

Clinical Evaluation of Medical Devices: So much more than “just” a report



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Overview

In 2016, the European Commission (EC) released MEDDEV 2.7/1 Revision 4 (MEDDEV) Clinical Evaluation: A Guide for Manufacturers and Notified Bodies Under Directives 93/42/EEC and 90/385/EEC, which was the first indication of sweeping regulatory changes that would occur in Europe affecting medical devices. This guideline was published and went into immediate effect without a transition period. Medical device manufacturers have struggled to understand and implement the guidance, which has some ambiguity and has left manufacturers with different interpretations. Manufacturers were still evaluating the changes from the MEDDEV when the EC officially published the EU Medical Device Regulation (MDR) 2017/745 in the Official Journal of the European Union on 05 May 2017. This regulation came into force on 25 May 2017 and has a deadline for compliance by 26 May 2021. The regulation affirms the expectations of the MEDDEV and expands on the clinical data requirements. This white paper will explain the key changes in this regulation and review the phases for clinical evaluation and expected documentation to clarify this somewhat ambiguous and highly scrutinized process.

Key changes

The MEDDEV was an expansion from a prior guidance and provided specific expectations for the clinical evaluation process for medical devices. Clinical evaluation is defined as “a methodologically sound ongoing procedure to collect, appraise, and evaluate if there is sufficient clinical evidence to confirm compliance with the relevant essential requirements for safety and performance when using the device according to the manufacturer’s Instructions for Use”.¹

Prior to Revision 4 of the MEDDEV, clinical evaluation was generally considered a report completed as a part of the technical file, often by the regulatory department. This report was updated when changes were made to the device. This all changed in 2016 with the MEDDEV release. A quick PubMed search and a simple report were no longer adequate for clinical evaluation reports (CERs). The clinical evaluation is now a process made up of 5 stages that need to demonstrate the safety and performance of the device.

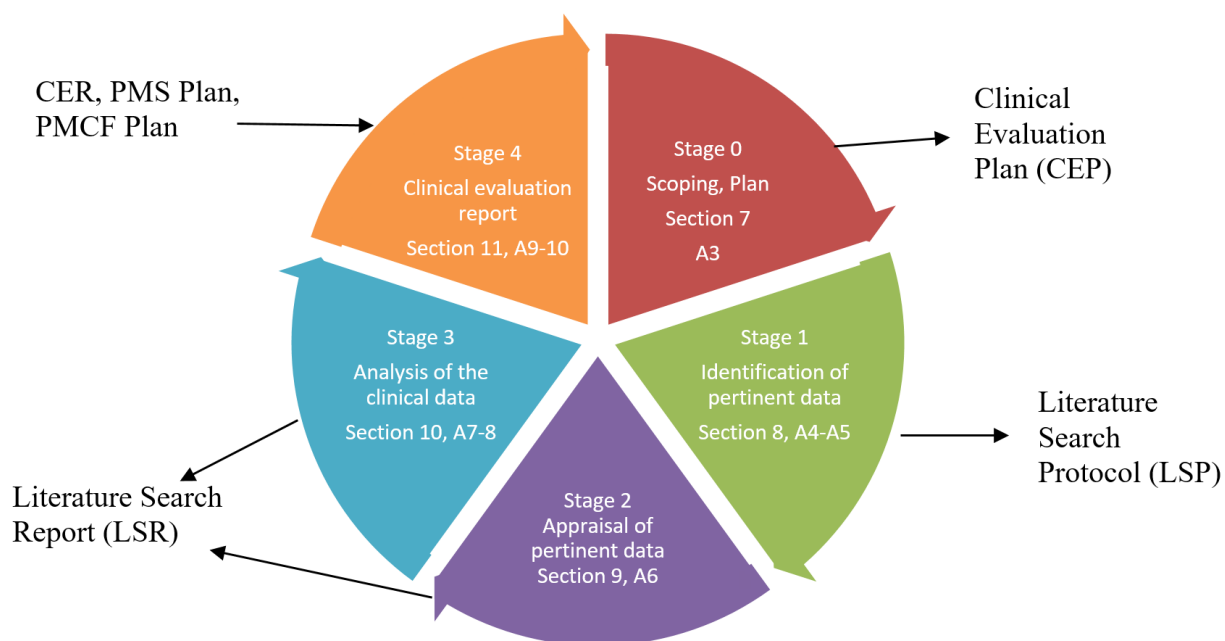
A “notified body is an organization that assesses the conformity of medical devices before being placed on the EU market. The notified bodies seem to also have stricter expectations for the clinical evaluations. One manufacturer stated, “these reports are being ripped apart” and others have had to remediate their reports within 30 days or risk losing their Conformité Européenne (CE) mark.

