



# Clinical data in support of U.S. FDA 510(k) submissions

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

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# More Clinical Data for FDA 510(k) Submissions

The U.S. Food and Drug Administration (FDA) requires evidence that a medical device is as safe and effective for its intended use as a legally marketed device. Generally, 510(k) submissions are used for certain devices, mainly those considered to present moderate risks (Class II), but also some low-risk (Class I) and high-risk (Class III) devices. These medical devices are submitted to the FDA for evaluation and clearance prior to marketing. Because 510(k)s are intended to demonstrate that a device is “substantially equivalent” to a legally marketed predicate device in safety and effectiveness, after receiving FDA clearance, the device becomes acceptable for use.

Most 510(k)s rely on non-clinical testing to demonstrate this equivalency, including conformance to standards recognized by the FDA. The testing required depends on the specific risk and generic type of the device.

The FDA requires clinical data for approximately 10%-15% of 510(k)s. This helps the FDA confirm that the device truly is as safe and as effective as a predicate device in cases where non-clinical data alone has not been deemed sufficient.

The FDA is expected to apply the least burdensome approach that is adequate to address safety and performance when evaluating medical device submissions, including clinical requirements. Therefore, they may consider both real-world evidence and clinical studies specifically designed to support a specific submission. Real-world evidence is clinical evidence from products that are in use and is generally most applicable for products that have been on the market in other regions or for products where a new intended use is desired.

## Conducting human clinical studies

Conducting a human clinical study is a significant and expensive undertaking. Prior to conducting a study, the sponsor should endeavor to understand exactly what needs to be answered in a clinical trial, if there are other options for obtaining clearance and the regulatory requirements pertaining to their clinical study.



**Failure to understand clinical study requirements could lead to the FDA rejecting the results, wasted money and significant delays in placing the device on the market.**

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 and/or feasibility with a relatively small sample size (similar to a Phase 1 drug study), while later, generally larger studies, termed pivotal studies, usually focus on effectiveness (similar to a Phase 3 drug study). In many cases, when clinical studies are used to support a 510(k), only a single study is necessary.

# Determining the clinical data necessary to support a 510(k)

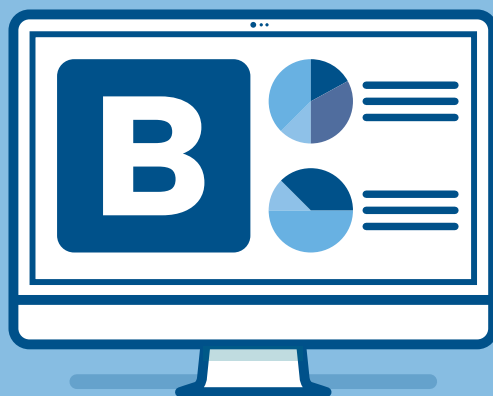
## 1. Determine if the 510(k) requires clinical data

The first step is to determine if your device requires clinical data and, if it does, the general question that it needs to answer. This requires that your company understand the generic device classification your device will be considered, as indicated by an FDA product code. Use the product code and generic device classification to identify applicable guidance documents and consensus standards. Additionally, review recent 510(k)s for products in that device classification to determine if clinical data was required, which will be included in the 510(k) summary if provided to the FDA.

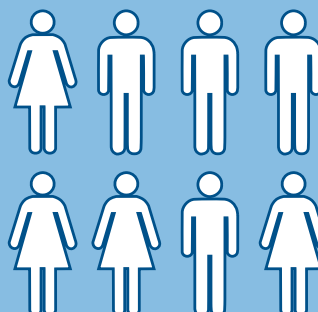
If any of the relevant guidance documents, consensus standards, or recent 510(k)s indicate that clinical data was necessary, it is likely that clinical data will be required for your device as well. In general, some indication as to the reason for that study is also provided. A clinical study is generally used to determine safety and/or effectiveness.



60%



80%





## 2. Determine if real-world evidence supports substantial equivalence

If clinical data is required, real-world evidence can be considered to determine if it might provide the necessary information. In general, this will only be applicable if the device is already marketed, either in a different market or for a different intended use.

