

The Clinical Evaluation Report: Bringing it Together

In light of recent regulations, it is important to discuss the general aspects and strategies for writing and compiling a CER

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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 and, 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 in the field, using evidence actively acquired by the manufacturer during the post-marketing clinical follow-up.

The CER has proven a challenge to medical device manufacturers and the regulators (the notified bodies [NBs]) alike. 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

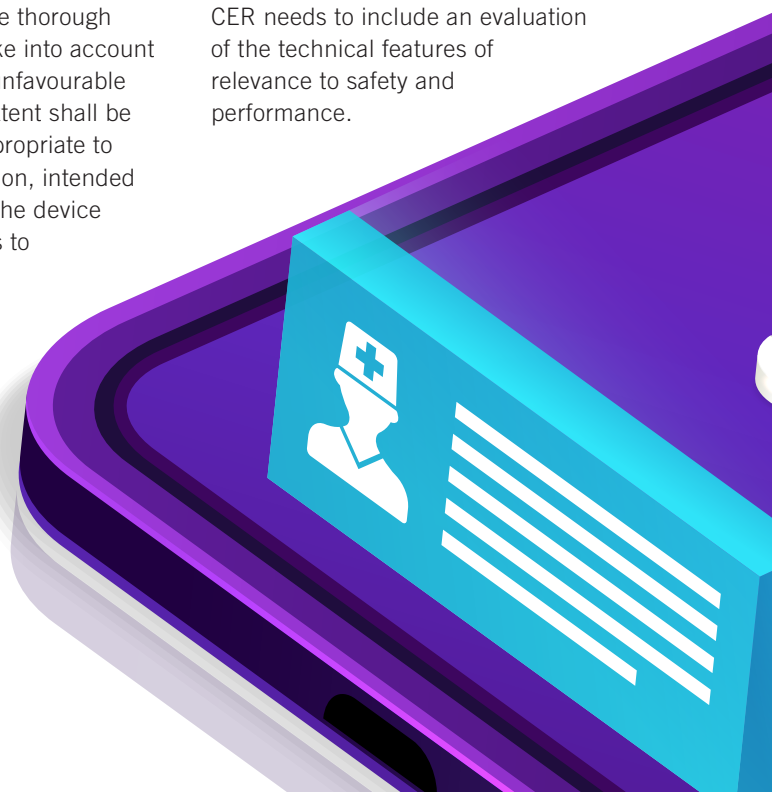
Medical Device Regulations (MDR), released in 2017, with its increased requirements for clinical evidence acquisition and documentation. The challenge for manufacturers is now greater than before.

Structure and Content of the CER

The CER describes the clinical evaluation of the medical device and, according to Annex II, Part A of the Medical Device Regulations 2017 (MDR), “shall be thorough and objective, and take into account both favourable and unfavourable data. Its depth and extent shall be proportionate and appropriate to the nature, classification, intended purpose and risks of the device in question, as well as to the manufacturer's claims in respect of the device”.

Therefore, the CER contains an analysis of the clinical data concerning the safety and

performance of the medical device, and of any other equivalent or similar device when ‘equivalence’ is claimed to another device already on the market or when the device under evaluation is a modification of an already licensed device. All relevant published and proprietary clinical data are to be reviewed in the CER. Depending on the type of device, its clinical safety and performance may critically depend on the technical features of the device. Therefore, the CER needs to include an evaluation of the technical features of relevance to safety and performance.



'Usability' is a technical aspect that is critical to the clinical utility of many devices. For example, the usability of pre-filled self-injection devices can determine dosing accuracy or patient compliance. For such devices, human factor studies are required that test the 'usability' of a device for the specific user, and the results of such studies need to be reviewed in the CER.

The CER must also include a review of the 'state of the art' (SOTA) of the relevant clinical field, including a general assessment of the expected or proven clinical utility of the device, such as in terms of the unmet clinical need to be met or being met by the device.

The CER is a mandatory requirement for all medical device licence applications in Europe. It is a stand-alone document and is submitted as an attachment to the technical file.

