Tips for writing high quality clinical evaluation reports (CERs)

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Abstract

Clinical Evaluation Reports (CERs) are required for all medical devices where manufacturers are seeking approvals or renewals for CE marking. European Union (EU) Medical Device Regulation (MDR) (EU2017/745) imposes strict requirements regarding the contents of CERs. Format, contents, process and details expected in CERs are described in MEDDEV 2.7/1 Rev 4. As per this format, CER for a medical device is an integrated report including data from various sources like clinical investigations, risk assessment, post marketing surveillance, post marketing clinical follow-up plan, literature searching and regulatory databases. Thus, in order to prepare high quality CERs that adequately represent a medical device's benefit risk profile, CERs should be prepared by a strong team who not only understand about the medical device, but also have good understanding of the clinical condition and potential patients/ users, and ability to review and appraise the data collected from various sources so that CERs correctly capture the benefits and risk associated with the medical device with due considerations to the current state of the art technologies and therapeutic options available for the patients/ users.

Keywords: Clinical Evaluation Reports, CERs, Medical Device Regulation, MDR, Medical Devices Directive, Medical Devices, MEDDEV 2.7/1 Rev 4, PMCF, PMS, Post marketing Clinical Follow-up, Post Marketing Surveillance, CE marking

Introduction

Trans-fats in Indian scenario

A Clinical Evaluation Report (CER) is a comprehensive analysis of pre-market and post-market clinical data relevant to a medical device. The CER forms part of the Technical File submitted to the Notified Bodies (NBs) for CE marking (Conformité Européenne (French for "European Conformity") approvals. Compliance with the requirements to prepare and regularly update CERs is mandatory for CE marking. Requirements, content and format of CERs are provided in MEDDEV 2.7.1 rev.4. Medical device companies need to take several measures to make sure that their CER is well-prepared as per the content and formats provided in the MEDDEV guidance document.

As the name suggests, CER documents the assessment of the clinical evidence supporting the safety, efficacy, equivalence or comparison of the medical device with other state of the art alternatives. Such an assessment is critical for receiving CE marking for the device and its subsequent renewal. A detailed CER with positive conclusions on the benefit risk assessment must support any medical device approved for sale in Europe. The report includes an analysis of clinical performance and clinical safety of the medical device.

The contents of CERs are clearly described in the EC guideline, MedDev 2.7/1 revision 4 (June-2016) and the Europe's Medical Device Regulation (MDR) (EU 2017/745) levies strict requirements regarding the same. The level of detail contained in a CER depends on the device. A detailed CER with annual update will be required for a medical device that has more potential risks for patients. Clinical evaluation involves the assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device. The document should contain appropriate and sufficient clinical evidence that establishes compliance to the Essential Requirements (ERs) in MEDDEV

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2.7/1 Rev. 4 Annex 1 (Safety and Performance Requirements in the MDR). The CER should also describe the physical and technical aspects and composition of the device, along with the instructions for use (IFU).

The sources for the input data for CERs include data from the clinical investigations conducted by the company, data from the existing literature- also include data on the equivalent devices, post marketing clinical experience, post marketing surveillance and data from safety databases like Manufacturer And User facility Device Experience database (MAUDE). A CER is required to be prepared and submitted with the technical file for CE Marking/conformity assessment process for initial approvals and renewals.

Importance of clinical evaluation reports

Clinical evaluation is required to be conducted throughout the life cycle of a medical device, as an ongoing process. Usually, it is first performed during the development of a medical device in order to identify data that need to be generated for market access. Clinical evaluation is compulsory for initial CE-marking procedure. This evaluation must be actively updated thereafter, on a regular/ periodic time-intervals. Clinical evaluation is necessary and important because it ensures that the evaluation of safety and performance of the device is based on sufficient clinical evidence throughout the lifetime that the medical device is on the market. This ongoing process enables manufacturers to provide notified bodies and competent authorities with sufficient clinical evidence for demonstration of conformity of the device with the Essential Requirements throughout its lifetime (for example for CE marking, fulfillment of post-market surveillance (PMS) and reporting requirements, or during surveillance procedures).

