Clinical Evaluation Reports from the medical writer's perspective!

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Abstract
Clinical evaluation is a structured ongoing procedure to collect, appraise and analyse clinical data pertaining to a medical device. The clinical data include current knowledge of the condition to be treated, published literature about the target device and any equivalent devices, information held by the manufacturer about pre-clinical and clinical investigations, risk management, post-market surveillance, and the instructions for use. The clinical data are analysed for consistency between them to identify any gaps or uncertainties that require further evaluation, and to show conformity with the Essential Requirements of the Medical Devices Directive (to be superseded by the Medical Devices Regulation). The clinical evaluation report (CER) is the document containing this information to support initial CE-marking or CE renewal. The guideline determining the structure and content of the CER is MEDDEV 2.7/1 Rev. 4 (June 2016). This article provides an overview of how to write a CER according to this guideline.

What is clinical evaluation?
Clinical evaluation is a structured ongoing procedure to collect, appraise, and analyse clinical data pertaining to a medical device. The purpose of the evaluation is to assess whether the available clinical evidence is sufficient to confirm compliance with relevant Essential Requirements for safety and performance when using the device according to the manufacturer's instructions for use (IFU).[1] The stages of clinical evaluation are presented in Figure 1. Clinical evaluation is an ongoing process conducted throughout the life cycle of a medical device: the data collected are updated whenever new post-market surveillance (PMS) information is received that changes the current evaluation, annually when the device carries significant risks or is not yet well established, or every 2 to 5 years if the device does not carry any significant risks or is well established.[1]

Stage 0:	Scope and plan
Stage 1:	Identification of pertinent data
Stage 2:	Appraisal of pertinent data
Stage 3:	Analysis of the clinical data
Stage 4:	Clinical evaluation report, including PMS/PMCF plan

From: MEDDEV 2.7/1 Rev. 4 (June 2016) Section 6.3
PMS = post-market surveillance;
PMCF = Post-market clinical follow-up

Figure 1. Stages of clinical evaluation

The clinical evaluation report (CER) is the document containing this information, and is intended for review by the Notified Body (NB), who assess medical devices for initial or renewal of market approval (the CE-mark). The CER will form part of the Technical File or, for class III devices, Design Dossier submitted to the Notified Body. The guideline determining the structure and content of the CER is MEDDEV 2.7/1 Rev. 4 (June 2016).[1] This article provides an overview of what is included in a CER and how to write one according to this guideline.

The medical writer's role is to collect, assimilate, and objectively present data about the medical device in accordance with the requirements of MEDDEV 2.7/1. This will require input from other experts, e.g. the manufacturer for technical information about the device, librarian or information scientist for literature searches, quality specialist for complaints data, and safety scientist for PMS data.

How is the CER written?

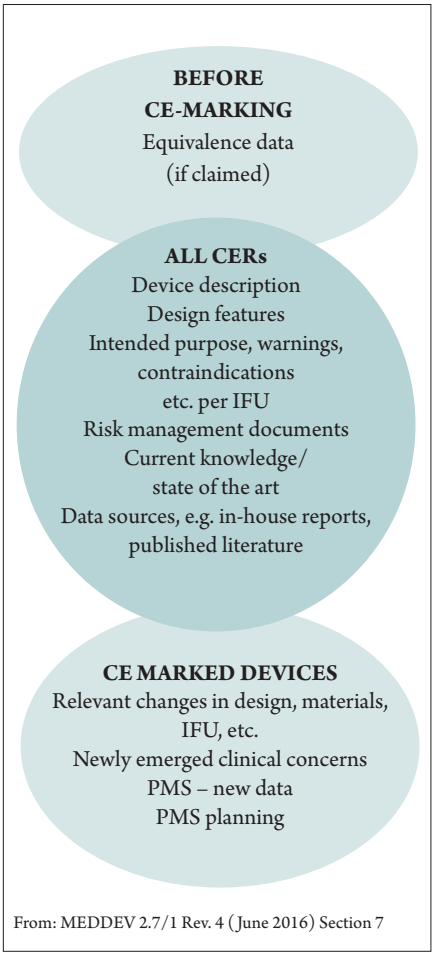
MEDDEV 2.7/1 Rev. 4 gives some indications for a structure for the report, but does not mandate one, and a proposed table of contents for a CER is shown in Figure 2. Some sections will contain more or less data depending upon the time-point in the product life cycle, e.g. in development, and what data are available e.g. published literature, clinical investigation data, post-market surveillance (PMS) information.

