US

Clinical Data in Support of US FDA 510(k) Submissions

How to ensure you are collecting the right data needed to support your US medical device regulatory submission



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More Clinical Data for FDA 510(k) Submissions

Recently, you may have noticed that FDA is requesting prospective human clinical data for some 510(k) submissions. The 510(k) program is designed to use "substantial equivalence" to a predicate device to demonstrate clinical efficacy, while conformance to the required consensus standards and technical equivalence to the predicate device demonstrates product safety. Despite this, the FDA requires clinical data for Class III devices, and more recently for some Class II devices (particularly for OTC devices).

Conducting human clinical studies

Conducting a human clinical study is a significant and expensive undertaking. Prior to conducting a study, the sponsor should understand the regulatory requirements pertaining to their clinical study.

Failure to understand these requirements could lead to the FDA rejecting the clinical study results, a large waste of money and significant delays in obtaining marketing approval.

Failure to comply with clinical regulatory requirements can also, depending on the nature of the issue, result in serious compliance actions.

It's important to note that clinical studies may be conducted at more than one point in time. Initial studies may evaluate safety or even feasibility with a relatively small sample size, while later studies, termed pivotal studies, frequently focus on efficacy. This is somewhat analogous to the Phase 1, Phase 2 and Phase 3 studies used in drug development, but is not standardized for device studies.

Developing an Outline for the Clinical Research Protocol

Developing an outline for the clinical research protocol is a critical first step, as the clinical protocol drives every other aspect of the study. Once many of the issues discussed below are resolved, a plan for moving forward with the study can be completed. A third-party Clinical Research Organization (CRO) can be very helpful in guiding a sponsor through various requirements and assist in protocol preparation, IDE applications, etc.

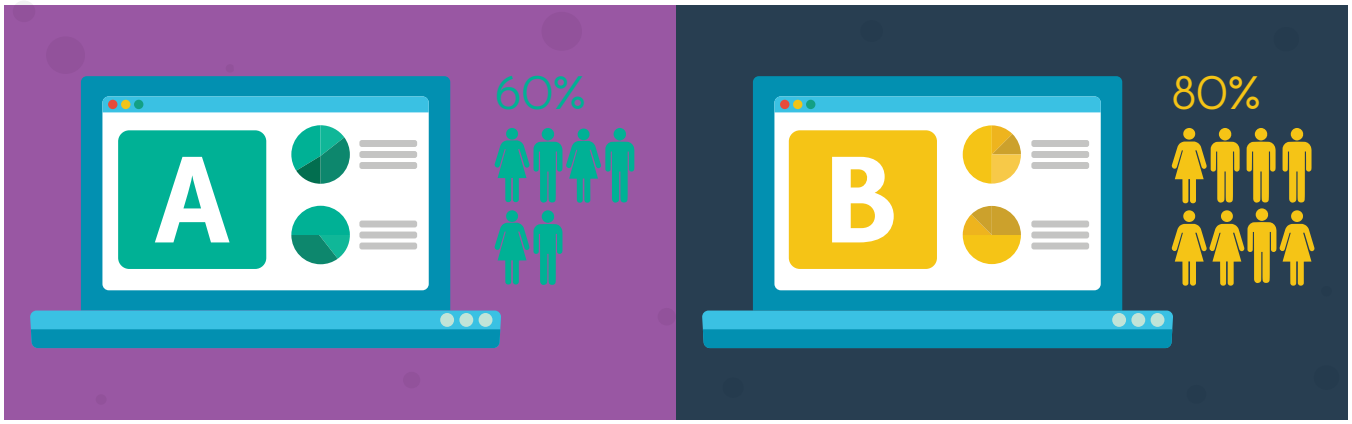
1. Develop the research question

A clinical study must be designed to address one or more specific questions. For example: Is my device safe to use as described in the indications for use? Does my device achieve its intended purpose (efficacy)? Is my device as good as (or perhaps better) than the current standard of care?

There are several different approaches to this. While a primer on protocol writing is beyond the scope of this white paper, the most common and straightforward approach is the comparator study. In such a study, the sponsor will compare the use of its device to another device. This comparator device is frequently the device that is currently the "standard of care" for the intended therapeutic or diagnostic purpose. If this device is also your chosen predicate for a Class II device, all the better.

In a comparison study, there are two common options. One option is termed a "superiority study," where the hypothesis being tested is that the sponsor device is better than the comparator device. These parameters, referred to as end points, must be very clearly described and must be important to clinical efficacy. The other common option is the "non-inferiority" trial. In such a trial, the sponsor is hoping to show that his device is at least as good as the comparator device.

To blind or not to blind? In many studies, the identity of the research product and comparator product are hidden from the subject (single blind); the subject and the Principal Investigator (PI) (double blind); or subject, PI and sponsor (triple blind). While blinding a study helps reduce the possibility of various biases, it is difficult to do with a device. Medical devices are much more obvious than, for example, one pill compared to another. Therefore, many device studies are not blinded and known as open label studies. Consider whether having the identity of the device known will be a possible source of bias that could affect the outcome of the study.



2. Determine the sample size for the study

Once the basic research question is posed, you must determine how large of a sample is needed. The sample size is driven by exactly what the study is trying to prove. The larger the expected difference between the research device and the comparator device, the smaller the sample size may be. However, there are many critical variables involved in determining the appropriate analyses, number of subjects required, etc.

