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Monitoring with an Auditing Mindset

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Monitoring and auditing are complementary activities that ensure clinical trial compliance. The ICH GCP definitions are provided below:[1]

> **Monitoring** is the act of overseeing the progress of a clinical trial and ensuring it is conducted, recorded and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s). (ICH GCP 1.38)
>
> **Auditing** is 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 GCP 1.6)

The goals of both auditing and monitoring are the same: to ensure that the trial is conducted properly, that participant safety is protected, and that data integrity is secured.[2] Monitoring visits are normally performed on a periodic basis as the trial progresses. The monitor reviews all aspects of the trial according to the monitoring plan, including essential documents, product accountability, informed consent documents, eligibility criteria, adverse event reporting, source documents, and case report forms. Additionally, the monitor attempts to work with the site to resolve any findings during the visits.

Auditing visits are normally performed at most once during a trial. These visits employ a top-down, systematic evaluation of trial processes, documents and data. Whereas monitors focus on new data at each visit, auditors review a wider sample of information to evaluate trends and find anomalies.

While monitoring primarily focuses on details in the documents, auditing primarily focuses on processes. Although monitors generally do not have time during routine monitoring visits to perform the additional activities of an auditor, monitoring with an auditor's mindset can improve site performance and reduce the monitor's work at subsequent visits.

In addition to identifying discrepancies and assisting with corrections, monitors can consider whether their findings indicate broader issues. In particular, is there a problem with a process that could be fixed to prevent recurring problems? When such an issue is identified, the monitor can employ CAPA (Corrective And Preventive Action) methodology to address it.[3]

Six Questions

To employ an auditor's mindset while monitoring a site, ask the following six questions when a possible issue arises:

1. **Was the issue a one-time occurrence?**

How prevalent is the issue? Have you observed it just once, or multiple times?

2. **What is the impact of the issue?**

What is the impact of the finding on participant safety and data integrity? Is it a minor, administrative error, or is it more consequential?

3. **What is the *potential* impact of the issue?**

Even if a single incident is not important, would repeated occurrences have a significant impact? Does this particular issue raise the possibility that other, more significant issues might be occurring?

4. **What caused the issue?**

What caused the discrepancy? For example, is the case report form confusing? Is the study coordinator's workload too heavy? Is the protocol especially complex? Does the protocol ask too much of the participants?

5. **Could the issue happen again?**

How likely is it that that this issue might occur again?

6. **What preventative measures should be taken?**

Can this issue be prevented, and is it worth the effort?

Example A: Updated Informed Consent Form

To illustrate the auditor's mindset, consider this example about informed consent:

> During a site visit, the monitor is reviewing a consent form and notices that the previous, out-of-date version of the informed consent was used for the most recently enrolled subject. The only change in the new version is that the site had recently moved to a new address. The error is only administrative, since it has no impact on participant safety, study data, or study conduct. No other consenting errors were noted during the monitoring visit. The research coordinator agrees to correct the issue by having the participant sign the current version at the next visit.

Ordinarily, the monitor would consider this issue closed and move on, but a monitor with an auditor's mindset should ask the following questions:

1. **Was the issue a one-time occurrence?**

Yes, this issue occurred with only one participant.

2. **What is the impact of the issue?**

There is little impact. The participant had visited the current offices, so he or she knew the new address of the site. None of the other information about the study changed.

3. **What is the *potential* impact of the issue?**

While the change in address has little impact, what if the change had been more important, e.g., disclosing a new risk or additional procedures that might affect the willingness of patients to give consent? In other words, the issue is not that something trivial changed but that the site's procedures might be inadequate for handling more important changes.

4. **What caused the issue?**

Why was the old version even available? Was the person obtaining consent informed that there was a new version? What about other people delegated the task of obtaining consent?

5. **Could the issue happen again?**

Looking at the issue more broadly, what is the site's process when a new consent form is approved? Is there a checklist or standard operating procedure (SOP)? How is the study team notified when new consent forms are available for use? How are old versions of consent forms made unavailable for future use?

6. **What preventative measures should be taken?**

Depending on the answers to the previous questions, the monitor can work with the site to determine what preventive measures should be taken, if any. If correct procedures are in place but just weren't followed, re-training might be sufficient. Otherwise, the monitor could work with the site to create or update an SOP for consent form revisions.

Example B: Missing Lab Values

To further illustrate the auditor's mindset, consider this data collection example:

> A study requires two blood draws from study participants. The study nurse performs one of the draws but participants have to visit a local lab for the other draw, which is relevant only for a secondary endpoint, not safety. During the first site monitoring visit, the monitor notes that one of 20 participants is missing the second blood draw. At the second monitoring visit, the monitor notes that two of 20 participants are missing the second draw. Copies of the lab orders document that the research coordinator correctly ordered the blood draws. All the relevant documentation is clear and in order. The site logged the deviations without prompting.

Ordinarily, the monitor would document the missing data clearly in the trip report and ask the site to look for the missing reports, find out what happened, and minimize future occurrences. The monitor would note that the site is in compliance, since the labs were ordered, and it is the lab's responsibility to draw the blood, run the tests, and report the results.

1. **Was the issue a one-time occurrence?**

No, but it was not a frequent occurrence.

2. **What is the impact of the issue?**

The impact is minimal, since only three of 40 lab reports are missing, and missing the blood draws does not put the participants at risk.

3. **What is the *potential* impact of the issue?**

Although only three lab reports are missing, it is troubling that the number did not decline but doubled from the first to the second visits. Is it a trend?

4. **What caused the issue?**

Most likely, the study coordinator gave the lab order to the participants and asked them to take it to the lab after leaving the investigator's office. So, some questions to ask are: How far away is the lab? Did the lab always draw blood promptly? Was the lab closed when some participants arrived? Are some participants needle-phobic? Was bad weather an issue?

These and other questions might need to be asked to understand what is causing the problem.

5. Could the issue happen again?

Since it's happened three times, it can probably happen again. An investigation should reveal the cause(s).

6. What preventative measures should be taken?

Three missing lab reports do not constitute a significant problem, but if the investigation reveals that the problem might continue or grow, preventative measures might be worthwhile for this particular study. Based on the above investigation, perhaps visits should not be scheduled late in the day. Perhaps someone should escort certain participants to the lab. (Escorting every participant to the lab might be overkill.) Perhaps the study coordinator should notify the lab to expect a participant within five minutes and report back if the person does not arrive. Perhaps the study coordinator could perform the second draw and send it to the lab.

Conclusion

Monitors have a lot of work to complete during site visits, so digging into what appears to be a small data problem to possibly find a larger process problem may not be a priority. However, when an issue arises, asking these six questions might reveal important problems that should be corrected and perhaps save the site monitor time over the course of a study. It might even help identify and remedy a problem occurring at other sites, as well.

The above examples demonstrate that a seemingly innocuous issue might indicate the presence of a serious, continuing problem. Or, it might just be a minor, one-time occurrence. By asking a few, quick questions that an auditor might ask, a site monitor can determine whether further investigation is required, potentially leading to a better process. An experienced auditor develops a sixth sense about process issues that deserve exploration and correction. With practice, site monitors can do the same.

When sites review any issues raised by a monitor, they, too, can investigate further. They need not wait for the site monitor to raise an issue that the site, itself, observes.

References

1. Good Clinical Practice: Consolidated Guidance (ICH-E6): April 1996
2. IMARC Research, Inc. Auditing vs. Monitoring in Clinical Research Studies. Available: www.imarcresearch.com
3. "Site Visit Follow-Up," Amy Adams and Rosanne Petros, Journal of Clinical Research Best Practices, February 2012

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