The EU MEDDEV Guideline 2.7/1 rev 4 (2016) remains the currently accepted guidance on the requirements that are to be met in the clinical evaluation of medical devices. It includes, in Section 11, guidance on the structure and content of the CER. It proposes a table of contents for the CER in Appendix IX, which has become the accepted, if not mandatory, CER structure, as viewed by the NBS.

A detailed description of the procedures required for a proper clinical evaluation of a medical device are provided in sections 7-11 of the guideline under the following headings:

- Section 7: definition of the scope of the clinical evaluation (stage 0)
- Section 8: identification of pertinent data (stage 1)
- Section 8.1: data generated & held by the manufacturer
- Section 8.2: data retrieved from literature
- Section 9: appraisal of pertinent data (stage 2)
- Section 10: analysis of the clinical data (stage 3)
- Section 11: the clinical evaluation report (CER, stage 4)



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Thus, according to the guideline, the writing of a CER is considered the final stage of the clinical evaluation process. However, the author of the CER needs to become familiar with all of the above listed sections of the guideline, because the CER needs to report on stages 0-3 of the clinical evaluation, and the reviewer at the NB will be looking for these aspects in the CER. In addition to considering these general aspects, the author needs to be aware of the specific issues and features of the device and its use that are likely to be of special interest to the reviewers at the NB. These need to be signposted within the document. It is easiest to signpost in the section of the CER on the scope of the clinical evaluation (stage 0 in the guideline), by cross-referencing to the sections that report on stages 1-3 of the guideline.

As a result of the 'sea change' in the European medical device sector caused by the introduction of the MDR in 2017, medical device licence applications are now being reviewed by the NBs 'to the letter' of the MDR, and in regard to the clinical evaluation, 'to the letter' of the MEDDEV 2.7/1 rev 4 guideline. So it is now important, more than ever, to directly reference within the CER the relevant sections of regulations, guidelines, and standards, quoting the exact wording of key points.

Equivalence, if claimed, is a key issue to be addressed in the CER. Most devices already on the market and seeking relicensing claim equivalence to other devices that are similar or identical, and which are supported by published data. For such devices, the CER needs to review the evidence and provide the argument to justify the claimed equivalence. The MDR (2017) includes a more detailed discussion of equivalence than the previous EU MEDDEV Guideline 2.7/1 rev 4 (2016). It also places an emphasis on the need to highlight and discuss what differences exist between the device under review and the claimed equivalent device. It is recommended

to include in the CER a table listing the differences in the technical, biological, and clinical characteristics of the two devices – indicating whether or not these differences impact on the safety and performance of the device, with a rationale for any claimed lack of impact.

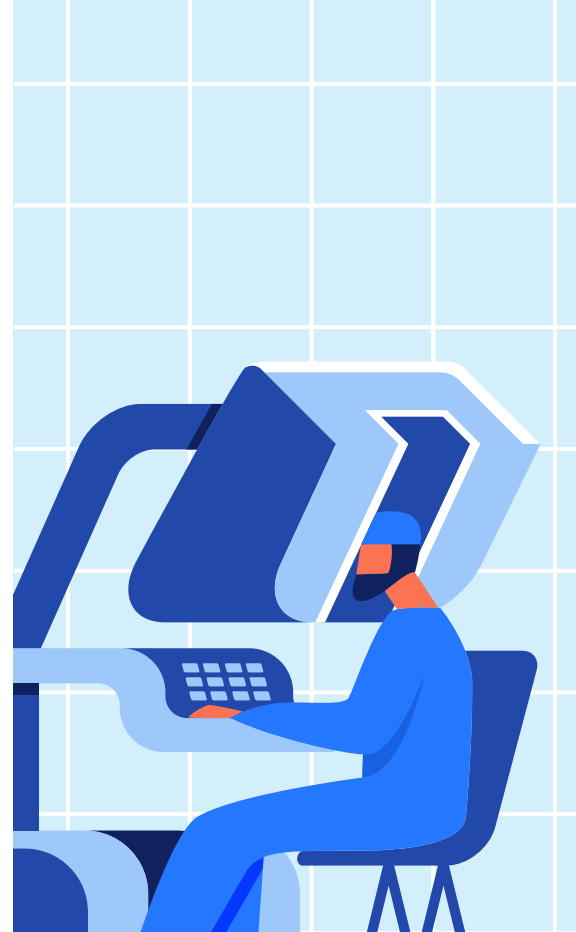
Writing and Compiling the CER

As the CER is a living document, it should ideally be brought to life at the beginning of the clinical evaluation process and compiled and updated throughout this process and the post-marketing period. However, very often, the CER is written after the device is considered by the manufacturer to be ready for the market.

