Devices: Clinical Evidence gaps matter & how to close

Finding evidence on a clinical topic is often challenging. The number of medical articles published in MEDLINE increases annually. Searching for the hypodermic needle in the thickening evidence haystack takes time, resources, and considerable skill in devising the right searches and inclusion criteria to answer a clinical question. Ways to maximize the yield of relevant studies while excluding irrelevant ones have evolved over time. Yet identifying relevant studies is easy compared with showing the alternative – that there is a gap in the evidence for the topic.

To put the problem into a medical context, finding just one of those thousands of clinical studies is relevant and you know there is at least some evidence to answer your question; but to be sure there is none, be prepared to screen a lot. Fortunately, it is possible to identify a gap in the evidence without having to process every article ever published. However, a systematic approach is necessary to be sure that a gap really does exist, and to minimize bias in coming to the conclusion - in other words, systematic reviews for identifying such gaps are definitive, rather than just informative , narrative assessments.

Why do evidence gaps matter?

Knowing early on in the product development process that there are gaps in the evidence gives manufacturers time to generate the evidence needed to demonstrate the value of their product. If, for instance, identification of an evidence gap relating to a specific subgroup could facilitate the design of a study to fill that gap. This might give a new product and edge over competitors with no specific evidence of benefit in such patients. Another example is the evidence on the prevalence or incidence of conditions, which is often sparse and incomplete for all populations and regions of interest. Identifying and addressing the gaps here can ensure up-to-date evidence exists for the relevant patients by the time the product is ready for launch.

What is evidence gap?

A complete lack of studies on a topic is clearly a gap; but how much information is required to be confident in making a decision? In other words, how do we know that we don't yet know? One approach to working this out with regards to date on efficacy is to summarize the available evidence as follows.

- **Study Results** are highly unlikely to be changed by future studies
- **Plausible Results** are consistent, based on numerous observational studies, which would probably not change significantly if evaluated through clinical studies.
- **Uncertain Results** would most probably change, in both size and direction of estimate, if evaluated through clinical studies
- **Unknown Results** are those for which no studies have been identified.

Topics with uncertain or unknown results would, by this classification, be evidence gaps, as there is not yet enough evidence to know the answer for sure.

Where should we look for evidence?

For most medical topics, searching the PUBMED/MEDLINE database will identify around 80% of all known clinical and economic studies. However, for some topics, other database maybe more useful than MEDLINE for European studies and topics relevant to common family disorders or orthopaedic and rheumatology topics; There are several other country and therapeutic specific databases that you can search further.

How should we search?

Literature reviewers spend substantial time devising search strategy for electronic databases that identifies as many relevant papers as possible (maximum sensitivity), while minimizing the number of irrelevant abstracts that has to be screened out (maximum specificity). Where the review is to inform national guidance on management of a condition, Maximum sensitivity is usually a requirement.

For most other situations, though, a more pragmatic approach is sufficient. Accordingly, several studies have identified that most effective balance is to aim for around 80%-90% sensitivity and 80% specificity.

Other approaches advocated by the Cochrane Collaboration and NICE can help to identify additional evidence, but have often been found to offer a poor return on the substantial investment required. These include the searching of additional databases, the examination of citation lists of included studies, the hand searching of key journals, the searching for conference abstracts, and contacting authors of included studies for suggestions of additional unpublished data: that is, many of the emblematic features of a “gold standard” review. It would seem sensible to limit these methods to more complex topics where it is difficult to develop a structured search.

To conclude, it is crucial for the manufacturers to identify relevant evidence gaps early in the development process of a new product. A pragmatic approach to systematically searching for evidence and identifying the gaps is possible, and, if implemented sensibly, can provide a rigorous, transparent and timely answer to inform future evidence generation.

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