

KAI RESEARCH

Risk-Based Monitoring: Maximizing Efficiency While Maintaining Quality

Scott Brand, PhD

Director of Strategic Planning
and Quality Assurance
sbrand@kai-research.com

Patti Shugarts

Vice President and Chief
Operating Officer
pshugarts@kai-research.com

KAI Research, Inc., an Altarum Company

11300 Rockville Pike
Rockville, MD 20852
Phone: 301-770-2730
www.kai-research.com



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Before the advent of clinical trial electronic data capture (EDC), data were collected on paper case report forms (CRFs). The paper forms were then sent to a Data Management Center for the double data entry. Double data entry was not immediate, and the sponsor or contract research organization (CRO) might not receive the completed CRFs for weeks after the participant was seen. This lag in receiving the CRFs, entering the data into the computer system, and generating data queries was long enough that errors could go undetected and potentially threaten or at least delay the outcome of a trial. This lack of access to the data was the primary reason that a sponsor or CRO would send clinical research associates (CRA) on frequent scheduled and unscheduled site monitoring visits to verify source data and confirm that good clinical practices were being followed. Intensive monitoring was essential to the success of a clinical trial.

The necessity for intense monitoring has been ingrained into every sponsor and CRO and has become the “security blanket” that allows them to feel secure in the integrity of the study processes and data. The Food and Drug Administration (FDA) reinforced this view of monitoring in the *Guidance for Industry, Guideline for Monitoring Clinical Investigation (1988)*, when it indicated the most effective way to monitor a study was to “maintain personal contact between the monitor and investigator throughout the clinical investigation.”

This process of intensive monitoring changed little with the early use of EDC, even though data review could be conducted as soon as the data were entered. To satisfy the FDA requirements and reassure themselves of the integrity of the data, sponsors continued to send monitors to the sites to confirm that the stored data matched the source documents and that the protocol was being followed correctly. It could be said that clinical trial research had one foot in modern technology and the other stuck in traditional practices.

What did serve as a stimulus to change monitoring practices was the rising cost of clinical trials as they included larger numbers of subjects at more sites in a wider geographic area. The expense of sending monitors on frequent visits to widely dispersed sites, including many international sites, could no longer be justified when EDC facilitates immediate central review and data editing. Combining the EDC with Web-based clinical trial management systems (CTMS) also made it possible to generate metric reports to track sites’ performance (e.g., time to data entry, quality of entered data, participant accrual) and compliance with protocol requirements. A second impetus for adjusting monitoring has been the acceptance of the adaptive approach to clinical trials. The adaptive design increases

the efficiency of clinical trials by adjusting the treatment administered based on interim analysis. This is an example of putting effort and money in study arm(s) that have a better chance of success. Researchers take advantage of the available information obtained during the study and adjust processes to achieve a better result. This same approach could be applied to monitoring: deploying monitors where and when the risk is greatest. The EDC and CTMS provide the needed information to guide and adjust the monitoring effort.

Technology (EDC and CTMS) facilitates accurate real-time assessment of study and site status, and the acceptance by regulatory agencies of the risk based approach (European Medicines Agency, 2011) has helped sponsors feel confident that risk based monitoring can increase efficiency while not reducing study quality.

FDA GUIDANCE

Recently, the FDA published *Guidance for Industry Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring (2011)*. This guidance document proposes that monitoring plans be responsive to the advantages that technology provides and the reality that not all sites have equal experience, capabilities or recruitment potential. These site differences correspond to variability in risk, and the degree of monitoring at each site should reflect this variability. Similarly, the status of a site can change with staff turnover, unanticipated increase in rate of recruitment or rate of dropouts, unexpected adverse event pattern, or lack of responsiveness to sponsor or CRO inquiries. These changes make it essential to reevaluate sites’ risk and adjust the monitoring required. While the doctrine has been the FDA expects 100% data verification, this guidance for industry states otherwise: “There is a growing consensus that risk-based approaches to monitoring, such as focusing on the most critical data elements, are more likely to ensure subject protection and overall study quality and will permit sponsors to monitor the conduct of the clinical trial more effectively.” This further reinforces the view that the maximum effort should be put in the area where the risk is greatest. Complete verification is essential for adverse-event and eligibility data, which are important to patient safety, as well as data used to support primary and secondary study endpoints. The variables that require 100% verification should be clearly addressed in the protocol and in the monitoring plan.