For innovative medical devices, the CER is often written and compiled by the writer working with the team from the manufacturer that developed and tested the device. Such teams usually include specialists with experience in identifying, evaluating, and collating clinical data. However, especially for devices already on the market, the CER author is often solely responsible for writing and compiling the CER. This is because many manufacturers lack experience in identifying, evaluating, and collating clinical data.

The content of the CER is heterogeneous, containing preclinical, clinical, and technical data, and strategies are needed for document compilation and internal review. As the currently accepted format of the CER lacks a modular format, such as that of the common technical document used in drug licence applications, it is usual for it to be reviewed as a single document. However, it is advisable to send critical sections of the CER separately to the relevant specialists at the manufacturer for review prior to completion of the first draft.

According to Annex IX of the MDR, the manufacturer should submit, as part of their documentation of the quality management system,



a clinical evaluation plan for review by the NB. This plan outlines the procedures used in the clinical evaluation of the device and can be a very useful source for the CER author. The strategy outlined in the clinical evaluation plan should present the device-specific issues that are key to determining the safety and performance of the device. It should also include the scientific rationale for the design and mechanism of action of the device, taking into account the SOTA. For some devices, particularly those already on the market, a clinical evaluation plan may not exist. However, preparing a *post hoc* plan prior to writing and compiling the CER can be a useful strategy for focusing the specialists on what issues and arguments need to be presented and substantiated in the CER.

A key part of the CER is the section containing the claims being made by the manufacturer concerning the performance and safety of the device. These are usually included in the label and will be a special focus of the NB's review of the CER. Therefore, these need to be carefully worded and the author of the CER should assess early on whether they are supported by the non-clinical and clinical data

