Centralized Monitoring for Optimizing Clinical Trials A Discussion on the FDA Draft Guidance: "Oversight of Clinical Investigations - A Risk Based Approach to Monitoring"

For clinical trial sponsors, making sure that their studies are being conducted properly is key to the reliability of the trial data. For this reason, sponsors spend a large portion of their study budgets on monitoring. Common monitoring practices vary, depending on the kind of study being conducted.

The FDA has released a draft guidance to introduce the concept of centralized monitoring, a more streamlined approach that would allow remote monitoring for most clinical trials. The purpose of this publication is to review and discuss key elements of the draft guidance entitled "Oversight of Clinical Investigations-A Risk Based Approach to Monitoring." It will address the concepts and practices of centralized monitoring, as it is described in the guidance.

Sponsors spend up to 15% of their clinical trial budgets on monitoring.

The paper will conclude by describing Clinilabs' approach to centralized monitoring, using a proprietary system developed by Clinilabs in 2009, called Clinical InSite™. The system is a technology platform designed to support monitoring for multi-centered studies, whether they are done in the United States or in other parts of the world. To conclude, data will be shown to emphasize the possible cost savings that can be brought on by switching to a centralized monitoring system, like Clinical InSite™.

What is Monitoring?

In clinical trials, monitoring can be determined in a variety of ways, dependant on the context to which it is being used. One way in which it can be defined is as the assessment of clinical investigator conduct, oversight, and reporting of any findings within a clinical trial.[1] It may also refer to an ongoing evaluation of safety regulations, including a risk/benefit profile of an investigational product. Monitoring can also be defined as the oversight of processes and systems that are integral to the proposal, design, performance, recording, reviewing, or reporting of clinical investigations.[1] However, within this publication, monitoring will refer to the methods used by sponsors or CROs to oversee the conduct of clinical investigations, as well as the reporting of any data collected.

It is important to note that monitoring is just one component of a multi-factorial approach to ensuring the quality and integrity of clinical trial data. Another crucial aspect of these studies is the protocol, generally used to ensure that the scientific and operational protocols are accurate. As is often said, "You can't solve a science problem with a business solution." Proper scientific practices must be set in place in order to ensure that the overall quality of the data is correct.

Subject safety is the main priority of clinical trial monitors.

The experience and training of the investigators is another part of this complex system. The actual design of source documents is also important to the overall integrity of the study. Finally, the monitoring plan itself. As the guidance indicates, no single approach is necessary or appropriate for every trial. This means that monitoring plans must be specifically tailored for each study or population. Identifying the key data and processes that should be monitored is extremely important as well.

The FDA wishes to encourage more effective monitoring of clinical trials.

FDA Draft Guidance
"Oversight of Clinical Investigations - A Risk Based Approach"

A recent draft guidance, published by the FDA on August 24, 2011, addressed the concept of centralized monitoring in clinical trials. The guidance was meant to assist sponsors in developing risk-based monitoring approaches and plans for investigational studies. The purpose of this publication was to introduce the method of centralized monitoring and offer guidelines on its implementation. The overarching goal is to enhance the safety of the human subjects, while improving the overall quality of the clinical trials. [1]

The FDA expressed its intentions for the draft, by making it clear that sponsors can use a variety of approaches to fulfill the responsibilities related to monitoring clinical trials, while offering suggestions of two specific methods of monitoring. The first was the use of a modern, risk-based approach to monitoring. This type of approach focuses on the identification of critical study parameters and their assessment. This method is also likely to rely on a combination of monitoring activities to oversee a study. The second method discussed revolves around the use of centralized monitoring methods. [1]

It is expected that sponsors of clinical trials provide oversight of the clinical study. This oversight must ensure that the rights, welfare, and safety of the human subjects are protected; as well as the quality and integrity of the data collected. All of these responsibilities can be retained by either the sponsor, or be delegated to a CRO. The regulations are not specific as to how sponsors should conduct this monitoring, therefore a wide range of approaches have been used.

Many sponsor's outsource their monitoring to CROs.