The FDA guidance actively promotes centralized monitoring: “FDA encourages greater reliance on centralized monitoring

practices than has been the case historically, with corresponding less emphasis on onsite monitoring,” thus decreasing the reliance on visiting the site. This centralization is feasible if the entered data and source data can be accessed electronically by the monitor. However, verification of EDC data originating from hardcopy medical records or other forms requires that the hardcopy source documents be reviewed. Source documents could be scanned and sent over a secure Web site or through a virtual private network; however, questions of security and privacy arise as source documents contain personal identifiers (e.g., names, birthdates, medical record number). Most likely, ethics committees will require adequate proof that privacy and confidentiality are protected and that access to and transmission and storage of scanned source documents be clearly defined. It seems doubtful that data in any format with subject identifiers would be authorized for release to such systems by ethics committees until suitable technology and safeguards are implemented and validated (unpublished discussion, Cindy Tryptten, Can-Med Clinical Research, Inc., 2011).

There is a bright spot for total centralized monitoring, which could eliminate the security and privacy issues. Data collection using extraction of selected data elements, free of personal identifiers, directly from an electronic medical record (EMR), produces a clinical trial database without manual data entry. The data would need to be edited only to identify issues that were both in the source and clinical trial data, a predominately data management task. It appears that the FDA guidance is pointing toward the future where the EMR systems replace the dedicated clinical trial EDC system.

Currently centralized monitoring is a hybrid, made up of centralized viewing and editing of the EDC data and as-needed onsite monitoring, making the process more efficient and cost-effective than the traditional structured monitoring approach. The efficiency and reduced cost comes in large part from the reduction of nonmonitoring time (e.g., travel, document retrieval, working around the site’s schedule). Once centralized monitoring is maximized, an initial site visit would be necessary to ensure that the site is prepared to initiate the study and that staff are properly trained. A subsequent visit would have to confirm that processes are being carried out correctly, that the drugs are accounted for, and that documents are being tracked and stored according to the protocol.

GOOD CLINICAL PRACTICE (GCP) MONITORING PLAN

Any risk-based monitoring approach has to be documented and justified in the GCP monitoring plan. The monitoring plan should describe the approach that will be taken to verify data and GCP practices at the clinical trial sites based on how risk has been determined or measured—as stated in the FDA guidance, “definitions of events or results that trigger changes in the planned monitoring activities for a particular clinical investigator.” One such trigger could be a lack of expected adverse events or a large quantity of an unexpected adverse event that is not evident at other sites.

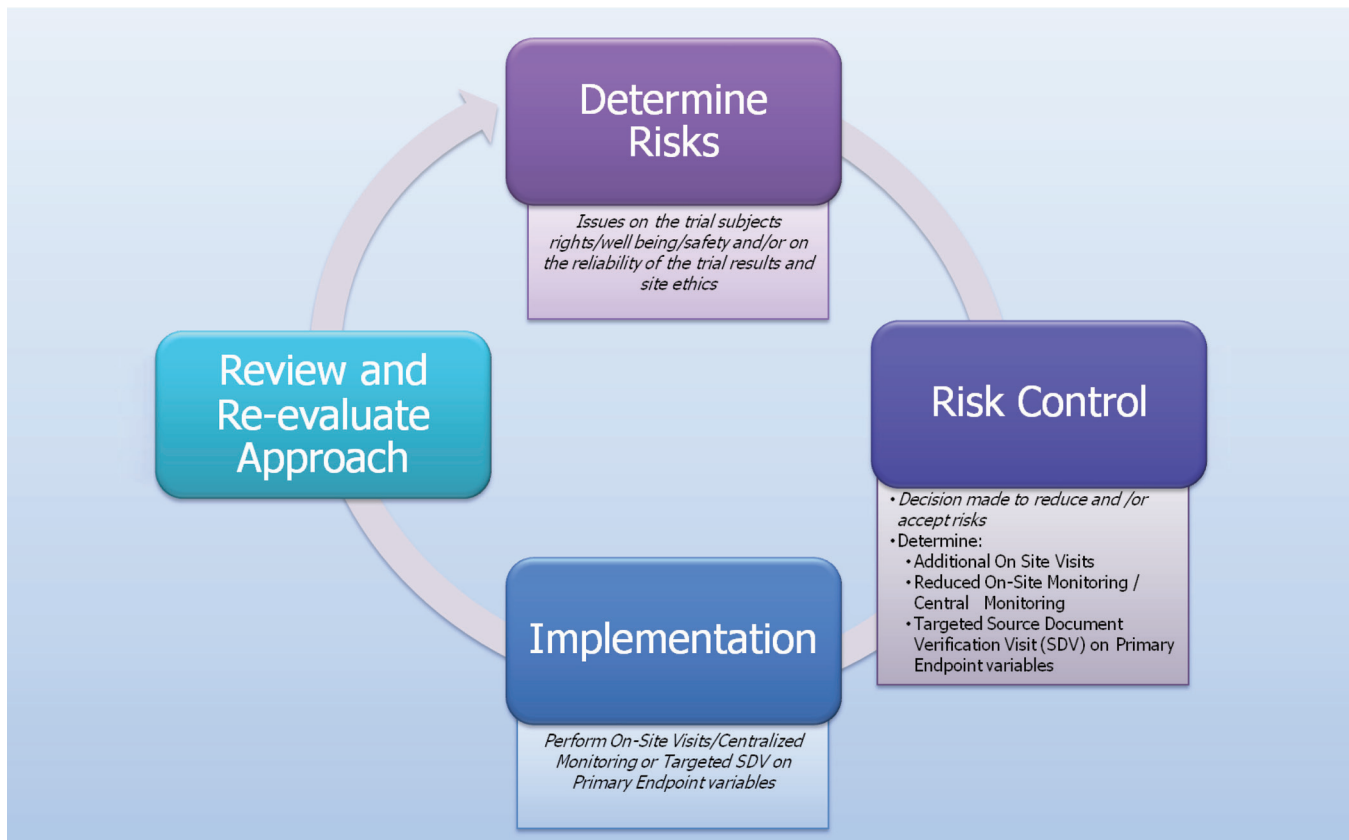
The GCP monitoring plan should address the following:

- ▲ The data elements that require 100% verification (e.g., endpoints, safety)
- ▲ Study complexity (e.g., adaptive design, multiple stratification factors, crossover)—the greater the complexity, the greater the risk
- ▲ Factors that may affect the level of risk
 - Experience of sites and staff
 - Medication or device (e.g., addictiveness, serious side effects, level of expertise needed to administer)
 - Unexpected adverse event signals, how they would be determined
 - Stage of the study (complexity and procedures performed can vary at different periods)
 - Vulnerable study population
 - Rate of early terminations
 - Staff turnover and reliability
- ▲ Required monitoring visits and what onsite monitoring visits must be carried out at all sites (e.g., site initiation, after first three subjects recruited, closeout visit)

While some of these risk triggers are quantitative, such as adverse-event signal and rate of early terminations, others are more qualitative, such as lack of responsiveness from the coordinator or slow or inadequate responses to questions.

The monitoring plan should be developed in association with the project manager, CRAs, data manager, biostatistician, statistical programmer, and sponsor. CRAs have hands on experience and can assess when a site visit is warranted. Similarly, the biostatistician and the data and project managers who assisted

Exhibit 1.



in the creation of the electronic CRFs and protocol can point out the data elements that require 100% verification or complexities in the protocol that increase the risk of erroneous data. The statistical programmer can then develop reports to ascertain trends or possible data discrepancies. This group approach is the best path to a realistic and efficient monitoring plan that takes into account all vital information. It is also beneficial to graphically display the triggers or decisions that can be used to focus the monitoring in reaction to increased risk (Exhibit 1). A complete diagram can communicate the concept of risk-based monitoring to the Institutional Review Board.

SUMMARY

Risk-based monitoring is an approach in response to technological innovation that allows both faster data access and application of quality checks. From a centralized data coordinating center, data managers can use the available information to make decisions on where to focus the monitoring effort. This approach will save money and time and still provide high-quality data.

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ABOUT KAI RESEARCH

KAI Research, Inc. (KAI), an Altarum Company, was formed in 1986 to provide clinical studies operations and quality assurance, data management, coordination of center services, and scientific infrastructure and management support to health research organizations. During the past 25 years, KAI has established itself as a high-quality research firm, providing research support services to the FDA, National Institutes of Health (NIH) and other government agencies, pharmaceutical and biomedical corporations, academic institutions, and associations. KAI was purchased in January 2008 by Altarum, a nonprofit organization that adds resources and depth to KAI in the areas of health care delivery and health services research.

KAI currently supports seven NIH institutes or centers: the National Institute on Aging; the National Institute of Arthritis, Musculoskeletal, and Skin Diseases; the National Institute of Neurological Disorders and Stroke; the National Institute of Child Health and Human Development; the National Institute of Mental Health; the National Institute on Drug Abuse; and the National Center for Complimentary and Alternative Medicine. We also support numerous pharmaceutical and biotech companies as well as several academic institutions and associations.

KAI RESEARCH, INC.

11300 Rockville Pike
Rockville, MD 20852
Phone: 1-301-770-2730
Email: marketing@kai-research.com

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