

Investigator preparedness for monitoring and audits

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Abstract

Monitoring and audits are two distinct processes that ensure that the rights and safety of the participants are protected, and data integrity is maintained. The present narrative summates authors' experiences with monitoring and audits by sponsor along with challenges faced by the site. It also offers potential solutions for challenges faced during the process of monitoring and audits. It is important to remember that no monitoring or audit can ever substitute for a well-designed and articulated protocol. In addition, a determined approach by the investigator and his/her team to ensure that all aspects of the protocol are adhered to in totality will go a long way in assuring quality.

Keywords: Investigator's responsibilities, quality assurance, quality control, site preparedness

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INTRODUCTION

Conducting clinical research is a highly complex and difficult endeavor. It mandates that the Principal Investigator (PI) constantly ensures oversight with regards to the study protocol, good clinical practice (GCP) guidelines, standard operating procedures (SOPs) of the site, institution and sponsor, requirements laid down by the Institutional Review Boards (IRB)/Institutional Ethics Committees (IECs), before, during and after conduct of the study. Monitoring and audits are two distinct processes that ensure that the rights and safety of the participants are protected, and data integrity is maintained. The latter is important so that the trial yields valid regulatory data in case of regulatory trials. Together, they have an additive impact on the data quality. A third process that can at times be associated with the two is an inspection. The present articles primarily focus on our experiences with monitoring and audits by a sponsor and/or a Contract Research Organization (CRO).

MONITORING AND AUDITS-DEFINITIONS

Monitoring

The International Council of Harmonization (ICH)-GCP defines monitoring as an act of overseeing the progress of a clinical trial, so as to ensure that the trial is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirement(s).^[1]

Audit

An audit, on the other hand, 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 SOPs, GCP, and the applicable regulatory requirement(s).^[1]

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THE DISTINCTION BETWEEN MONITORING AND AUDIT

Monitoring and audits are similar in that they both protect the rights, safety, and well-being of study participants as well as data integrity. However, they are different with respect to responsibilities of the different stakeholders and the frequency with which these processes are carried out. For studies funded by the pharmaceutical industry, the responsibility for monitoring lies with them. For academic studies, it lies with the PI. Thus, for every study, the responsibility of ensuring monitoring rests with the “sponsor” and in the case of academic studies/Investigator Initiated Studies, the PI becomes the sponsor.

Monitoring is a regular activity done at predefined frequencies spelt out in a predefined monitoring plan. The

process of monitoring ensures that study activities are being carried out as planned and deficiencies addressed and corrected promptly. It is thus a quality control tool. An audit, on the other hand, is not frequent. It can be done at any time during the conduct of the study (*ad hoc*) or “for cause” (for a specific purpose). An audit is essentially a quality assurance activity undertaken by personnel independent of the trial.

THE PROCESS OF MONITORING BY THE SPONSOR

Monitoring is necessary for all clinical trials regardless of whether they are academic studies or funded by the pharmaceutical industry. The monitoring plan for a particular research study should be made based on the study’s complexity and envisaged risks. For Investigator-Initiated

