CENTRALIZED VS ONSITE MONITORING: A SPONSOR'S BALANCING ACT

Applying a Risk-based Approach

Introduction

Since the August 2011 release of the draft guidance document by FDA on a risk-based approach to monitoring[1], there has been a lot of buzz in the industry about how to apply the approach in clinical trials. Perform a quick Google search online for "risk based monitoring" and over 255,000 results are provided for blog postings, webinars, and even conferences on the topic. While many ask the question about how this risk-based approach may reduce the costs of clinical studies by requiring less on-site monitoring of data, it's also important to ask what the risk is for not going on site.

Start with the regulations

First, the regulations for conducting medical device clinical trials should be considered. Within the regulations, the sponsor is given the responsibility of ensuring proper monitoring of an investigation (21 CFR 812.40). More specifically, 21 CFR 812.46(a) requires that sponsors secure compliance by stating:

> *A sponsor who discovers that an investigator is not complying with the signed agreement, the investigational plan, the requirements of this part or other applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or FDA shall promptly either secure compliance, or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation.*

Although this requirement is just one of the many responsibilities the sponsor is given, it is an area where sponsors spend a great deal of time throughout the conduct of an investigation. The regulations provide little detail as to how a sponsor should secure compliance; however, guidance documents released by FDA represent current thinking on a topic and oftentimes these documents become the roadmap for study conduct.

Guidance for Industry: Then and Now

In 1988, the FDA provided a guidance document entitled, *Guidance for Industry: Guideline for the Monitoring of Clinical Investigations*[2], which outlined acceptable monitoring approaches for the industry. It stated that the "most effective way" to monitor clinical investigations was to "maintain personal contact between the study monitor and investigator throughout the clinical investigation." This led to the practice of frequent on-site monitoring visits with 100% data verification. These periodic on-site visits were often made on a fixed schedule, such as every 4-8 weeks, regardless of enrollment. Every site was treated the same, without special considerations for how much data was submitted or was outstanding, how many queries were issued, how many findings were recorded on previous monitoring reports, if there were any staff or site issues, etc. Fast-forward to the present, and many companies still use this same monitoring approach.

What does the monitor do during site visits?

During visits, the monitor conducts a variety of activities to ensure proper conduct of the clinical study. In essence, the monitor serves as the "eyes and ears" of the sponsor on-site, and serves an important role in the sponsors' responsibility to ensure that the site is complying with the regulations, as noted above. One major function of the monitor is to verify the sites' data with the source and study documentation; often this activity consumes the majority of time spent on-site. In addition to verifying study data, the monitor carries out these additional tasks:

- Reviewing informed consent documentation;
- Reviewing enrollment information, including subject recruitment and eligibility criteria;
- Assessing the site's familiarity with the protocol and required procedures;
- Reviewing essential regulatory documents and assessing the site's familiarity with study agreements, required IRB policies, and applicable FDA regulations;
- Assessing investigators' involvement with the study, in particular, Principal Investigator oversight;
- Conducting investigational product accountability;
- Reviewing adverse events;
- Reviewing protocol deviations; and
- Building working relationships with the Principal Investigator and site staff, among others.

This approach has become the standard for many in the industry; however, it may not be the most cost effective or efficient. Depending on the research site, complexity of the clinical investigation or patient enrollment, a study monitor could make many trips to the site to perform source data verification over the course of the study, which can become very costly for a clinical trial. In addition, frequent monitoring visits are sometimes considered very disruptive and time consuming to the research study personnel.

How does the new risk-based draft guidance affect monitoring?

The 1988 Monitoring Guidance document was replaced in August 2011 with the *Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring (DRAFT)*[1] to adapt to the changing environment of clinical research. In summary, the 2011 FDA draft guidance describes "strategies for monitoring activities that reflect a modern, more risk-based approach that focuses on critical study parameters and relies on a combination of monitoring activities to oversee a study effectively." In addition to removing the stigma that 100% source data verification is the only way to product approval, FDA is encouraging sponsors to take credit for activities that are conducted throughout the study that contribute to the responsibility of monitoring investigations. Many of these activities take place in-house outside of the traditional field monitoring role and are referred to as "centralized monitoring." (See our white paper "Monitoring as a Mindset" which discusses other activities that contribute to the monitoring of investigations[3]).

