Is Your Trial Complex? The Top 5 Trial COMPLICATIONS

Introduction

Over the years, many clients have discussed their medical device trials with us in terms of complexity, oftentimes specifically noting how much more complex device trials are today versus the past. It's true – recent widespread recalls of medical devices have led to harsher scrutiny and stricter rules from the Food and Drug Administration (FDA). Steps taken to prepare for trials in the past are no longer enough. 510(k) equivalency is much harder to come by. Start-ups and even seasoned healthcare companies embarking on their first medical device trial face an immense laundry list of requirements and regulations. One wrong step can mean going back to the drawing board, or for many, going out of business.

Following are five key areas that can complicate medical device trials. In all of these scenarios, the path to FDA approval requires tremendous organizational skills and attention to detail to navigate.

NUMBER ONE

How much experience do you have with medical device trials?

Medical device trials are unique, even for companies who have experience moving through pharmaceutical trials. If your company has never been through a device trial, that in and of itself would make your trial complex.

The chief difference between devices and drugs, and the one that in part is driving much of the increased FDA scrutiny, is the fact that the device often requires surgical implantation. If a problem were to occur, a second surgery may be necessary. Many recent high-profile and widely publicized recalls have forced the FDA to take action and have spawned class-action lawsuits largely due to complications such as infection that occurred due to the necessity of a follow-up surgery. *F.D.A. Orders Surgical Mesh Makers to Study Risks*, *New York Times*.

If this is your first trial, chances are that you have been focused primarily on your product's design, functionality and, if you've had time after those things, its potential market. The following is just the beginning of a list of things you'll need to add to your plate as you prepare your trial:

- Selecting sites
- Recruiting patients
- Providing training (initially and ongoing)
- Monitoring and reporting – knowing the regulations AND enforcing them
- Determining how the trial will be designed
- Planning and executing a pilot study or studies

NUMBER TWO

Who is involved in your trial?

Depending on your device, the number of people and entities (such as hospitals, long-term care facilities, etc.) varies enormously, presenting another complexity. While some devices may be able to get the data they need with only a few sites (and possibly only one), most cases utilize in the neighborhood of 20 and some companies require 100 or more sites to draw significant data. With each site you have a number of individuals who touch the trial:

- Patients
- Physicians
- Nurses
- Physician assistants
- Lab technicians
- Imaging technicians
- Administrative staff

After doing the difficult work of recruitment and gaining buy-in from all necessary parties, your company faces another challenge; counting on these individuals to accurately and consistently record and report clinical trial data.

Turnover rates among healthcare workers is still high, for instance the rate for both physician assistants and nurse practitioners is 12.6 percent. This turnover points to a common area where trials go wrong. Often, a company commits to training the staffs at its trial sites at the beginning, but does not follow up with additional training or re-training during the course of the trial.

Also, the ancillary staff is often missing from study-specific training, leading to non-compliant testing. For instance, when imaging technicians miss training sessions, the result can be unnecessary exposure to radiation when x-rays are taken according to the standard of care rather than per trial protocol requirements.

One sure indicator that additional training or re-training is necessary is when you observe a sudden drop-off in the quality of data from any given site, particularly if this data is not reflective of other, similar trial sites.

Given the fact that many device studies require long-term follow-up (up to five years), you can clearly see how the high turnover rate combines with a lack of training to create multiple scenarios for noncompliance.

NUMBER THREE

Are you planning on acting as both sponsor and clinical investigator of your trial?

Many who seek to bring a new medical device to market choose to act as both sponsor and clinical investigator for their trial. It often means both initiating the trial and overseeing its investigation, however this requires addressing new layers of complexity.

As the investigator, you will have a great deal of responsibility for ensuring that the trial remains compliant. Add to that the dual responsibility of fulfilling the FDA's sponsor requirements and you have more than doubled your workload while creating new opportunities to fall out of compliance. The recording responsibilities of the investigator and sponsor are different and many companies who seek to serve in both roles simply aren't aware of the differences and often miss crucial details. From the FDA:

> *Sponsors are responsible for selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained, submitting an IDE application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation. (Regulation 21 CFR 812.40)*

To improve your performance serving in both roles, you must strive to think and act like two separate entities. Don't let your knowledge as the investigator impact how you record and report data as the sponsor, as this can lead to incomplete recording. For instance, in your role as sponsor, you must collect information that proves you are qualified as the investigator as well, this means collecting CV or resume information on yourself and your staff. While this may seem simple, it is overlooked often.