MEDDEV 2.7/1 rev. 4 guidance for CERs

This guidance promotes a common approach to clinical evaluation for medical devices regulated by the Directives 90/385/EEC and 93/42/EEC. The depth and extent of clinical evaluations should be flexible and appropriate to the nature of the device, intended use of the device, and benefit- risk considerations of the device under assessment. This guidance does not impose device-specific requirements. Manufacturers of the device should prepare CERs that are appropriate for the device as per associated potential risks.

As per the guidance 'MEDDEV 2.7/1 revision 4 (June 2016)', clinical evaluation is a methodologically comprehensive ongoing procedure to collect, appraise and analyse clinical data pertaining to a medical device. The depth and extent of clinical evaluations should be flexible and appropriate to the nature of the device, intended use of the device, and benefit- risk considerations of the device under assessment. This guidance does not impose device-specific requirements. Scope of clinical evaluation is restricted to evaluating the compliance with relevant essential requirements for safety and performance only when the device is used according to the manufacturer's instructions for use. Writers should also assess and document whether there is sufficient clinical evidence to confirm the safety and performance. If IFUs are not required (in exceptional cases), the assessments are conducted considering generally recognized modalities of use by the healthcare professionals and/ or patients/ users. Periodic CERs are required for all classes of medical devices3. The evaluation should be appropriate to the device under evaluation, its specific risks/ benefits, and its intended use.

Besides EU, Competent Authorities from several other countries like China, Australia critically review the CERs for approvals and to critically evaluate the benefits and risks associated with the device.

Stages of preparation of clinical evaluation report

CER documentation typically comprises of several distinct stages [1] as explained below.

Stage 0 Scope and plan: This stage involves identifying and defining the scope of the clinical evaluation of the particular medical device and the CER to be generated thereof. The plan for the clinical evaluation that need to be addressed from a clinical perspective is determined. This is also referred to as scoping. The scope serves as a basis for next steps for example developing literature search strategy for the identification of relevant data. A detailed description of the device including models or videos should be provided to the team working on the clinical evaluation report. The clinical evaluation is ought to be critical and so, needs to identify, appraise and analyse both favorable and unfavorable data. The depth and extent of clinical evaluations should be flexible and appropriate to the nature of the device, intended use of the device, and benefit- risk considerations of the device under assessment. This guidance does not impose device-specific requirements. Depending on the stage in the lifecycle of the product, considerations for setting up a clinical evaluation plan would include different aspects. During this stage, evaluators and medical writers should be trained on the medical device and the equivalent devices. In the CER, the device should be described in sufficient detail so that compliance with Essential Requirements can be assessed. Photographs and diagrams of the device should be included. If the device will be marketed based on Equivalence to another device, Equivalence needs to be demonstrated on all key aspects including clinical, technical and biological characteristics. To be equivalent, all three characteristics must be fulfilled. The scope serves as a basis for next steps for example developing literature search strategy for the identification of relevant data. A detailed description of the device including models or videos should be provided to the team working on the clinical evaluation report. Full details of the equivalent device and reasons why it is considered equivalent to the subject device should be

provided. Clinical, technical and biological characteristics that need be demonstrated when equivalence is claimed by the manufacturer [1], are outlined as below (**Table 1**).

Table 1. *Clinical, technical and biological characteristics that need be demonstrated when equivalence is claimed by the manufacturer.*

Equivalence Claimed	**Clinical**	• used for the same clinical condition, not only for the disease but also the severity and stage of disease, age group of the patient population should be considered
		• used for the same intended purpose
		• used at the same site in the body
		• used in a similar population (age, gender, anatomy, physiology, etc)
		• not foreseen to deliver significantly different performances (in the relevant critical performances such as the expected clinical effect, the specific intended purpose, the duration of use, etc.)
	Technical	• be of similar design
		• used under the same conditions of use
		• have similar specifications and properties (physicochemical properties such as type and intensity of energy, tensile strength, viscosity, surface characteristics, wavelength, surface texture, porosity, particle size, nanotechnology, specific mass, atomic inclusions)
		• use similar deployment methods (if relevant)
		• have similar principles of operation and critical performance requirements
	Biological	• Preferably, the same materials or substances are used in the device as Equivalent device, especially those parts of the device that are in contact with the same human tissues or body fluids

