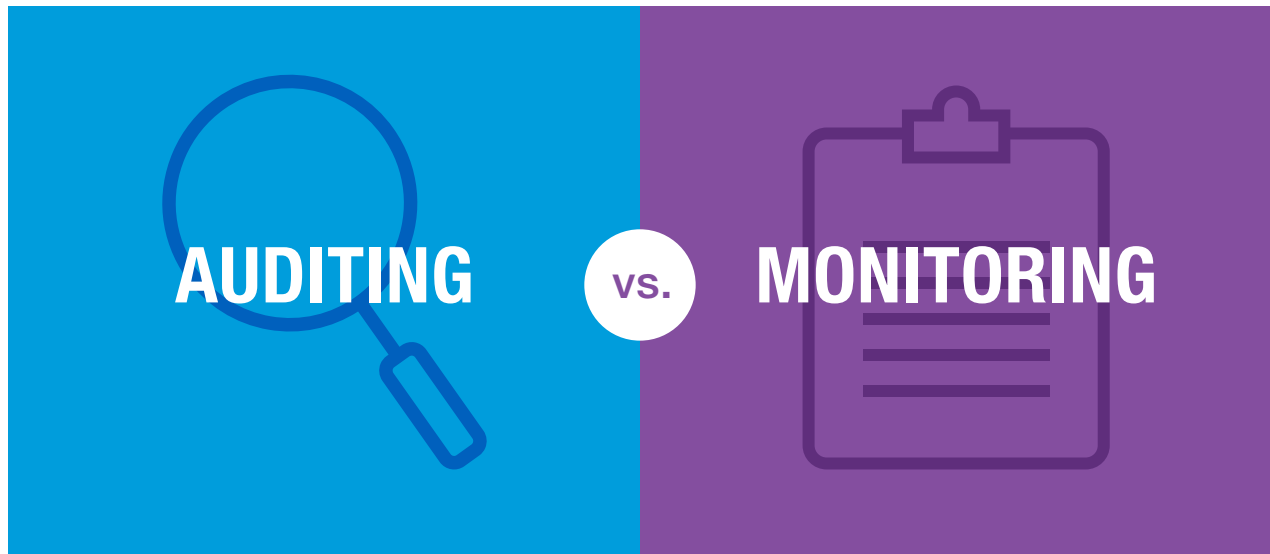


Introduction

Many professionals working in the clinical research arena may not appreciate or understand the roles and differences between clinical research auditing and monitoring, two distinctly different functions. Or if they do, they may not understand that the two functions can have an additive rather than redundant impact on quality. Conducting clinical studies is a complex endeavor, involving oversight of clinical investigators with respect to the protocol, Good Clinical Practices (GCP), governing regulations, conditions of Institutional Review Boards and/or Ethics Committees, and institutional Standard Operating Procedures before, during and after conduct of the study.



The study data that are generated must be of the highest quality; data must be accurate and evaluable in support of marketing clearance/ product approval and collected in a manner that protects the rights, safety and welfare of properly consented trial participants. Both monitoring and auditing can provide this oversight, albeit in different ways. The purpose of this whitepaper will be to define monitoring and auditing, compare and contrast them, and propose that the combination of monitoring and auditing in a clinical trial setting can have an additive impact on the overall quality of a clinical trial.



DEFINITIONS

To begin to understand the differences between auditing and monitoring, we need to define a few terms. Let's examine four terms defined in the Good Clinical Practice Consolidated Guidance (ICH-E6, April 1996) as follows:

- **Quality Assurance (QA)** is defined as “all those planned and systemic actions that are established to ensure that the trial is performed and data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirement(s)” [ICH1.46];
- **Quality Control (QC)** is defined as “the operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities are fulfilled” [ICH 1.47];
- **Monitoring** is defined as “the act of overseeing the progress of a clinical trial, and ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures(SOPs), GCP, and the applicable regulatory requirement(s)” [ICH 1.38]; and
- **Audit** is defined as “a systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor’s standard operating procedures (SOPs), GCP and the applicable regulatory requirement(s)” [ICH 1.6].

Elaborating on these definitions will lay the groundwork for understanding the differences between auditing and monitoring.



DIFFERENCES BETWEEN

AUDITING VERSUS MONITORING:

Looking at the Forest versus the Trees

Starting with the familiar expression “[he/she can’t] see the forest for the trees,” we adapt it to become “the forest versus the trees” as an analogy for the different functions of auditors and monitors. In this illustration auditing is represented by the forest and monitoring is represented by the tree. *It turns out you can see both the forest AND the trees if you utilize each compliance function!*



Monitoring is a quality control function where study conduct is routinely assessed on an on-going basis at every step of the trial. Using the tree analogy, a monitor looks in detail at each leaf on the tree. During a monitoring visit, all aspects of the study at a specific site will be checked in accordance with a monitoring plan, including informed consent documents, eligibility criteria, protocol compliance, source document verification for data accuracy, query resolution (clarification or correction of inaccurate data), occurrence and reporting of adverse events, test article accountability, maintenance of essential documents, and oversight of the Clinical Investigator and IRB. Monitors must ascertain that the Clinical Investigator is adequately informed of his or her responsibilities to recruit eligible subjects and to collect high quality data. Monitoring of clinical research studies is mandatory per federal regulations (21 CFR 812.3 (j)),

812.25, 812.40 and 312.50). During the course of a U.S. regulatory audit, FDA has access to monitoring reports and their associated action items.

