

MONITORING FOR QUALITY

Innovative and Traditional Resources in a Risk-based Monitoring Program

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The monitoring of any clinical study is designed to ensure that investigators are appropriately selected and trained to complete the proposed protocol-driven research, and that appropriate subject (patient) protection standards are in place. The “gold standard” for monitoring studies traditionally uses Clinical Research Associates (CRAs) as monitors who are dispatched to the investigative site every 4 to 8 weeks to perform an on-site assessment of the facility, conduct and review training, verify that appropriate subject protection standards are observed, that source document data matches the data entered into the case report forms (CRFs) and perform drug accountability verification when applicable. This continues to be the standard most commonly used throughout biopharmaceutical research, particularly in pivotal research to support a product’s approval. Monitors examine the performance of the site by examining screening logs, review of subject enrollment data, comparison of CRFs (or eCRFs) to the source data (the subject’s clinical record), visualization of subject consent documentation, interviews with research staff

and the principle investigator, drug/device accountability and visual inspection of the research facility.

This model has worked well, though not flawlessly, to produce high quality data to support the claims of efficacy and safe use of products intended to treat patients across the spectrum of disease, disability and nutrition.

The current regulatory environment, as well as the general public’s demand for more long-term safety data, is requiring an ever larger number of subjects in both pivotal trials and in the post-marketing safety trials that are now increasingly included as commitments for drug approval. Even with the potential for introducing “conditional approval,” the amount of subjects required for both initial (conditional) marketing approval and long-term unrestricted approval is likely to increase. This creates serious pressure on the research enterprise to sustain the cost of research using traditional tools such as CRAs described above.

CENTRAL MONITORING

Several years ago Quintiles began to develop a central monitoring capability as a method for monitoring larger studies, particularly on approved products in which the risk to the subjects in the study was considered to be minimal, and where there were already accepted community standards for the use of the products. Quintiles applied the concept of central clinical and data monitoring and established a group organized around the concept of a Project Coordination Center (PCC). The PCC is staffed with Research Coordinators (RCs) who function in part as in-house monitors but who also are cast in a data-quality support role. The Research Coordinators, using a variety of tools, play a significant role in routine site management, data cleaning and maintenance of study documentation. The PCC Research Coordinators are trained in the same Good Clinical Practice standards as CRAs, with selection based on the ability to understand and articulate complex concepts (such as a clinical protocol) and customer service skills. Prior research experience, particularly within the site-based study coordinator or CRA ranks, is also a consideration.

HYBRID APPLICATION OF CENTRAL MONITORING

Central monitoring exists on a spectrum of application. It can be applied with no on-site monitoring, typically in very low-risk studies with a non-interventional study design and a sufficient number of subjects to allow biostatisticians to

GLOSSARY

- **Risk-based Monitoring:** a quality circle program of risk assessment for clinical conduct and gathering of clinical data for any study that applies available monitoring resources according to the risks identified and reassesses those risks on a regular basis. The risk management monitoring program is documented in the Clinical Management Plan.
- **Hybrid Monitoring:** the selective application of on-site monitoring by CRAs combined with central (remote) monitoring by in-house Research Coordinators providing an integrated program of site management services, clinical conduct assurance, support for clinical data gathering, and patient protection/GCP compliance.
- **Progressive Source Data Verification:** a controlled sampling methodology for selecting source data to be verified in any clinical trial. The timing and number of subjects selected for source data verification and the frequency of repeated source data verification are established by the monitoring risk assessment documented in the Clinical Management Plan.

easily correct any missing data. More commonly, central monitoring is applied in a “hybrid” fashion by combining it with the use of on-site monitoring. In this model, Research Coordinators collaborate with their on-site counterparts (CRAs) to provide a blended approach and bring the benefits of both models to bear on the study. This approach permits the addition of strong site management support to shift the burden away from the investigative sites and provides a ready reserve of help and knowledge. Support from an RC is more immediately available than is possible when the only site management services available are from a CRA who is supporting several sites, traveling and trying to return calls and provide assistance while at the same time taking on responsibilities at new sites.