Current Monitoring Practices

While the overall goal of monitoring a clinical trial is the same across all investigations, there are some variations Even though centralized monitoring is growing in popularity, the predominant industry practice still involves periodic visits to each clinical investigator site. [1] This is done to evaluate the conduct of the investigators and review any source data obtained from a specific trial. Monitoring visits are typically conducted every 4 to 8 weeks, dependant upon the type of study being conducted. For each visit the monitor must travel to the designated testing facility, spend a considerable amount of time at the site, possibly meet with the investigator, and complete a monitoring report.

Monitoring methods can differ in focus, intensity, and methodology.

This process, which has developed over the years, has been based on the perception that frequent on-site visits, with 100% source document verification, is the FDA's preferred standard. As recent trends have shown, this may not be the case.

Within their August 2011 guidance, the agency cites many organizations that have used less frequent monitoring visits or methods other than those which are commonly applied within the industry. The FDA goes even further in their guidance, by indicating that the use of alternative monitoring approaches should be considered

by sponsors, including commercial sponsors, when developing risk-based monitoring strategies and plans.

The FDA has issued several drafts in the past, regarding clinical trial monitoring practices.

Other draft guidances were issued by the FDA, in reference to monitoring, beginning in 1988. The draft stated that the most effective way to monitor an investigation was through "personal contact between the monitor and the investigator." [1]

Today, the FDA recognizes the growing consensus that risk-based approaches to monitoring may provide a higher standard of subject protection and study quality, resulting in the withdrawal of the 1988 guidance.

At the time this guidance was issued, sponsors had limited ways to effectively and meaningfully communicate with investigators and over see their work. Due to this, the only possible way to oversee a trial properly was to visit the site. Another guidance issued in 1996 addressed monitoring in a more contemporary and flexible way. It advised sponsors to consider the objective, purpose, design, complexity, size, and endpoints of the trial in determining the extent and the nature of monitoring for that specific trial. [1]

Issues Facing Monitoring

Globalization has led the FDA to change their opinion on centralized monitoring.

One of the many issues facing sponsors, and CROs, is that clinical trials have become much more complex. As the number of clinical investigators continues to increase worldwide, the variability in their education and prior experience has diversified. The geographic dispersion of investigators is another factor that challenges conventional monitoring approaches, as it can be difficult to cover all sites, in all countries, at any specified period of time. Clinical study protocols also vary in complexity, presenting possible monitoring issues. Repercussions of such complexities include the excess usage of time and money required to conduct the study effectively.

As the industry of clinical trials becomes more global, it is simply impossible for the FDA to monitor all investigators involved in a clinical trial. Because of this, responsibility delegations, as well as human subject protection, are absolutely critical to data quality.

A key concept derived from the issuance of this guidance gives a clear sense that human safety and quality oversight should be achieved through a systems' approach that is integrated into an enterprise solution held by the sponsor or CRO. [1]

What has the FDA done to Facilitate These Changes?

The agency is leading the way in risk-based alternative methods to monitoring.

Along with withdrawing their 1988 draft guidance, pushing sponsors to use on-site visits, the FDA has issued a new document stating an alternative. The guidelines of the draft encourage the use of risk-based monitoring, including alternative methods.

The administration has also established compatibility between guidance manuals related to monitoring, such as CPGM 7348.810 and 7348.811.

The administration is also attempting to ensure that all affected program areas in the FDA are aware of the goals and purposes of this draft. Finally, the FDA is considering establishing a CDER review process for monitoring plans. [1]

Two Types of Monitoring

Conventional On-Site Monitoring

This traditional evaluation method consists of monitors making routine visits to the sites. On site monitoring provides insight into site performance, practices, and quality of documentation.

Centralized Monitoring

Centralized monitoring can provide many of the capabilities of on site monitoring, while being performed remotely. Centralized monitoring provides monitors with many positive functions, which were identified in the FDA's 2011 draft guidance. This method replaces the need for many on site visits and allows for augmentation of on site monitoring needs, providing sponsors with the chance to double their monitoring capabilities. Investigators have the opportunity to address possible anomalies with the investigator site, prior to their visit. [1]

Electronic centralized monitoring also provides real time data access and review, streamlining the entire clinical trial process. [1] Real data access allows monitors to capture any problems what may arise in the beginning of the trial, eliminating the replication of errors. It enables monitors to view a problem early on, identify it, and ultimately address is. Statistical analysis of large amounts of site data is highly simplified through centralized monitoring. [1] Using this type of monitoring system makes comparative assessments of site-by-site data quality much more efficient. Lastly, the implementation of centralized monitoring can help with the improvement of administrative and regulatory functions (i.e. archiving documents).