Phases of clinical evaluation

The MEDDEV describes clinical evaluation as consisting of 5 stages. The stages include stage 0, scoping the plan; stage 1, identification of the pertinent data; stage 2, appraisal of the pertinent data; stage 3, analysis of the clinical data; and stage 4 that encompasses the clinical evaluation report, the post-market surveillance plan (PMSP), and the post-market clinical follow up plan (PMCFP) (Figure 1).

Figure 1.

Stages of the clinical evaluation and documentation¹



Also refer to EU/MDR Annex XIV (clinical evaluation and PMCF) and Annex XV and Articles 61-82 (clinical investigations)²

CER = Clinical evaluation report, PMS = Post-market surveillance, PMCF = Post-market clinical follow up

Stage 0: Defining the scope

Stage 0 consists of scoping the clinical evaluation and the plan for each step of the clinical evaluation. This stage of the evaluation and the expectation for a documented clinical evaluation plan (CEP) are new expectations in this revision of the MEDDEV. The need for a CEP is emphasized in Section 7 with details outlined in Appendix 3 of the MEDDEV. The CEP defines the scope of the clinical evaluation and how it will be performed from a clinical perspective and needs to take into consideration the type of device and its history. It should include a general overview of the device (Section 7). The CEP will identify if the CER will rely on equivalence (the test and reference devices are similar to the extent that there would be no clinically significant difference in the safety and clinical performance of the test device) and/or clinical data and the types of clinical data that will be presented (ie, bench-top testing,

clinical studies, or literature). Additionally, the CEP will list the sources that will be referenced such as risk assessments, instructions for use (IFUs), and literature and post-market surveillance (PMS) databases. The CEP does not have a timeframe for mandatory updates but should be updated as needed when there are changes to the device, current knowledge/the state-of-the-art, applicable standards/guidance documents, new information relating to the medical condition managed with the device, or new medical alternatives.

The CEP is an overview of the devices including the description, design features, indications, intended purpose, warnings, potential complications, and target population. The manufacturer should also state any claims on clinical performance and clinical safety of the device. This section gives an overview of current regulatory approvals as well as any changes since the last report.

Stage 1: Identification of the pertinent data

The data to be reviewed as part of the clinical evaluation will be identified and gathered in stage 1. Clinical data should include preclinical studies, clinical studies, and clinical literature. Clinical literature needs to be identified in a systematic way and clearly described in a literature search protocol (LSP). The MEDDEV states an LSP should clearly define the methodology and sound strategy for the search and provide examples of methods including PICO (patient characteristics, type of intervention, control, and outcome queries), PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), and MOOSE (meta-analysis of observational studies in epidemiology). The LSP should include the search methodology, sources of the literature, database search strategy, extent of any internet searches, search terms and limits, timeframe for the search, inclusion/exclusion criteria, and appraisal plan. The search for data may also include scientific databases, internet searches, non-published data, and citations referenced in the scientific literature. Appendix 4 of the MEDDEV states MEDLINE or PubMed are a good place to start. But to ensure adequate coverage of devices and therapies in use in Europe, consider using Embase, Excerpta Medica, and the Cochrane CENTRAL trials register.