Quality assurance encompasses and is built upon good quality control. **Auditing, a quality assurance function, is an independent, top-down, systematic evaluation of trial processes and quality control.** In our analogy, auditing involves looking at the forest as a whole. Using tools such as FDA's BioResearch Monitoring Program Guidance Manual, auditors can assess a wider study sample than monitors and can help evaluate trends at various levels by auditing a single or multiple sites, trial vendors and/or the sponsor. Auditors may look at study design, site/data management, statistical analysis and the Clinical Study Report. In general, auditors evaluate compliance to recognized standards, i.e., FDA's Code of Federal Regulations, International Conference on Harmonization, International Standards Organization and Standard Operating Procedures. Audits are not done continuously the way that monitoring is performed during a study, but instead are compliance snapshots in time. In addition, audits are not required by the U.S. regulations, but are voluntarily performed. Other countries may require audits, like Japan and those conducting trials under ISO 14155 [section 6.11]. Finally, during the course of a U.S. regulatory audit, FDA would not have access to an auditor's findings.



IF I HAVE GREAT MONITORS, WHY SHOULD I AUDIT?

A common mistake that many study teams make is to put the entire weight of the quality of a study on one team member – the monitor. Collectively, all members of the study team who interact with the various sites play some role in monitoring a site's compliance, whether it is a research assistant who reviews consent form changes that are submitted prior to IRB approval, or a project manager who talks to investigators about enrolling ineligible subjects. Many hands touch and contribute to the oversight, monitoring, and progress of an investigation. Yet, when the study is nearing completion and FDA inspections are imminent, there is often an unspoken sentiment that if FDA should find anything wrong it was because the monitor did not do his or her job. While it is possible that the monitor may have been less than adequate, it is also possible that any member of the study team may have failed in some manner as well.

What may be confusing is that, from afar, auditing an investigative site looks exactly like monitoring. They both schedule and confirm visits with the site. They both review subject records. They both review the regulatory binders. They both talk with the staff. They both generate reports. But because the auditor is looking more at processes– both the site's processes and the sponsor's processes as depicted by the site documentation – rather than focusing on individual data points, the outputs will be different. Some considerations as to why a study team should consider adding auditing to their quality plan are detailed on the next page.

Avoid common warning letter findings

If routine monitoring is adequate, why audit? Perhaps a more fundamental question is how adequate has clinical research monitoring historically been? Examining Warning Letters, issued from 2007 through 2012, posted on FDA's website has found that, year after year, the most common sponsor-monitor deficiencies noted during FDA inspections (See Table 1) are inadequate monitoring, failure to bring investigators into compliance, and inadequate accountability of investigational product.

Table 1:

Most common FDA Findings During Sponsor-Monitor Inspections						
Findings	2007	2008	2009	2010	2011	2012
Inadequate monitoring	✓	✓	✓	✓	✓	✓
Failure to bring investigators into compliance	✓	✓	✓	✓	✓	✓
Inadequate accountability for investigational product	✓	✓	✓	✓	✓	✓

Source: US Food and Drug Administration (2012). BIMO Inspection Metrics. Retrieved from <http://1.usa.gov/HLS1Lt>.

Hence, the most common findings against sponsors become the biggest liabilities in conducting clinical trials. Including early auditing as part of the quality plan can help identify ineffective monitoring practices and help a project team correct deficiencies if necessary.

Determine monitoring effectiveness

Even in cases where monitoring is thought to be robust and effective, however, auditing can certainly add value by bringing in a set of eyes that is focused on the “forest” and who has an objectivity that is difficult for study team members who are involved in the day to day management of study activities. Imagine a scenario wherein a monitor conducts periodic visits to a site throughout a trial, and as part of his routine, he verifies consent forms of newly enrolled subjects at each visit. At some visits, there may have only been one additional subject enrolled, and at other visits, there may have been several. In either case, the monitor reviews the consents of the newly enrolled subjects to confirm that the correct version was signed, that the subject signed and dated it prior to his procedure, and that all the necessary signatures were obtained. In essence, the monitor is examining the consenting “leaf” on the tree.

