

The Hidden Value of Onsite Monitoring

PEER REVIEWED

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Electronic data capture (EDC), central monitoring, and risk-based monitoring (RBM) have been disruptive to the entire clinical research enterprise. These new technologies and processes offer the potential to increase efficiency while reducing onsite monitoring and data management costs. Sponsors and contract research organizations (CROs) are crafting standard operating procedures (SOPs) which will allow these changes to occur in their organizations, and they have been discussed extensively at professional meetings and in publications

Rarely discussed, however, is the role onsite monitoring plays in detecting high-level problems with the design of investigational test products, with the clinical protocol, and with site noncompliance or fraud.





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Given recent and ongoing developments in monitoring practices, is traditional study site monitoring an historical anachronism? Would it be better if onsite monitoring were only applied to a few unique situations? These provocative questions are being discussed throughout the clinical trial enterprise. Indeed, with the growing adoption of EDC in conjunction with the increase in computer-assisted centralized monitoring and RBM processes, one might logically raise the question whether onsite monitoring should be significantly scaled back or totally abandoned.

Our view is that clinical monitoring operations have been significantly disrupted by the acceptance of these new and partially automated processes by regulatory bodies and their growing adoption by sponsors, CROs, and sites. In this article, we describe aspects of the overall topic that are rarely discussed, with special focus on the risks that accompany these trends and the underestimated value provided by onsite monitoring.

Purpose of Traditional Monitoring

Traditionally, a significant proportion of onsite monitoring has been devoted to ensuring that central site study files and source documentation are in place to safeguard human rights and verifying that all study information is accurate and properly documented.¹ Checking every datapoint in the sponsor's database against patient charts and other records is a major activity of traditional monitoring models representing a large proportion of the work done during most site visits.

In addition, monitors perform verification and accountability of study drugs or devices to confirm protocol adherence. Ultimate goals include confirming that the study was conducted per protocol, gaining an increased assurance that the safety and human rights of subjects were protected, and ensuring a diminished likelihood that auditors will find deficiencies in the study conduct.

Evolution of the New Processes

Given the intentions stated above, what are the key advantages offered by the new processes and technologies impacting monitoring styles? The Clinical Trials Transformation Initiative (CTTI) has addressed many of these factors with one key conclusion from this source being that the amount

of effort required in traditional onsite monitoring did not justify the resources applied to this activity. Part of this conclusion was based on economic and statistical arguments. Specifically, it was asserted that the occasional random error that occurs during a large clinical study should not make an appreciable or statistically significant difference to bottom line determinations of safety and efficacy.²⁻⁵

These conclusions, along with public comment, were incorporated into the 2011 U.S. Food and Drug Administration (FDA) guidance on RBM.^{6,7} The guidance states that there are "a variety of acceptable approaches to fulfill monitoring responsibilities," and that monitoring should be focused on critical, higher risk clinical sites and data that impact subject safety and data reliability. Also, it emphasizes that monitoring plans should be dynamic and reflect the discovery of new information.

The implications of the guidance on monitoring, as well as those of similar International Council for Harmonization and International Organization for Standardization documents, have been published extensively in this journal and elsewhere.^{1,8-17} Sponsors are slowly implementing changes that have the potential to significantly impact long-held practices, and monitoring organizations are carefully adjusting their SOPs and (hopefully) watching out for unintended consequences.

We are in the midst of a "formative" period—one in which sponsor/CRO processes can be influenced; therefore, before the new monitoring practices become standardized across the industry, it is important to raise concerns, some of which have hardly ever been discussed or published.

This new paradigm envisions a monitoring and database validation process with a higher level of efficiency and reduced cost, as well as the following advantages:

- If site personnel are responsible for entering data directly into electronic systems, transcription errors will be reduced significantly, compared to the process of using paper case report forms (CRFs) and other hard copy study documents as source documentation.
- Out of range or inconsistent data values can be proactively rejected prior to data being saved, as they would be identified by automated, pre-identified edit checks and/or centralized data reviews.

Since clinical monitoring is one of the most time-consuming and expensive product development activities, even a small change in the amount of onsite monitoring will have a large impact on product development costs.

- Essential study documents can be stored in central repositories that provide site personnel, monitors, and sponsors with remote electronic access.

Since clinical monitoring is one of the most time-consuming and expensive product development activities, even a small change in the amount of onsite monitoring will have a large impact on product development costs.^{1,18,19} Monitors will have more time to concentrate on problematic subjects or entire sites identified remotely by the new systems. On a higher level, RBM and properly applied centralized monitoring has the potential to identify anomalies at both the site and study levels that might not be apparent without automated processes.

Benefit of Onsite Monitoring

While the new processes have several important advantages, those already provided by traditional onsite monitoring models must be addressed. The following sections expound on these advantages, which are summarized in Table 1.

