, with an update of MEDDEV 2.7/1, rev. 4, and a definition of orphan devices and clarification on their use in the EU. The article provides useful information for manufacturers and highlights published expert scientific opinions aimed at notified bodies. It also discusses the expanding use of real-world data and evidence (RWD and RWE) for confirming the safety and performance of medical devices, especially in postmarket clinical follow-up (PMCF).



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## Clinical evaluation in the EU

The EU Medical Devices Regulation (EU MDR), also known as Regulation (EU) 2017/745,<sup>1</sup> has more detailed and specific requirements for evaluating clinical data compared with the EU Active Implantable Medical Devices Directive (EU AIMDD; Directive 90/385/EEC)<sup>2</sup> and the EU Medical Devices Directive (EU MDD; Directive 93/42/EEC),<sup>3</sup> which were repealed under the EU MDR in May 2021.

over two stages, with the date of completion currently set for the end of 2024.

The updates during the first stage are expected to clarify some common terms used in the EU MDR but not defined in Article 2 of the regulation, for example, *indirect clinical benefit*. The updates will also provide clarity on conducting clinical evaluations and using data from different types of clinical investigations, such as retrospective studies or the additional clinical studies mentioned in Article 82 of the EU MDR. Notified bodies are currently reviewing a high number of retrospective studies conducted by manufacturers trying to improve their sufficiency of data by analyzing retrospective data sets, such as patient chart reviews, to supplement the data required under the former EU MDD and EU AIMDD.



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There are many regulatory projects globally and in the EU that aim to harmonize the interpretation of the clinical evaluation across industry and notified bodies. Within the EU, there are planned updates to existing guidance and projects focused on new guidance to facilitate the implementation of the EU MDR. The most significant change in the EU relates to the update of the 2016 MEDDEV 2.7/1, rev. 4, guidelines for medical devices to align them with the requirements of the EU MDR. The updates are expected to be completed

The second stage of updates to the document will further clarify the clinical



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evaluation process and address the changing clinical evaluation landscape. The updates will include new information on sufficient clinical data for orphan devices and define the criteria mentioned in Article 61(10) of the regulation when clinical data are not deemed appropriate to show conformity with the general safety and performance requirements. These efforts should help align manufacturers and notified bodies in their interpretations of this clause.

Notified bodies now also have to assess medical devices that include artificial intelligence (AI) that go beyond machine learning and medical device software containing AI, including next-generation AI. One challenge is establishing sufficient clinical data levels for AI in learning models that will accurately reflect the target patient population and not increase exposure to risks that may not be evidenced within the data model sets. The updates to MEDDEV 2.7/1, rev. 4, are also expected to clarify the clinical evaluation process for devices using AI.

The EU-funded Coordinating Research and Evidence for Medical Devices (CORE-MD)<sup>4</sup> consortium is reviewing the methodologies for the clinical evaluation of high-risk medical devices and suggesting new designs to ensure patient safety and clinical effectiveness of the devices developed in this innovative and rapidly advancing landscape. Participants in the consortium include medical professional societies, notified bodies, academic institutions, manufacturer groups, regulators, and health agencies. The CORE-MD project was launched in April 2021 and will be completed in 2024. In essence, it is looking at the application of regulatory science methods to clinical evaluation of these devices.

The findings of the projects within CORE-MD are expected to raise awareness of the limitations of past methodologies and advise on how the limitations can be improved by establishing best practices in collecting pre- and postmarket evidence. Conclusions from the CORE-MD research are expected to result in significant updates to MEDDEV 2.7/1, rev. 4.

*The increased regulatory burden for devices under the EU MDR and the potential low return on investment for manufacturers are usually cited as reasons for removing devices from the market.*

The removal of devices for rare diseases from the EU market remains a central concern for the medical community. The increased regulatory burden for devices under the EU MDR and the potential low return on investment for manufacturers are usually cited as the reasons for removing these devices from the market.<sup>5</sup> The European Commission and the Medical Device Coordination Group (MDCG) have recognized these concerns, as outlined in an MDCG position paper on the transition to the EU MDR.<sup>6</sup> The two entities have initiated a task force to examine how best to manage the clinical evaluation of orphan devices, especially with the limited availability of clinical data and reduced opportunities for postmarket data collection because of the low usage of these devices. The task force's efforts have been prioritized, and a final guidance paper is expected to be released in early 2024.