Summary

Although it is the first section to be read, the summary is the last to be written. The summary should give a succinct overview of the clinical condition and state of the art; brief details of the subject device and its indication; conclusions of the evaluation pre-clinical studies, pre-market clinical investigations, risk management, PMS, and published literature; risk-benefit profile conclusion. The summary is usually up to two pages in length.

Scope of the clinical evaluation

The scope sets out the objectives of the CER, what is included and which guidelines, standards and reference materials have been used. The objective is to support conformity of the device with the essential requirements for safety and performance as per the European Medical Devices Directive (MDD) 2007/47/EC, to be superseded by the Medical Devices Regulation (MDR). It should be stated whether the CER is in support of initial CE-marking, a CE mark renewal, or is at the request of the Notified Body (NB). The documents required for all CERs and those additional documents specific to CE-marked devices or to new devices, where equivalence with another devices is being claimed, are listed in Figure 3.



From: MEDDEV 2.7/1 Rev. 4 (June 2016) Section 7

Figure 3. Information to be included in the CER

1.	Summary
2.	Scope of the clinical evaluation
3.	Clinical background, current knowledge, state of the art
4.	Device under evaluation
	4.1 Type of evaluation
	4.2 Demonstration of equivalence (only if claimed)
	4.3 Clinical data generated and held by the manufacturer
	4.4 Clinical data from literature
	4.5 Summary and appraisal of clinical data
	4.6 Analysis of the clinical data
	4.6.1 Requirement on safety
	4.6.2 Requirement on acceptable benefit/risk profile
	4.6.3 Requirement on performance
	4.6.4 Requirement on acceptability of side-effects
5.	Conclusions
6.	Date of the next clinical evaluation
7.	Dates and signatures
8.	Qualification of the responsible evaluators
9.	References

From: MEDDEV 2.7/1 Rev. 4 (June 2016) Section A9

Figure 2. CER table of contents

Guidance documents used in addition to MEDDEV 2.7/1 include the following:

- EN ISO 14155:2011 – Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice;
- EN ISO 14971:2012 – Medical Devices – Application of Risk Management to Medical Devices;
- MEDDEV 2.12/2 rev2 Post Market Clinical Follow-up – A guide for manufacturers and Notified Bodies (January 2012; to be superseded by MDR Annex XIV);
- NB Med 2.12 Rec1 – Post Marketing Surveillance (February 2000; To be superseded by MDR Annex III).

Depending upon the type of medical device other guidelines might also be relevant, e.g. MEDDEV 2.1/6 Quantification and Classification of Stand Alone Software (January 2012).

Reference materials used in preparing the CER include the IFU, literature review, clinical

investigation reports, risk management reports, PMS reports.

Clinical background, current knowledge, state of the art

Describing the current knowledge, or state of the art, has assumed much greater importance in the CER since the introduction of MEDDEV 2.1/7 rev. 4. A literature search is required in order to determine the state of the art for the subject device. This literature search is separate from the systematic literature search conducted to appraise the subject device. As it is intended to define the state of the art, the search terms should be broad and the timeframe recent, e.g. up to 2 years. NB – keep the state of the art bibliography separate from the literature review bibliography, even if there is some overlap between them.

Practice and consensus guidelines, health technology assessment reports, systematic review databases e.g. Cochrane, and Competent Authority websites and registries can be useful starting points when writing this section. Describe the condition to be treated, provide epidemiology data, explain how the disease is classified and managed, justify the choice of clinical endpoints and identify potential clinical hazards. What is the 'gold standard' treatment? What other treatments are available? This should include medical, surgical and other alternative forms of treatment for the target condition. What are the pros and cons of these treatments in different patient groups? What is the benefit/risk profile of other devices and treatments? How does the subject device compare with the state of the art? Information about competitor products and equivalent devices should also be obtained and any knowledge gaps identified.

Device under evaluation

The MEDDEV 2.4/1 Rev. 9 (June 2010) guideline (to be superseded by MDR Annex VIII) is used to determine device classification and contains the Rules by which devices are classified based on risk as I, IIa, IIb or III.[2]

The device should be described in sufficient detail so that compliance with Essential Requirements can be assessed. Always include photographs and diagrams of the device. The details to be provided are shown in Figure 4. Most of the information will be found in the IFU and, depending upon the nature of the device, additional information may be available in a Surgical Guide. The intended purpose should use the same wording as the IFU; this is because the IFU is part of the Essential Requirements of the MDD.