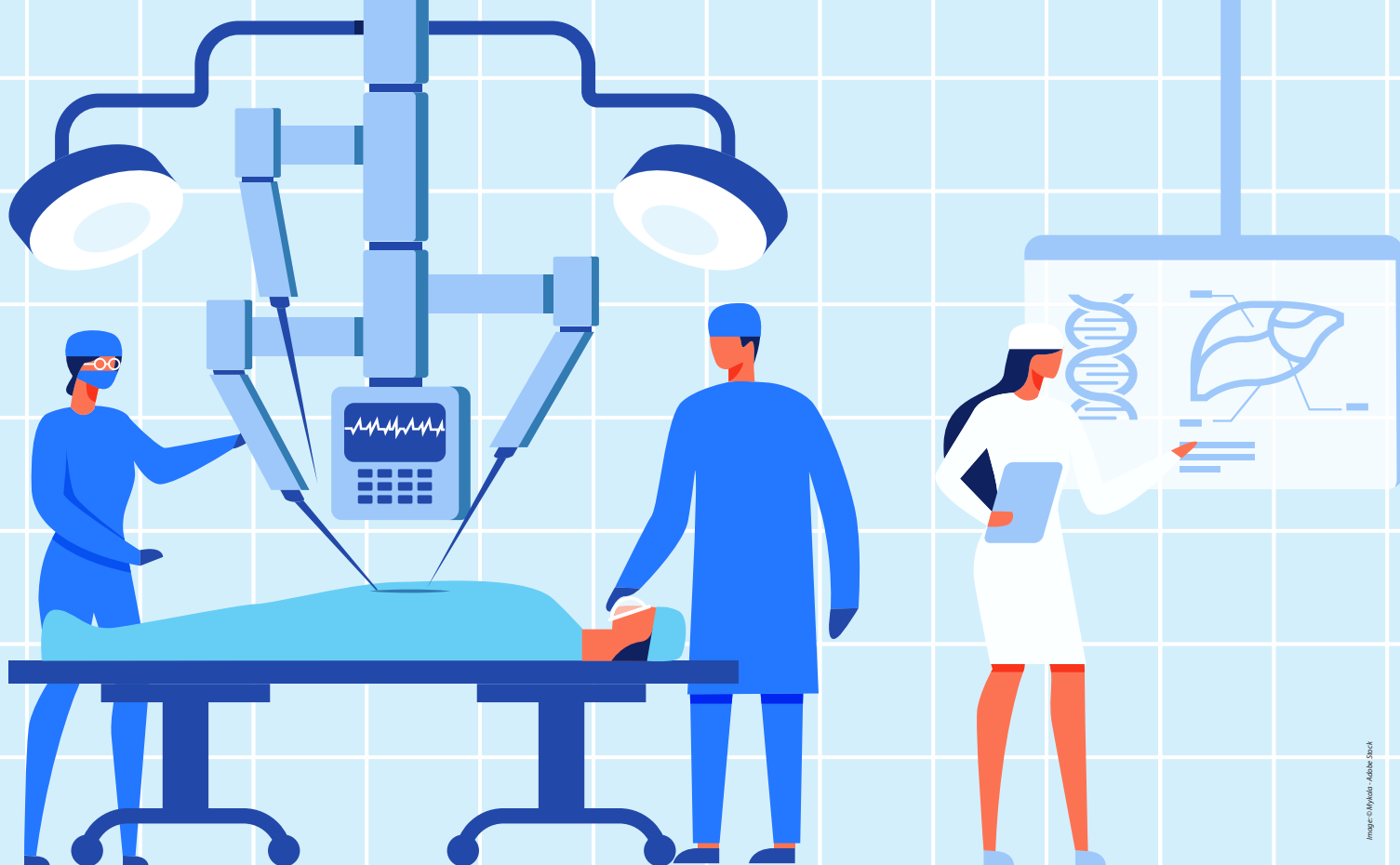


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that are to be presented in the CER. Claims are also often dependent on preclinical data and the results of technical testing, which would also need to be reported in the CER. Early on in the process of compiling the CER, detailed prior discussion with the manufacturer concerning the claims for the safety and performance of the device is necessary. It is wise to start writing the claims section of the CER first and to send this section for an initial review by the manufacturer, including an outline of the supporting evidence. In this way, agreement with the manufacturer can be obtained early on in the process.

Another section that could be sent out for early review by the manufacturer is the SOTA section. This describes the clinical setting in which the device is being or is proposed to be used. This section should succinctly review the current knowledge of the target medical condition. It should reference relevant guidelines, any relevant international standards, and current treatments. It should precisely describe and justify the current clinical need that is being met or would be met by the device. Important source documents for the SOTA review are the most recent

systematic reviews, the current clinical guidelines, any relevant international standards, and perhaps solicited clinical expert statements.

As with any regulatory submission for a medicinal product, writing and compiling a medical device CER requires the author to interact with specialists involved in the clinical and technical development, regulatory development, clinical testing, and marketing of the device. These specialists need to be identified or designated as responsible for reviewing the specific sections relevant to their expertise. This is a first step that allows a granulated approach to the review process prior to completion of a first draft of the CER. It is also important early on to identify what source documents are needed. These can include clinical guidelines and standards, preclinical and clinical reports, the device's instructions for use, any post-marketing surveillance reports, the post-marketing clinical follow-up plan, and relevant technical reports.

The general approach to writing and compiling a CER described here will not be unfamiliar to medical writers experienced in writing and compiling

marketing authorisation applications for medicinal drugs. Therefore, manufacturers lacking experience in identifying, evaluating, and collating clinical data and requiring a CER should look to experienced medical writers for expert help.



Gerry McGregor received his PhD in Human Physiology at Imperial College London in 1984, before taking up a post-doctoral position at the Max Planck Institute of experimental medicine in Göttingen, Germany. During several years in medical research at Marburg University, Germany, Gerry published extensively in scientific journals. In 2000, he joined the pharma industry (Head of Medical Sciences at Pascoe Pharmaceuticals), where he began medical regulatory writing. In 2008, he joined a small CRO in Geneva as Head of Medical Writing. During the last eight years, he has written and compiled several CERs for medical devices. Since May 2017, he has been a Principal Medical Writer at **Trilogy Writing & Consulting** and is based in Germany.