Clinical evaluation reports:
6 years after the introduction of MEDDEV 2.7/1 revision 4

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Abstract
MEDDEV 2.7/1 is the European guideline about the clinical evaluation of medical devices. The 4th revision, in 2016, updated how clinical evaluation should be conducted and reported, thus paving the way for clinical evaluation under the Medical Device Regulation (MDR) 2017/745. Transitioning directly from MEDDEV 2.7/1 revision 3 to the MDR would have been a huge leap; revision 4 has provided a stepping stone along the way to the MDR. This article considers how clinical evaluation and clinical evaluation reports (CERs) have evolved since 2016 and why MEDDEV 2.7/1 revision 4 is still in use today.

MEDDEV 2.7/1 is the European guideline about the clinical evaluation of medical devices. The 4th revision, in 2016, updated how clinical evaluation should be conducted and the main changes are described in this article. The implementation of the Medical Device Regulation (MDR) 2017/745 has brought further changes in how clinical evaluation is conducted and these are also described.

MEDDEV 2.7/1 Rev. 4 (2016)

The European guideline MEDDEV 2.7/1 rev. 4, introduced in 2016,[1] updated the clinical evaluation process for medical devices. This revision confirms that clinical evaluation is a planned, continuous, and iterative process throughout the life cycle of a medical device. Guidance is provided on how to conduct clinical evaluation, including how to identify, appraise, and analyse clinical data; demonstrate equivalence to other medical devices; conduct literature reviews; and structure a clinical evaluation report (CER).

The main changes however, between revisions 3 and 4 of the MEDDEV 2.7/1 guideline, are the introduction of the clinical evaluation plan (CEP), expanding the current knowledge and determining the state of the art, and providing more detailed methods for conducting literature reviews (LRs). In practice, revision 4 made it more difficult to claim equivalence to other marketed medical devices (also known as predicate devices), as it put more emphasis on the need for clinical investigations, which aligns with the MDR 2017/745 requirements. These changes are discussed in more detail below.

Clinical evaluation plan: Before MEDDEV 2.7/1 rev. 4 was introduced, clinical evaluation comprised three stages, namely, the identification, appraisal, and analysis of clinical data.[2] Revision 4 introduced an additional stage, Stage 0, that defined the scope and planning of the clinical evaluation. Before revision 4, CERs were produced when required and summarised the clinical evidence available up to that point in time. Therefore, the introduction of the CEP was a significant change in the clinical evaluation process.

The CEP sets out the scope of the clinical evaluation based on the Essential Requirements that need to be met. Note that Essential Requirements have been superseded by General Safety and Performance Requirements in the MDR. In the same way that a protocol or clinical

Box 1. Changes to clinical evaluation introduced by MEDDEV 2.7/1 revision 4:

- Introduction of the clinical evaluation plan;
- Expanded current knowledge section and determination of the state of the art in the CER;
- Objective literature review methodology;
- More difficulty claiming equivalence to other medical devices; and
- Increased emphasis on clinical investigations.

investigation plan describes how a clinical trial or investigation will be conducted, the CEP sets out how a clinical evaluation will be performed. It describes the medical device being evaluated, including its indication, intended purpose, contraindications, warnings, and any design changes; information on equivalence to other medical devices (if claimed); the current knowledge and state of the art; sources and types of clinical data, including newly generated data to be used in the evaluation; and post-market surveillance (PMS) activities, including post-market clinical follow-up (PMCF). The CEP is used to determine what data are available; if there are any gaps in the data – and if so, how and when these gaps will be filled; and whether the data are suitable for evaluation. The CEP is reviewed and updated regularly, and in particular, before generating a CER. The CEP evolves as the medical device progresses through its life cycle and remains in use even after the initial conformity assessment and CE-marking. (See section 7 of the MEDDEV 2.7/1 rev. 4 for more guidance on scoping of the clinical evaluation and CEP content.)

In practice, revision 4 made it more difficult to claim equivalence to other marketed medical devices (also known as predicate devices), as it laid more emphasis on the need for clinical investigations, which aligns with the MDR 2017/745 requirements.

Current knowledge and state of the art: What disease is the medical device intended to treat? How is this condition currently treated? For example, are there other medical devices, surgical, pharmaceutical, or non-medical treatments in use? Which treatments are suitable for which patients? Are there any problems or unmet clinical needs with currently available treatments? What treatments are in development? All of these questions, and more, should be addressed in the current knowledge section, which is a broad description and assessment of the epidemiology of the disease being treated and its diagnosis and pathology, including disease classification; treatment guidelines; and objectives and endpoints used in clinical investigations. Having reviewed all of this information the current state of the art is determined. The state of the art embodies what is currently and generally accepted as good practice in technology and medicine; it is not necessarily the most technologically advanced solution.[3]

MEDDEV 2.7/1 rev. 4 expanded and placed more importance on the current knowledge part of the clinical evaluation and determination of the state of the art. It plays an essential role in determining the development strategy of a medical device and features prominently in both the CEP and CER. For the medical writer, considerably more time is now required to write the current knowledge and state of the art sections of the CEP and CER.