Table 1: Preparedness for monitoring by the sponsor

How to ensure site preparedness	
Prestudy monitoring	<ul style="list-style-type: none"> • Keep the SOPs of the site ready and ensure that all SOPs are current and valid • Ensure that the staff who will form part of the study are trained in the SOPs and the training log is kept ready • Ensure staff training for ICH - GCP, India GCP guidelines, Schedule Y and ICMR 2017 guidelines and keep training log ready • Keep the IEC SOPs ready/URL where they can be found • Have adequate knowledge of the IEC meetings and turnaround time • Ensure that all instruments relevant to the study and refrigerators (if applicable to the study) are calibrated and the calibration certificates are ready for inspection by the monitor • Ensure controlled access for all study areas (audio-video consenting area, pharmacy room, document archival area, clinical pharmacology unit/outpatient department, etc.,) and evidence thereof • For high-risk studies such as first in human studies, ensure emergency tray is equipped, and all requisite instrumentation calibrated and function (e.g., ECG, defibrillator, and ventilator) so that these can be checked and verified by the monitor • Keep data ready on number of potential participants who can be recruited in a given time frame, and attrition due to laboratory tests or lost to follow-up
Site - initiation visit	<ul style="list-style-type: none"> • Conduct multiple protocol readings so that the team members become familiar with every aspect of the study before the initiation • Prepare-specific questions related to operational aspects of the study which can be discussed with the sponsor at the time of the site initiation • Ensure that the entire team is present on the day of the site initiation • Confirm supplies received (IP, TMF, laboratory kits, etc.,) from the sponsor/CRO and discuss storage and use on that day. Do dry runs in the sponsor’s presence • Ensure that any deficiencies identified during the pre-study visit have been addressed • Ask for a report of the site initiation visit report. When received, file in the TMF
Routine monitoring visit	<ul style="list-style-type: none"> • Confirm a clear understanding among the team members of individual roles and responsibilities • Ensure that all study team members are available • Ensure a quiet area is available for the monitoring • Ensure proper documentation of CRF including signatures, updated TMF and other study related logs • Arrange all case sheets, CRFs and TMFs clearly and sequentially • Orient the monitor to appropriate areas of the site • Enquire regarding findings at the end of the visit • Ensure that medical records and files are kept in a locked room, if monitoring lasts for multiple days • Discuss the findings and schedule the next visit, on a mutually agreed date, at the end of visit • File the monitoring report sent by the monitor in the TMF
Close out visit	<ul style="list-style-type: none"> • Ensure that all study team members are available • Ensure a quiet area is available for the monitoring • Make necessary arrangements for retrieval of pending study related documents • Provide secured area for archiving relevant documents for a specific period as per sponsor’s SOP • Confirm that all CRFs are retrieved and queries resolved • Ensure whether all extra CRFs, study supplies and laboratory kits returned to the sponsor/CRO • Ensure that all biological samples have been shipped or back-up samples are destroyed as per site SOP • Make sure that the final report provided by the monitor be placed in the TMF • Send a copy of the final monitoring report to the IEC

SOPs=Standard operating procedures, ICH=International Council of Harmonization, GCP=Good clinical practices, ICMR=Indian Council of Medical Research, IEC=Institutional Ethics Committee, URL=Uniform resource locator, TMF= Trial master file, IP=Investigational product, CRO=Contract research organization, CRF=Case report form, ECG=Electro Cardiogram

studies, the PI is responsible for having a written monitoring plan before study initiation. These studies should be monitored by someone independent of that particular study but may be part of the investigator's overall team. For industry-funded studies, the PI is responsible for ensuring that the sponsor or CRO, (when monitoring is outsourced), provides a monitoring plan for the study before its initiation. He/she must also ensure his team's familiarity with it.^[2]

The monitoring process is usually undertaken in three phases – before, during, and after the study. Before the study, a pre-study qualification visit is done where the capability of the investigator is assessed, and facilities scrutinized. Post-IEC approval, a site initiation visit is done. Here, the protocol is discussed threadbare and key elements reiterated to minimize errors and the monitoring plan presented. Subsequently, monitoring is done at regular intervals as the study progresses. The last monitoring visit is a “close out” visit when a final check is done, and the data securely archived. Preparedness for all three stages of monitoring at the site is given in Table 1.

AUDIT

The purpose of an audit as mentioned earlier is to evaluate that the trial is conducted in compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements and it is a quality assurance tool. Audits are usually conducted by the sponsor and/or the regulatory authorities. The PI is usually notified about an audit in advance. Measures to ensure site preparedness (there is some overlap of preparedness for an audit with monitoring) for an audit is depicted in Table 2.

INSPECTION

An inspection is a regulatory audit. It is conducted by the regulatory authority and assesses whether the investigator and sponsor are conducting the study as per applicable statutory and regulatory requirements. Rule 122 DAC of Drugs and Cosmetic act 1940 states that the regulator is authorized to conduct trial site inspection at any time.^[3] In the event that noncompliance is found, the regulator can suspend/cancel the trial and even debar the sponsor and/or investigator from conducting future studies. Thus, preparedness of the study site at all times must be ensured, as unlike audits and monitoring; an inspection can be sudden or with very little warning. The preparedness for inspection is in no way different from that of an audit or monitoring.