Stage 1 Identification of pertinent data: This stage involves identifying and validating clinical data (both relevant pre-market and relevant post-market clinical data). The PMS should include Post-Marketing Clinical Follow-up studies (PMCF) including post market clinical investigations, registry studies and observational studies/ data collections planned or sponsored by the manufacturer, the literature search and literature evaluations conducted as part of the PMS, trend reports, incident reports and complaints received by the manufacturer along with the manufacturer's own evaluation and reports. PMS data shared with CER writers should also include details of all field safety corrective actions and, complaints regarding performance and safety received by the manufacturer even when the device is used as a custom made device or under compassionate use. Complete data should be entirely disclosed and made available to the evaluators which comprises of data from Europe and other countries inclusive of clinical studies as well as well as user-usage data. All data sets should be adequately summarized, appraised, analysed and referenced in the CER.

Data retrieved from Literature: Literature search is used to identify data that is not held by the manufacturer, but essential for the clinical evaluation. Literature searching identifies potential sources of clinical data and establishes clinical data relevant to the device under evaluation. Literature search should aim to search data that relate to the device under evaluation as well as data of the equivalent device (if equivalence is claimed). A dedicated literature search should be performed to capture the information regarding the current knowledge and the state of the art. This includes applicable standards and guidance documents, data that relate to benchmark devices, equivalent device and other devices. The data are typically looked-for in order to describe the clinical background and identify the current knowledge/ state of the art in the corresponding medical field. Along with benefits, literature search should also be planned to identify potential clinical risks including risks due the materials used, impurity profiles and technology related risks ies, Literature should also be collated to justify the validity of criteria used for the demonstration of equivalence (if equivalence is claimed), and to justify the validity of surrogate endpoints (if surrogate endpoints are used).The searching strategy should be thorough and objective (to be able to identify all relevant favorable and unfavorable data).

For some devices, where there are no clinical investigations conducted as part of PMCF, clinical data generated through literature searching will be the only data representing the clinical evidence, whereas for others, literature search will be one of the sources for the clinical data. So, when conducting a literature review a comprehensive search should be conducted. If a comprehensive search is not considered necessary, reasons should be clearly documented and appropriately justified.

Several searches with different search criteria or focus are usually necessary to obtain the necessary data. A literature search and other retrieval of data are carried out based on a search protocol. The search protocol documents the planning of the search before execution. Once the searches have been executed, the adequacy of the searches should be verified and a literature search report should be compiled to provide details of the process followed and all any deviations from the

literature search protocol should be listed along with the final summarized results of the search (**Table 2**).

Table 2. *Essential Elements in Literature search performed for CER*

Essential Elements in Literature search performed for CER	
Scientific literature databases	• MEDLINE or Pubmed can provide comprehensive data
	• Local European Journals
	• Additional databases should also be checked to ensure adequate coverage of devices and therapies in use in Europe, for example trial registers
	• Information coverage and search features available in scientific databases always do change with time; criteria for selecting adequate databases, so should be defined and re-evaluated on a regular basis as a mandate
Internet searches	• Provide reliable data on:
	• Harmonised standards and information on clinical performance and clinical safety
	• Field safety corrective actions for the equivalent devices (can be found on the websites of European Competent authorities, the U.S. Food and Drug Administration (FDA))
	• Implant registry reports
	• Documents available in systematic review databases (e.g. the Cochrane Database of Systematic Reviews, Prospero international prospective register of systematic reviews)
	• Expert documents produced by the professional medical associations/ These documents and clinical practice guidelines that are important for assessment of current knowledge/ the state of the art therapies available
	• Meta-analyses and reviews of health technology assessment (HTA) institutes
	• Identification of studies via the WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov
Non-published data	• Retrieval of such data should be considered, including for monitoring of any changes:
	• The label and IFU of the equivalent device (if equivalence is claimed by the manufacturer) and/or of benchmark devices and other devices
	• Data provided to manufacturers from implant registries
	• Data presented at congresses
Citations referenced in scientific literature	• Are important and should be screened as a mandate:
	• Literature found to be relevant are likely to cite other literature that could of direct interest to the manufacturer
	• may be necessary to retrieve some of the referenced literature in order to appraise the scientific quality of a document

It is important that the literature search be documented to such degree that the methods can be appraised critically, the results can be verified thereof, and the search reproduced if necessary. Some essential points to be taken into consideration when a large section of CER is based on literature search/ data published in public domain [1]. The literature search and literature review protocol should refer to the background and the objective of the review, focusing on the literature review questions/ queries and the methods for identification, selection, collection and appraisal of the relevant publications judged to essential to address these questions/queries.

It should include the literature search methodology (preferably recognized as the "Literature Search Protocol"). The protocol should specify & focus all the vital aspects addressing the background of literature search, objectives of the search and Medical Subject Heading (MeSH) terms. Protocol should list in detail the methods for identification, selection or rejection and collation of the relevant publications to address the literature review questions. The selection of literature should be objective and justified, i.e. include all relevant data for the device and equivalent device including all favorable and unfavorable. With respect to the clinical evaluation, the evaluators should assess the extent to which the selected papers indicate the intended application/ use of the device. Objective, non-biased, systematic search and review methods [1] should be used.

Stage 2 Appraisal of pertinent data: This stage includes analyzing & appraising each identified data set for scientific validity, relevance to particular clinical evaluation, and weightage to the final report and interpreting it to see if it meets all the requirements. The value & significance of the data identified in stage 1 can be determined only when each individual document is appraised in terms of its contribution to the evaluation of the clinical performance and clinical safety of the device. The evaluators should go through each document to identify the relevant information contained in each document and evaluate the methodological quality of work done by the authors. The scientific validity4 and the relevance of the information to the clinical evaluation should be determined and the contribution of each data set to the

clinical evaluation should be systematically assessed to provide weightage/ score.

The appraisal plan should typically include criteria for determining the methodological quality and the scientific validity of each data set, criteria for determining the relevance of the information to the clinical evaluation (relevance to the device considering its intended purpose) and criteria for scoring the contribution of each data set to the overall clinical evaluation.

The appraisal should be thorough and objective. It should identify and attribute adequate weightage to both to favorable and unfavorable aspects of each document. The criteria adopted for the appraisal should reflect the nature, history and intended clinical use of the device. They should be documented and justified on the basis of current knowledge / the 'state of the art' therapies/ medical devices and applying accepted clinical and scientific standards. There are many acceptable ways, both qualitative and quantitative, by which the appraisal can be carried out

The complete appraisal plan should be defined clearly and documented in the CER. The evaluators should follow the pre-defined appraisal plan strictly and apply its criteria consistently throughout the appraisal. Their appraisals should not be based on the abstracts or summaries, rather based on the full text of publications All of the contents should be reviewed including the methodology employed, the reporting of results. the validity of conclusions drawn from the investigation, including careful assessment of any limitations and potential sources of error in the reported data.

The appraisal should be documented in the clinical evaluation report to the extent that it can be critically reviewed by others. If any clinical investigation has been carried out by or on behalf of a manufacturer, all the details related to the study design, ethical and regulatory approvals, conduct, results and conclusions of the investigation, as appropriate, should be also considered under clinical evaluation. Another important consideration of the evaluation should be to assess whether the conduct of the investigation/ study/ trial was as per the rules laid down by the applicable regulations, and in accordance with the current applicable ethical standards that have their origin in the Declaration of Helsinki. Clinical investigations/ study details that are not in compliance with applicable ethical standards, medical device standards (for example EN ISO 14155 or comparable standards) or regulations should not be used for demonstration of performance and/or safety of the device and so should not be included in the CER.

