Clinical Evaluation Reports – Tying it All Together (article 2 of 3)

Forward:

MEDIcept, an international medical device consulting firm is presenting this as an ongoing series of articles focused on Clinical Evaluation Reports in the medical device industry.

Our team at MEDIcept has worked with a variety of manufacturers to develop Clinical Evaluation Reports (CERs) for a wide range of devices and device classifications; with these articles, we will provide an overview of the steps for completing a CER and describe the benefits of bringing clinical and safety data, risk analyses, and product literature (e.g. labeling and manuals) together in one place to provide an objective, transparent evaluation of device safety and performance. The last article gave a quick overview of CERs and the need for an internal Standard Operating Procedure. This article will discuss the elements of the CER.

If you have questions or comments on the issues discussed, or if you have recommendations for topics to consider in the future, please let us know. 508-231-8842.

Clinical Evaluation Report Elements

Clinical Investigations:

The element of the CER that gets the most attention is the Clinical Literature Review. While it is an important piece of the puzzle, it’s not the whole report. Just to de-emphasize it a bit more, we’ll start this section with a discussion of Clinical Investigations.

Clinical Investigations are clinical studies conducted by the manufacturer to assess the performance of the subject device (or an equivalent device) for its intended use. Clinical Investigations are not required elements of the CER, but when they are available, they provide valuable information to evaluator. Since the Clinical Investigation typically focuses directly on the subject device, the results can provide valuable evidence of device efficacy and safety.

When including a clinical investigation in a CER, the guidance requires that the author also include supporting information to describe the conduct of the study (e.g., study protocols, evidence of IRB approval, etc.). While the clinical investigation report (or reports) will typically be presented as an appendix to the CER and will contain more detailed background information when compared to clinical literature, it will ultimately be appraised in the same manner as other clinical data (more on that later). That said, since the clinical investigation report typically addresses the exact same device that is the subject of the CER, it will typically be considered a key element of the overall evaluation.

Clinical Literature Review:

The Clinical Literature Review is an important, and usually the most time consuming, portion of the clinical evaluation process. In a nutshell, the clinical literature review is the process of identifying
relevant, published clinical studies, screening and appraising those studies for relevance and data quality, and summarizing the results in a complete and unbiased manner. The following are the key steps in the clinical literature review process and a few recommendations for how to complete each step in a complete and efficient manner.

- **Literature Search**: This first step in the process includes developing a literature search strategy and conducting the search. The output is a list of citations to be screened and appraised. The challenges that you will run into when conducting the literature search will depend upon the technology being evaluated. If the technology has a long history of clinical use with limited innovation, you may have difficulty finding any relevant clinical literature – it’s just not a technology that clinicians spend time researching. Many Class I and some Class II devices fall into this category. At the other extreme, if a large body of literature has been published for a more novel device, the challenge may be to design a search that effectively identifies relevant studies, thereby reducing the time and effort associated with screening abstracts in the next step of the process. In all cases, we recommend that evaluators consider the following:

  - **Search terms**: It is best to involve individuals with direct clinical expertise when developing search terms not only to help identify terms to identify which articles to include; but also to identify terms to help exclude articles (particularly when there is a large body of literature). Typical exclusion terms include non-human studies, single-subject case studies, indications that are not intended and publication dates constraints (e.g., limiting the timeframe to a period most relevant for the subject device).

  - **Search strategy**: Involve the talents of the literature search expert at MEDIcept. Individuals with expertise in developing search strategies i.e., accessing the right databases and constructing the Boolean search logic (which must be reported in the CER), will help to ensure that your search is comprehensive and that the output is on target. Literature searches are like casting a net into the ocean, without the right expertise you may not get what you want at all, or you may get what you want, but you end up having to sort through a lot of “carp” (sorry about that). MEDIcept will typically also have access to Embase, which provides a more global view of the available research compared to Medline or PubMed. That said, we have found that searches of multiple databases can be valuable.

- **Screening**: Even the best search strategy will return citations to studies that are not relevant for your device. Each abstract will need to be reviewed for relevance. As you identify studies that don’t fit, keep track of the rationale for exclusion. To ensure the transparency of the process, you’ll need to be able to identify in the final report why specific studies were excluded.

