Introduction to Clinical Trials Management

Table of Contents

Purpose of this workbook and how to use it

Welcome, you have an idea for a medical device! As part of your product development, it's important to determine if you need a clinical trial in order to get the product on the market, and also to obtain optimal reimbursement once you do.

In this playbook, we discuss when to start thinking about clinical trials and how to determine the right clinical trial for your product.

Collaboration

This playbook is written in collaboration with Boulder Clinical Science, a clinical research organization that specializes in clinical trial protocol design and implementation. They have vast experience with both the drug and device development cycles and can execute a clinical trial that best suits the product development strategy. For information about developing and executing clinical trials, you can email Bcs.Contact@Boulderclinicalscience.com.

Here's how to get the most out of this workbook:

Download/Print this workbook onto your desktop.

Email support@enzyme.com for any questions.

Now let's get started!

Overview

Clinical trials are a complicated weave of science, clinical medicine, logistics, contract negotiation/business, and most importantly ethics. Many companies underestimate the difficulty and cost associated with implementing a clinical trial successfully.

A clinical research trial is just that; research with a null hypothesis. The outcome is not certain, and the first clinical trial is essentially a big "bet" that your device will be safe and/or efficacious. Sometimes, the gamble may be so large that in fact, if the trial fails, likely so does your product and/or company.

Medical Device clinical trials are expensive and can range from at least 1 million USD to greater than 10 million USD each[1]. Hence it is important to start planning early so that the adequate funds can be raised to support the trial(s).

Planning early allows your company to devise a strategy that can reduce both trial cost and time. In turn, this can reduce your time to market. Depending on your designation (Class II/501(k) or class III/PMA), the FDA (or your government's notified body) will want to see varying levels of evidence that your device is safe and effective.

Furthermore, your investors and board will want to know that you have an internal clinical team, or Clinical Research Organization (CRO), or both, to design and implement the clinical strategy and trails.

Investors will shy away from inexperience, equivocal/poor trial results, or a device that has a difficult reimbursement path. Any potential future acquisition deals will benefit from higher pricing for a device that has proven value to the payers. Once on the market, the payers (Medicare/Medicaid and/or private insurance companies) will need clinical evidence of value to support reimbursement.

If your regulatory and/or strategic path includes the need for clinical data, there are ways that an experienced CRO can help your company mitigate the risk, and go into the trial with the best possible design.

[1] Makower et. al. FDA Impact on U.S. Medical Technology Innovation: A Survey of Over 200 Medical Technology Companies. November 2010 http://www.mddionline.com/blog/devicetalk/how-much-does-510k-device-cost-about-24-million

Product Risk Classification

The first step to developing a clinical trial strategy is to determine your product classification which impacts the design and implementation of the clinical trial.

The Food and Drug Administration (FDA) has well-written guidance on how to determine your product classification.

There are three categories, or classes, of medical devices that are designated based on risk and the controls required to ensure the safety and efficacy of the device.

Class I devices are the lowest level of risk and require the lowest level of regulatory control. Some examples of Class I devices are: adhesive bandages, sunglasses and dental floss.

Class II are more complicated than Class I devices and at slightly higher risk than Class I devices. Thus they require more stringent regulatory controls to provide assurance of their effectiveness and safety. Some examples of Class II devices are x-rays, ultrasound diagnostic equipment, and pregnancy testing kits. In addition, in order for a device to qualify for a Class II designation, it must either have been on the market, or be "substantially equivalent" to a device that was on the market before 1976.

Class III devices are the highest risk and therefore require more stringent regulatory controls to provide assurance of their effectiveness and safety. Some examples are implantable pacemakers, balloon catheters, and breast implants.

It is important to be aware and realistic about your product's classification as you may waste time and resources attempting to convince FDA to grant a Class II designation for a device that may have a better business case as a Class III. The indication/intended use sought for the device weighs heavily in device classification.

You can also learn more in the Product Risk Classification course on Enzyme Community.

Clinical Trial Design

Clinical trial design and execution requires several different areas of expertise, including clinical science, medicine, biostatistics, logistics, and in addition, it is experiential. Regardless if you are a small or large company, the success of your clinical trial depends on the team you partner with.