Table 2: Site preparedness for a sponsor or a regulatory audit

How to ensure preparedness

- Ensure a secure room and study team availability on the day of audit
- Ensure that the TMF is updated with the latest IEC approved version of the protocol, ICDs, and investigator brochure along with the previous versions
- Keep updated curriculum vitae (signed and dated) and GCP certificates of all study staff on TMF
- Ensure subject enrollment log and the staff signature log include delegation of responsibility are up to date
- Keep the initial IEC approval letter on TMF and latest amendment approvals if changes have been to the study
- Ensure whether all correspondence (signed/dated applications, responses, and e-mails) to and from the IEC and sponsor are filed
- Ensure re-consenting (if applicable) has been completed and documented
- Make sure protocol deviation/violation report has been submitted to the IEC and the IEC correspondence is filed in the TMF
- Ensure all IEC correspondence of adverse event/SAE reports, if there are available in the TMF
- Ensure that samples are collected, transported and stored as per site SOP and GCP guidelines and documentation is complete
- Ensure data collection, source documents and IP accountability log for each subject is up to date
- Make sure that the audit log is up to date in case the site was audited previously
- Keep a copy of normal laboratory values, if applicable
- Keep all study hard copies in a cupboard with restricted access
- Ensure that access to electronic study records and files are password protected

TMF= Trial master file, IP: Investigational product, IEC= Institutional Ethics Committee, ICDs = Informed consent documents, GCP= Good clinical practices, SAE= Serious adverse event, SOP= Standard operating procedures

CHALLENGES FACED BY INVESTIGATOR FOR THE MONITORING AND AUDITS AND PROPOSED SOLUTIONS-A PERSONAL PERSPECTIVE

Table 3 lists all the challenges that were faced by the authors with regards to monitoring and audits. Most or all of these challenges can be addressed through mutual understanding, appropriate communication, and adequate training of all stakeholders involved.

Potential solutions to address challenges faced during monitoring and audits

The solutions for ensuring effective monitoring and audits lie with all stakeholders involved. The relationship between the stakeholders should be one of mutual respect. At the level of the sponsor, following measures can be initiated:

- a. Establish effective communication between all the stakeholders involved
- b. Avoid frequent change of monitors
- c. Have an SOP to ensure uniform quality of monitoring in case of repeated monitor changes
- d. Every monitor should be knowledgeable about the site-specific protocol and related documents and establish clear and coherent communication channels with the PI and his/her team

Table 3: Challenges faced by investigator for the monitoring and audits

- Poor coordination between the sponsor and the CRO, when the monitoring is outsourced to a CRO
- Miscommunication between PI and sponsor resulting from PI communicating with CRO alone and CRO subsequently communicating with the sponsor
- Repeated monitor changes during the study
- Lack of preparedness on part of the monitor leading to less than desirable quality of monitoring
- Uneven quality of monitoring across different monitors
- Varying monitoring requirements among different sponsors
- Leaving the trial-related documents in a less than desirable state at the time of leaving the site
- Failure to readily communicate a change in the scheduled monitoring plan by the monitor
- Attrition of designated study team member for a particular role during the course of the trial leading to difficulties with the newly appointed person's interaction with the monitor

CRO=Contract research organization, PI=Principal investigator

At the level of the investigator,

- a. Appoint an internal monitor, even for regulatory studies, to oversee the trial-related activities on a periodic basis
- b. Maintain a site-specific SOP to ensure continuity of trial in case of study staff attrition
- c. Conduct assessment test at specified intervals for the study team to ensure better compliance with the protocol and amendments.

CONCLUSION

Effective monitoring is crucial to data integrity and human rights protection. It is, however, important to remember

that the most effective tool for this is a well-designed and articulated protocol. Subsequent to this is a determined approach by the investigator and his/her team to ensure that all aspects of the protocol are adhered to in totality. A study by the authors that analyzed warning letters issued to investigators by the US Food and Drug Administration showed that the most common reasons for these letters were failure to adhere to the investigational plan (81%), failure to maintain adequate and accurate case histories (58.1%) followed by informed consent issues (48%).^[4] Thus, while monitoring and audits are quality tools, true quality comes from adherence to the protocol and attention to detail.

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Conflicts of interest

There are no conflicts of interest.

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