PROBLEMS TO BE DISCRETE ABOUT

Onsite monitoring is often responsible for identifying high-level issues that impact the outcome of entire projects, and which often are only discussed behind closed doors. Frequently, these tales concern inadvertent noncompliance, known but uncorrected errors, or outright fraud by site

personnel. These incidents are not often discussed publicly for obvious reasons, as the reputations of sponsors, clinical research associates (CRAs), and sites are at risk.

A false accusation or the promulgation of a rumor can have significant consequences on organizations and individuals. There are often moral, legal, and financial implications, including delays in or rejections of regulatory marketing approvals when data from a single site are excluded.

For example, if a study site’s data are suspect, a company may elect to present two analyses of the study results—one with the suspect data included and one without. Preparation of two analyses requires a significant amount of additional resources. There is also the possibility that the smaller database will have an insufficient number of study subjects to meet *a priori* statistical objectives. In this case, the sponsor may be forced to re-open enrollment to recruit additional subjects for meeting the needs of statistical analyses.

PROBLEMS DIFFICULT TO DETECT

Seasoned monitors often identify significant issues that can never be detected in databases. Three problems are particularly difficult to detect from a distance:

- First, there can be problems encountered by subjects or site personnel when attempting to use investigational products. Ease of use, malfunctions, or other investigational product-related difficulties encountered by end-users are often important factors not sufficiently captured in electronic or paper questionnaires. Crafting the perfect CRF or patient-reported outcome questionnaire is often very difficult until the investigational product has been used by hundreds of subjects. In the case of rare events (e.g., 0.01% incidence), an observation might not occur during the entire clinical development program. Basically, you don’t know what you don’t know. If a drug is too hard to mix or apply, or if a device is too difficult to operate, compliance can be significantly impacted. Perhaps the greater risk is that poor product design will be tolerated in the clinical study setting, but will be rejected once the product is approved, released, and marketed.

TABLE 1: Relative Effectiveness of Monitoring Technique

Type of Issue	Relative Effectiveness (★ = minimum; ★★★★★ = maximum)	
	Electronic Data Capture/ Central Monitoring/ Risk-Based Monitoring	Traditional Onsite Monitoring
Inconsistencies within the database	★★★★★	★★★★
Inconsistences between source documents, study site trial master file, and database	★★★★★	★★★★
Noncompliance by end-user conduct	★★★	★★★★
Noncompliance by site personnel	★★★	★★★★★
Detecting problems with the protocol or investigational product	★★★★	★★★★★
Clinical supply accountability	★★★★★	★★★★



- Ironically, the second type of problem that is not easily detected remotely involves site personnel and study participants dutifully executing the procedures as described in the protocol. The number of procedures mandated in each protocol has increased, and study visits have become longer and more complicated.^{1,18} This has several potential effects, including how, for study subjects and site personnel, excessively long study visits can lead to fatigue and inaccuracies in both objective and subject test results. The duration of office visits can make recruitment more difficult and inadvertently impact the type of subjects who elect to enroll. For the study monitors, more errors lead to excessive time devoted to reconciling databases with source documentation, which poses an unnecessary distraction. An increase in data variability, especially if concentrated in one of the treatment groups, makes it more difficult for sponsors to detect important safety and efficacy signals. Onsite monitoring is a very effective method for recognizing that study visits are too long or procedures too complex.
- The third type of issue that is difficult to identify from a distance covers insufficient investigator oversight, fraud, and noncompliance. This includes confirmation that the principal investigator (PI) understands and is properly carrying out his/her responsibilities. The same applies to sub-investigators, study coordinators, and other site personnel. Too many monitoring visits (and FDA inspections) reveal that PIs have inappropriately delegated key activities to site personnel or not maintained active control. These important noncompliance incidents can be detected by the good detective work provided by experienced monitors.

AN INSPECTOR CALLS...

The FDA's website²⁰ has many examples of issues discovered at study sites by their inspectors; however, these reports have been heavily edited and do not emphasize the impact on study sponsors. Here are some real-life examples from our personal experiences that may help communicate these concerns:

- Several years ago, we learned about a study that seemed to be progressing quite nicely based on the receipt of CRFs and periodic remote contact. The PI was conducting the study at two urban offices. Enrollment had progressed reasonably well and the number of database errors was proportionately appropriate. While the source documentation matched the CRFs, a routine monitoring visit uncovered some serious concerns. An examination of the front desk calendar revealed that the PI, the only individual authorized to perform several key medical procedures, was at the wrong office on several study visit days. The CRF visit days did not match the front desk calendars. This was a significant deviation that invalidated a significant number of datapoints and raised concerns about all study data. Ultimately, the site's participation in the study was prematurely terminated.
- In another case, a six-month study had progressed well with a good start-up visit followed by good enrollment. Overall, the responsiveness of the site to phone calls and other contacts with the sponsor was outstanding. CRFs were unremarkable. At the Month-3 milestone, a routine monitoring visit uncovered a significant problem. The study coordinator pulled the monitor aside and demonstrated that the investigational medical device malfunctioned when the instructions for use were followed. Specifically, the combination of two investigational products led to excessive foaming that spilled the investigational solution out of the designated vial and left it puddled on the table. This had not been previously reported to the sponsor because there was no place on the CRF to report this type of event, and the site had not reported it in any communication to the sponsor. The study was terminated early and the project abandoned.
- In another occurrence, a large study was close to meeting its enrollment goal when sponsor audits revealed that many adverse events and serious adverse events found in source documentation had no follow-up documentation and/or had not been reported. This caused a significant delay in the study timelines and raised many quality issues that had to be ironed out.