Real-world evidence may be derived from electronic health records, data from product and disease registries, patient-generated data, or any other source that can substantiate information regarding the usage, potential risks and potential benefits. It is much cheaper and generally faster to collect and analyze data that can provide real-world evidence than to run a new clinical study, where applicable. However, real-world evidence can be of variable quality. If the intent is to use this to support a submission, the sponsor should first review it for alignment with the FDA guidance “Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices.”

Because of the likelihood that a 510(k) would either be found not substantially equivalent or need to be withdrawn if the FDA does not accept this evidence, it is highly recommended that the sponsor engages with the FDA in a Q-Submission prior to 510(k) submission to gain alignment on the acceptability of the evidence.

## 3. Describe the research requirements

A clinical study can be thought of like other design requirements for a medical device. First, determine the user need and/or design input that drives the need for the clinical study and the necessary acceptance criteria. Is the reason a clinical study is necessary described in a guidance document, consensus standard or by a predicate device? Is the need for a clinical study because you have made some changes, such as to the surgical technique to implant a device, and you need to confirm that this modification does not create new questions of safety or effectiveness?

In some cases, the clinical trials required to support a 510(k) are not required to be statistically significant pivotal trials, but rather are smaller trials intended to confirm a specific question. For example, studies in alignment with the FDA’s early feasibility studies program often do not need to be statistically significant. Therefore, determining if statistical significance is required is important as a basic design input for the clinical trial.

If the research requirements are not clearly specified, then the clinical trial cannot be designed in a manner to provide the evidence that the FDA believes is necessary to demonstrate substantial equivalence.

# Developing a clinical research protocol

## Develop a clinical research protocol

Developing an outline for the clinical research protocol is a critical 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. This study needs to address the question(s) that have been determined necessary to support substantial equivalence.

The best references to help clarify clinical requirements are those from the applicable guidance documents, consensus standards and predicate device 510(k) summaries. One or more of these resources will often provide details about the study type, statistical evaluation used and sample size.

A full primer on protocol writing is beyond the scope of this white paper, but this provides an outline of points to consider. A third-party clinical research organization (CRO) can be helpful in guiding a sponsor through various requirements and may assist in protocol preparation, IDE applications and more. The National Institutes of Health (NIH) has several clinical research protocol templates available on its website that may be utilized.

Because of the great cost and time resources associated with conducting a clinical trial, before a trial is initiated, it is recommended to engage with the FDA in a Q-Submission prior to beginning the study to gain alignment on the likely acceptability of the results of the clinical research if conducted in the manner described in the protocol.

### 1. Determine the study type

The most common and straightforward approach is a comparator study. In such a study, the sponsor will compare the use of its device to another comparator device. In most cases, this should be the predicate device to which the sponsor intends to present their

device as being substantially equivalent. It would generally be within the same product code and have the same intended therapeutic or diagnostic purpose. The comparator may be considered the current “standard of care” and must already be legally marketed.

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’s device is better than the comparator device. These parameters, referred to as endpoints, must be very clearly described and must be important to clinical effectiveness. The other common option is the non-inferiority trial. In such a trial, the sponsor is hoping to show that its device is at least as good as the comparator device. Either type is generally acceptable to support a 510(k). A superiority study may allow additional marketing claims, which can be important in market acceptance. Generally, this requires more patients to reach statistical significance, leading to a longer and more costly study.

To blind or not to blind? In clinical studies, the identity of the research product and comparator product may be 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 may be difficult to do with a device. Medical devices are usually much more obvious than, for example, one pill compared to another. Therefore, many device studies are either only single-blind or are not blinded, known as open-label studies. Consider whether having the identity of the device known will be a possible source of bias that could affect if the study can adequately answer the questions it needs to address.



## 2. Define statistical requirements

The statistical evaluation of the data must be pre-defined and described in the protocol. In some cases, statistical significance is not required for studies that are intended to support a 510(k). However, in general, a statistically significant trial is expected.

There are many varied statistical tests, from the relatively easy and straightforward to the very complex. It may be advantageous to consult with the biostatistician to ensure that the correct statistical tools are selected.

## 3. Determine the sample size

The sample size is driven by determining exactly what the study is trying to prove and the statistical requirements that are necessary to support the submission. The larger the expected difference between the research device and the comparator device, the smaller the necessary sample size. There are many critical variables involved in determining the number of subjects required, including the study design, the hypothesis being tested (superiority versus non-inferiority), the primary endpoint, the clinically significant difference margin, the necessary level of significance (usually 5%), the necessary power of the study (usually  $\geq 80\%$ ), the expected drop-out rate of subjects, and the expected percentage of data that will be usable (within the required follow-up times, etc.). In general, the FDA accepts smaller studies for rare conditions based on the feasibility of the study. The FDA has also started to consider whether a patient would consider a difference to be significant, independent of what might be considered clinically significant.