Post-market performance data should also be identified and include manufacturer complaint and recall data, information from the Manufacturer and User Facility Device Experience (MAUDE) data (US), Bundesamt für Arzneimittel und Medizinprodukte/Federal Institute for Drugs and Medical Devices (BfArM) (Germany), Healthy Canadians (Canada), Swiss Medic (Switzerland), and any other pertinent databases including Eudamed (when it is available). For new devices, all data should be included. For updates to existing devices, coordination with the notified body and enough data should be included to show trends in the post market data. Identification of the data needs to be thorough, reproducible, and should justify inclusion and exclusion.

Stage 2: Appraisal of the pertinent data

Once data is identified, it needs to be appraised for inclusion or exclusion based on its contribution to the evaluation of the device's safety and performance. The appraisal process should include a review of the information in each of the identified documents for its quality, validity, and relevance. Next, it should be weighed for contribution to the clinical evaluation using a systematic approach (Figure 2). The appraisal process should be transparent and ensure that all high-quality data, favorable or unfavorable, are included.

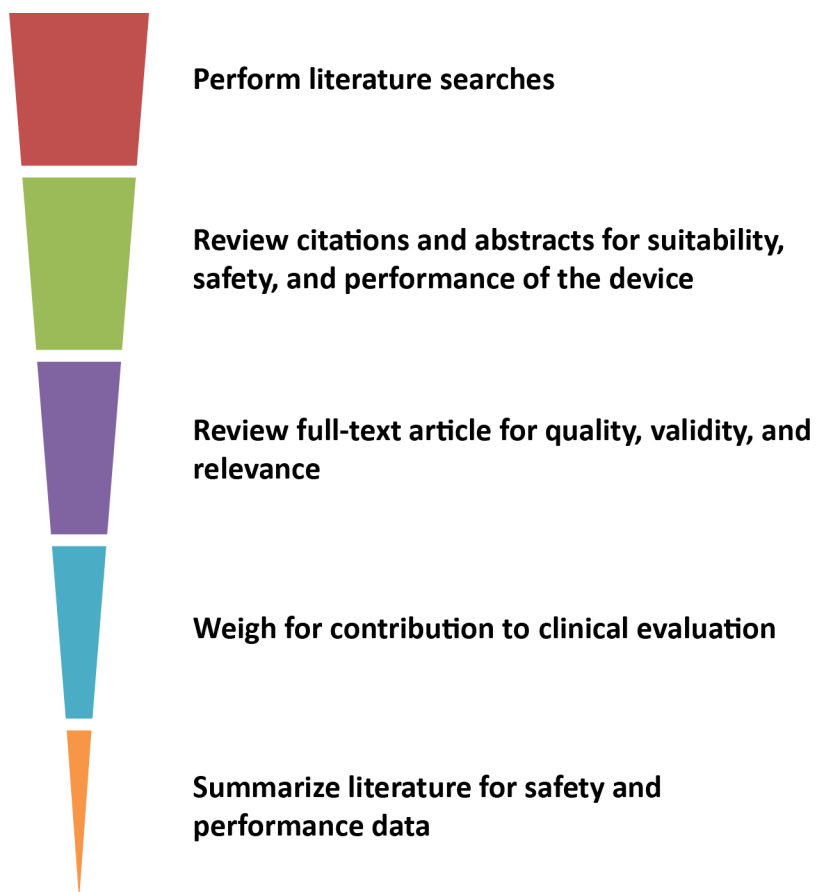


Figure 2.
Systematic review of the literature

Include an appraisal plan to ensure an unbiased appraisal of the clinical data. The appraisal plan should include methodologically sound selection criteria. Appendix 6 of the MEDDEV provides examples of studies that lack scientific validity for demonstration of adequate clinical performance and/or clinical safety. Exclusion examples include publications that omit methods, products used, number of patients, clinical outcomes, and confidence intervals or statistical significance. Inclusion criteria may depend on the amount of data returned. For example, some devices may have hundreds of meta-analysis and randomized clinical trial data, whereas others have only single-center observational studies.



