Demystifying devices: clinical evaluation reports in the EU

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Abstract
Clinical evaluation of medical devices has been thrust into the headlights following the publication of the EU Medical Device Regulation and MEDDEV 2.7.1 rev 4. The clinical evaluation report is compulsory, so how should companies approach it? This short article aims to point out the steps involved to create a compliant clinical evaluation report.

MEDDEV 2.7/1 Rev 4 published in July 2016 defines a clinical evaluation as: "A methodologically sound ongoing procedure to collect, appraise and analyse data pertaining to a medical device and to evaluate whether there is sufficient clinical evidence to confirm compliance with relevant essential requirements for the safety and performance when using the device according to the manufacturer's Instructions for Use".[1]

The clinical evaluation process involves an assessment and analysis of clinical data pertaining to a medical device to verify its clinical safety and performance. The output of this process is the clinical evaluation report (CER) which is required for all devices and – depending on the risk classification – may be simple or extensive. It is an important element of the CE marking procedure and will be reviewed with the technical file as part of the certification process. It is an objective review and serves to either provide adequate data to support safety and performance claims or to highlight shortfalls that will need to be addressed to achieve or maintain compliance.

The publication of MEDDEV 2.7.1 revision 4[1] raised the status of the CER in the ongoing evaluation of safety and efficacy of a device in anticipation of the considerably more rigorous demands of the Medical Device Regulation[2] (MDR 2017/745). Although new requirements are in fact few, there is detailed guidance on how to carry out a robust and systematic analysis including how a manufacturer may assess the scientific validity of its data and conclusions.

The MEDDEV[1] is very clear that "clinical evaluation is conducted throughout the lifecycle of the medical device, as an ongoing process". Therefore it is preferable for manufacturers to plan the initial CER during the development phase and update it regularly thereafter, based on regulatory requirements, ie, annually for higher risk devices, less frequently for lower risk ones, or on identifying new risks or new competitor technologies via post-market clinical follow-up studies and post-market surveillance (PMS) activities

The data to be evaluated in a CER can come from existing literature, clinical experience, clinical trials, or any combination of these according to the MEDDEV,[1] and should provide proof that the device meets its performance claims without exposing users and patients to unnecessary risks. In practice the CER is a living document, providing a summary and analysis of data from different sources and in turn providing input for further clinical evaluation and design improvement as shown in Figure 1.

So where does one begin when developing a CER?

With any project, it is best to start by thinking about what you hope to achieve. In this case you will want to assure the notified bodies (NBs) that you have:

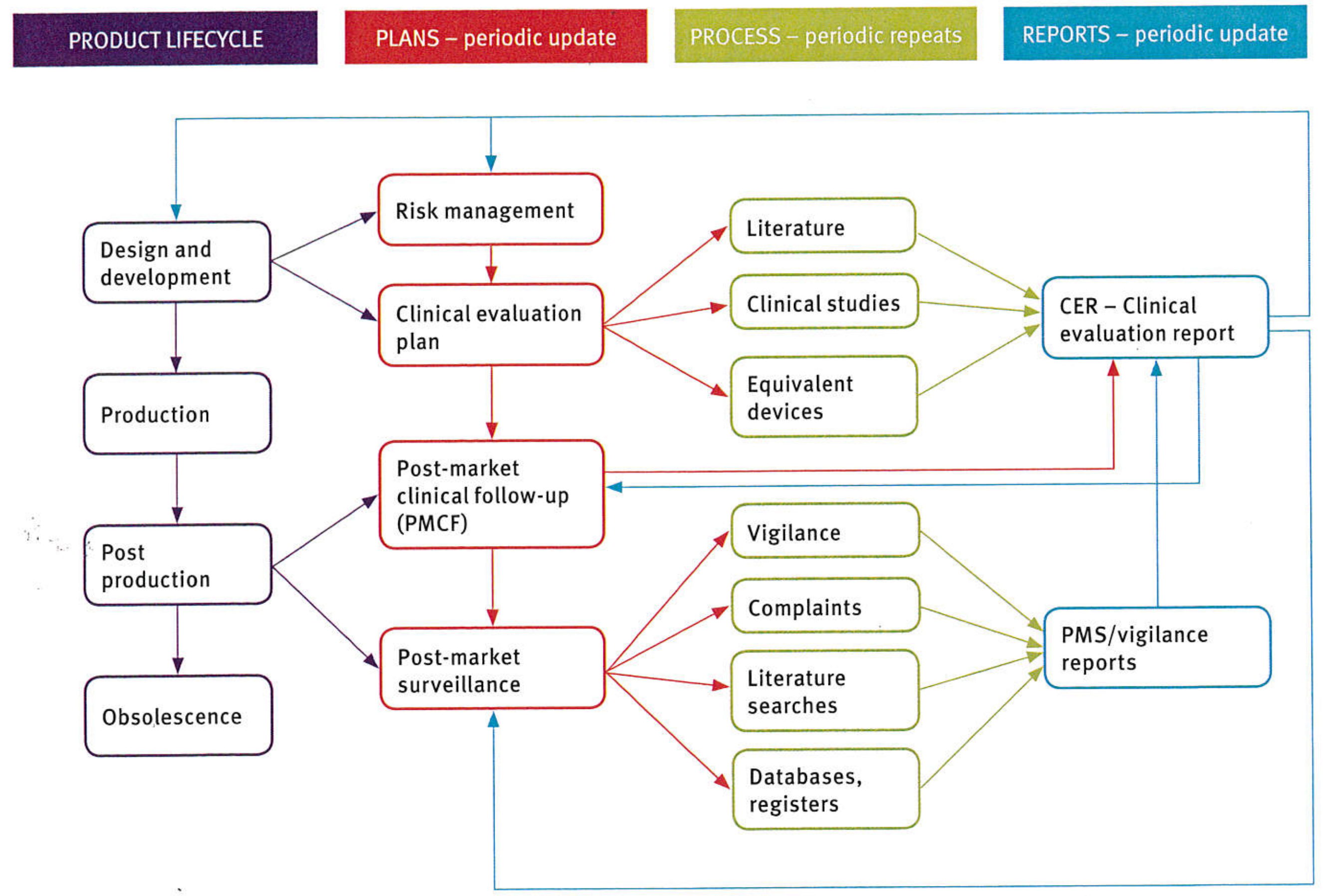
- Established a benchmark against which the clinical benefits and risks of a device may be assessed
- Demonstrated compliance with the relevant Essential Requirements (ERs) in the Medical Device Directive (MDD) or the General Safety and Performance Requirements (GSPRs) in the MDR
- Shown that the device achieves its intended performance under normal conditions of use
- Minimised, as far as possible, all foreseeable risks and adverse events from using the device and that the overall patient benefit outweighs any remaining risk
- Provided data to support any claims made about the performance and safety of the device – for example, in the labelling or instructions for use (IFU).

Once the outputs have been identified, it is necessary to consider the process for CER development. It consists of the following five basic steps, which are described more fully in the MEDDEV:

1. Stage 0 – Scoping: Defining the scope and planning how the clinical evaluation will be conducted. It is here that one should identify relevant ERs (GSPRs in MDR) requiring support with clinical data and any areas of potential concern such as vulnerable patient groups or drug-device combination products, etc.
2. Stage 1 – Identification of pertinent data: This part has a dual purpose, firstly to research the current state-of-the-art regarding the clinical management of the medical conditions for which the device is indicated and secondly to identify clinical data that is relevant to the device itself.

   The state-of-the-art review is the benchmark against which the device under evaluation is assessed. This will serve to identify any new technologies that may potentially make older devices

Figure 1: Relationship between the CER, product lifecycle and continuous data collection.



obsolete or provide pointers for design upgrades. This is usually based on published literature and guidelines from professional bodies.