As you build your team, it is important to consider a team who can mediate between the clinical trial site and your company. The site's priority is its patients and your company needs data. Therefore, you need someone who can ensure both are accounted for.

If you don't have the right individuals or team, you may end up collecting insufficient data, which in the long run will have high remediation costs.

Therefore it is imperative to have an experienced team (internally or CRO) that can identify the right goals for the trial and execute it effectively.

Trial Location

Site screening and qualification are crucial aspects of any clinical trial. There are many factors that should be considered when determining the appropriate site(s) for your clinical trial.

- Experience of their clinical research department and staff at the site
  It is important to select a site that has staff who have experience in implementing clinical trials. It's also important to have a professional team so that challenges can be identified and addressed swiftly.

- Experience of the principal investigator
  It is important to select a principal investigator (internal or CRO) at the clinical site that understands the distinction between research and clinical standard-of-care medicine.

- Bandwidth of the principal investigator
  When selecting the investigator, it's important to discuss the number of studies they are implementing. Verify if they have the bandwidth to oversee your clinical trial and if their other trials compete with yours for patient enrollment.

- Patient population at the site
  Verify if the site has enough of a patient population needed for your clinical trials.

- Institutional Review Board (IRB)
  Verify if the site has a local or central IRB representative they work with. The IRB verifies that the study's approach is ethical and considers the safety and well being of the patients enrolled.

- Contract negotiation
  Determine how easily you can negotiate a contract with the site. Some university sites are very difficult to negotiate with and this can delay your trial. In turn, this can add cost and delay the release of your product.

- Indirect Costs
  As part of the contract negotiation, it is important to confirm and document all costs associated with the trial. Some sites may have indirect costs which may not be reflected in your contract. This can become an additional financial burden to your company.

Estimate Costs

There are several factors that influence the cost of the clinical trial

- Size of the study
  The larger the number of patients enrolled in the study, the more it will cost. There are some new innovative ways to reduce the trial size using statistical methods.

- Length of the study
  The longer the patient follows up, the more it will cost. If possible, consider an alternative end point that could shorten the length of the study and still provide the data you need.

- Clinical care
  If your clinical trial requires a “non-standard” clinical care, then your company will have to pay for it. For example, if your study requires an MRI, an extra day in the hospital etc. that wouldn’t otherwise be prescribed to the patient, you will have to account for that cost in your trial.

- Data capture
  Determine how you will capture the clinical data, If you utilize electronic data capture tools, they must be HIPPA compliant and can be expensive.

- IDE applications
  Be sure to add the cost of the application.

Software as a Medical Device (SaMD) Companies

The FDA defines a SaMD as a “software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device."

SaMD companies are subject to the same design control requirements (CFR 820.30) as traditional medical device companies. The FDA has developed General Principles of Software Validation (GPSV) to validate SaMD products.

The FDA has identified three levels of software testing requirements: system, integration and unit level.

- System Level testing is essentially black-box testing. It looks only at inputs and outputs and does not validate how the software works internally.
- Unit Level testing investigates the basic functions and building-blocks or the individual components and classes of software.

- Integration testing is between the two levels. FDA hasn't provided specific guidelines on integration testing so companies can determine how to address this.

Clinical studies are of utmost importance for SaMD companies as the FDA will focus on them to ensure and efficacy of the software. They will also want to confirm that the company has addressed and mitigated cybersecurity issues. The clinical trial should address intended user needs, networking activities and how cloud-based/wireless devices are impacted by software updates.

Next Steps

The next steps are to

- Develop your clinical strategy either internally (if you have the team) or with clinical research organization (CRO).
- Utilize clinical experts to help build your reimbursement, regulatory and investor pitch decks.

Let us know if you have any questions - support@enzyme.com

Reference Terms

SaMD	Software as a medical device guidelines by FDA
Software Validation	FDA Guidelines for software Validation
Study Protocols	Master Protocols to study multiple therapies
Device Classifications	FDA's guidelines on device classifications
Institutional Review Board (IRB)	Defined by the FDA as a committee or group designated by an institution to review and approve of research of clinical trials.
Protocol	A plan that details how a research study will be conducted to answer a question.