- **Appraisal**: Each study will need to be appraised for relevance and data quality. For this step, the full text of the article is needed. A complete appraisal requires knowledge that you are unlikely to find in a single individual. An individual with clinical expertise is needed to assess the relevance of the identified studies (or at least review and approve the overall appraisal) while a
biostatistician is a valuable asset when reviewing the study design and analytical approach. MEDIcept has access to multiple biostatisticians with experience in CERs. The guidance provides suggested criteria to use in this appraisal, but other approaches are acceptable—as long as they meet the spirit of the guidance and are approved by company management (typically in the CER SOP).

- **Clinical Literature Summary**: Once the relevant, high quality studies are identified, it’s the evaluator’s job to summarize the findings. We’ve found that pulling key information from the studies into a table prior to drafting the prose summary is a valuable step. The table supports both the objectivity and the transparency of the report, by presenting both positive and negative results in a similar manner—there’s no opportunity to emphasize one set of results over another. Also, the table serves as a helpful tool prior to drafting the prose summary (particularly when there are a lot of studies to summarize) — helping to make sure that important information doesn’t get lost along the way.

**Internal and External Safety Data**

Just as Clinical Investigations and Clinical Literature respectively provide internally and externally generated efficacy (and safety) data, post-production feedback (i.e., complaints) and Regulators’ safety databases (e.g., FDA’s MAUDE) provide internally and externally generated safety data.

For currently marketed devices, your internal complaints management system should be able to provide very relevant data related to the types of operational failures and user errors that are associated with your device. If your device is new to the market, your complaints database can still be valuable. Feedback on other devices in the same product family can provide valuable insight into the types of problems that should be expected with the new device.

It’s important to present the data in a manner that provides the evaluator with a clear understanding of the rate at which different device problems occur. Typically, these data should be presented in terms of the number of uses of the devices (e.g., 1 complaint per 10 or 1,000 or 1 million uses). With data in this format, the evaluator can confirm whether the assessment made in the risk analysis is accurate (see the discussion of reviewing the risk analysis below). Remember, the objective is to weigh the risks of the device against its benefits. While you don’t need to reassess the full risk analysis, you do need to make sure that the current risk analysis accounts for all of the safety issues identified in the clinical evaluation.

External safety data is not as reliable (and potentially not as relevant) as internal data, but it can provide valuable insight into safety issues that may otherwise be missed. The FDA’s MAUDE database is the main source for information on device failures and product recalls. The MHRA’s Medical Device Alert (MDA) system can have some useful information, as can Health Canada’s Recall Listing, but neither provides the depth of information that is available in the MAUDE database. That said, the MAUDE database is a largely unfiltered repository for potentially serious, but sometimes irrelevant, erroneous, and/or
duplicative allegations. The results of a MAUDE search can provide an indication of the types of failures and harms that could result from the use of a particular device or family of devices; however, it provides no sense of the rate at which these problems occur.

In our evaluations, MEDIcept typically checks to ensure that the risk analysis addresses the major types of failures/harms associated with a device (particularly those alleged to cause an injury or death). If we find evidence that some of these risks are not addressed in the risk analysis, it suggests that the risk profile of the device is not up to date and needs to be revised before the assessment of risks and benefits can be fully evaluated.

**Risk Analysis and Product Literature Review**

Once the clinical data are collected, it’s the job of the evaluator to review the risk analysis to ensure that it addresses all of the safety issues observed with fielded devices, and the product literature to ensure that it clearly communicates the intended use of the device, contraindications, and appropriate usage directions and warnings. If the evaluator finds that all of the safety issues identified in the clinical investigation, clinical literature, and internal/external safety sources are captured in the current risk analysis, he/she can begin drafting a final report with confidence that the company has been diligent in its efforts to assess risk. The greater the number of safety issues missing from the risk analysis, the lower the evaluator’s confidence in the overall risk assessment.

The CER is, in fact, a very important check on the risk assessment. When preparing a device to be released to the market, the CER should be completed in parallel with the risk analysis so that issues identified during the clinical evaluation can be fed into the risk assessment. Later in the lifecycle of the device, updates to the CER are important inputs to the risk assessment to be sure that it addresses the full range of issues observed in the field.

The review of product literature is conducted to ensure that the indications for use and product claims are in line with, and supported by, the clinical data. If the product literature contains specific indications or claims and there is no evidence that those indications/claims are supported by clinical data, it’s time to take a step back and reassess the product literature. Similarly, if the risk analysis contains significant risks and the only mitigation (or perhaps the major mitigation) is communication through product literature – it’s important for the evaluator to check to ensure that those messages are clearly stated.

MEDIcept is a medical device consulting firm dedicated to helping pre-revenue and established medical device manufactures with the complexity of international regulatory requirements.

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