Another development within the EU relates to the qualifying criteria for having a contract between manufacturers when one seeks product equivalency with another's device. Under the EU MDR, if a manufacturer of Class III and implantable devices wants to bypass premarket clinical investigations and instead claim equivalence with another manufacturer's device(s), there should be a valid contract between the two parties to ensure the manufacturer pursuing the equivalence route has ongoing access to the other manufacturer's technical documentation. This requirement has reduced the number of claims of equivalence under the EU MDR for these specific devices. In addition, manufacturers that successfully claimed equivalence under the former directives but could not complete their PMCF activities and gain sufficient data on their device at the time of

EU MDR application may not be able to transition to the EU MDR successfully. That is clearly a concern for regulators and industry regarding the availability of certain devices.

An MDCG draft guidance is currently available for comments and feedback from interested parties. The document addresses whether there is a need for a contract between manufacturers for devices that were certified under the former directives. It challenges requirements in Article 61(5) and whether legacy or well-established technology devices mentioned within Article 61(6) are exempt from a contract when claiming equivalence, given that they do not need to conduct clinical investigations to establish data sufficiency.

The International Organization for Standardization's ISO/AWI 18969<sup>7</sup> is a new standard in development for clinical evaluation that aims to provide a horizontal standard to the clinical evaluation approach. The anticipated standard, due for completion in 2024, will explain the scientific steps required to conduct a robust clinical evaluation of a medical device and is not expected to introduce any additional requirements. The hope is that the horizontal standard will be the basis for developing vertical standards for specific device groups to facilitate a more predictable clinical evaluation for common standard-of-care devices, similar to the EU MDR's common specification requirements.

### Published scientific opinion from EC expert panels

The EU MDR has introduced an additional level of scrutiny with the clinical evaluation consultation procedure (CECP) in Article 54 and requirement for expert panels<sup>8</sup> to support and advise on the scientific assessment of medical devices and in vitro diagnostic medical devices. These additional steps are to enhance the transparency of clinical evaluation assessments of high-risk devices by notified bodies.

Only Class III implantable and Class IIb active devices that administer and/or remove medicinal products are applicable for CECP.<sup>9,10</sup> Legacy devices modified to comply with EU MDR requirements are exempted

from CECP under Article 54(2)b. In addition, MDCG 2019-3, rev. 1, which provides an interpretation of Article 54(2)b, clarifies that the requirement does not apply to devices being modified outside of strict EU MDR compliance and that Article 54(1) applies to them.<sup>9</sup>

*Thematic expert panels disagreed with 9 of the 10 most recent notified body assessments, noting concerns related to available clinical evidence, the evaluation methodology, and PMCF strategies and plans.*

The notification for a CECP is triggered after a notified body issues a final positive clinical evaluation assessment. The notification package includes the clinical evaluation assessment report (CEAR) and the manufacturer's clinical documentation, including the clinical evaluation plan and report and the PMCF plan and report. In compliance with Article 54(3), CECP notification is done through the European Database on Medical Devices, or EUDAMED, to the European Medicines Agency. After a feasibility check of the submitted documentation, the file will be passed on to a screening panel, which will decide within 21 days of receipt of the notification whether a thematic expert panel should give a scientific opinion on the notified body's CEAR, based on three screening criteria<sup>10</sup> – the device's novelty and resulting impact; scientifically valid health concerns; and significantly increased incidents. If any of those criteria apply, a scientific opinion by the expert panel will be issued within 39 days of initial receipt of notification, making the CECP a 60-day process after receipt of the dossier. Scientific opinions will be published on the European Commission website, with anonymized manufacturer and device information.<sup>11</sup> The expert panel will then use the scientific opinion to decide whether to agree or disagree with the outcome of the notified body's clinical evaluation assessment of the device.

As of October 2023, 10 scientific opinions had been issued since 2021 under the CECP.<sup>11,12</sup> Of those 10 opinions, the thematic expert panels agreed with only 1 of the notified body assessments, meaning they disagreed with 9 assessments. The expert panels' key concerns were similar in all negative opinions and related to the clinical evidence available, the evaluation methodology in general, and the PMCF, specifically:

In most opinions, the expert panels disagreed with the notified body's assessment that the clinical data were quantitatively and qualitatively sufficient. They noted that patient numbers, study design, and level of evidence included with the studies were limited and did not substantiate the claimed indications. Furthermore, long-term follow-up data was found to be poor or completely absent.

*The expert panels found essential aspects of the clinical evaluation methodology lacked systematic soundness, and that literature search methodologies were unsystematic and had inadequate search periods and search terms.*

Essential aspects of the clinical evaluation methodology, which a notified body had approved, were found to lack systematic soundness. The expert panels found that literature search methodologies were unsystematic and had inadequate search periods and search terms. They also found that inconclusive inclusion and exclusion criteria meant that current pivotal scientific publications were not included in the search, and their data were therefore excluded from analysis in the clinical evaluation report. In addition, the expert panels identified that state-of-the-art evaluations did not always reflect the most current state of the art for the device in question.