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, resulting in the necessity for an additional clinical study.

## 4. Determine clinical data management

The next step is to determine:

- i. What data will be collected.
- ii. The time intervals in which data will need to be collected.
- iii. Who will collect the data.
- iv. How will the data be recorded and what forms will be necessary.

Do not forget to consider how the data will be received and analyzed. Unless a company has a specific, highly skilled department to address this requirement, it is 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 to be considered.

Some studies may also utilize an independent third party, called a data and 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.

## 5. Determine if an adaptive design will be utilized

In certain cases, the FDA allows for prospectively planned modifications to be made to a clinical study design during the study itself. Usually this is not necessary for a clinical trial to support a 510(k), but a sponsor may wish to consider this and is advised to reference the FDA's guidance "Adaptive Designed for Medical Device Clinical Studies" if interested in pursuing this tactic.



When finalizing a clinical research protocol, it is highly advisable to engage with the FDA via a Q-Submission meeting to ensure that the FDA agrees that the study will meet their expectations to decide on whether the device is substantially equivalent to the predicate device.

# Defining clinical research regulatory requirements

Some regulatory requirements are necessary for any clinical study to be in alignment with Titles 21 and 45 of the Code of Federal Regulations. Among these are:

1. Obtaining institutional review board (IRB) and approval of the clinical protocol to conduct the trial according to the protocol. Most major institutions that regularly conduct clinical investigations, such as universities and teaching hospitals, have IRBs. There are also commercial IRBs that may be utilized. Note that changes to protocols need to be submitted, reviewed and approved by the IRB.

**The FDA has published multiple guidance documents to communicate IRB responsibilities.**

2. Obtaining informed consent from all subjects prior to beginning any testing. This is critically important and a legal requirement, except in certain narrowly defined cases which are usually outside of the realm of a study to support a 510(k). 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.

**If a sponsor believes that it is impractical or impossible to gain informed consent, refer to the FDA guidance “IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More than Minimal Risk to Human Subjects” for information on if a waiver may be acceptable.**

3. 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 conducted. A medical professional appropriate to the study design and therapeutic area is required to manage the actual clinical setting. This may be a surgeon, physician, dentist, or similar medical professional as applicable to the medical device evaluated.

**Various information will need to be gathered from the investigators, including their qualifications, financial disclosure, etc.**

4. Studies must be monitored according to a formal documented monitoring plan. This is where a person independent from the study investigator(s) reviews the study data to ensure that the data is genuine, the proper documentation is collected, informed consents are on file, etc. For small companies, this is usually outsourced to organizations that specialize in this area, such as a CRO.
5. Sponsors must have approved, documented procedures covering good clinical practice (GCP) in compliance with 21 CFR 812. These procedures supplement the quality management system (QMS) and are controlled in the same manner as the rest of the QMS. Functional and compliant design controls are required before a medical device to be used in a human clinical trial is manufactured. The International Council for Harmonization (ICH) provides additional guidance in ICH E-6 Good Clinical Practices.
6. 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.



**All clinical studies intended to determine or confirm the safety and/or effectiveness of a medical device need to be overseen by an IRB (known as an Ethics Committee outside the U.S.), which reviews and monitors clinical studies to protect the rights, safety and welfare of human research subjects.**