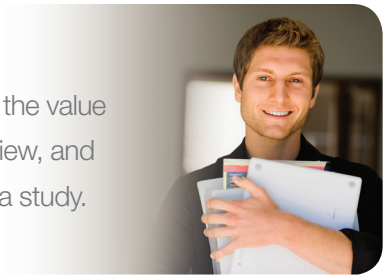
What can be done using centralized monitoring?

Per the new draft guidance, "centralized monitoring is a remote evaluation carried out by sponsor personnel or representative (e.g., data management personnel, statisticians, or clinical monitors) at a location other than the site(s) at which the clinical investigation is being conducted."[1] With centralized monitoring, sponsors could perform the following tasks remotely:

- **Identify non-compliances or training deficiencies in real time**
  - Sponsors can review screening logs in-house to identify high screen failure rates, and in-house review of the data may identify a high number of study eligibility violations. These findings may lead to re-training of sites or amending the protocol requirements to increase enrollment numbers. Additionally, sites with delayed data entry, or a trend of out-of-window visits can be identified by regular review of the data.
- **Perform data checks for completeness and consistency**
  - Queries can be generated for missing fields or out of range data as the data is entered.

- **Review study-wide data for inconsistencies**
  - Through clinical review of data, the sponsor may identify and investigate overall trends across sites. Such trends may not be identified during on-site monitoring, reviewing one site's data at a time.
- **Verify source data remotely, provided that both source data and CRFs can be accessed remotely**
  - Source verification is often the most time consuming part of a monitor's job. If the site can provide the monitor with source documents and CRFs, source verification can be done in-house.
- **Complete regulatory reviews and updates**
  - Regular inventory of sites' files can be conducted by using a shadow file of documents submitted by the site to ensure current and complete records. Regulatory review can include, but is not limited to, the following:
    - Review of IRB approvals to ensure that lapses in approval have not occurred;
    - Informed consent review to ensure that all essential elements are included in the document, that the correct version is being used, and that the informed consent document has been approved by the IRB
- **Determine which sites need on-site review**
  - Based on real-time review of data coming in (or not coming in!), the sponsor can decide that an in-person visit may assist the site in becoming compliant with their responsibilities.

Do we still need on-site monitoring visits?



While it is true that much of the study oversight and review can be done in-house, the value of being on-site cannot be denied. Consider the following scenarios for on-site review, and whether centralized monitoring would be enough to solidly secure compliance for a study.

- **Reviewing informed consent documentation**
  - The informed consent is arguably one of the most important parts of a clinical trial. Per ICH E6: the rights, safety and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society. It is important for the monitor to ensure the patient has voluntarily provided informed consent, and that the subject signed and dated the informed consent document prior to performing any study-related procedures. Reviewing a copy of the consent alone is not enough to show that the site obtained proper consent. *cont. on next page*

On site, the monitor can go one step further to verify the patients' signatures against other documents to ensure the patients signed the consent themselves. In addition, the on-site monitor can review operative reports and the dates and/or times of other test results to ensure that no study procedures were performed prior to obtaining consent. Finally, the monitors can discuss with research personnel how the informed consent process takes place and view any additional consenting source documentation that may be present on-site to confirm the activities were carried out in accordance with the regulatory and site requirements.

- **Reviewing enrollment information, including subject recruitment and eligibility criteria**
  - If a site provides source documents to the sponsor to conduct remote verification of data, how can the sponsor ensure all source was provided? On site, the monitor is able to thoroughly review all medical records, whether paper or electronic, to ensure each patient has met inclusion/exclusion criteria.
- **Assessing the site's familiarity with the protocol and required procedures**
  - The site's reaction to queries and clarifications to the data during visits can give the monitor insight into the comfort the site has with the study and its requirements. It is critical for the study staff to fully understand the protocol and what is required to prevent non-compliance, ensure patient safety and protect the integrity of the data. If deficiencies are noted while on-site, the monitor may provide immediate training to the staff in deficient areas to improve compliance at the site.
- **Reviewing essential regulatory documents and assessing the site's familiarity with study agreements, required IRB policies, and applicable FDA regulations**
  - The monitor can ensure the site is in compliance with Federal Regulations and the site's Institutional Review Board, as well as ensuring the site has received all of the necessary documents to conduct the study while reviewing regulatory documentation. The research coordinator may have an overwhelming list of responsibilities and regulatory documents can be in disarray. With the monitor being on-site, a full inventory of paperwork can be performed, and misplaced or lost documentation can be addressed. In addition, the monitor can assess how well the site research personnel are aware of their own IRB policies and study agreements.
- **Assessing investigators' involvement with the study; in particular, Principal Investigator oversight**
  - Monitors normally request to meet with the PI at every monitoring visit. If the PI consistently does not make time for the monitor, his/her involvement in the study may be questioned. Additionally, the monitor can often get a feel for the PI's involvement by reviewing the documentation and in observing the relationship between the PI and study staff.