It is highly recommended to consult a biostatistician to determine the appropriate sample size. Too small a sample size, termed an underpowered study, can invalidate the study results.

Also, account for the fact that not every subject will complete the study and not all data will be useable. Again, consult a biostatistician.

3. Implement clinical data management

The next step is to determine the following issues:

- What data will be collected,
- The time intervals in which data will need to be collected,
- Who will collect the data,
- How will the data be recorded and what forms will be needed.

Do not forget to consider how the data will be received and analyzed. It is highly recommended to outsource clinical data management to a competent data management company that is in the business of collecting, managing and outputting clinical data. There are many complexities as well as computer and software validation requirements involved.

Some studies may also utilize an independent third party, called a Data Safety Monitoring Board (DSMB), which serves to protect the subjects should the data indicate a safety issue. Each of the functions requires fees which are borne by the clinical sponsor.

4. Define statistical evaluation of data

The statistical evaluation of the data must be pre-defined and described in the protocol. There are many varied statistical tests, from the relatively easy and straight forward to the very complex. Depending upon the type of study to be conducted, consult with the biostatistician to assure that the correct statistical tools are selected.

These are a few of the concerns to consider when creating the research protocol. A CRO may be very helpful in preparing the protocol; the National Institute of Health (NIH) also has several templates available on their website.

Defining Regulatory Requirements

Once the protocol outline is created, the regulatory requirements can be defined. There are two main options:

- Studies involving significant risk require an Investigational Device Exemption (IDE) from the FDA before the clinical study may begin.
- Studies determined to be non-significant risk may be conducted without an IDE.

In the US, a duly authorized Institutional Review Board (IRB) determines whether a study is significant risk.

ALL studies need to be overseen by an IRB (Ethics Committee outside the US). In some cases, the IRB may determine and document that a study is non-significant risk and may proceed without an IDE approval from FDA.

Note that most major institutions, such as universities and teaching hospitals, have IRBs. There are also commercial IRBs that may be utilized. In all cases, utilizing an IRB is required and involves payments to the IRB. Note that once the protocol is finalized, it must be submitted to the IRB for approval. Each and every revision to the protocol likewise needs to be submitted and approved by the IRB.

If an IDE is required, this involves a lengthy process where FDA will review the proposed protocol and determine if the study may proceed.

Quality Requirements for Clinical Studies

Once approved, with IDE if required, the study may begin. Similar to device manufacturing, clinical studies have their own set of quality requirements or "good clinical practices." These are defined for medical devices partially in 21CFR 812, but additionally in ICH E-6 Good Clinical Practice. While there are minor differences between these two requirements, both should be consulted.

As defined in both the CFR and ICH, sponsors have a defined set of requirements. Among these are:

1. Obtaining informed consent from all subjects PRIOR to beginning any testing. This is critically important and a legal requirement. Use of children in a clinical study comes with additional requirements. Failure to strictly follow informed consent requirements is a serious issue and can lead to having the study invalidated, and sanctions against the sponsor.

2. Carefully evaluating the person(s) who will conduct the study, referred to as the "Principal Investigator." Qualifications must be documented and should be appropriate to the study being conducted. A medical professional (not necessarily a physician) appropriate to the study design and therapeutic area is required to manage the actual clinical setting.

3. Studies must be monitored according to a formal documented monitoring plan. This is where an independent person reviews the study data to ensure that the data is genuine, the proper documentation is collected, informed consents are on file, etc. This is best outsourced to organizations that specialize in this area, such as a CRO.

4. Sponsors must have approved, documented procedures covering good clinical practice. These procedures supplement the Quality Management System (QMS) and are controlled in the same manner as the rest of the QMS. A functional and compliant QMS is a requirement BEFORE a product to be used in a human clinical trial is manufactured. These products are used on humans; for medical devices, only design controls (820.30) are required. This contrasts with pharma, where late-stage studies require full GMP compliance.

5. Clinical studies are also subject to FDA inspection. During inspection, an FDA investigator may review the sponsor's and Principal Investigator's adherence to regulatory requirements. Failure to comply, particularly with the requirements pertaining to subject safety, carry significant penalties including debarment, large fines and even criminal prosecution in extreme cases.

Compiling and Analyzing Data

After the data is collected, it must be compiled and analyzed per the pre-defined statistical analysis plan and a report must be issued. It is critical that ALL data is presented.

"Cherry picking" only the favorable data is a serious offense.

If including clinical data in a 510(k) submission, assure that the study report is complete, has been reviewed by someone competent to do so, the conclusions are clear and support the research question, the conclusions are well-supported by the data, and the various FDA forms (financial disclosure, ClinicalTrials.gov) are included in the submission.

Conclusion

When considering the financial investment required and the scientific and regulatory complexity involved, early involvement of vendors such as CROs, data management companies, statisticians and the FDA (Pre-Sub Meetings) are highly recommended. Addressing concerns prior to initiating the study is a much better strategy than attempting to fix it after the data is generated.

Learn more about the FDA testing requirements

If you enjoyed this whitepaper, we know you will like our in-depth whitepaper explaining FDA requirements for usability studies. We discuss how to conduct a usability study, the difference between usability studies and clinical studies, when these studies are necessary, and much more.

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About the Author

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