Inconsistencies in knowledge between the two roles is easy to understand. The investigator role often comes more naturally, as the site's first priority is patient care and recording patient data is of course a part of that. In order to have a complete understanding of your role as sponsor, you will need to ramp up on the unique FDA requirements for sponsors, then work to view your trial from this perspective separately.

NUMBER FOUR

How complex is your medical device?

For drug trials, complexity of use is not typically an issue. Pills and injectable drugs require only the one step – getting the medicine into the patient. This is another area where medical device trials are very different from drug trials. Both the complexity of the device design and how the device is to be used create numerous opportunities for mistakes.

What makes a device complex?

- **Device requires that the physician receive training to use**
- **Device requires patient-specific customization prior to use**
- **Device is implantable**
- **Device interacts with software or other electronics, requiring training**
- **Device utilizes materials or technology that physicians are unfamiliar with**

Medical device makers are using emerging technologies to address more and more health issues. While this is great news for the future of patient care, it means that devices are being created with more moving parts that often require more steps be taken for the device to work effectively. Unfortunately, more moving parts also means more things you need to record for compliance. Before your trial begins, you need to be aware of each step necessary for your device to work. This will help you to be comprehensive in your recording of trial data.

NUMBER FIVE

Will your study be based solely in the U.S. or will it be global?

As one can imagine, doing business globally presents many challenges, regardless of industry. In terms of medical device trials, navigating the regulatory environment of a single country represents a significant amount of work. Adding countries can increase trial complexities exponentially due to a number of factors:

- **Language differences**
- **Cultural differences, such as work styles**
- **Logistical challenges due to distance, time zones, etc.**
- **Labeling requirements that could complicate shipping**
- **Different governing and regulatory bodies**

Cultural idiosyncrasies mean that developing relationships with physicians and others tasked with overseeing facets of your trial will be very different from one country to the next. Processes will likely take longer and misunderstandings will occur. The key is to identify the right people and entities that can help you minimize the challenges of global studies, which can be accomplished by taking steps such as recruiting sites that have taken part in previous global studies and seeking partners that are knowledgeable of both foreign and domestic regulations.

So, how do you manage your complex trial?

Medical device trials require constant vigilance and the capability to capture even the smallest details and act on them if necessary. Compliance failures, whether through grossly inadequate monitoring or something as simple as using an outdated patient consent form, account for most FDA warning letters.

Training and re-training of the individuals responsible for carrying out the study, and also documenting the efforts, is critical to demonstrating compliance with the criteria set by the FDA. Patient safety is the ultimate driver of this scrutiny, as the FDA seeks to make sure all steps are taken to protect both the trial patients, but also any patients who may receive the device following its approval. To accomplish this, device makers must carefully assess all those who touch the trial process, gathering the right group of professionals and then creating a system of checks to ensure that all runs smoothly and within compliance. For a more in-depth look at FDA documentation protocols, please refer to our white paper *Documentation in Device Studies*.

The compliance program a device maker creates will work to meet some key needs:

- Ensuring that all trial patients have given their informed consent
- Constantly monitoring and evaluating data to ensure its integrity
- Ensuring compliance with all FDA regulations, and securing compliance when noncompliance is discovered
- Assessing device accountability
- Reviewing overall site capabilities (in general and by site)
- Reviewing all essential documents

The amount of data that requires near constant review and evaluation to ensure compliance presents great complexity to even the most seasoned device makers. Failure to actively and adequately monitor trial data represents the most common causes when clinical trials go wrong. From the FDA:
Most Common Clinical Investigator Deficiencies:

- Failure to follow the investigational plan and/or regulations
- Protocol deviations
- Inadequate recordkeeping
- Inadequate accountability for the investigational product
- Inadequate communication with institutional review board
- Inadequate subject protection – including informed consent issues

While some larger companies may have the ability to absorb the costs of FDA failure, many device makers get only one or two chances at the approval their entire business hinges upon. The number of moving parts that begins with recruitment, carries on through careful monitoring and ends with presentation for FDA approval can be overwhelming, and preparing for the complexities is paramount to gaining approval for your device. Truly, nearly any medical device trial presents complex challenges, but with the right preparation and commitment to compliance, all of these challenges can be overcome.

References:

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Sandra Maddock, CEO and President

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coronary and peripheral stents, angioplasty balloons, combination products, thrombolytics, chemotherapy agents, endovascular grafts for treatment of thoracic and abdominal aortic aneurysms, wound care, and dura mater replacement grafts. Whether serving as a global auditor for a device study across the U.S., Japan and Germany, or working with U.S. sites establishing GCP Compliance in preparation for an FDA Inspection, Sandra's hands-on approach has become her trademark.

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