Usability testing of the device is a new requirement in MEDDEV 2.7/1 rev. 4 introduced because usability factors have either caused or contributed to many incidents. This means demonstrating that the device design and any risks relating to its use have been minimised, that the residual risks are acceptable, and that the information materials e.g. IFU, training guide, are suitable for use by the intended users.

If the device will be marketed based on equivalence to another device this must be demonstrated on the basis of clinical, technical and biological characteristics (see Figure 5). To be equivalent, all three characteristics must be fulfilled. Full details of the equivalent device and reasons why it is considered equivalent to the subject device should be given.

Clinical data generated and held by the manufacturer

This includes data from pre-clinical studies (e.g. bench testing), pre-market clinical investigations, risk management and PMS – see examples in Figure 6. All data should be made available, not just those data generated in Europe, and they should be summarised, appraised, analysed and referenced in the CER. Risk management and PMS reports are usually large documents containing spreadsheets of quality control reports, complaints, sales figures, and also information from external national databases, e.g. MAUDE in the US, MHRA device alerts in the UK. Obtaining these data requires liaising with various groups within the manufacturing company to ensure that reports are available in time for inclusion in the CER and to meet submission timelines, especially for CE-mark renewals with specific timelines.

Clinical data from the literature

The clinical literature review (LR) is a substantial section which can take as long to write as the rest of the CER. The LR can either be part of the CER or a separate document which is summarised in the CER. A separate LR has the advantage of limiting the size of the CER and making it more navigable: an LR can easily run to 100

- Name, models, sizes, components of the device, including software and accessories
- Device group to which the device belongs (e.g. biological artificial aortic valve)
- Whether the device is being developed/undergoing initial CE-marking/is CE-marked
- Whether the device is currently on the market in Europe or in other countries, since when, number of devices placed on the market
- Intended purpose of the device
  - exact medical indications (if applicable)
  - name of disease or condition/clinical form, stage, severity/symptoms or aspects to be treated, managed, or diagnosed
  - patient populations (adults/children/infants, other aspects)
  - intended user (use by health care professional/lay person)
  - organs/parts of the body/tissues or body fluids contacted by the device
  - duration of use or contact with the body
  - repeat applications, including any restrictions as to the number or duration of reapplications
  - contact with mucosal membranes/invasiveness/implantation
  - contraindications
  - precautions required by the manufacturer
  - single use/reusable
  - other aspects
- General description of the medical device including
  - a concise physical and chemical description
  - the technical specifications, mechanical characteristics
  - sterility
  - radioactivity

From: MEDDEV 2.7/1 Rev. 4 (June 2016) Section A3

Figure 4. Device description – information to be included

Clinical

- Used for the same clinical condition (including similar severity and stage of disease), and
- Used for the same medical indication, and
- Used for the same intended purpose, and
- Used at the same site in the body, and
- Used in a similar population (e.g. age, gender, anatomy, physiology etc.), and
- 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, and
- Used under the same conditions of use, and
- Have similar specifications and properties (e.g. 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 such as nitrocarburising, oxidability), and
- Use similar deployment methods (if relevant), and
- Have similar principles of operation and critical performance requirements.

Biological

- Use the same materials or substances in contact with the same human tissues or body fluids.

From: MEDDEV 2.7/1 Rev. 4 (June 2016) Section A1

Figure 5. Demonstration of equivalence – characteristics

pages. The main disadvantage of a separate LR is the need to ensure consistency between the LR and CER.

Unlike pharmaceutical development, few clinical investigations are conducted during medical device development and so the published literature is an important source of clinical data for equivalent devices during CE-marking/ renewal and for the subject device itself during CE-renewal.

MEDDEV 2.7/1 rev. 4 places increased emphasis on a quality assessment of the available evidence from the literature and on the scientific validity of the LR itself.

- Post-market clinical follow-up (PMCF) studies, device registries sponsored by the manufacturer
- PMS reports, including vigilance reports and trend reports
- The literature search and evaluation reports for PMS
- Incident reports sent to the manufacturer
- Complaints regarding performance and safety sent to the manufacturer
- Analysis of explanted devices (as far as available)
- Details of all field safety corrective actions
- Use as a custom made device
- Use under compassionate use/ humanitarian exemption programmes
- Other user reports

From: MEDDEV 2.7/1 Rev. 4 (June 2016) Section 8.1

Figure 6. Risk management and PMS – examples of data

Literature review protocol

An LR protocol should be developed which is consistent with the scope of the clinical evaluation and which uses objective, non-biased, systematic search and review methods, e.g. patient characteristics, type of intervention, control, and outcome queries (PICO process). Inputs for the review questions are found in the IFU and include the device description, its intended performance, any claims on clinical performance and safety, and information from the risk management process. The review questions should also address any gaps in the clinical evidence, e.g. comprehensiveness of the data, number and severity of adverse events. Example review questions might include: What interventions characterise the state of the art? What comparators can be identified? What clinical data are there to assess safety and performance and is the evidence sufficient for the clinical evaluation?