Lastly, PMCF strategies presented within the PMCF

plan and considered appropriate by the notified body were found to lack a comprehensive description of the planned postmarket activities. The PMCF activities were also considered insufficient for meeting the PMCF objectives, including the generation of long-term follow-up data.

Apart from challenging the manufacturer's clinical evaluation and the notified body's assessment, the expert panels also challenged the documentation of the assessment results in the CEAR. In particular, they concluded that:

- The CEARs did not sufficiently focus on the device's novel aspects;
- The stratification of the clinical evidence to the individual indications was insufficient; and
- The methodology for collecting preclinical data with clinical relevance lacked transparency.

The expert panels also identified a lack of robust and plausible justifications for why limited clinical data available for specific claims should be acceptable in conjunction with suitable PMCF activities.<sup>12</sup> In conclusion, having clinical evaluation assessments of high-risk medical devices under the expert supervision of a third party imposes additional challenges for all stakeholders but needs to be seen as a significant asset in the continuous improvement and harmonization of clinical evaluation assessment provided by the notified bodies.

### Real-world evidence as PMCF

RWD and RWE have been discussed as potential sources of clinical data for the clinical evaluation. Several countries have undertaken efforts to implement frameworks for gathering and using RWD and RWE for medical devices.<sup>13,14</sup> RWD are not new for medical devices, but they are known as a data source used in regulatory decision making for medicinal products. RWD are data related to a patient's health status or delivery of healthcare and that are collected during routine clinical practice and manifold sources other than traditional clinical trial settings.<sup>15</sup> Device registry data, patient self-reported data, data generated by mobile devices,

and data from medical insurance or hospital medical records could be categorized as RWD. In recent years, sources of clinical data obtained from patients using medical devices have expanded significantly with the evolution and digitalization of medical devices. RWE is the result of the analysis of RWD as part of the clinical evidence needed to comply with the EU MDR clinical evaluation requirements.

The need for quantifying the clinical benefit and safety of medical devices has been described in the MEDDEV 2.7/1, rev. 4, guidance document currently under revision. The emphasis on clinical evidence based on clinical data in the MEDDEV guidance has been carried over into the EU MDR, which also reinforces clinical evaluation to improve health and safety, among other aims. RWE may contribute to inform decisions in medicine, specifically in line with the clinical evaluation requirements of the EU MDR.

RWE is generally considered a complement to traditional clinical evidence and not a replacement of it.<sup>16</sup> In particular, for Class III and implantable devices, it is evident that RWD and RWE alone are not sufficient to fulfill all clinical evaluation-related EU MDR requirements when setting up the clinical development plan for such devices. RWD under the regulatory framework of the EU MDR has been mentioned in the MDCCG 2020-6 guidance document<sup>17</sup> for legacy devices previously CE marked under the EU MDD and AIMDD and exhibiting an indirect clinical benefit (i.e., devices that require combined use with another device to achieve the intended purpose, such as guidewires).

RWD fill in data gaps and provide complementary data that can help answer remaining scientific questions related to the inherent limitations of premarket clinical investigations. These limitations could include selection bias or rare side effects that are unquantifiable because of the low number of participants; device interactions; and the evaluation of human factors, including learning curve effects. RWD and RWE may also deliver additional evidence for devices with limited premarket clinical evidence, for example, orphan, pediatric, and

breakthrough devices. In summary, as part of the cumulative evidence gained during the pre- and postmarket phases, RWD can be expected to reinforce the robustness of the evaluation of clinical benefit, performance, and safety of the use of the device in question.

*Any acquisition of clinical data, including RWD, should be methodologically sound and include, but not be limited to, protocol documentation and the identification and control of any risk for bias.*

RWD fitness for purpose must be appraised to evaluate the suitability of the data obtained. In this context, any limitations of the different data sources must be evaluated. Typical measures to control the risk for bias in a study, such as blinding, randomization, or including a control group, are missing in RWD and RWE. Therefore, any acquisition of clinical data, including RWD, should be methodologically sound and include, but not be limited to, protocol documentation and the identification and control of any risk for bias. As a general rule, the manufacturer must be able to justify the contribution of any clinical data used as part of the clinical evidence under the EU MDR in relation to the device's risk and use.