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- Elsewhere, six weeks after institutional review board (IRB) approval and receipt of investigational products, an onsite visit revealed that no one had enrolled in a study despite frequent dialog with the site personnel claiming that 12 subjects had been enrolled and randomized (Note: The new processes cannot totally eliminate this problem, since the availability of an EDC system does not guarantee timely data entry by site personnel).
- Then there was the case in which an onsite visit revealed that the duration and complexity of the office exams was excessive—twice as long as planned—and may have led to excess fatigue and data variability.
- An onsite visit regarding another study revealed that site personnel had prepared their own set of in-office written instructions for site personnel and subjects that had not been vetted by the IRB or the sponsor.
- During an onsite visit elsewhere, it was noted that a site staff member with many years of clinical research experience used pencil to document all study data. Per the study coordinator, this would allow her to erase “mistakes” and write over the correct data with a pen.

Remote communication processes between the site and the sponsor/CRO that would detect these types of incidents are often not in place, or are inadequate. The same can be said with cross-checks within electronic databases. In addition, once these deviations are detected, the processes used within sponsor or CRO organizations to manage these events are of potential concern.

Sponsor/CRO organizations typically have well-developed SOPs that specify that noncompliance or suspected fraud must be immediately reported to management and quality assurance departments. Such SOPs mandate many well-defined steps to protect all parties: the monitor, the sponsor, the site, and the subject/public good. However, critics can easily identify conflict of interest factors.

These study site incidents are often complex and rarely receive external visibility due to confidentiality and liability concerns. Feedback to sites suspected of significant noncompliance is often kept intentionally vague. Perhaps more importantly, bad apples often remain in the barrel.

The original sponsor may not use the site again, but a competitor may. Confidentiality concerns and the competitive environment are often barriers to the free exchange of this information.

Best Practices

What is the ideal? What are best practices? The potential for improving our processing using EDC, central monitoring, and RBM is extraordinary. It is a significant modernization that needs to move forward. The clinical research enterprise needs to leverage the use of automation to improve efficiency and reduce costs.

However, practical experience accrued from years of traditional monitoring indicates that these new technologies and processes only make sense when used in conjunction with monitoring and data management plans that allow for customization. The customization needs to address:

1. the challenges presented by each specific protocol (e.g., complexity; development stage; project criticality; safety risk);
2. the experience and skill of the site personnel (e.g., certified personnel or novice);
3. the experience of the sponsor or the sponsor/CRO's organization with this type of study;
4. the experience of the specific personnel assigned by the sponsor/CRO to the project; and
5. any new evidence of major noncompliance found during the course of the study.

Frequent onsite monitoring with 100% source data verification should be required at all sites unless evidence is presented to support another approach. Essentially, clinical study managers should build their plans by assuming that noncompliance will occur if the site were allowed to operate without intense intervention (guilty unless proven innocent). Less intensive onsite monitoring should occur only when it is justified, and all monitoring plans periodically reviewed based on available evidence.

Finally, the quality and frequency of site visits needs to be addressed. Quality is highly dependent on the detective work provided by CRAs who have a strong foundation of extensive training and experience. ACRP's Certified Clinical Research Associate (CCRA[®]) program has recognized the requisite skill sets, and most organizations impose a field-training element.

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The full utilization of a CRA's skills requires a good relationship between the monitor and the site personnel; however, the concern amongst many clinical research professionals is that the new monitoring models will reduce the number of site visits and contact time with key site personnel.^{13,21} Success building professional relationships may be adversely impacted if visits are inappropriately reduced.

Many of the noncompliance incidents described above were uncovered when CRAs asked questions that were not specified in monitoring plans. The discoveries relied on personal relationships developed over time. Sponsors and CROs should be concerned that the pressure to reduce onsite monitoring time combined with high turnover rate amongst monitors will spur unwelcome consequences in product development.

Summary and Conclusions

The potential for efficiency improvements using the new data monitoring tools and processes is significant. There is an opportunity to significantly reduce development costs and improve data quality. However, the clinical research literature has rarely focused on the problems that cannot be detected without the onsite presence of a skilled monitor.

While the safety risk to individual subjects or the risk to the project may appear to be small, the hidden, underestimated value provided by onsite monitoring is significant. Companies should seek the appropriate balance between remote and onsite monitoring that will take advantages of new technologies while maintaining the benefits provided by site visits.

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