MRM Step Monitoring Method™: "A Step in the Right Direction"

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FDA Warning Letter "Failure to ensure proper monitoring of the clinical investigations"

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Monitoring without adequate CRA training, including competency assessments and a monitoring methodology, can spell disaster! The safety of subjects and, of course, millions of dollars could be at stake. MRM performed a review of several FDA Monitoring Warning letters and found the following examples: "Monitors failed to secure compliance", "Inaccurate monitoring reports", "Monitors not properly trained", and "Failure to follow up." Such warning letters demonstrate the vital importance of quality monitoring, especially those aspects of monitoring most often mentioned in a 483. A recent Warning Letter cited a sponsor for "failure to ensure proper monitoring of the clinical investigations." This is and has been for many years the most common citation for a sponsor-monitor warning letter. A large organization recently received an FDA Warning Letter stating "failure to ensure that an investigation was conducted in accordance with the general investigational plan and protocols, as specified in the IND [21 CFR 312.50]." Other areas that have received a great deal of attention from the FDA include HIPPA violations, informed consent issues, subject eligibility, and device/drug accountability. Such actions by the FDA are avoidable.

On the Job CRA Training vs. Comprehensive CRA Training

Many CRAs are provided with ad-hoc, on the job training and, if they are lucky, a two day seminar. This hardly scratches the surface of what a competent CRA needs to know to properly monitor a clinical trial. In 1999, Medical Research Management created the 140 Hour CRA Certificate Program with three examinations including a vital monitoring competency exam. The CRA completes 70 hours of e-learning followed by two weeks of hands-on training in a class room setting employing the MRM Step Monitoring Method™. During the two weeks, the CRAs monitor 5 subjects across two different protocols. Each subject is a completed case with 7 visits per case. The protocols selected are relatively complex and the cases are specifically designed with an increase in issues and GCP non-compliance.

MRM provides such an intense program because training at a high level of complexity and dealing with difficult issues found during QA/FDA audits provides the CRA with the ability to develop critical thinking skills and the application of GCP. MRM's purpose is to provide extensive education: acquiring knowledge and applying that knowledge with hands on training. MRM uses three examinations: a core knowledge exam to validate the e-learning; an FDA GCP & ICH GCP examination to evaluate regulatory knowledge; and a monitoring competency examination to evaluate the application of the training. During the monitoring competency examination the CRA monitors a completed case along with the Investigator Study Binder and must receive an 80% or better to pass the class.

The Case for Using a Monitoring Method

The MRM Step Monitoring Method™ provides a methodical and standardized approach to monitoring. Based on feedback from industry professional, the MRM Step Monitoring Method™ demonstrates a higher level of thoroughness and consistency compared to didactic training with minimal hands-on experience.

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A Comparison

MRM Step Monitoring Method™

1. Reviews source document by itself to identify omitted data
2. Defines points of ICF/HIPAA Compliance Verification
3. Tools to aid in eligibility verification, accurate reports, CAPA plan development, and managing follow up action items.

Ad-Hoc Monitoring with SDV only

1. May miss omitted raw data which is key in supporting subject eligibility
2. Varies with the CRA and can lead to document inventorying
3. Use of Post It notes only can lead to inaccurate verification, monitoring reports and failure to mange follow up action items or verify if corrections are completed properly.

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The first step of the MRM Step Monitoring Method™ is *Source Document Review.* The purpose is to verify that the raw data is accurate and complete; supports eligibility; and demonstrates fulfillment of the Investigator's supervisory role to document that the subject is eligible to engage in the study. During this step, the CRA verifies what MRM refers to as the 8 points of consent GCP compliance and the 5 points of HIPAA compliance. Using such points of compliance prevents the CRA from merely inventorying the presence or absence of documents. In performing this step, the CRA uses a subject worksheet, monitoring notes, and an ICF/HIPAA verification log. This step performed with tools and without reviewing the CRF permits the CRA to focus on core compliance areas found in typical QA/FDA audits. Often CRAs may go directly into performing source documentation verification. Although the CRA may find transcription errors, they may not identify missing source necessary to support eligibility because it was not required to be transcribed into the CRF. Not all data, merely a simply check list, is recorded in the Case Report Form.

The second step of the monitoring method is *Source Documentation Verification*. Performing this step after *Source Document Review* confirms the accuracy of the information. During the verification step the CRA verifies from the source document into the CRF and organizes the flow of the verification via the CRF pages. Since the source is the raw data it is logical to verify it in this manner. During verification of medical history, medications, and adverse events, the CRA uses the list recorded on the subject worksheet because these items may be scattered throughout a medical chart. Listing them in one location makes verification easy and efficient. For example, if the CRA verifies from the CRF AE log into the source they may miss the AEs that were not transcribed.

Depending on the CRF transmission as monitored or unmonitored, a third step, *CRF Review* may be applied. The purpose is to review cross checks, data rules, and other known edit checks to prevent query generation. This will save time and money by reducing the number of queries which are estimated to cost the sponsor/CRO roughly $65 per query and a total cost for paper CRF at $300,365 per study[i]. This cost does not take into account the time spent resolving queries.

The key to the success of the MRM Step Monitoring Method™ is a systematic method utilizing tools oppose to using Post It notes only. The tools implemented are critical to writing though monitoring reports, developing Corrective and Preventative Action (CAPA) plans to secure GCP non-compliance, and managing outstanding monitoring action items from visit to visit.

A CRAs Perspective

From the perspective of a CRA, the course prepares a future monitor to enter the field. According to Brenda Anderson, RN, MSN, CCRA and a graduate of the Medical Research Management 140 Hour CRA Certificate Program, the course enabled her to "hit the road far and above colleagues." She says, "It is a difficult industry to get your foot into. The course assures perspective employers that you know what you are doing." She adds that "you always have access to MRM's expertise once one has completed the course."

Quality and Cost Savings

The MRM Step Monitoring Method™ may be applied to all clinical studies regardless of phase or therapeutic area. Utilization of this technique helps sponsors, sites, and CROs to maintain the highest standards for human subject protection, data quality, and ultimately, cost savings.

[i] Applied Clinical Trials, April 2010 pg 54

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