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Monitoring as a Mindset

Effective Monitoring for a Medical Device Trial

Demonstrating the safety and effectiveness of new medical devices through clinical trial work is a critical part of the development process. Obtaining solid data, achieving international acceptance and ensuring patient safety requires implementation of a quality monitoring system. While this certainly involves having standard operating procedures for monitoring and putting a monitoring plan in place for a clinical trial, it also involves empowering those who are involved in the every day management of the trial to understand their role as "monitor." The art of effective monitoring requires more than just an individual or a title, more than just a comprehensive procedure or checklist – it requires a mindset on the part of everyone who touches that clinical trial.

The purpose of clinical trial monitoring is:

- To ensure protection of the rights and well-being of study subjects
- To ensure data integrity
- To ensure compliance with federal regulations, agreements, clinical investigational plan (CIP), and the requirements of the Institutional Review Board (IRB)
- To identify and address non-compliance
- To improve quality and promote high standards
- To identify research misconduct or fraud

The U.S. Food and Drug Administration (FDA) defines monitoring as the act of overseeing an investigation. In addition, the FDA requires sponsors to not only identify investigators who are not complying with the federal regulations, the agreements, the clinical investigational plan (CIP), or the requirements of the Institutional Review Board (IRB), but they are also required to secure compliance or discontinue shipments of the device (21 CFR 812.46).

The International Organization for Standardization (ISO), the organization that provides international guidance for the medical device industry, further describes monitoring as not only the act of overseeing a clinical investigation, but the act of ensuring "that it is conducted, recorded, and reported in accordance with the CIP, written procedures, this International Standard, and the applicable regulatory requirements" (ISO 14155:2011(E), 3.29).

Traditional Monitors

The industry recognizes CRAs or Field Monitors as the “traditional” monitors tasked with overseeing the study at a site level. Some work regionally while others work in-house, but all travel to the investigative sites periodically to pour through the clinical study records in an effort to ensure data integrity and identify non-compliance. Finding qualified monitors with a clinical and/or scientific background and documented experience and/or training in regulatory requirements, CIP, device knowledge, and sponsor procedures is essential. A weakness in any of these areas should be addressed prior to monitoring and additional training, if necessary, should be undergone by the monitor.

Monitoring by a qualified person and/or entity is important in several areas:

- Assessing data integrity
- Ensuring proper informed consent
- Ensuring protocol compliance
- Reviewing essential documents
- Assessing overall site capabilities
- Assessing device accountability

Types of visits that a monitor might be involved in include site assessment (or qualification) visits, site initiation/training visits, periodic monitoring visits, and/or close-out visits, guiding site teams through the clinical trial process from Day 1 through comprehensive training, and then course correcting as needed throughout the clinical trial. Through medical chart review, monitors are able to assess data integrity by ensuring information submitted to the sponsor matches source documentation on file at the site. The monitor will work with site personnel, for example, to correct conflicting dates for an X-ray, or to verify that all adverse events that are present in the chart are reflected on the data forms submitted to the sponsor in accordance with the requirements in the protocol.

The medical chart review also allows the monitor to focus on eligibility criteria. If the clinical trial criteria excludes patients with a history of congestive heart failure (CHF), for example, and a chart review revealed a patient enrolled in the study who has CHF in their medical history, the monitor would communicate this finding to the site personnel and work with them to institute a corrective and preventative action plan to prevent future enrollment of ineligible patients. The field monitor's role is nicely suited to not only identify areas of non-compliance, but to work with the site personnel to secure compliance. An example of this is highlighted in the table below.

Identification of non-compliance	Efforts toward securing compliance
The CIP excluded subjects who had a history of CHF. During a periodic monitoring visit, the monitor discovered that subject 12-345 had a history of CHF.	The monitor discussed this with the site and developed a corrective and preventative action plan to prevent future enrollment of ineligible patients. For example, involved personnel will be retrained and an eligibility checklist will be completed and signed by the enrolling physician prior to enrolling future subjects into the trial.