Literature review: That LRs should be based on an objective research question, conducted systematically, have a literature search protocol, and generate a search report was stated in MEDDEV 2.7/1 rev. 3 and reiterated in rev. 4. Note that the guidelines refer to "the literature review", suggesting that only one LR protocol, search strategy, search report, and LR are required. In practice, because the literature search needs to be tailored to the purpose of the LR more than one literature search is required. Therefore, to identify appropriate literature for the current knowledge and state of the art sections and the device under evaluation or equivalent device (if claiming equivalence), separate protocols, strategies, and search outputs are required. Additional literature searches may also be performed to support PMS activities.

Individual articles about the device under evaluation (or equivalent device) are appraised,

i.e., assessed for their weighted contribution to the evaluation of clinical safety and performance in a methodological and documented way. MEDDEV 2.7/1 rev. 4 does not give any examples of appraisal methods, but it does refer to the widely used Appendix D from the Global Harmonization Task Force (GHTF) clinical evaluation guideline,[4] now Appendix F in the updated International Medical Device Regulators Forum (IMDRF) guideline.[5] Once appraised, articles to be included in the clinical literature about the device under evaluation are presented in a data extraction table, summarised, and analysed. Narratives of individual literature reports disappeared with the introduction of MEDDEV 2.7/1 rev. 4. Instead, an overall critical and objective analysis of the literature is expected, which in turn contributes to the assessment of clinical safety and performance.

Equivalence: Claiming equivalence to another medical device became much more difficult with the introduction of MEDDEV 2.7/1 rev. 4 and the MDR. Not only did the strict criteria for clinical, technical, and biological equivalence have to be fulfilled, but for class III devices in particular, access to the technical file and a contract with the manufacturer of the equivalent device are now also required.

Clinical investigations: There was always a requirement for clinical investigations for class III and implantable medical devices and for devices where gaps in clinical data could not be filled in other ways. As MEDDEV 2.7/1 rev. 4 has made claiming equivalence to other devices increasingly difficult, more clinical data now needs to be generated from clinical investigations.

Medical Device Regulation 2017/745

As a consequence of the pandemic, the transition to the MDR[6] was delayed by a year until May 2021. Thus manufacturers and notified bodies had 5 years from the introduction of MEDDEV 2.7/1 rev. 4 to adapt their practices and prepare for the MDR. In addition to the changes in clinical evaluation already described, the MDR placed more emphasis on risk assessment, especially benefit-risk analysis, and the need to show that the benefits attributed to a medical device were supported by data. It also reaffirmed the need for PMCF.

Risk assessment: Bringing together and analysing all clinical data is what clinical evaluation is

Box 2. Changes to clinical evaluation introduced by MDR 2017/745:

- More extensive risk assessment and benefit-risk analysis;
- Benefits identified and supported by data; and
- Importance of PMCF reaffirmed.

all about. Since the introduction of MEDDEV 2.7/1 rev. 4, this has become a much more extensive task that involves a benefit-risk analysis of the medical device. In the past, the focus was very much on the risks associated with the device, but the introduction of the MDR meant that the benefits of using the device also have to be demonstrated and all claims substantiated.

Although the CER table of contents in Appendix A9 of MEDDEV 2.7/1 rev. 4 is still followed, section 4.6 (Analysis of Clinical Data) often needs to be expanded and adapted to meet the requirements of the MDR.

Post-market clinical follow-up: There has always been a requirement for PMCF;[7,8] this is confirmed by MEDDEV 2.7/1 rev. 4 and reinforced by the MDR. Consequently, much more detail about PMCF studies is now expected in the PMS section of the CER with references to the PMCF plan and report.

Conclusions

It has been 6 years since MEDDEV 2.7/1 rev. 4 was introduced and 1 year since the MDR came into force. Both have affected how clinical evaluation is conducted. Most notably, MEDDEV 2.7/1 rev. 4 introduced the CEP and emphasised that clinical evaluation is a continuous process and not just a report produced at intervals, and it also made equivalence a more difficult route to CE-marking. The MDR has expanded risk assessment, with more focus on the benefits of a medical device and more emphasis placed on PMCF.

For the medical writer, the CER is now closely linked to the CEP, which has a much more extensive current knowledge and state of the art sections; more objective and analytical LR; and more extensive risk assessment, PMS, and PMCF sections. As a result, CERs require more time to write (sometimes twice as much) than was the case with MEDDEV 2.7/1 rev. 3. However, the whole clinical evaluation process is now a much more planned, objective, robust, and comprehensive assessment than it used to be.

The MDR does not give guidance on how to perform clinical evaluation or how to write a CER. Consequently MEDDEV 2.7/1 rev. 4 is still very much in use today.

Disclaimers

The opinions expressed in this article are the author's own and not necessarily shared by EMWA.

Disclosures and conflicts of interest

The author declares no conflicts of interest.

Data availability statement

N/A.

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