Several publications suggest that data anomalies may be more readily detected by centralized monitoring.

Clinilabs' Push for Centralized Monitoring

The growing need for a streamlined, centralized monitoring method has led Clinilabs to create a web based, proprietary document management tool called Clinical InSite™. This system offers a user friendly interface that requires no special training, along with user defined design structures, for all electronic study files. Clinical Insite™ also captures electronic images of paper trial documents as they are being faxed or scanned.

Clinical Insite™ can be accessed from any electronic platform.

The system has improved the overall monitoring of clinical study workflow by converting source documents, at investigator sites, to electronic versions. Clinical InSite™ also allows monitors to complete source document verification remotely. It was designed to be fully compliant with the standards of handling and transferring of electronic data.

Ultimately, the implementation of Clinical Insite™ can reduce the overall number of onsite visits. This, along with a single repository for document storage has enhanced communication and collaboration at Clinilabs. Reducing the number of visits allows monitors to focus their attention on tasks that can only be completed in person, like drug accountability. Ultimately, Clinical InSite™ may reduce "monitor burnout."

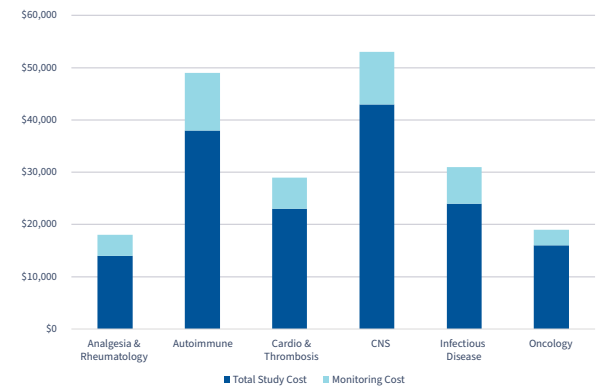
Cost Savings with Clinical InSite™

Clinical InSite™ has shown to reduce costs by an average of 15% across many therapeutic areas, like CNS and infectious disease. Graph A will show the average cost per patient, per therapeutic area, in a Phase III study. [2]

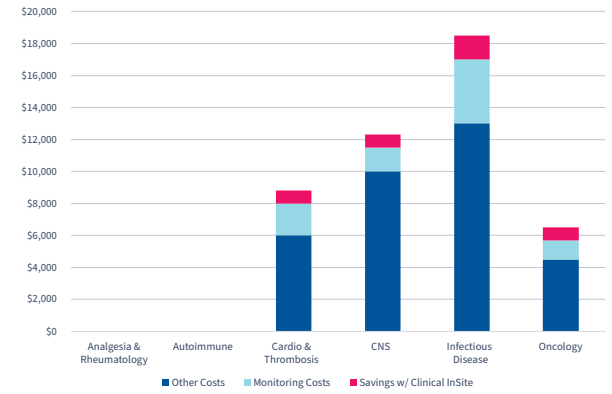
From the data it is evident that conducting a Phase III trial in any of the listed areas can be quite costly, with the least expensive beginning at $15,000. With monitoring fees consuming up to 20% of most clinical trial budgets, a 15% reduction in monitoring costs is one of the many advantages of using a centralized monitoring system.

Graph B will indicate the total study costs that are estimated for Phase III studies in any given therapeutic area. This will show the total costs of completing a Phase III trial. The light orange area demonstrates the potential savings that are a direct result of utilizing centralized monitoring systems, like Clinical InSite™. These cost saving alternatives are just some of the advantages that are available when working with Clinilabs.

Graph A: Average Monitoring Cost per Patient



Graph B: Estimated Savings with Clinical InSite™



References

[1] Guidance for Industry: Oversight of Clinical Investigations - A Risk Based Approach to Monitoring, August 2011.

[2] 14 Parxel's Bio/Pharmaceutical R&D Sourcebook, 2008/2009 pg. 181.