Table 1. Example of securing compliance through medical chart review

Aside from medical chart review, the monitor will assess site compliance while on site with a review of:

- Essential documentation, including consent forms, IRB correspondence, company correspondence, lab certifications, curriculum vitae, training records and other pertinent documentation;
- Overall site capabilities, periodically touring procedures rooms, device storage areas, research documentation storage areas and patient follow-up areas;
- Resourcing issues at the site (often through staff interviews) to determine if they are devoting enough time to the study, whether there is adequate staffing and if staff are properly qualified, etc.;
- Investigational product accountability, reconciling what was sent vs. what was used vs. what is in stock at the site, as well as determining who received, used and returned the devices.

To facilitate the monitoring process, field monitors generally utilize checklists targeted at source data verification and essential documentation. These checklists will vary from study to study and will be largely protocol-specific.

Perhaps the most important tool in a monitor's toolbox, however, is the cell phone. Generally speaking, there is a whole team of people working on a study who are prepared to support the field monitors when needed, including project managers, research assistants, statisticians, medical reviewers, data managers, IRBs, and other entities. It is the people on the other end of that cell phone that can be combined into the group called "non-traditional monitors."

Beyond "Traditional" Monitors

In this highly technological world where communication and information flows freely in many directions, companies are beginning to rely on remote or centralized monitoring for some studies. A recently released draft guidance document from the FDA entitled "*Guidance for Industry – Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring*" further confirms this melding of approaches, recommending a combination of both remote monitoring and traditional on-site monitoring be utilized in clinical trials. Many different individuals and entities have some shared responsibility in overseeing the progress of a clinical trial, including sponsor personnel, IRBs, Data Safety Monitoring Boards and Clinical Events Committees, among others.

Sponsor personnel

Through site interactions and review of incoming data and essential documentation, team members who have never been inside a medical institution can play an integral role in study monitoring. If, for instance, the site submits data via an electronic data capture system, someone sitting in a cubicle can identify inconsistencies or blanks long before a field monitor makes a visit. The reviewer can then communicate with the site via a data query to resolve the deficiency. A research assistant tasked with maintaining IRB correspondence from the sites could certainly play an integral role in identifying deficiencies related to IRB requirements, including such issues as a potential lapse in IRB approval, patients being enrolled before full approval granted, etc. Data managers who are looking at data trends can alert the rest of the study team if they are seeing the same laboratory values missed across multiple sites, or if sites seem to be recording weight in pounds instead of kilograms, thereby assisting in securing compliance.

Through their many interactions with the sites, each person at the sponsor level has the potential to identify issues. Be it through a document that they received, a phone discussion they had, or a film they were reviewing, identification of errors is everyone's responsibility. The monitoring, or oversight, that happens at that sponsor level cannot just stop at the fact that a document or film was received. For it to be effective, the review should be purposeful. Each individual who touches a study document, a study film, or communicates in some way with the site, should ask him or herself what the significance of this is, and then review it accordingly.

IRBs

IRBs – an independent group charged with protecting the safety of human subjects enrolling in clinical trials – conduct initial and continuing reviews to determine whether a study can proceed. Sites are responsible for submitting annual renewals to the IRB, along with adverse event and/or protocol deviation information. In turn, the IRB issues a written response indicating approval or disapproval of the study.

Through this process, the IRB is essentially "monitoring" the progress of the trial with a particular interest in protection of the subjects enrolled in the trial. A savvy IRB will request additional information from a site that submits a renewal for an implantable cardiac medical device, for instance, indicating that no adverse events occurred in the previous 12 months, no protocol deviations occurred in the previous 12 months, and no patients withdrew or were lost to follow-up in the previous 12 months. While it may be possible that there were absolutely no issues with the study, it is highly unlikely, and a good IRB will research the situation a little more before reviewing a checklist, noting "no problems" and granting approval. Perhaps an IRB would even observe the consenting discussion to ensure that the requirements of 21 CFR 50 are satisfied. Again, the key to an IRB's monitoring contribution in a clinical trial is that their actions be purposeful.