Choosing the right search terms, developing the search strategy and knowing how to search databases are essential for a successful literature search. The review questions above and previously conducted searches will inform the terms.

It is important to search more than one database. MEDLINE or PubMed have the advantage of being free to access and fairly easy to search but the search features are not sophisticated and there is incomplete coverage of some European journals. Therefore additional databases such as EMBASE/Excerpta Medica (https://www.elsevier.com/solutions/embase-biomedical-research/) and Cochrane Database of Systematic Reviews (http://www.cochranelibrary.com/cochrane-database-of-systematic-reviews/) should also be used. CDSR is free to access but EMBASE is not. The search strategy should define which databases will be searched and the time period to be covered. A ten year time period is reasonable for initial CE-marking whereas for CE-renewals the literature search is from the date of the previous search.

Having defined the search terms, the databases to be searched and the time period, the next step is to apply "limits", e.g. language, type of article, to the search results in order to retrieve a manageable number of relevant articles; thus the search strategy is developed. Literature searching is an iterative process and the strategy is adjusted until the researcher is satisfied that as many relevant papers as possible have been retrieved. It is strongly recommended that the search strategy is tested by ensuring that known key papers are consistently identified by iterations of the search; if not, the search strategy must be modified until they are found. 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.

The literature search, screening and appraisal process is illustrated in Figure 7.

Appraising the literature

It is recommended that reference management software, e.g. EndNote™ (www.endnote.com) is used to manage the literature search results. Abstracts are initially screened for eligibility in order to exclude those that are obviously not

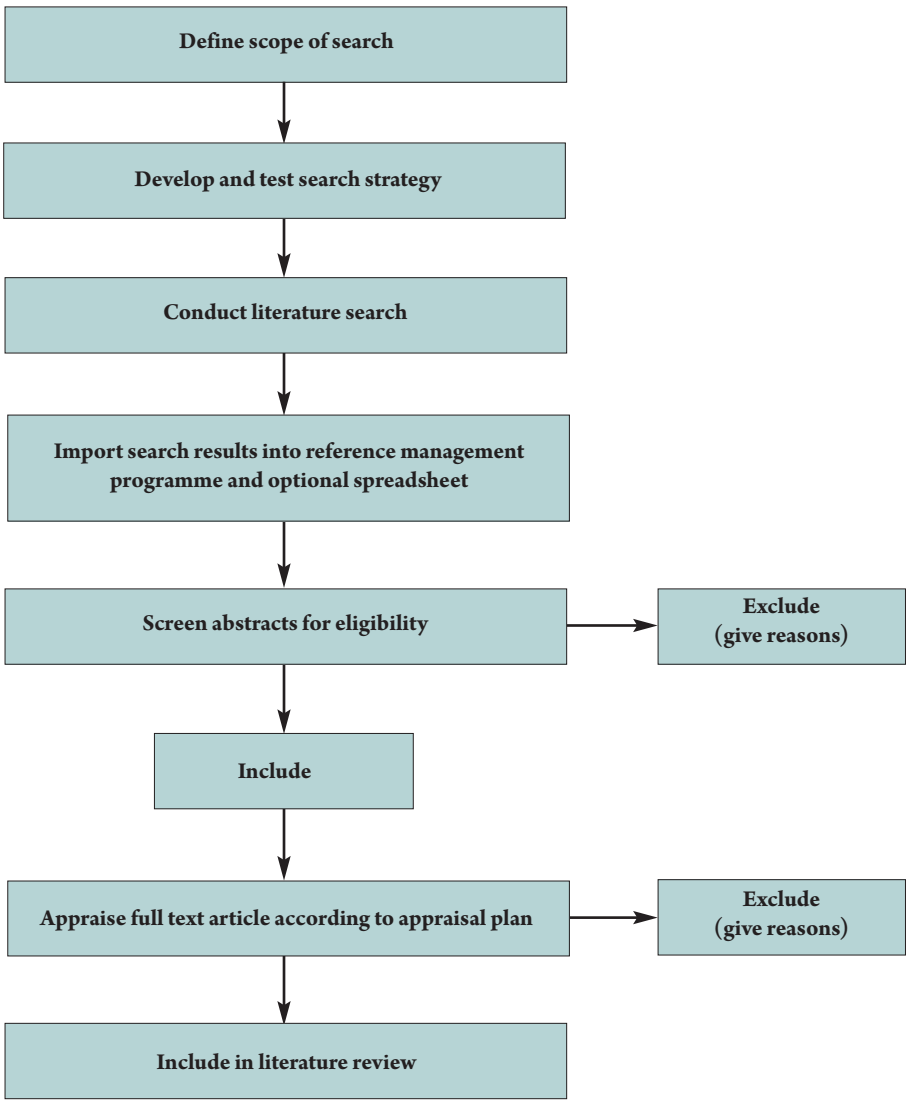


Figure 7. Literature searching, screening, and appraisal process

relevant. The full text articles are obtained for the remaining abstracts and assessed for relevance, i.e. do they directly demonstrate adequate clinical performance and clinical safety of the device (pivotal data), or do they serve an indirect supportive role. Questions that help determine whether data are relevant are listed in Section 9.3.2.c of MEDDEV 2.7.1 rev. 4 and are summarised 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?

Having established that an article is relevant its contribution to the clinical evaluation is weighted. There is no single, well established method for weighting clinical data and a method appropriate for the target device should be chosen, e.g. the OCEBM levels of evidence.[3] The OCEBM considers a systematic review of randomised trials to be the highest level of evidence. In practice, clinical evidence from systematic reviews may only be available for those conditions with an abundance of published literature e.g. heart valve replacement surgery, and most of the evidence will be from randomised controlled trials (Level 2) and non-randomised controlled cohort studies (Level 3).

Reasons for excluding papers might include lack of information about the study e.g. unable to extract safety or performance data, too few patients e.g. case reports, improper statistical methods, lack of adequate controls. The disposition of screened and appraised articles should be recorded; a spreadsheet or other programme, e.g. DistillerCER (www.evidencepartners.com), is a convenient way of doing this. The number of included papers and excluded papers, with the reasons for exclusion, can then be tallied and must be the same as the number of articles identified by the literature search.

The list of excluded papers with reasons for exclusion is attached as an appendix to the CER. The included papers are presented in a bibliography which should be separate from the state of the art bibliography. Note that the full text articles (as pdf) are part of the clinical evaluation and must be provided with the CER.

Analysing the literature

The goal of the analysis stage is to determine if the appraised datasets 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.[1]

Data from the appraised literature are extracted into tables, summarised and analysed. Data extraction tables are a convenient way of presenting papers; they give an overview of the literature and facilitate comparisons between papers but lack narrative detail. Due to their size data extraction tables are usually presented as an appendix to the CER and may be split into smaller tables in order to fit A4 page width. Tables can be presented as follows:

- Study details, e.g. evidence weighting, study design, treatments/interventions, devices used, follow-up period;
- Patient population, e.g. number of patients, demography, baseline disease characteristics;
- Performance, e.g. endpoints as determined by the disease under study;
- Safety, e.g. post-operative complications/adverse events, deaths.

Papers can be presented in groups, e.g. by study design, or simply listed alphabetically by author

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or listed by publication year.

The data are analysed as a whole across the dataset so that comparisons can be made between studies and summarised in the CER. The analysis is objective and critical. A combination of descriptive text and in-text tables is used to present the data and to explain the outcome measures used. Narratives of each study are not required, but presenting important pivotal studies is helpful.

Analysis of the clinical data

Analysis of the clinical data explains if and how the information provides sufficient clinical evidence to demonstrate the clinical performance and clinical safety of the device under evaluation. The analysis also describes the benefits and risks of the device and explains the acceptability of the benefit/risk profile according to the state of the art. The analysis should also look for consistency between the clinical data, the IFU, risk management documentation and the state of the art to identify any gaps and discrepancies, residual risks and uncertainties or unanswered questions (such as rare complications, uncertainties regarding medium- and long-term performance, safety under wide-spread use) that should be further evaluated during PMS, including in post-market follow-up (PMCF) studies.

Conclusion

The current guidance on clinical evaluation of medical devices, MEDDEV 2.7/ rev. 4, explains how an evaluation is performed, what information is required and how this information should be analysed and presented in the CER. The importance of an overall evaluation of the device is emphasised with particular focus on ensuring that clinical data are evaluated in a systematic and objective way, that the benefit/risk profile is acceptable and that any knowledge gaps are identified and addressed.

Experienced medical writers have an important role to play in the clinical evaluation of medical devices. ■

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Conflicts of Interest and Disclaimers

The author writes CERs and LRs for various medical device companies.

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