Data specific to the device can be generated by the manufacturer or retrieved from the literature. In practice, it is becoming increasingly difficult to justify a purely literature-based approach without clinical data due to the stricter criteria required to establish substantial equivalence with other devices. (For this reason, it is wise to identify any requirements for clinical studies as soon as possible in order to be ready for the transition to MDR.)

The manufacturers' data may include pre-market clinical investigations and data from risk management activities. For devices already on the market, all available data from post-market clinical follow-up (PMCF), data from device registries, details of field safety corrective actions, complaints and other PMS) activities must be included. A systematic literature search should identify all clinical data relevant to the device under evaluation and any equivalent devices. Both favourable and unfavourable data must be included; and as per all data searches, a search strategy should be documented in advance.

3 Stage 2 – Appraisal of pertinent data: Each data type must be evaluated appropriately. For the literature searches, a report must be documented, looking at the adequacy of the search and its results. Some data will be more relevant than others and should be weighted to reflect this, ensuring that more emphasis is placed on the most important data for the product.

4 Stage 3 – Analysis of the clinical data: Here one should evaluate all the data from Stages 1/2 in the context of establishing safety and performance and also compliance with the ERs (GSPRs). Any residual risks or uncertainties need to be highlighted and either addressed in premarketing studies or, if low risk and not mitigated at the time of CE marking, consideration should be given to evaluating these in post-marketing studies.

5 Stage 4 – Final stage: Where all available data are collated to reach conclusions on safety and performance. MEDDEV[1] states that: "The clinical evaluation report should contain sufficient information to be read and understood by an independent party (eg, regulatory authority or NB). Therefore, it should provide sufficient detail for understanding the search criteria adopted by the evaluators, the data presented, all assumptions made and all conclusions reached." It is important to clearly explain what has been done by documenting details of each stage of the evaluation within the report itself.

While seemingly straightforward, various nuances must be considered at every step of the way. At the outset, the scope of the clinical evaluation must be planned. To do this effectively, full details of the device – its use, history, problems encountered, etc – must be collected. Next, the manufacturer needs to identify existing data (from literature, bench experiments, clinical studies), relevant ERs (GSPRs) and all pertinent standards. Then an appraisal needs to be conducted of each individual data set for relevance, applicability, quality and clinical significance. Finally, an analysis of individual data sets needs to be undertaken to arrive at performance conclusions, safety conclusions, labelling, and patient information. Once the CER is written, you may find that certain questions posed in the scope remain unanswered, requiring the generation of additional data from a clinical investigation, which will then lead to a revision of the CER following the steps already undertaken.

A suitably qualified individual or team should be identified to write the CER. You must justify your choice of evaluator with respect to their qualifications and/or experience, for example, a relevant degree plus five years of experience or ideally ten years of experience. However, in general evaluators should have knowledge of:

- The device technology and application
- Research methodology (ie, investigation design, biostatistics)
- Diagnosis and management of the conditions intended to be treated.

This demanding list of attributes can often be best met by creating a team of individuals who have these skills between them. A well-qualified regulatory affairs consultant could be a good addition and may be able to augment the manufacturer's deep knowledge of their technology with the search engines, commercial information, clinicians, biostatisticians, medical writers and regulatory affairs professionals needed to develop the most complete and robust CER possible.

The data to be evaluated in a CER can come from existing literature, clinical experience, clinical trials, or any combination of these according to the MEDDEV, and should provide proof that the device meets its performance claims without exposing users and patients to unnecessary risks

And finally, what does the NB do with your CER? They have a role in the assessment and verification of the reports, both methodology and conclusions, to ensure manufacturers are indeed complying with the ERs or GSPRs or where this is not possible or appropriate, to assess the reasons why and ensure this is borne out by the risk analysis that has been completed. ■

References

1. MEDDEV 2.7/1 Rev 4, September 2016.
2. Medical Device Regulation 2017/745, May 2017.