- **Conducting investigational product accountability**
  - If the site only submits confirmation that product is received throughout the trial, can the sponsor ensure the proper storage and use of investigational product? During the product accountability process on-site, the monitor is able to tell if the product is stored in a secured, locked location according to the sponsors' requirements, and verify that the product the sponsor shipped to the site has indeed been received and logged in appropriately. Additionally, the monitor can take repeated inventory to ensure no product is misplaced or misused on non-study patients.
- **Reviewing adverse events**
  - Reviewing adverse events, whether related or not related to the investigational product, helps to protect patient safety. By having access to the full medical record, the monitor is able to review for unreported adverse events occurring during, or in between, study visits that may have been overlooked by the research coordinator. In addition, the monitor may better be able to ascertain whether or not these adverse events were reported to the site's IRB, per their IRB requirements, and if not, work with the site to ensure that this is done appropriately.
- **Reviewing protocol deviations**
  - Protocol deviations may or may not affect patient safety; for major deviations affecting the safety and welfare of study subjects, the on-site monitor can work with the site to report these to the sponsor and site's IRB, as applicable. Additionally, repeated discovery of protocol deviations may lead the monitor to provide retraining on deficiencies or to review difficult protocol requirements with the sponsor in consideration for amendments.
- **Building working relationships with the Principal Investigator and site staff**
  - This can be a priceless asset to any study. Instead of a study monitor or research coordinator being a "face-less name" on an e-mail address, having on-site monitoring visits can enable the study monitor and the site to develop a working relationship. Oftentimes, the monitor becomes the first point of contact for the research coordinator and/or Principal Investigator for any questions throughout the study. The site personnel may also be more willing to work with the monitor and sponsor (for example, to address queries in a timely manner, or to promptly submit data for a data lock), if they see the monitor in person and view them as more of a "helper" rather than a "nuisance". This relationship helps the monitor gain valuable information from the study staff that otherwise would not be known. For example, during casual conversation, the monitor can learn things about the site staff such as their knowledge of the protocol and regulations, their responsibilities outside of the clinical trial that may prevent them from giving 100% effort to the trial, or their process for obtaining informed consent and assessing adverse events.

The following table summarizes the differences between centralized and on-site monitoring, and illustrates how both add significant value:

Item Reviewed	Centralized Approach	On-site Approach
Informed consent	Review copies of signed informed consent documents sent from site. Confirm that all required elements are included in the consent, that the correct version of the consent is used, and that signatures are present.	Review source documentation to confirm the patient's own signature, that the patient was consented prior to study procedures, and that proper consent processes were followed by the site.
Eligibility criteria	Verified per source sent from site.	Verified per source review of ALL available medical records (paper and/or electronic).
Protocol procedures	Review of CRFs/source sent by the site to ensure the site is following the protocol.	Verification of CRFs with source, ability to assist site with query resolution, obtaining outstanding data, etc. Assess site's comfort level with protocol requirements through dialogue.
Regulatory documents	Keep a "shadow file" of sites' regulatory files, per documents sent from the sites.	Review of all regulatory documents to ensure maintenance of accurate, current, and complete records. Assist the site in addressing any deficiencies or missing documents. Confirm that the sponsor has a copy of required documents.
Investigator involvement	Discussions via telephone or e-mail to follow-up on study progress or to answer questions.	In-person meetings allow the monitor to ascertain important site/staff issues that may not be obvious otherwise.
Product accountability	Verifying product log against shipping records and possibly product labels on patient source documents sent from site.	Verifying product log against sponsor shipping records, device labels in patient source, products in stock, as well as product storage location.
Adverse events	Remote review for AEs submitted by the site.	Review of all available medical records (paper and/or electronic) for additional unreported AEs, discussion with site regarding the reporting of the AEs to the IRB.
Protocol deviations	Remote review for protocol deviations submitted by the site.	Review for additional unreported protocol deviations, discussion with site regarding the reporting of deviations to the IRB, and assessment of whether or not additional training is required.
Relationship with site staff	Limited when only communication is via telephone and e-mail.	In-person visits put a face to the monitor/ sponsor, and a more comfortable working relationship may be formed.