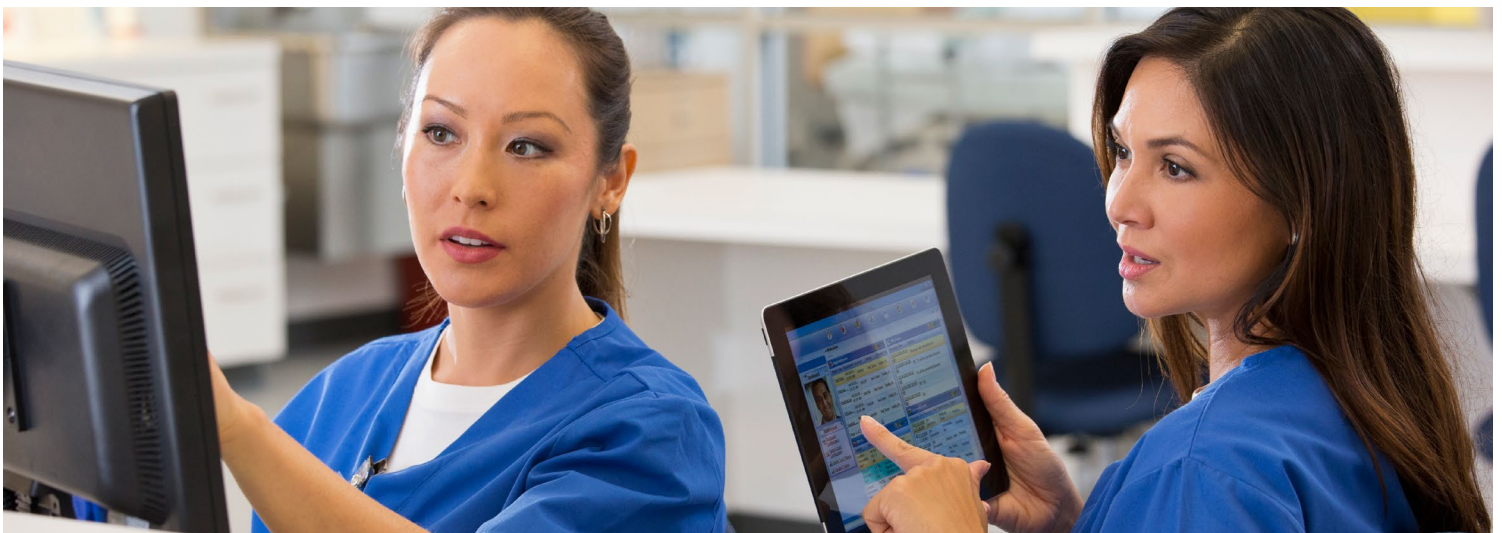
The main regulatory requirement variable involves Investigational Device Exemption (IDE) requirements, in alignment with 21 CFR 812. Studies that involve significant risk, as described in the FDA guidance “Significant Risk and Nonsignificant Risk Medical Device Studies,” require that an IDE submission be made to the FDA and approval be granted from the FDA prior to the beginning of the clinical trial as well as periodic progress and/or a final report. Studies that are determined to present nonsignificant risk do not require a submission

to the FDA prior to study initiation and do not require periodic or final reports, but must follow other requirements, often referred to as abbreviated requirements.

The sponsor is responsible for making the initial determination on whether the study is a significant risk or nonsignificant risk study, and the IRB is responsible for making the final determination prior to study initiation. The FDA is available for consultation and retains ultimate authority on this determination.

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

Once IRB and, if necessary, FDA approval has been granted, a study to support a 510(k) must be registered with [clinicaltrials.gov](https://clinicaltrials.gov). After this is done, the clinical trial may begin.



## Submitting clinical data

After the data is collected, it must be compiled and analyzed per the pre-defined plan and a report must be issued. It is critical that all data is provided to the FDA and has been summarized accurately.

When including clinical data in a 510(k) submission, ensure 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.



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





# Conclusion

Clinical studies are expensive, require significant time and are complex. When a clinical study is required to support a medical device regulatory submission, it is important to understand exactly what questions need to be addressed to satisfy the FDA's expectations. Therefore, involvement by specialists who can confirm the regulatory requirements, determine if real-world evidence can be used to provide the necessary evidence, help design the clinical protocol and monitor the clinical trial are recommended. Additionally, meeting with the FDA via a Q-Submission is highly recommended. Modifying a protocol to address potential FDA concerns prior to finalizing a study protocol can help ensure that the clinical trial will allow the FDA to clear a 510(k) in a timely manner and minimize the chance of needing to conduct an additional clinical trial.

# Learn more

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## About the author

**Robert Seiple, RAC (U.S.)** is a senior regulatory consultant at Emergo by UL. He has over 35 years of experience with quality assurance and regulatory affairs in regulated industries, including medical devices, pharmaceuticals and clinical research. His areas of expertise include 510(k) submissions, CE marking, quality system implementation, training and auditing.

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