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Monitoring with an Auditor's Eye

By Linda C. Rudolph

> Is the standard monitoring report template (e.g., a form with multiple check boxes) inhibiting monitors from seeing the "big picture"?
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> How confident are study sponsors that problems occurring at clinical sites are being identified and corrected sufficiently to demonstrate compliance and the quality of clinical data to regulatory authorities?

These were two questions a senior project manager posed after reviewing a 20-page monitoring report of checklists and comments. Although the report detailed numerous problems with documentation, protocol compliance, and good clinical practice (GCP), the report did not provide an explanation for why all the problems occurred or what should be done about them. The report raised more questions than answers and left the manager feeling uneasy about the adequacy of the monitoring and the investigator's involvement in the conduct of the clinical trial. It was like reading a good book that was missing the final chapter. The report did not reach conclusions or even raise explicit questions about investigator oversight of the clinical trial, even though there were many signs pointing to this conclusion. Despite all the evidence, the monitor could not see how the pieces fit together.

In today's regulatory environment, sponsors need assurance that the site understands what went wrong and what needs to be done to fix the problem. For serious problems, developing a "CAPA" (Corrective Action, Preventive Action) plan can make sure the problem has been corrected and does not happen again. The process is not always easy and requires looking beneath the surface to find the root cause.

Most sites are not familiar with the term "CAPA" unless a sponsor has required the site to provide corrective actions in response to an audit. Monitors can improve the effectiveness of monitoring by adopting an auditor's perspective to addressing problems in their report.

The Role of the Site Monitor

Most monitors are skilled in finding deficiencies in source documents, regulatory binders, and drug accountability logs. However, focusing on the details makes it difficult to step back and see the bigger picture. This lack of a broader, action-oriented perspective usually is not their fault; monitors are probably doing exactly what management asks them to do. Many sponsors and contract research organizations (CROs) require monitors to use a monitoring report template (form) that consists of numerous check boxes and text fields. These templates generally focus on detailed findings, rather than on root cause analysis and CAPA plan development.

The FDA's "Guideline for the Monitoring of Clinical Investigations" gives a good description of the monitor's primary responsibilities:[1]

> The monitor should visit the investigator at the site of the investigation frequently enough to assure that:
>
> - Facilities used by the investigator continue to be acceptable for purposes of the study.
> - The study protocol or investigational plan is being followed.

- Changes to the protocol have been approved by the IRB and/or reported to the Sponsor and the IRB.
- Accurate, complete and current records are being maintained.
- Accurate, complete and timely reported are being made to the sponsor and IRB.
- The investigator is carrying out the agreed-upon activities and has not delegated them to other previously unspecified staff.
- The monitor or the sponsor should maintain a record of the findings, conclusions and action taken to correct deficiencies for each on-site visit to an investigator.

The key text here is: "conclusions and any actions taken to correct any deficiencies noted during the visit."

The ICH E6 Good Clinical Practice: Consolidated Guidance similarly describes what should be included in monitoring reports:

> Reports should include a summary of…the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to secure compliance. (5.18.6 (c))

Thus, the report needs to include more than a list of deficiencies. Monitors need to draw conclusions about the cause of significant deficiencies and record any actions taken to correct them and prevent them from reoccurring. Monitors can improve the value of the report by identifying the root causes and working with the sites to develop CAPA plans.

The Role of the Auditor

The auditor's role is to ascertain whether the monitoring was adequate, systems worked, and the study was conducted in compliance with the protocol, GCP and applicable regulations. Auditors should be independent from the project team so they can offer a "fresh set of eyes." Both monitors and auditors play vital roles in assuring that quality is built into the clinical trial; however, the purpose of auditing is not to "re-monitor" the trial data.

The ICH E6 Guidance defines auditing 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), good clinical practice (GCP), and the applicable regulatory requirement(s). (1.6)

In addition, auditors review study records and visit reports to look for trends or patterns of non-compliance. The auditor formulates questions for further investigation or discussion with the investigator and site personnel. For example, if an auditor notes frequent missing data (i.e., expiration date of the pregnancy test kit) in the source documents, he or she might question whether the site disposed of the test kits before recording the lot#/expiry. A quick conversation with the study coordinator can confirm the theory or point to a different cause. For example, the information might have been recorded on a log that was not provided to the auditor with other study records.