Put it into Practice – Consider the Risk

In practice, on-site monitoring visits should be considered early on in a study. Having a monitoring visit after the first patients have been enrolled allows the sponsor to determine whether the site fully understands the protocol and other study requirements. After a successful first monitoring visit, subsequent monitoring visits may not be needed at a high frequency, and 100% of source data verification may not be necessary. However, if issues are identified during an early visit, the sponsor can focus efforts on the sites that need them to obviate future risks to subject safety or data integrity.

If early monitoring, either on-site or remotely, uncovers multiple unreported protocol deviations or violations with the Federal Regulations, the site may be deemed high-risk and require on-site monitoring visits. Or if a site reports multiple serious adverse events, on-site monitoring may be necessary for a full medical chart review. Communication is a must for centralized monitoring to succeed. If a site fails to send essential regulatory documents, source documents or CRFs, or doesn't complete EDC entry in a timely manner, on-site monitoring visits may be necessary.

Instead of making frequent periodic site visits every 4-8 weeks, on-site monitoring visits could be performed at flexible intervals, based on objective information about each site's performance and risk level as the study progresses. Sites deemed high-risk would be visited more often, and sites deemed low-risk less often. The table below demonstrates how a site could be evaluated as high-risk or low-risk:

High-Risk Site	Low-Risk Site
Large number of subjects	Low subject enrollment
High number of errors	Not many errors
Frequent staff turnover / personnel inexperienced in research	Staff continuity / experienced staff
Many protocol violations	Low number of protocol violations
Out-of-window visits	Follow-up visits being conducted within windows
High rate of subject drop-outs or withdrawals	Not many drop-outs or withdrawn subjects
Unresponsive to queries and other sponsor requests	Responsive and cooperative to sponsor requests

This means that there is no "cookie cutter" approach to monitoring clinical trials. Every trial may require a different approach to monitoring, and each site may require a different approach to monitoring. At some point during a trial, a site that was operating in the Low-Risk category may become a High-Risk for one of the reasons mentioned above, requiring a mindset shift in how monitoring should be conducted. But regardless of the hybrid approach that is implemented, the regulation remains the same; through monitoring efforts, the sponsor should ensure the proper conduct of a study, the protection of the rights, safety and welfare of study subjects, and the integrity of data they plan to submit to the FDA.

Conclusion

Although in theory, a centralized approach to monitoring may reduce short-term costs, excluding on-site monitoring altogether may prove to have long-term consequences. Centralized and on-site monitoring are not meant to be mutually exclusive; instead, on-site monitoring combined with an overall centralized review process and excellent communication throughout, results in a high-quality, risk-based approach to identifying and securing compliance. In turn, this balanced approach can give sponsors confidence that patients enrolled in their trials have been protected, their data is accurate, and that their investigational product can reach the finish line.

References:

[1] U.S. Department of Health and Human Services, Food and Drug Administration. (2011). Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring (DRAFT) (On-line). Available: *www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=risk-based monitoring guidance&utm_content=1*

[2] U.S. Department of Health and Human Services, Food and Drug Administration (1988). Guidance for Industry: Guideline for the Monitoring of Clinical Investigations.

[3] IMARC Research, Inc. Monitoring as a Mindset – Effective Monitoring for a Medical Device Trial. Available: *www.imarcresearch.com*

[4] International Conference on Harmonisation of Good Clinical Practice (1996). Available: *www.ichgcp.net*.

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