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Clinical Study Clean-up:
How to get your study back on track

Introduction

Every year, the U.S. Food and Drug Administration (FDA) releases metrics detailing the outcomes of the Bioresearch Monitoring (BIMO) inspections done at facilities conducting clinical research within the previous year. Of the 104 Sponsor/Monitor/Contract Research Organization (CRO) inspections done in fiscal year 2017, 36 percent were found to have some type of deficiency, resulting in either a Voluntary Action Indicated outcome or an Official Action Indicated outcome.

These outcomes often demonstrate that deficiencies in complying with the regulations were observed. In some cases, the deficiencies may be minor in nature, and in other cases, the deficiencies may be more severe, pointing to data integrity conflicts or even a human subject protection issue. These more severe types of deficiencies are usually evidence of a study that has gone "off the rails" for one reason or another. Maybe you've been part of a study team that allowed for study conduct to get out of control, or maybe you've "inherited" a study mid-stream that seemed disorganized and chaotic.

Detailed below are seven common causes of a non-compliant study, along with five suggestions for getting your study back on track.

7 Common Causes

1 Poorly Written Protocol

Perhaps the biggest, and potentially most frustrating risk that could lead to a poorly run study is a poorly written protocol. Having a poorly written protocol may leave what should be straightforward protocol questions up for interpretation. The protocol is typically the gold standard reference document for study teams, and if everyone is interpreting the same document in different ways, this can lead to inconsistency in the messaging between the study team and with the study sites. Protocols written with this "gray-area" interpretation can cause differences in study conduct among sites and potential loss of data.

2 Mismanaged Study Team

Whether the study team on your project is within your company or contracted externally to a CRO, they need to be managed. An inexperienced or ill-equipped study team can have a negative impact on overall study conduct. The monitoring team is the sponsor's eyes and ears in order to maintain human subject protection and data integrity. Setting clear guidelines on how study teams should conduct potential site assessments, site initiation visits, periodic monitoring visits, close-out visits, and general site management will enable an effective delegation of responsibility and appropriate oversight.

3 Inadequate Training

Training is the foundation to clinical trial management. If the study team is not knowledgeable in the protocol, applicable regulations, standard operating procedures, national and international guidelines, the investigational product under study, and any reviewing IRB/EC requirements, then inevitably mistakes will be made, and study mis-management is likely. An untrained study team will not have the basis in which to adequately face challenges that arise throughout the clinical trial.

4 Inadequate Documentation

There is a common adage known to many researchers: "If it's not documented, it's not done." Inadequate documentation will not allow for the traceability required in clinical trials. Unfortunate consequences of poor documentation can include questions from an FDA auditor that you are unable to explain years after their occurrence. This may be most commonly noted in those "inherited," long-term ongoing clinical studies.

5 Lack of Resources

Both appropriate monetary and personnel resourcing are important for the success of a study. Lack of communication, a lag in enrollment and failure to address issues in a timely manner, among other issues, can quickly combine to push the study out of control from a budgetary standpoint. In addition, it is not uncommon for study teams to be consistently pressed for time and working on numerous trials. The research sites may not always have the infrastructure or resources to promote timely data entry or completion of protocol-required follow-up visits. This could lead to issues with obtaining informed consent, delays in enrollment, inadequate data entry, inadequate product accountability, failure to identify adverse events, lapses in IRB/EC approval and more. Each of these could lead to potential data integrity and/or human subject protection issues that, if left unaddressed, could cause issues with the overall study.

6 Ineffective Leadership

Strong leadership to motivate a study team toward a common goal is vital to keeping a clinical trial on track. Ineffective leadership can be detrimental to a clinical study and typically starts with inadequate communication and a lack of management of vendors, sites, and CROs. A lack of oversight and leadership to contest the potential lags in enrollment, protocol changes and unexpected issues known to arise in the clinical trial process could cause a wide array of deficiencies within your clinical trial.

7 High Turnover

Sponsor, site, and monitor turnover is common within the research field, especially for those clinical trials with long-term follow-up requirements. High turnover can lead to inconsistency in the running of the clinical trial, loss of historical knowledge of how something was handled, and a loss of efficiency from one person to another as the baton is passed.

Overall, the FDA's common findings following an inspection are the same from year to year and include failure to follow the investigation plan/agreement or regulations, inadequate record keeping, inadequate monitoring and failure to bring investigators into compliance. Identifying the common causes that may impact your study will enable you to better safeguard your study against pitfalls in compliance. However, despite best efforts, once your study is off-track, it's important to know "what's next" in study recovery.

Five Steps to Study Recovery

1 Mental Preparedness

It is important to remember that study clean-up will be a marathon and not a sprint. Focusing on the learning experience will allow you to embrace the time and efforts required in the process. Albert Einstein said it best: “The only source of knowledge is experience.” The innumerable lessons learned from the study clean-up process will inevitably only further your preparedness for future clinical trials.

Start the process with an “I get to” mindset, take a deep breath, and dive in.