Data Safety Monitoring Boards and Clinical Events Committees

Data safety monitoring boards (DSMB) and clinical events committees (CEC) also perform elements of monitoring specific to adverse event information. Both committees monitor the progress of a trial as it relates to safety. The DSMB is charged with "independent oversight and assurance of the safety of trial participants, both at the individual subject level and in aggregate" (Cutlip, D., et al., 2008) while the CEC examines adverse events on a more individual basis, providing an independent assessment of relativity to the investigational product. Both the DSMB and CEC work to provide safety monitoring during a clinical study and make determinations as to whether the risk/benefit ratio remains acceptable to continue the trial.

Melding Traditional and Non-Traditional Monitoring

Most investigators do not embark on clinical research with ill-intent, but many involved in clinical research are better clinicians than researchers. They depend heavily on the guiding hand of the clinical research team. It is for that reason that the entire clinical research team bears some burden in monitoring the progress of a clinical trial. Whether it is the field monitor who first identifies non-compliance through chart review, or a research assistant sitting back at the sponsor's office who picks up on the fact that patients may have been consented with an outdated consent form; everyone who touches a clinical trial has the potential to function in a monitoring, or oversight, capacity.

To reiterate the goals of monitoring outlined above:

- To ensure protection of the rights and well-being of study subjects
- To ensure data integrity
- To ensure compliance with federal regulations, agreements, CIP, and the requirements of the IRB
- To identify and address non-compliance
- To improve quality and promote high standards
- To identify research misconduct or fraud

These are certainly goals shared by the entire research team, and thus, responsibility for achieving them, through various methods of monitoring, is essential. While procedures, checklists, guidance documents, report templates and all sorts of other things combine to form the infrastructure for monitoring, what is possibly even more important is the shared mindset. The acceptance by all that regardless of the title, there is a shared responsibility in calling out issues, in looking purposefully at this document, in questioning that blank. The empowerment of others to assume the role of "monitor" every day they come to work in whatever capacity that is, will achieve the desired goals - protected patients, solid data, and international acceptance. To monitor is more than a title. It is a mindset.

Sandra Maddock CEO and President

Under Sandra Maddock's leadership, IMARC Research was founded in 1999 to deliver the highest-quality clinical research monitoring, auditing, training/development and consulting services.

Sandra offers IMARC partners years of expertise covering:
coronary and peripheral stents, angioplasty balloons, combination products, thrombolytics, chemotherapy agents, endovascular grafts for treatment of thoracic and abdominal aortic aneurysms, wound care, and dura mater replacement grafts. Whether serving as a global auditor for a device study across the U.S., Japan and Germany, or working with U.S. sites establishing GCP Compliance in preparation for an FDA Inspection, Sandra's hands-on approach has become her trademark.

For more information on how you can help prepare your sites for a better outcome, starting from Day One, please contact John Lehmann at 440.801.1540 or via e-mail at jlehmann@imarcresearch.com.

References:

Cutlip, D., Tcheng, J., Budreau, R., Fearnot, N., Snyder, S., Tacker, W. (2008). Chartering a data safety monitoring board. Applied Clinical Trials Online. Retreived from http://appliedclinicaltrialsonline.findpharma.com/appliedclinicaltrials/article/articleDetail.jsp?id=527737&sk=&date=&&pageID=1.

International Standard Organization. (2011) Clinical investigation of medical devices for human subjects - good clinical practice. ISO 14155:2011 (E).

U.S. Department of Health and Human Services Food and Drug Administration. (2011). Draft guidance for industry, oversight of clinical investigations – a risk-based approach to monitoring. Retrieved from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf.

U.S. Department of Health and Human Services Food and Drug Administration. (1996). Part 812 – Investigational Device Exemptions. Retrieved from http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm.