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5 STEPS to Make Your Monitoring Efforts Matter

Monitoring Defined

As discussed in a previous whitepaper, "Monitoring as a Mindset", monitoring is defined by the FDA as the act of overseeing an investigation. The International Organization for Standardization and the International Conference on Harmonisation further define monitoring as "The act of overseeing the progress of a clinical investigation and to ensure 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; ICH E6 1.38).

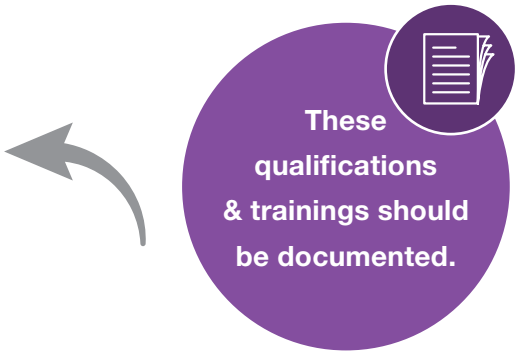
In order to comply with the applicable regulations and requirements as noted above, the intention of clinical trial monitoring is to protect the rights and well-being of study subjects, ensure data integrity, and ensure that the trial conduct is in compliance with the clinical investigational plan (CIP), agreements, GCP, requirements of the Institutional Review Board (IRB) / Ethics Committee (EC), and all applicable regulations. In addition, the goals of monitoring should include identifying and addressing non-compliance; improving quality and promoting high standards; and identifying research misconduct or fraud.

What 5 steps can be taken to ensure monitoring goals are achieved?

1 **Identify Qualified Monitors:** When choosing monitors to oversee the progress of the clinical study, a determination regarding their qualifications should be made as required in 21 CFR 812.43(d), which is described as follows.

Monitor qualifications should include:

- Regulatory knowledge
- Clinical/scientific knowledge
- Knowledge of the Investigational Plan
- Knowledge of the device under study
- Knowledge regarding sponsor procedures



CRAs or Field Monitors are perhaps the most recognized type of monitors. They may conduct site assessment visits, site initiation/training visits, periodic (interim) monitoring visits and/or close out visits. The majority of their work is done onsite at investigative sites involved in conducting clinical trials.

2 **Develop a Monitoring Plan:** a well-structured monitoring plan, created prior to the start of study enrollment, will further define the expectations of the monitors throughout a particular investigation and will help aid in ensuring a compliant clinical study.

Questions to ask when thinking through a monitoring strategy include:

- What type of study is being conducted? (IDE? 510k?)
- What is the risk of the study?
- How many sites and how many subjects will be involved?
- How complex is the study?
- What are the endpoints and measures? Are they quantitative or qualitative?
- How much data is being collected?
- How complex is the study population?
- What is the expected rate of enrollment?
- What is the experience level of the investigational site(s)?
- Where is the data being used?

Depending on the answers to the above questions, varying monitoring techniques may be employed, including frequent onsite visits for studies and/or sites that present higher risk, to less frequent onsite visits for lower risks. Including plans for remote, or centralized monitoring (i.e., review of IRB approval letters, review of submitted data, etc.), may also be appropriate depending on the risks as outlined above.

3 **Perform monitor training to ensure proper execution:** Training of monitors is an essential step in ensuring a well-controlled, well-run clinical study that results in protected human subjects and evaluable data. Being aware of their responsibilities and competent in the execution of those responsibilities is imperative for monitors to ensure compliance throughout a clinical trial. The monitors should minimally demonstrate a strong working knowledge of how to perform the following functions:

- **Ensuring proper informed consent:** First and foremost, the monitor reviews all informed consent documents, to ensure that the subjects were consented appropriately and that the process was documented. Any questions about the informed consent document or process should be discussed with the applicable site personnel, and corrective action plans may be suggested.

- **Assessing data integrity:** Through medical chart review, monitors are able to assess the integrity of the data by comparing what was submitted to the sponsor to what exists in the source documentation on file at the site. Any discrepancies between the source and the case report form is queried and discussed by the monitor and site personnel. In addition, monitors should clarify any questionable source documentation, to ensure that the data being submitted to the sponsor accurately reflects not only the appropriate source but the clinical condition of the study participant.

- **Assessing protocol compliance:** The monitors can determine whether or not a site is adhering to the procedures, as outlined in the protocol. If not, monitors may discuss with the applicable site personnel any corrective action plan to improve the site's process where it may be lacking. Monitors may work with a site a step further to determine whether the site is following the sponsor and/or IRB/EC-required procedures for reporting a protocol non-compliance.