You cannot actually control the clinical study outcome, and once the study is off the rails, identifying root causes and mentally accepting the status of the reality will help you plan for the clean-up process.

2 Garner Support

Executing a clinical trial takes a team and the clean-up process will as well. Embrace the fact that you cannot do it alone, and be your study’s advocate for what you need to get the job done. Additional resources are inevitable in projecting your needs for clean-up. Make a case for what the study needs and garner management support for the resources and budget needed for the clean-up effort. It’s important to have open discussions about the budget and resources required to get the study back on track.

Although the study is off track, this is a great time to re-assess any study-specific areas that were identified to have a lack of resources. Examples may include initiating a new DSMB/CEC, garnering additional CRO support, identifying a new Core Lab or image review team, etc. Amending your study’s needs and garnering the support and appropriate resources will help enable the clean-up process.

3 Establish a Prioritized Approach

Focus on tackling issues and then moving to the next. It is recommended to conduct an internal audit to establish your study gaps. Consider using a BIMO checklist as a resource to establish a baseline and determine your study clean-up requirements. The gaps identified will specifically relate to applicable questions an FDA inspector might ask, and may include a combination of the above warning signs. Lapses in site training, sponsor regulatory documentation and data entry, among others, may all be identified as being deficient; so where do you start?

Subcategorize into focused areas and tackle each subcategory with an outlined plan.

Fight fires as they come up, and strategize the best approach to meet goals. Having an underlying plan to gain control establishes clear expectations and a faster study rescue. Through the baseline audit process, you will need to fix what can be fixed, and accept what cannot. You cannot go back and re-create missing documentation, but finding the best way to explain the missing documents will become your new goal.

Areas to focus on are dependent on what the cause of your study derailment was, but in general, the following are key areas that require may require attention:

- Protocol amendments, as appropriate
- Adverse event reporting
- Investigational product accountability
- Protocol deviations
- Data entry (including follow-up visits, imaging requirements, etc.)
- Status of the Trial Master File
- Re-training sponsor/CRO personnel, as appropriate (i.e., protocol training, regulatory training, etc.)
- Re-training sites in areas of weakness (i.e., get the sites all on the same page about how to interpret a certain part of the protocol, reminding sites of the timeline for AE reporting, etc.)

4 Communicate Expectations Clearly

An important strategy during a clean-up effort is to be able to separate the "day-to-day" functioning from the study clean-up process. The study doesn't stop just because clean-up needs to be implemented. When outlining the clean-up approach, you may need an additional team member just to manage everyday site questions, review monitoring reports and maintain current protocol deviations. Outline scheduled study calls or meetings separate from the everyday study needs to touch base with a focused discussion on the progress with the study clean-up effort.

Dictate how updates should be provided and to whom. Be prepared to be the problem solver when clean-up delays inevitably come up. Garnering a team approach and maintaining open lines of communication gives you the opportunity to be the most effective and to keep all team members up to date with the current progress.

5 Set Timeline Expectations

Decide on a reasonable amount of time that it will take to complete your goal. Be aware of how much time during the week you and your team may be able to devote to clean-up versus the typical daily responsibilities.

Always give yourself extra time as the finish line will likely be a moving target.

You can repeat the preliminary internal audit or BIMO checklist six months after you have started study clean-up in order to monitor progress. Celebrate the successes along the way, and reward yourself and the team for the hard work accomplished. Embrace the learning experience and accomplishment in navigating your study rescue.

Being able to identify risks within your own clinical trials, as well as understanding the best practices for study recovery will help you ensure successful FDA inspections and efficacious future trials. There is no way to foreshadow a successful outcome of a clinical research trial, however utilizing FDA guidance and recognizing common causes of an "off-track" study may help with early identification and correction of any necessary study clean-up.

The FDA regulations that govern clinical research set a framework in which to protect human subjects and ensure quality data. It is up to us to utilize that framework in order to conduct and manage clinical trials. Using a team approach with clear communication and management buy-in can help get your study back on track. Embrace the learning experiences you will inevitably gain from a study rescue process and infuse it into future project development.

Kelly Jasko, Lead Clinical Research Associate

Kelly Jasko joined IMARC in early 2015 as a Clinical Research Associate, and currently serves as a Lead Clinical Research Associate, managing several IND studies, as well as continuing to monitor on device studies. Throughout her tenure here, Kelly has worked on a variety of studies across a range of therapeutic areas, including in vitro diagnostics (IVD), interventional cardiology, genitourinary, and women's health.

As a Lead CRA, Kelly guides her monitoring teams and works closely with her with clients on projects mainly focused on stress urinary incontinence. Kelly's monitoring experience has included working on IVD, 510(k), 522 post-market surveillance, IND, and IDE studies. Prior to joining IMARC, Kelly worked as an optometrist assistant and as a medical technologist in several medical center laboratories. Kelly has a Bachelor of Science Degree in Biology, as well as a Clinical Laboratory Sciences ACSP Certificate, both from Ohio Northern University.

To learn more about how we can help you get your study back on track, contact us today.

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