Experienced auditors are able to see beyond problems already documented by the monitor or site. With experience, they instinctively know "what's missing from this picture." For example, an auditor may notice that the investigator did not date/sign the consent form the same day as the study participant on several occasions. A quick review of the investigator's clinic schedule can verify whether the investigator was on site and forgot to sign it until later

or was actually not in the office when consent was obtained (a bigger problem). Over time, auditors know what to look for, including things that are not there.

Auditing Strategies for Monitors: Identifying Problems

Monitors can adopt the following strategies to use an "auditor's eye" in their work:

1. Occasionally, step back and take a "global" snapshot of how the trial is going at different stages. For example, during the screening and enrollment phase, did any of the following occur?
   - Lack of explanation of the reasons for screen failures
   - Screen failure rates significantly higher or lower when compared to other sites
   - Sponsor "waivers" allowing subjects not meeting inclusion criteria to be enrolled
   - Study-related procedures being performed prior to the consent being signed

   These observations may indicate a protocol violation, a departure from GCP, or a reportable deficiency in the study documents. Although an isolated instance may not require a CAPA plan, a pattern or trend may evidence serious or continuing non-compliance that requires immediate corrective measures.
2. Determine whether investigator involvement and oversight is evident.
   - Is it clearly documented in the source?
   - What percentage of the monitoring visits includes investigator participation?
3. Question whether "oddities" (e.g., unusual or non-conforming events) are red flags that may indicate a systemic problem. Common red flags include:
   - Delays or errors in addressing deficiencies identified in previous visit reports
   - Multiple errors or omissions in signing source documents
   - Too many notes to files (NTFs) located in study source documents and/or the regulatory binder that restate or explain the finding but do not address the underlying cause or how the problem was fixed
   - Delays in entering source data onto case report forms
   - Missed or incomplete study visits
   - A high dropout rate

   Issues like these can indicate that a study (or entire site) lacks adequate resources or support from management. It is also not uncommon to see problems emerge with personnel changes, especially with new study coordinators or subinvestigators.
4. Ascertain whether systems and processes are operating properly:
   - Does the site have and follow written procedures (SOPs) consistent with GCP?
   - Are incidents of non-compliance isolated or part of a pattern?
   - Is there evidence of process gaps or communication breakdowns?
   - Is there a general sense of disorganization at the site?

Auditing Strategies for Monitors: Solving Problems

No one appreciates criticism in the form of blaming or finger pointing, but most site personnel gladly participate in a constructive process of improvement. Monitors can use this process to build relationships with site personnel. Experienced monitors know the importance of maintaining open lines of communication, even in difficult situations.

Monitors can work with sites using the following four-step CAPA process to define, correct and prevent problems:

1. **Agree that there is a problem and what it is.** Define the problem based on the facts surrounding the deviation or deficiency.
2. **Determine the root cause(s).** Trace the problem back to its source, considering all contributing factors.
3. **Take corrective action.** Develop and implement a corrective action to immediately correct problems that have already occurred and mitigate their effects.
4. **Take preventive action.** Develop and implement preventive (i.e., proactive) action to minimize the chance that the same problem will occur in the future. Preventive actions are usually part of a continuous quality improvement program and require implementing systemic solutions, e.g., SOP development and training programs.

Sites will be expected to perform the corrective/preventive actions, while the monitor will follow-up to make sure actions taken by the site result in the desired outcome. As site personnel become more familiar with the CAPA process, they will be able to take a more active role in determining root causes and creating their own CAPA plans, as well.

Conclusion

Monitoring requires attention to detail — looking at "a lot of trees" — when reviewing study documents. Occasionally taking an auditor's forest-level perspective can help monitors see more pervasive problems. Utilizing CAPA strategies creates site reports that offer substantial value and increase sponsor confidence in the sites. By working with sites constructively, monitors can strengthen the sponsor/site relationship and improve the site's overall performance.

Note

1. The guidance has been removed from the FDA website and is currently under revision.

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