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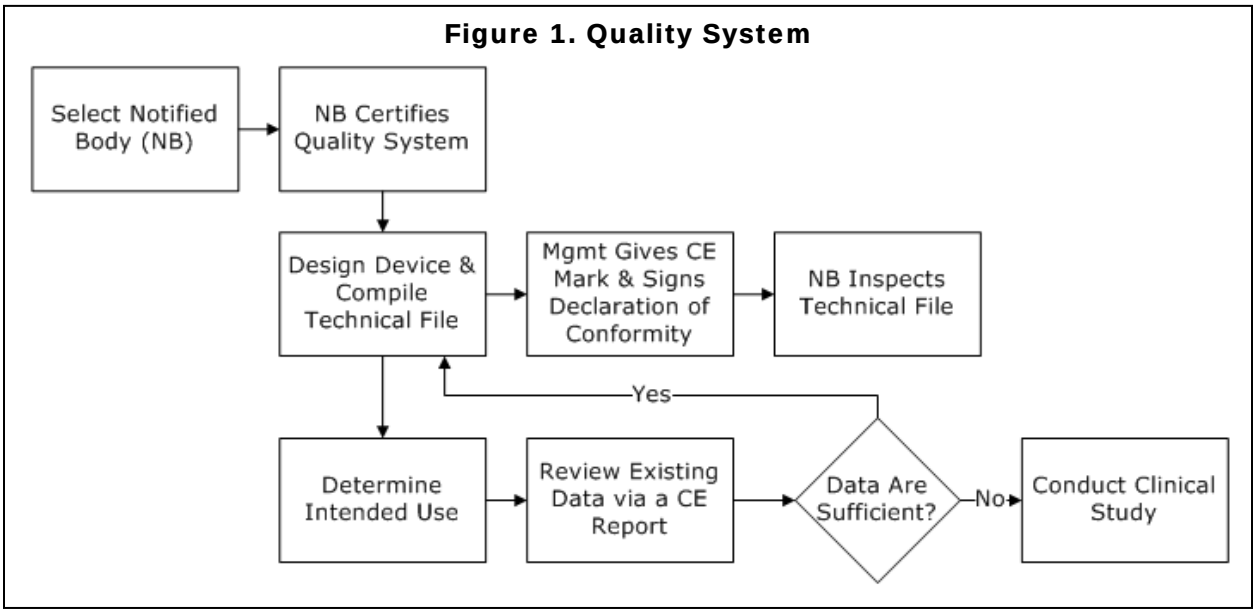
Clinical Evaluation Reports for Medical Devices: What Do Notified Bodies Want?

By Nancy J. Stark

Europe has come a long way in explaining what it expects in a Clinical Evaluation (CE) Report. If you are writing a CE Report for a new, pre-approval device, you are asking the question, "Do I need more clinical data for certification?" If you are writing a CE Report for a device on the market, you are updating your documentation. The CE Report is a key element in medical device quality systems. (Figure 1)

Figure 1. Quality System



How Long? How Much?

Top management will ask three questions about the CR Report:

- How long will it take?
- How much will it cost?
- What will the report say?

The answers depend on the device, its intended uses, and the amount of data available to review for the report.

Let's say you market a very nice ultrasonic toothbrush and you now intend to use it for cleaning road rash abrasions — the kind of abrasion you get when you lose control of your mint-condition 1995 Harley Bad Boy 1338cc, Springer Softail bike avoiding a family of raccoons and your skin grinds against the pavement. The toothbrush is very useful in removing the assorted detritus ground into the wound. However, this unusual intended use raises all kinds of questions, such as the following:

- Can the cleaning process damage the healthy tissue?
- Are there safety features to prevent over-brushing?

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- What is the effect of ultrasound on open wounds?
- How do the physical properties of wound tissue compare to gum tissue?
- What are the instructions for use?
- Does this method of cleaning improve clinical results?
- Are the raccoons OK?

For this device, a Clinical Evaluation Report for cleaning wounds will take longer and cost more than a report for brushing teeth. The findings of the report are also less predictable.

Clinical Evaluation Reports for Pre-Certification Devices

If you are still developing your device, begin by identifying its intended uses. Then evaluate the existing clinical data to determine if it is sufficient to support safety and performance per the essential requirements of EU Directive 93/42/EEC on medical devices (MDD) and EU Directive 90/385/EEC on active implantable medical devices (AIMD), or if you need additional clinical data. If additional clinical data are needed, you have the choice of revising the intended use or performing a clinical trial.