Stage 3: Analysis of the data

In this stage of the clinical evaluation, the data is appraised to evaluate compliance with the essential requirements (ERs) 1, 3, and 6 under the medical device directive (MDD) or general safety and performance requirements 1, 5, and 8 under the MDR (Table 1). The data should demonstrate that there is sufficient clinical evidence to meet the ERs or the general safety and performance requirements (GSPRs).

Table 1.

Medical Device Directive Essential Requirements and MDR General Safety and Performance Requirements³

Essential requirement	General safety and performance requirement
ER 1	GSPR 1 and 5
ER 3	GSPR 1
ER 6	GSPR 8

ER= Essential Requirement, GSPR=General safety and performance requirement

With each of the ERs and GSPRs, the clinical data needs to be analyzed to assess that it demonstrates the device is designed and manufactured such that patients' and users' safety is not compromised and that it accounts for the acknowledged "state-of-the-art" (products that are developed and approved for sale in the marketplace). The data should be reviewed with the risk management documents to ensure all identified hazards have been fully covered by the relevant standards, and any gaps are covered by clinical data. The manufacturer also needs to correctly identify the medical conditions and target groups that the device will treat and demonstrate through sufficient clinical evidence of the benefits to patients. In addition, the data should demonstrate an acceptable benefit/risk profile related to the intended purpose and that the risks are minimized and acceptable when weighed against the benefits to patients.

Post-market clinical follow up needs should be determined based on any residual risks and any uncertainties or unanswered questions.

Stage 4: The clinical evaluation report

Stage 4 is the culmination of the clinical evaluation where each phase is documented, and conclusions are made regarding the device's safety and performance.

In Appendix 9 of the MEDDEV, a sample table of contents is given and should be referenced for additional details. A brief outline of the table of contents is presented below.

1. Summary: This is a general overview of the report and should specify which guidance is being conformed to (ie, MDD or MDR), a determination of benefit/risk profile, intended target groups, medical indications for the device, and acceptability of the device profile based on the state-of-the-art in the medical field.
2. Scope of the clinical evaluation: The manufacturer should identify the products, accessories, software, name/address of the manufacturer, the physical and chemical characteristics of the device, and provide an image. Include additional information from the IFU such as indications, warnings, and complications here.
3. Clinical background, current knowledge, and state-of-the-art: This section should contain its own literature search with the methodology for how the information was retrieved, sources used, and appraisal criteria. The state-of-the-art section is essential in

establishing justification for the device in its intended market. In this section, describe similar and competitor's devices, as well as their risks and benefits. Also, include the following information:

- Description of the medical condition, natural course of the disease, and the population it is intended to be used with
- Alternatives to the device including non-treatment
- Risks and benefits of the device and the alternative devices
- Users of the device (ie, patients, nurses, physicians)
- Any unmet medical needs

4. Device under evaluation

4.1 Type of evaluation: State if the evaluation is based on scientific literature and/or clinical investigations or demonstration of conformity.

4.2 Demonstration of equivalence: Claiming equivalence is a difficult task for the manufacturer. They must have access to the technical file for the equivalent device, use that equivalent device, and demonstrate the following:

EU Substantial Equivalence ⁴
Clinical
Clinical condition - same
Medical indication - same
Intended purpose - same
Body site - same
Population - similar
Performance- similar
Technical
Similar design (per MDR)
Similar conditions of use
Device specifications - physiochemical properties - similar
Biological
Materials - same
Contact with human tissue or body fluids - same

4.2 (continued) Finally, conclusions whether equivalence is demonstrated or not should be included. If it is demonstrated, confirm that the differences are not expected to affect the clinical performance and safety of the device under evaluation (Appendix 9).