Stage 3: Analysis of clinical data: This stage identifies risks and uncertainties, which ought to be answered during PMS and construct the Benefit/Risk Profile, build in the residual risks and include all the unanswered questions as well. The goal of this stage is to determine if the appraised data sets available for a medical device collectively demonstrate compliance with each of the Essential Requirements pertaining to the clinical performance and clinical safety of the device, when the device is used according to its intended purpose, and also for the instances when the device is not used for its intended purpose or as per IFU. In order to demonstrate compliance, the evaluators should use sound methods; review the complaints and incident reports received, make a comprehensive analysis; determine if additional clinical investigations or other measures are necessary; and to determine PMCF needs.

In general, data that are not methodologically sound (such as single patient reports) should not be used for demonstration of adequate clinical performance and clinical safety of a device. Conformity assessment with requirement on performance - it is expected that the device achieves its intended performances during normal conditions of use, and that the intended performance is supported by sufficient clinical evidence. Conformity analysis/ assessment with requirement on acceptable benefit/risk profile includes: evaluation of the description of the intended purpose of the device; evaluation of the device's benefits to the patient; quantification of benefit(s) to the patients; evaluation of the clinical risks of devices; evaluation of acceptability of the benefit/risk profile.

Confirmation of usability, that the design of the device adequately reduces the risk of use-error as far as possible, and that the design is adequate for the intended users (lay, professional, disabled or other users, if applicable), adequacy of the information materials/ instructions for use supplied by the manufacturer, including if risk mitigation measures are correctly addressed in the IFU of the medical device like sections on handling instructions, description of risks, warnings, precautions, contraindications, instructions for managing foreseeable unwanted situations is mandatory.

Assessment should be carried out if there is uniformity and alignment between the clinical evaluation, the information materials supplied by the manufacturer, and the risk management documentation for the device under evaluation. All such discrepancies should be identified in order to ensure that all the hazards and other clinically relevant information have been identified and analysed appropriately. It should also be assessed if there is consistency between the documents mentioned above and current knowledge/ the state of the art. The evaluators should also include aspects such as rare complications, uncertainties regarding medium- and long-term performance, or safety under wide-spread use.

Stage 4: Finalize the clinical evaluation report: This is the last stage of Clinical Evaluation and involves finalization of the report by summarizing the entire data analysis and providing strong clinical evidence, for conformity assessment so the device can be approved for CE marking for sale in European markets. A CER shall be compiled to document the

clinical evaluation and its output. The report should outline the different stages of the clinical evaluation. This document needs to be dated and version controlled. The clinical evaluation report should contain sufficient information to be read and understood by the assessor of the Notified Body. Therefore, the CER should describe in detail the literature search criteria, all data that were available and reviewed, all assumptions made to arrive at the conclusions regarding the benefit risk profile. The contents of the CER shall be cross-referenced to the relevant documents that support them. It should be clear which statements are substantiated by which data, and which reflect the conclusions or opinions of the evaluators.

The CER should include references to literature-based data and the titles and investigational codes (if relevant and available) of any clinical investigation/ clinical study reports, with cross-references to the location in the manufacturer's technical documentation. The amount of information may differ according to the history of the device or technology. Where a new device or technology has been developed, the finalized CER should also include an overview of the developmental process and the points in the development cycle at which all clinical data have been generated.

Discussion

Who should perform the clinical evaluation & prepare Clinical evaluation reports?

Preparation of CERs is teamwork and a considerable amount of effort, time and expertise are all required to develop a high quality CER. Team for preparation of CERs includes suitably qualified and trained device experts, medical experts, medical writers with experience of writing CERs, literature review experts, biostatistician's clinical data analysts. The ultimate goal is to prepare a CER that is robust and includes verified and accurate data.

