Clinical Evidence Reports (CERs): The Insider’s Guide to Requirements and Process

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Thank you for joining us! We will begin at 12:00 Central Time.

Your phone line is currently muted.
Welcome

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Your phone line has been muted.

Type in any questions you have in the Questions box and we’ll have an audio discussion at the end of the presentation.

For technical difficulties, please call 952-746-8080.
Objectives

- Understand the importance of CERs to your business priorities.
- Describe key changes to the MDD and AIMDD related to CERs.
- Identify components of a successful CER.
What is a CER?

- A Clinical Evidence or Evaluation Report is a compilation of the clinical evidence demonstrating device safety and performance that is available on a medical device or system that has been granted CE Mark for sale in the EU.

- The evaluation of clinical evidence is a process; the output of the process is the CER.
Clinical evidence is the safety and performance information generated from the ongoing use of the device throughout its life cycle, and can be gathered from:

- New information gained from clinical use in the market.
- New clinical investigations, including post-market studies.
- Literature reviews of published clinical investigations of the particular device or devices that can be demonstrated to be equivalent.
- Unpublished manufacturer’s reports: updated risk analysis, complaints/MDRs/Vigilance Reports, bench testing, biological safety data, etc.
Regulatory Basis for Med Device CERs

- Report on the Functioning of the MDD (NBM/061/02) (June 2002) concluded that most manufacturers didn’t have adequate clinical evidence for their medical devices and that most Notified Bodies didn’t adequately verify the clinical evidence that was provided to them.

- The MDD was amended in 2007 to address these concerns:
  - Clinical Evidence Reports are now required for all medical devices in Europe, even Class I.
  - Every medical device sold in Europe, regardless of its classification, must have a CER in its technical file.
The 2007 amendment to the MDD 93/42/EEC became effective on March 21, 2010.


Annex I of the amended MDD now states the “Demonstration of conformity with the Essential Requirements must include a clinical evaluation (i.e.: the assessment and analysis of clinical data) in accordance with Annex X.”

Do not discuss/present “substantial equivalence” as a rationale for safety or performance.

Notified Bodies are requiring manufacturers to update or create CERs or their product(s) may be pulled from sale.
CERs and Business Priorities

No CER = No CE Mark = Pull product(s) from sales in EU!

- If you have multiple CERs to generate/update, prioritize based on your strategic business goals.
- Work with your Notified Body to extend timelines, if needed.
Clinical Evaluation

- Demonstration of conformity with Essential Requirements (ER) must include a clinical evaluation for all devices
  - Clinical data must now include acceptability of benefit/risk ratio.
  - Clinical investigations are required for Class III and implantable devices unless duly justified based on existing clinical data.
  - Clinical evaluations must include a post-market surveillance plan unless justified and documented.
  - Clinical evaluations must be actively updated with data obtained from the post-market surveillance.
Clinical Evaluation

- If clinical data are determined to not be necessary to demonstrate compliance to the ER, then justification based on risk management, device/body interaction, intended clinical performance, and claims must be considered.

- Adequacy of the pre-clinical testing must be substantiated.

- Serious adverse events must be recorded and immediately reported to all Competent Authorities (CA) in the Member States where clinical investigations are being performed.
Clinical Evaluation

- Member State (MS) shall inform all other Member States and the European Commission (EC) if an investigation is refused or halted.

- Member State shall inform all other Member States if an investigation is significantly modified or interrupted.

- Manufacturer or Authorized Rep must:
  - Notify CA of the end of investigation with a justification for early termination.
  - Notify MS and EC if terminated early due to safety concerns.
Components of a Successful CER

- Provides guidance to manufacturers on reviewing and analyzing clinical data to be presented to Notified Bodies.
- Must demonstrate that the intended purpose and claims for the device are achieved.
Components of a Successful CER

- Evaluation conducted by a “suitably qualified individual(s).”

- Knowledgeable about:
  - Device technology and application(s).
  - Clinical research methodology (especially literature reviews).
  - Diagnosis and management to the intended conditions.

- Typically a mid-senior level clinical researcher as either lead author or team leader.
Components of a Successful CER

- Develop a robust CER SOP and template.
- State compliance to MEDDEV 2.7.1 or GHTF guidance.
- Incorporate the Literature Review process and output format.
- Train staff on analysis of relevant information.
- Prioritize CERs to be completed.
- Develop a process and schedule for ongoing CER updates.
- OK to combine devices into “families” of similar device types, or write one CER for an entire system (primary device and accessories).
CER Components

- Device Description: model numbers, component descriptions
- Indications, contraindications
- Essential principals of operation
- Worldwide regulatory and marketing history
- Summary of the therapy and indication
CER Components

- Review of Internal Documents
  - Risk Analysis Summary (ISO 14971)
  - Report of sales
  - Review of complaints, Medical Device Reports (MDR) and Vigilance Reports
- Clinical Evidence
Clinical Evidence in the CER

Most important information in the CER to demonstrate device safety and performance

- Literature Review
- Review of market experience since last CER or CE mark approval
- Review of ongoing human studies (investigational or post-market)
- Verify compliance to MEDDEV 2.7.1 or GHTF guidance
Literature Review

- Must follow a systematic, consistent, organized approach.
- Incorporate into the CER SOP or create a stand-alone SOP.
- Must be balanced; favorable and unfavorable information about the device, competitors, outcomes, safety concerns.
- State the objectives for the Literature Review.
- Define the search protocol: date range, key terms, database(s), peer-reviewed journals.
- Databases must be scientific and controlled, i.e., Medline, Embase.
- Include competitive devices in search to ensure all relevant literature are found.
- Provide the criteria for article selection (accept/reject criteria): human studies only, originally published in English, etc.
- Acceptable to reject isolated case studies, opinions and letters, insufficient data.
- Acceptable to include systematic reviews and meta-analyses.
Literature Review

- Run the lit search; refine terms and limits if needed and run again.
- Review all abstracts; reject those that are irrelevant (out of date range, not human studies, not applicable device or indication).
- If in doubt, obtain the full article for review.
- Articles can be found via Pub Med links (some are free!), or obtain from your corporate library or an external source.
- Review articles for relevance; create a table to summarize accepted articles and another table for rejected articles.
- Include rationale for rejected articles (required by MEDDEV 2.7.1).
# Table of Accepted Literature

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Safety, Performance, or Both</th>
<th>Level of Evidence</th>
<th>Type of Study</th>
<th>Study Objective / Population</th>
<th>Effectiveness Outcomes</th>
<th>Safety Outcomes</th>
<th>Conclusions</th>
</tr>
</thead>
</table>
| Levinson, 2009 | Both | II | Case series on 48 patients. | To report on the development of a successful multivessel technique, including lateral wall grafting. Article specifically cited the use of the Acme retractor with the Coyote positioner. | - All patients were able to walk unassisted 24 hours post procedure without complaint of angina.  
- Very little narcotic analgesic was used for pain.  
- Patients was discharged an average of 4 days (2-8) post procedure. | One patient required two hours of vasopressin. No hemodynamic compromise was noted. | The authors conclude that the subxiphoid approach offers a step towards a less invasive surgical option for multi-vessel CABG. |
| Abraham, 2008 | Both | II | Case series on 20 patients requiring reoperation of the right coronary artery (RCA). | To develop and describe a technique to perform a reoperation of the RCA. The article cited the use of the Acme retractor. | Post-anastomosis flow measurements were acceptable. | No reported safety concerns or adverse events. | The authors concluded that this technique provides another approach to reoperative coronary revascularization of the RCA. |
## Table of Rejected Literature

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Rationale for Rejection</th>
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<tbody>
<tr>
<td>Miller, 2009</td>
<td>Irrelevant, does not include actual or comparable device.</td>
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<tr>
<td>Johnson, 2008</td>
<td>Not originally published in English.</td>
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Literature Review

- Provide a method to appraise and weigh the clinical data in the literature.
  - MEDDEV 2.7.1, Appendix D.
  - Create your own method; present it in the CER
- Present a discussion of key articles and their main points.
- Present a strong conclusion reviewing key points from the literature.
- Bibliography of all reviewed articles.
Clinical Data

- If the product is on the market, report data on actual use: how many people, geographic distribution.

- Note key safety and performance information.

- Provide information on ongoing clinical investigations and the post-market surveillance program of same device in all geographic regions: number of studies and their purpose(s), number of subjects, indications, and key safety and performance issues.

- If the clinical use is outside of the EU, demonstrate that the device and patient population are the equivalent to the EU market.

- If this is a new CER for initial CE mark approval, and no clinical investigation is justified, provide rationale.
CER Components (cont.)

- Statement of Evaluator Qualifications
  - Qualified by experience and education.
  - Include signature and date of signature.

- CER Conclusion
  - Must be strong and balanced.
  - Review key points from the entire CER (if this is the only section someone reads, will it be enough?).
  - Confirm device benefits outweigh risks.
  - Confirm demonstration of conformity to Essential Requirements.
Common NB Observations

- Risk management separate from clinical data
- Inadequate literature review
- Devices described as substantially equivalent without appropriate substantiation
- Conclusions based on non-completed clinical trials
- Inadequate Post Market Surveillance plans
- Inadequate/lack of post market clinical follow up
- Non-coherent CER
- Citing non-CA recognized clinical trials
- Lack of risk/benefit statement
- Inadequate review of device claims and labeling
Thank you for attending today’s webinar on CERs!

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