When the auditor comes in, she may open all the consent forms for the enrolled subjects and lay them out on a table, scanning them for trends in who consented the patients, similarities in handwriting, or any other glaring issues. This type of review is a luxury that was not afforded to the monitor who may

have only had one consent form to look at in isolation, among many other tasks to complete during a short visit. The auditor might then move to qualification documents, tracking back through all of the personnel who consented to ensure that they were adequately trained, taking special note of individuals who may only have consented one or two of the patients. From there, the auditor may question the investigator and the research coordinator separately about the consenting process, to ensure that the account of their consenting process is consistent with the documentation that the auditor is reviewing, and to ascertain the principal investigator's general oversight of the consenting process. The auditor may go from there to the hospital chart to review any documentation relevant to consenting, including what else was happening during the time that the patient was being consented (i.e., being prepared for surgery, having IV lines started, or signing hospital consents). If the auditor suspects that a patient was not given adequate time, she would then perhaps request to see an appointment book, sign-in log, or other documentation that would reflect the time that a patient arrived at the facility, comparing it with the procedural time, and then ascertaining what else occurred during that window of time. During this entire process, the auditor is checking for compliance with the reviewing IRB's policies, their own internal institutional policies, the sponsor's requirements, and the appropriate regulations. So you can see that the auditor is therefore examining the "whole forest" in order to make an assessment of compliance. The resulting finding could point toward a compliant site and effective monitoring practices, or a non-compliant site due either to ineffective monitoring or due to a site's unwillingness to make changes toward compliance despite a monitor's best efforts.

Determine study team effectiveness

Assessment of monitoring effectiveness is not the only reason to audit. Many individuals on the study team interact with the sites, requesting essential documents, discussing study status with the investigator, notifying the site of queries, and other seemingly unending requests. The monitor may even be communicating a site's non-compliance issues with the project manager who may be more focused on enrollment than on working with the sites to correct deficiencies. Perhaps the monitor has documented the non-compliance very clearly in the monitoring reports, but the project manager fails to react; this would be an internal process-level audit finding that would tell a sponsor that they have some work to do in terms of how they manage projects and monitor findings. Over the years, we have witnessed study teams take a "we'll fix that later" approach to study management so as not to impede enrollment. The risk of course is that issues may never be fully resolved and may eventually be identified by an FDA inspector. Auditing can uncover this type of system-level failure in a way that monitoring cannot.

Provide an independent assessment

If a Sponsor is utilizing internal monitors, hiring outside auditors adds an element of third-party oversight; this enables a sponsor to benefit from an independent set of eyes on a study. When the study team is in the middle of a busy clinical trial, bogged down with the myriad of daily tasks that are required in order to run the study, having objectivity to identify their own shortcomings or deficiencies would be difficult, if not impossible. As an analogy, imagine driving home after a busy day at work knowing that you have to get two kids to soccer, make dinner, help with homework, and attend an evening meeting. Would you even notice that you were speeding on the way home? Or that you didn't make a full stop at the stop sign? Or if you did notice, would you pull yourself over and give yourself a ticket? The answer is "no."

Manage non-compliant sites

Additionally, auditing can be used to help bring sites that are unresponsive to repeated actions taken by the monitors, the project manager, or other study team members into compliance. Sending an auditor to a site can create a "good cop-bad cop" scenario, in which the auditor can be as firm as necessary to emphasize the importance of coming into compliance, while at the same time, preserving the relationship that the study team has with that particular site or investigator.

Assess inspection readiness

Auditing is often used as a dress rehearsal aimed at high enrolling sites, sites with outliers in their data (i.e., large number of adverse events, large number of bail-out procedures, etc.), or sites with some type of financial conflict of interest. The auditor can perform a mock audit to mirror that of an FDA inspection. This prepares the sites for what to expect in the event of an FDA inspection, and primes the study teams for the types of questions and requests that may be forthcoming should one occur. The site and sponsor each gain confidence that they will know what to expect, outstanding issues are resolved, and required documents are confirmed as complete and correct. Potentially some minor administrative improvements could be put in place to help facilitate the actual regulatory inspection. This approach may fall short if deficiencies are identified too late in the game, and not much can be done to correct them, however, an audit can still be a valuable learning experience for all study members.



MONITORING + AUDITING = **SOLID ASSURANCE OF QUALITY**

Used effectively, monitoring as a quality control function can ensure the protection of research subjects, verify the completeness and accuracy of trial data and establish that the trial was conducted in accordance with the protocol, GCP, and pertinent regulations at a clinical site. Auditing is a higher-level process assessment, or quality assurance function, that provides an independent appraisal of data quality and integrity. Auditing critically evaluates the overall monitoring and regulatory compliance of a study by identifying potential system-wide problem areas.

While monitoring and auditing are distinct functions, together, they can complement each other to create an additive impact on the overall quality and integrity of a clinical trial.

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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 15-plus 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.

Mary Lewis, Chief of Clinical Operations

Mary Lewis comes to IMARC with over 30 years of clinical experience. She has held diverse positions of importance in the field which includes working as a Decentralized Senior Clinical Research Associate at Parexel International, as a Manager of Clinical Studies at NeuroControl Corporation, Director of Clinical Research at Fujirebio Diagnostics and Senior Director of Clinical Research at Stryker Orthobiologics.

Mary's clinical experience has covered various therapeutic areas including: spinal implant technology, biomarkers for epithelial ovarian cancer and malignant epitheloid and biphasic mesotheliomas, vertebroplasty in treatment of osteoporotic vertebral compression fractures, and post-stroke rehabilitation using functional electrode stimulation. Mary was recently named Chief of Clinical Operations for IMARC Research. She is responsible for the oversight of clinical operations at IMARC.



Want more information on how you can help prepare your sites for a better outcome, starting from Day One?

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