The manufacturer needs to take into consideration that the requirements of the report/ evaluation are clearly defined for the evaluators, in line with the nature of the device under evaluation and its clinical performance and risks. The manufacturer should justify the choice of the evaluators through reference to their qualifications and documented experience, and should present a declaration of interest for each evaluator. With respect to the device under evaluation, the evaluators should in addition have knowledge of the technology used in the device and its application;, knowledge of medical alternatives for diagnosis or management, treatment standards and other technologies A clinical specialist with clinical expertise in the relevant medical specialty should be a part of the team. The evaluators should have at least a degree from higher education in the respective field and 5 years of documented professional experience or 10 years of documented professional experience if a degree is not a prerequisite for a given task.

Major contents/ sections of CER: A plausible structure (or let us say, a template) for the CER is suggested in MEDDEV 2.7/1 Rev.4, but the guidance does not mandate it, and a proposed table of contents [2] for a CER can be as below.

Best practices in CER and medical writing: The preparation of a CER should have a Life cycle approach which means that CERs should be prepared before launch of the medical device and updated across life cycle of that particular medical device. Various sections of the CER should be carefully drafted and although Summary is the first section of the CER, typically this is the last section to be prepared. The Summary should briefly explain the clinical condition, give a succinct overview of the state of the art therapeutic options; provide brief overview of the subject device and its indication; outcome of the evaluation pre-clinical studies, pre-market clinical investigations, risk management, PMS, and published literature. Finally, summary should provide the conclusion of the writers regarding the risk-benefit profile of the device. The summary should preferably be of around a thousand words.

As literature review usually takes a lot of time and the section of literature review is usually long, up to a hundred pages, sufficient time should be planned for literature review and literature appraisal. Sometimes, when the literature review is too long, some writers do prefer to separately provide literature review to facilitate navigation through CER.

A Literature Review protocol should be developed consistent with the scope of the clinical evaluation and should utilize Objective, Non-Biased, Systematic Search and Review Methods, for example patient characteristics, type of intervention, control, and outcome queries (PICO process). Choosing the right search terms, developing the search strategy and knowing how to search databases are essential for a successful literature search. The final search strategy, date the search was conducted and the search results showing the number of articles identified at each step should be documented in the LR protocol so that the search can be reproduced if necessary.

CER is an integrated report that takes in to consideration the generated and held by the manufacturer including data from pre-clinical studies (e.g. bench testing), pre-market clinical investigations, risk management, incident reports, label updates, IFU changes and PMS. All data should be summarized, appraised, analysed and referenced in the CER. Risk management and PMS reports as well as information from external national databases, e.g. MAUDE in the US, MHRA device alerts in the UK should be included [3,4].

For Appraisal of the Clinical data, there is no single, well established method and so, a method appropriate for the target device should be chosen on a case-basis. Questions that help determine whether data collected or searched are relevant can be summarised2 as follows: To what extent

are the data generated representative of the device under evaluation?; What aspects are covered?; Are the data relevant to the intended purpose of the device or to claims about the device?; If the data are relevant to specific aspects of the intended purpose or claims, are they relevant to specific device models, user groups, medical indications, age group, and gender, severity of condition or time period? The list of excluded papers with reasons for exclusion should also be attached as an appendix to the CER2. The included papers should be presented in a bibliography that is separate from the bibliography prepared for the articles included in the main body of the CER to describe the State of the Art. The full text articles (as pdf) are part of the clinical evaluation to be provided with the CER [5,6].

Conclusion

CERs are one of the key documents included in the technical file that play a key role in facilitating initial CE marking approval and renewals. CERs are integrated reports that include information from clinical investigations, risk assessment, PMS, PMCF plan and literature and assess the consistency between the data generated from various sources and correct representation of the data in the IFU. It also takes into consideration the residual risks and uncertainties which need to be further evaluated during PMS, including the PMCF studies. Manufacturers should have adequate systems in place so that the team preparing the CERs has due access to the data from all sources. Further, to ensure the preparation of high quality CERs, manufacturers should engage appropriately trained and qualified professionals who have a strong ability to critically review and appraise data from various sources to correctly assess the benefit risk profile of the device and identify information gaps, if any for which additional data should be generated.

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Conflicts of Interest

No conflicts of interest.

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