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- 4.3 Preclinical and clinical trial data generated and held by the manufacturer
 - 4.4 Clinical data from the literature, specific to the device or equivalent device
 - 4.5 The literature for inclusion or exclusion should be summarized and appraised.
 - 4.6 Analysis of the clinical data: The data to substantiate the ERs and GSPRs are met by including the following:
 - 4.6.1 Requirement on safety: See Section 10 and Appendix 7.1. This section presents any safety concerns and whether they have been adequately addressed.
 - 4.6.2 Requirement on acceptable benefit/risk profile: See Section 10 and Appendix 7.2. This is a summary of the benefits and risks of the device, including the incidence rates from the PMS data and comparison to the risk documents.
 - 4.6.3 Requirement on performance: See Section 10 and Appendix A7.3. Does the device perform as intended and is that described appropriately in the IFU?
 - 4.6.4 Requirement on acceptability of side effects: See Section 10 and Appendix 7.4. Any side undesirable effects related to the device should be identified and evaluated for acceptability, with justification included.
 5. Conclusions: See Section 11. The conclusions of the CER should state compliance to the ER or GSPR, as well as acceptability of the benefit/risk profile according to the current knowledge and state-of-the-art. The manufacturer also needs to list how they will follow up on the report findings in the PMCFP.
 6. Date of the next clinical evaluation and an explanation of how it was determined based on the class of the device and how well established it is. See Section 6.2.3 of the MEDDEV.

Key additional considerations

As you initiate, prepare, and finalize your clinical evaluation, ask these key questions:

- Are your authors and reviewers “qualified” to perform the clinical evaluation?
- Have you included Curriculum Vitae and declarations of interest for each evaluator?
- Have you searched multiple databases and performed a methodologically sound clinical literature search for state-of-the-art and the clinical data?
- Is there “sufficient” clinical evidence to support the conclusions of the report?
- Is conformity to each of the relevant ERs or GSPRs clearly stated and discrepancies identified?
- Do you have a CEP, a PMSP, and a PMCFP?

Summary

In summary, many companies and their staff are struggling with these complex new regulations and all that the clinical evaluation now entails. The clinical evaluation process has expanded from a simple process and report, to a comprehensive justification of your medical device and critical appraisal of its safety and performance. The evaluation must be based on clinical data that may require conduct of a clinical trial or be supported through a systematic literature search. The clinical evaluation including the CEP, CER, literature protocol, and literature report are essential components of the summary technical documentation (STED) and a major hurdle in obtaining and maintaining CE marking. The MEDDEV 2.7/1 Revision 4 Clinical Evaluation: A Guide for Manufacturers and Notified Bodies Under Directives 93/42/EEC and 90/385/EEC **EU Medical Device Regulation (MDR) 2017/745** had a compliance deadline of 26 May 2021. If you have been certified or recertified under the MDD, your focus now needs to shift to compliance with the MDR. Manufacturers with EC certificates issued prior to 25 May 2017 will remain valid until they expire or until 27 May 2024, whichever comes first.

If you need assistance with understanding the regulations, performing your literature searches, or writing your CEP or CERs, contact us at <https://www.certara.com/regulatory-science/regulatory-consulting-regulatory-affairs/>.

References

1. Commission E. Guidelines on Medical devices. MEDDEV 2.7/1 Revision 4. DG internal Market, Industry, Entrepreneurship and SMEs: Health technology and Cosmetics; 2016.
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3. Macomber LS, A.; . General Safety and Performance Requirements (Annex I) in the New Medical Device Regulation. 2018. Accessed March 2020.
4. Group MDC. MDCG 2020-5 Guidance on Clinical Evaluation-Equivalence A guide for manufacturers and notified bodies. 2020.

About the Author



Angela Siebeneck, MSN, RN, Director of Regulatory Strategy and Policy for Medical Devices at Synchrogenix, a Certara company, has more than 30 years of clinical and medical device experience. She provides global medical device regulatory strategy, consulting, medical writing, and submission support from development to post-marketing follow up.

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