CONTINUUM OF MONITORING

We have since seen the central monitoring method move from its original employment in the post-approval period to extend to earlier phase studies as well. The benefits apply to both areas. When applied together, the two resources—CRAs and PCC-based RCs—co-exist on a continuum of variable application. On one end, high levels of on-site monitoring are combined with the site management benefits of central monitoring. This provides not only the data assurance required in a complex research environment such as a randomized clinical trial, but the employment of burden-shifting and site management tools that permit the best possible research experience for the site-based investigators and research staff that are the

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backbone of the research enterprise. This is particularly important when a study uses research sites not familiar with the demands of clinical research. On the other end, RCs in the PCC provide the bulk of the monitoring contact, particularly in studies with a large number of research-inexperienced or non-traditional sites.

SELECTION CRITERIA FOR CENTRAL MONITORING

Appropriately applying central monitoring delivered through Quintiles' Project Coordination Centers (PCC) is based upon the following criteria:

- Number of Subjects
- Research experience of investigators and site resources
- Protocol complexity
- Protocol with low recruitment expectations
- Electronic data capture (EDC)
- Duration of study

This approach is designed to: 1) increase site satisfaction, engagement and data quality; 2) prompt site adherence to the protocol; and 3) assist in timeliness of data entry and query resolution. Implementing a site management design that leverages central monitoring in conjunction with CRAs allows the field monitors to stay focused on site-specific issues when on-site, spending the majority of the time on source data verification and supporting the oversight of operational logistics.

PROGRESSIVE SOURCE DATA VERIFICATION

Quintiles has developed a model called Progressive Source Data Verification to make the most efficient use of the hybrid approach of combining central and on-site monitoring to space on-site visits more widely apart than would be the case in traditional models. In this model, the study's clinical lead guides a team of both central RCs and on-site monitors (CRAs) assigned to the study.

Site visits may occur at longer intervals, with a maximum time on-site designed to achieve the targeted level of source data verification. All status reports for on-site visits—whether selection visits, initiation or interim—are available immediately to the PCC-based RCs assigned to the study through a commonly shared clinical trial management system with the RCs coordinating and driving the follow-up responsibilities for any actions identified during the on-site visit.

RISK MANAGEMENT CLINICAL MONITORING PROGRAM

Incorporating a hybrid model of site monitoring (central plus on-site) together with Progressive Source Data Verification produces the twin pillars of a risk management approach to clinical monitoring.

Performing a careful monitoring risk assessment is critical to ensure that all of the monitoring objectives are achieved; namely, protection of subjects, adherence to the protocol, ensuring optimal data quality and providing a satisfactory research experience for the investigative site.

Once a monitoring strategy is selected and documented in the clinical monitoring plan, it is imperative that adherence

to that plan be strictly observed. If modification is necessary—based on risk information obtained during site visits or in central monitoring findings—then the plan may be modified as required. This traditional quality circle ensures that risks identified are managed appropriately, and new risks evaluated and quickly addressed. Failure to strictly adhere to the plan can result not only in improper monitoring and compromised data, but increases the likelihood of negative findings during any potential regulatory audit.

SUMMARY

At Quintiles, we have found that implementing a hybrid of central (PCC) and on-site monitoring, together with Progressive Source Data Verification, creates an effective risk management approach to clinical monitoring. The intent of this design is to continue to ensure protection of subjects in studies, obtain the highest quality data achievable, and whenever possible, to shift the administrative burden of the study from the research site to the PCC. It is also intended to provide immediate assistance to sites, thereby attempting to reduce both protocol deviations and the number of uncompleted data queries. Lastly, this model seeks to provide a successful research experience for the investigator and the site staff by engaging and supporting them with central RCs and on-site CRAs. We believe that the combination of PCC and risk management-based monitoring is one of the strongest tools to help make that happen. Important cost benefits of this approach also accrue, but vary with the monitoring risks identified and relative application of PCC and CRA resources.



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