The EU MDR requires an analysis of all relevant clinical data to reach conclusions about safety and clinical performance. For devices that already have market experience in non-European markets, RWD and RWE may exist and be relevant when the initial application is lodged with the notified body. In such cases, the manufacturer may be required to justify not considering these data as part of the clinical evaluation under the EU MDR. For example, the appraisal of the data includes a review of regional factors, such as differences between healthcare systems, that may affect the transferability of the data obtained outside of Europe to the European market.



The use of RWD and RWE is expected to increase, given their greater availability and the potential benefits of using them for the clinical evaluation of medical devices. However, there are technical, ethical, and legal challenges in implementing the collection of RWD for clinical evaluation under the EU MDR, such as those related to the feasibility of data access and availability of hospital data sources. Furthermore, the EU General Data Protection Regulation (EU GDPR), in combination with national laws, limits the use of RWD. An EU GDPR-conforming complete anonymization might render the datasets unusable for confirming the safety and performance of medical devices – for example, age information or the medical history of the patient may be needed to evaluate observed side effects appropriately. As such, notified bodies will require substantiated demonstration of the feasibility and sustainability of planned postmarket data collection as part of their assessment of the PMCF plan for conformity with the EU MDR.

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In general, patient health data are sensitive and confidential and should be securely stored and protected and available only to users with permission to access them. That means that access to data may be limited, which could significantly limit the availability of RWE. The systematic evaluation of deidentified, but not anonymized, patient data requires adherence to data protection requirements and analysis and application of the relevant recognized ethical principles for medical research. To that end, an example of a standardized broad consent that is compliant with the EU GDPR has been developed to enable the secondary use of such data for regulatory purposes.<sup>18</sup>

The clinical evaluation requirements of the EU MDR include the consideration of suitable sources of post-market clinical data, specifically mentioning registers as an example of RWD. This is part of the EU MDR's legal requirements, but access to such data for manufacturers and notified bodies is limited by administrative hurdles, access restrictions, and/or insufficient resources for healthcare providers to record clinical experience data systematically during clinical practice. Further efforts involving legislators, authorities, certification organizations, and device manufacturers might facilitate access to RWD in the future.

#### Additional takeaways

There were numerous takeaways from the question-and-answer session after the presentation, including:

- The European Association of Notified Bodies (Team-NB) has introduced regular meetings between notified bodies to ensure they align on the interpretation of clinical evidence and clinical evaluation as presented in the EU MDR. Speakers involved in these meetings noted the interpretative alignment between the notified bodies had improved through the meeting discussions.
- When conducting a pre- or postmarket clinical investigation, it is important to do a comprehensible sample size calculation that factors in different patient subpopulations and the different indications for a medical device during clinical investigations.
- Manufacturers planning to conduct specific PMCF activities, such as a PMCF study or high-level survey outside of the EU, must consider the transferability of the clinical data to the European population.
- Under the MDCG 2022-14 guidance, notified bodies and manufacturers are encouraged to have a structured dialogue before and during the conformity assessment process to facilitate the efficiency and predictability of the process.<sup>6</sup> The notified bodies are investigating how to set up the necessary internal processes for such dialogue with the manufacturers.

## Conclusion

It is important that there is a continuous exchange between various stakeholders and notified bodies outside of the normal conformity assessment process. In the current transition phase from the EU MDD and AIMDD to the EU MDR, there is a steady need to understand the notified bodies' interpretation of topics related to clinical evidence and the clinical evaluation process. With the introduction of the CECP, the legislation introduced another level of scrutiny, specifically on the work of the notified bodies but also of information on the quality and quantity of clinical data through published scientific opinions. RWD and RWE are becoming increasingly relevant for medical devices and could reduce the number of patients and the follow-up time required for specific PMCF activities. Finally, there will be a long-awaited update of the MEDDEV 2.7/1, rev. 4, guidance on clinical evaluation that will also provide some clarification on uncertainties in the interpretation of some requirements of the EU MDR.

## Abbreviations

**AI**, artificial intelligence; **CEAR**, clinical evaluation assessment report; **CECP**, clinical evaluation consultation procedure; **CORE-MD**, Coordinating Research and Evidence for Medical Devices; **EU AIMDD**, EU Active Implantable Medical Devices Directive; **EU GDPR**, EU General Data Protection Regulation; **EU MDD**, EU Medical Devices Directive; **EU MDR**, EU Medical Devices Regulation; **MDCG**, Medical Device Coordination Group; **PMCF**, postmarket clinical follow-up; **RWD**, real-world data; **RWE**, real-world evidence; **Team-NB**, European Association of Notified Bodies.

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