

Get the writing right

Gerry McGregor, a principal medical writer at **Trilogy Writing & Consulting**, explains how experienced medical writers can help medical device manufacturers meet the new regulatory demands of producing clinical evaluation reports.

In Europe, a clinical evaluation report (CER) is now a key element in assessing the fitness of a medical device for clinical use. It documents the clinical evidence that supports a medical device licensing application. After a successful application, it is regularly updated to enable the medical device to remain on the market. The updated CER contains a reassessment of the device's safety and clinical performance, using evidence actively acquired by the manufacturer during the post-marketing clinical follow-up (PMCF).

For device manufacturers, and indeed for the regulatory assessors (notified bodies), the CER has always been a particular challenge. Prior to 1993, documentation of a medical device's clinical efficacy and safety was given much less attention than the documentation of its manufacture and quality. Since the release, in 1993, of the EU Directive 93/42/EEC, the importance of clinical evidence in the licensing of medical devices has increased as the directive went through subsequent amendments and the MEDDEV series of EU guidelines were released.

Now, there is the EU Medical Device Regulations (MDR), released last year, with its increased requirements on clinical evidence acquisition and documentation. The challenge for manufacturers and assessors is now greater than before.

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A thorough understanding

The clinical evidence acquisition and documentation requirements of the EU MDR are essentially derived from the EU guideline, MedDev 2.7/1 revision 4 (EU-2016), released in 2016, which provided much needed guidance on the process of clinical evaluation and on the content of the CER. Appendix A9 of the guideline provides details on the content and format of the CER, which had been missing in previous versions.

However, much of what is prescribed concerning CER content is very familiar to medical writers experienced in writing submission documents for medicinal drugs. The processes described in the 2016 guideline are rooted in the principles of evidence-based medicine, which are being applied on a daily basis by medical writers who

create regulatory submission documents for medicinal drugs, such as the clinical overview of the ICH-CTD.

Similar to the clinical overview, the CER contains an evidence-based assessment of efficacy and safety, and a benefit-risk analysis. It also contains a state-of-the-art review of the clinical setting in which the device is to be used. It succinctly reviews current knowledge of the targeted medical condition, with reference to relevant guidelines or international standards, current treatments and precisely what existing clinical needs would be met – or, in the case of a licence renewal, are being met – by the medical device under review.

Source documents include the most recent systematic reviews, current clinical guidelines and relevant international standards, and, possibly, solicited clinical expert statements.

For licensing, the safety and clinical performance of a medical device must conform to specific 'Essential Requirements', as discussed in Appendix A7 of the 2016 EU guideline. It identifies four aspects of a medical device's safety and clinical performance that are to be evaluated and then reported in the CER:

- **Conformity assessment with requirement on safety:** the CER indicates how the instructions for use (IFU) are consistent with the clinical evidence, including that they correctly identify all hazards associated with the use of the device. Reference is made to international standards relating to the use of the device. Medical device standards are listed on the European Commission website but other international standards may also be relevant.
- **Conformity assessment with requirement on acceptability of undesirable side effects:** the guideline states that “any undesirable side effect must constitute an acceptable risk when weighed against the performances intended”. This is addressed in the CER with a comparison of the risk associated with the alternative treatment options currently available for the target patient population.
- **Conformity assessment with requirement on performance:** the CER presents the clinical evidence of how the medical device achieves the intended clinical aims. The evidence of clinical efficacy needs to be presented and critically reviewed.
- **Conformity assessment with requirement on acceptable benefit to risk profile:** the CER presents the benefit-risk relationship of the device. >>



The daunting task of preparing a CER that meets all current regulations can be made much easier with the help of experienced medical regulatory writers.

The guideline states that the “depth and extent of clinical evaluations should be flexible and appropriate to the nature, intended purpose and risks of the device in question”. The depth and extent of the clinical evaluation is largely, though not exclusively, governed by the medical device class.

Other factors are also relevant, such as whether another identical or similar device is already on the market and in clinical use, which reduces the level of risk of introducing the new device and, consequently, reduces the required degree of clinical evaluation.

Keeping up to date

During the PMCF, all four aspects of the medical device's safety and clinical performance are reassessed and the results are incorporated into the CER. This includes an updated systematic review of the published literature, including any new clinical guidelines and standards. For some devices, the manufacturers must also initiate clinical investigations.

In the CER, the new data is assessed in regard to whether it affects the IFU or impacts on how well the device meets the relevant requirements. Submission of an updated CER is required annually for high-risk or relatively new devices and less frequently for others, with the frequency of updating decided in discussions with the notified body.

Required content varies

The CER is a major part of the clinical evaluation and, in many cases, the sole component. Here are three different possible scenarios that would determine the CER content:

- **For new innovative Class III medical devices, the clinical evaluation is a prospective series of clinical tests of the device:** the CER is usually compiled when the manufacturer decides that the

device is ready for the market and that a licensing application is to be made. Therefore, the CER is the last stage of a long process of clinical evaluation. In this case, the author of the CER is a member of a team, working with the clinical developers, statisticians, medical advisers and possibly others.

- **The clinical evaluation process is quite different for a medical device that is similar or even identical to another product that is already on the market:** such devices include commonly used devices in Class I, IIa or IIb, and require no prior clinical testing of the device itself. The clinical evaluation of such devices solely depends on an up-to-date, systematic review of the literature that is represented by the CER. In such cases, the author of the CER is likely to be solely responsible for the literature review and, thus, effectively performs the clinical evaluation.
- **There are devices across all classes that are similar to devices already on the market but require some degree of clinical testing:** for example, a device incorporating an innovative, partial improvement of an existing, licensed device. Here, the CER reviews the proprietary clinical data and presents an up-to-date systematic literature review. The author will liaise with clinical investigators and others but is likely to be solely responsible for the larger part of the CER – the literature review. This will need to be more extensive and detailed than that required for commonly used devices, because an evidence-based argument needs to be crafted to explain how the new device provides a significant clinical improvement in the treatment of the target patient population.

The CER author needs to be aware of the assessors' expectations when deciding the scope of the CER. Ideally, the CER author should have direct contact with the notified body but, if not, will need information from the manufacturer on any prior discussions with the designated CER reviewer.

It is particularly important to clarify the extent of the systematic literature review. The guideline refers in detail to the procedures and guidelines for conducting a ‘thorough’ systematic literature search. But it is crucial to define what constitutes ‘all relevant data’, as this determines the focus and extent of the literature search. A thorough literature search is often not warranted and an abbreviated search – for example, using PubMed and Google scholar – may be sufficient, but a justification must be given in the CER.

Preparing a CER that meets the current regulations may appear daunting to medical device manufacturers, but help is available from experienced medical regulatory writers that have the skills to get it right. ■

Further information
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