- **Reviewing essential documents:** The monitor also spends time reviewing essential documentation, IRB correspondence, Sponsor correspondence, lab certifications, CVs, training records, and other pertinent documentation. One tool that monitors may use is the list of Essential Documents, as found in The FDA Guidance for Industry ICH GCP E6, Sections 8.2-8.4 or the ISO 14155:2011(E) Annex E.

- **Assessing overall site capabilities:** In addition, monitors assess the overall capabilities at the site, periodically touring areas such as procedure rooms, device storage areas, research documentation storage areas, and patient follow-up areas, and assessing resourcing issues at the site through interviews with staff (i.e., do they have enough time to devote to the study? Has any new staff been added? Is additional training needed for anyone?). Monitors should make recommendations to the sites in order to enhance any areas that may need improvement, such as moving study files to a more secure location to assist with maintaining confidentiality.

- **Assessing device accountability:** Monitors conduct investigational product accountability, reconciling what was sent from the Sponsor, versus what was used or returned, versus what is in stock at the site. Monitors should also assess who received, used, and returned the devices to ensure that only appropriate study personnel had access to the investigational product, that the devices were only used in study subjects who signed informed consent, etc.

4 **Identify and Document Findings:** Identifying non-compliances requires that a monitor have a thorough understanding of what compliance means for this particular site on this particular study. One cannot identify a non-compliance without first knowing all of the requirements. Per 21 CFR 812.110 (b), "An investigator shall conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, this part and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA." It makes sense then, that in order for a monitor to assess compliance in those areas, he or she needs to have a thorough understanding of each of them.

A monitor generally documents his or her findings through written reports that get distributed to the study team and through a follow-up letter that is sent to the site(s). In addition, a high performing team relies heavily on site and/or study team discussions, working together to problem solve ways to secure compliance, escalating issues as needed.

5 **Secure Compliance:** Once a non-compliance has been identified, the responsibility for securing compliance then falls on the sponsor. Per 21 CFR 812.46, "A Sponsor who discovers that an investigator is not complying with the signed agreement, the investigational plan, the requirements of this part or other applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or FDA shall promptly either secure compliance, or discontinue shipments of the device…." Many times, the sponsor's approach to securing compliance is through monitoring efforts, be it through additional training, corrective action plans, increased levels of monitoring, or other actions determined to be appropriate for the particular issue. If compliance cannot be secured, devices should be removed from the site, as stated in the regulation.

Does Monitoring Matter?

Of course monitoring matters! Compliance needs to be secured at even the best of sites from time to time. In addition, warning letters continue to flow out of the BIMO division of FDA, with the Number 1 finding in 2013 being failure to comply with federal regulations, agreements, investigational plan, and requirements of the IRB. Most people conducting research are not setting out to be malicious or do harm to anyone. But many involved in clinical research are probably better clinicians than they are researchers, and they depend heavily on monitors to steer them in the right direction.

There are extreme cases, however, in which monitoring and securing compliance is critical. In the Ketek Case1, involving Sanofi-Aventis as a sponsor and PPD as a CRO, a monitor uncovered fraud during a routine monitoring visit. Her findings along with her subsequent interactions with the FDA eventually landed the physician in jail. In this example, human subject safety was obviously an issue.

In the Schering-Plough fraud case2 involving a ragweed allergy study, a physician and research coordinator allegedly enrolled staff members, made up names, and lied about ages for financial gain. Both pleaded guilty to one count of conspiracy and one count of failing to maintain records in a clinical trial. They were sentenced to one year on supervised release and ordered to pay restitution of more than $36,000.

The importance of the monitoring function in clinical trials cannot be underestimated. The end-goal is to ensure a well-controlled, compliant clinical study in which human subjects are protected and the resulting data is evaluable. Achieving this goal takes diligent efforts on the part of sponsors, monitors and investigational site staff working together as a study team.

To set your next trial up for success from Day 1, consider taking these 5 steps for monitoring:

- Identify Qualified Monitors
- Develop a Monitoring Plan
- Perform Monitoring Training to Ensure Proper Execution
- Identify and Document Non-Compliance
- Secure Compliance

In doing so, you may avoid costly clean-up efforts, prevent a warning letter, ensure that data is credible and reliable, and ensure that all human subjects were protected throughout the process. Monitoring definitely matters.

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.

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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.

Reference:

1 Ross, David B. The FDA and the Case of Ketek, N Engl J Med 2007; 356:1601-1604