Once you believe the data are sufficient, ask management to grant a CE Mark ("Conformité Européenne") and sign the Declaration of Conformity to your quality management system. When a Notified Body inspector comes to call, you will get your "grade."

Clinical Evaluation Reports for Marketed Devices

The more common situation is that your device is already on the market in Europe and the Notified Body has informed you that your Clinical Evaluation Report is overdue. He or she will give you a grace period that can be considered final. You follow the same process of evaluating the existing data to determine if it is sufficient to support safety and performance for the intended uses. Should the report conclude that the existing data are insufficient, you are in a difficult situation; you'll need to suspend sales until additional data are acquired.

Because the consequences of determining that the data are insufficient are so financially damaging to your firm, and the consequences of determining that the data are satisfactory are so financially favorable, keep the report writers independent from the device developers to ensure an objective report.

Resources

To write the report, you need a team of at least three people: a medical writer, an information specialist, and a statistician.

In addition, you need a written procedure for CR Report writing, a report template (recommended but not required), and access to literature databases, such as PubMed and Embase (for marketed devices). PubMed is operated by the U.S. National Library of Medicine and is accessible through an Internet browser. PubMed provides free access to abstracts from 5,400 worldwide journals in 39 languages, dating from 1947 to the present.

Embase, on the other hand, is not free. It provides access to an additional 2,000 European medical journals, and thus is indispensable since the purpose of the report is to enable marketing of the device in Europe. Embase access costs at least $7,000 per year, so contracting for the search or sub-contracting the time from a third-party may be more economical.

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A Three-Legged Stool

First Leg: Literature Review

The first leg of a Clinical Evaluation Report is to evaluate the existing literature to determine if it supports the safety and performance of the device for its intended use. For better or worse, investigators unknown to you may have volunteered their services in testing your device. The Global Harmonization Task Force (GHTF) Study Group 5 document "Clinical Evaluation" and MEDDEV 2.7.1 Rev 3 guidances describe how to perform literature reviews.

The medical writer, with your assistance, will follow these steps:

1. Define the key questions.
2. Identify the databases to search (e.g., PubMed, Embase, MAUDE, Cochrane).
3. Define the scope of the search and search strategies using a qualified information specialist.
4. Scan through the abstracts to identify articles for review.
5. Acquire the full text of the articles.
6. Weight the articles based on technical significance and discard the least significant ones.
7. Have a statistician weight the remaining articles based on statistical significance and discard the least significant ones.
8. Evaluate in detail only the highest-weight articles, perhaps five to 25 per intended use.

Although not required, prepare a literature review annex to the main CE Report to document the literature review process. It includes several required elements, such as the search strings used by the information specialist, a list of abstracts scanned, a list of articles reviewed, their weights and justification for those weights, and full-text copies of the articles.

Second Leg: Sponsored-Study Review

The second leg of the CE Report is for the writer to review any existing clinical investigations that your firm has sponsored. Review these data separately from the literature because you have access to more details. In addition to the results, confirm that the studies complied with applicable regulations. Ask questions such as, "Was the Declaration of Helsinki followed?" and "Were adverse events resolved?" If a study was not compliant, mention it in the report without using the data, and explain why you are not using the data.

The writer then evaluates the valid study results to see if they support the safety and performance of the device for its intended use.

Although not required, prepare a separate sponsored study review and attach it to the main CE Report as an annex.

Third Leg: Risk Management Review

In the third leg, the medical writer examines the complaint file from the risk management system. Does the file indicate that the device is safe and complaint handling, as dictated by the risk management system, supports the safety and performance of the device for its intended use?

Although not required, a table of the complaints reviewed and methods for mitigation may be annexed to the main report.

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The CE Report

With these three reviews in hand, the medical writer determines whether the combined data support the device's safety and performance for the intended use, or if additional clinical data are needed. If new clinical data are needed, management will have some decisions to make.

The Technical File

If the data are sufficient, file the CE Report in the device's Technical File. File a document describing the writer's evaluation process in the quality management system. Wait for a visit from a Notified Body investigator.

Author

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