**Topic: Monitoring & Auditing**

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Introduction
Welcome to the Topic: Monitoring and Auditing.

This topic will give you information on monitoring and auditing activities for a clinical study.

You will need approximately 25 minutes to review the topic.

Why is this Topic important?

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<th>Short Version (Page text)</th>
<th>Long Version (Audio text)</th>
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<tr>
<td>The Sponsor is responsible for ensuring that studies are conducted, and that data is generated, documented/recorded, and reported in compliance with the protocol, ICH GCP, Standard Operating Procedures (SOPs), and applicable regulatory requirement(s). Monitoring and auditing are 2 different activities which enable Sponsors to fulfill these responsibilities. Per ICH GCP 4.1.4, the Investigator/Institution should permit monitoring and auditing by the Sponsor, and inspection by the appropriate Regulatory Authority(ies).</td>
<td>Hi, I'm Dr. Paul Wang. I've been working as an Investigator for the last ten years. Sponsors are responsible for ensuring that studies are conducted, and that data is reported in compliance with the study protocol, with ICH GCP, Standard Operating Procedures or SOPs, and with any applicable regulatory requirements. Monitoring and auditing are two different activities which enable Sponsors to fulfill these responsibilities. As Investigators, we should permit monitoring and auditing activities to occur at our facility. This topic will explain the activities of monitoring and auditing and what you can do to prepare for these visits when conducting a study.</td>
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### Definition of Monitoring

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

Per ICH GCP 5.18.1, the purposes of trial monitoring are to verify that:

- The rights and well-being of human subjects are protected.
- The reported trial data is accurate, complete, and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

### Types of Monitoring Visits

Sponsors may delegate the task of monitoring to internal personnel or hire a Contract Research Organization, or CRO, to conduct monitoring activities.

There are primarily four different types of monitoring activities:

1. Qualification or Pre-study selection Visit,
2. Initiation Visit,
3. Interim Monitoring Visit, and,
4. Close-out Visit

We will now review each visit type in more detail.

### Qualification or Pre-Study Selection Visit

The first visit type may be the Qualification or Pre-Study Selection Visit.

**Purpose:**

The purpose of a qualification or pre-study selection visit is for the Sponsor to assess:

- The suitability of the Investigator, study staff, and facilities for a clinical study.
- The ability of the Investigator to recruit qualified subjects into the study.
- The ability of the Investigator to adhere to the protocol requirements.

**Remember:** Contact your Sponsor Representative immediately if you plan to move or change locations anytime during the study. The proposed facility may require inspection prior to the move.
Activities during visit:

During this visit, the Sponsor Representative will:

- Tour the facilities to inspect any areas where study activities will occur, including the pharmacy/study drug storage area.
- Verify the suitability of equipment and calibration status in accordance with protocol procedures.
- Meet with the Investigator to review the available protocol information and discuss the potential for recruiting qualified subjects.
- Collect any additional information needed to assist the Sponsor in the selection of qualified Investigators.

Preparation for visit:

As an Investigator, you can prepare for this visit by:

- Reviewing previously provided study materials in advance of the visit.
- Setting aside sufficient time to complete all activities.
- Having your equipment calibration records and written SOPs available, if applicable.
- Arranging the facilities tour.
- Providing any additional materials and completing activities as requested by the Sponsor Representative conducting the visit.

Tip: You can increase your chance of selection for the study by being prepared, engaged, and by asking questions. This is also your opportunity to learn more about the Sponsor activities and what to expect during the clinical study.

Initiation Visit

If you are selected for the study, you may be asked to participate in an Initiation Visit.

Purpose:

The purpose of the Initiation Visit is to prepare the Investigator and study staff to conduct the study according to the protocol. An Initiation Visit may be conducted by the Sponsor Representative(s) just before enrollment is scheduled to begin at your site.

Who will be involved?

- Investigator
- Primary Study Coordinator
- Other key Investigator and study staff as determined by the Investigator and/or Sponsor

Remember: The Initiation Visit occurs after all necessary approvals and agreements are in place. This may include the receipt of any Sponsor supplies and materials as applicable.
Activities during visit:

During this visit, the Sponsor Representative will:

- Confirm that the information collected at the Qualification/ Pre-Study selection visit, including information on study staff, facilities, and equipment, has not changed.
- Provide training on Protocol and any other training required to Investigator and study staff.
- Determine enrollment projections and recruitment strategies.
- Review essential documents (Investigator Site File or ISF) and conduct an inventory of available study supplies.
- Provide answers to questions.
- Verify Investigator and study staff access to systems and vendor portals such as IXRS.

Preparation for visit:

As an Investigator, you can prepare for this visit by:

- Ensuring that you and your staff have completed any required training in advance of the meeting.
- Have the ISF, training records, study supplies, and any other materials requested by the Sponsor Representative available for review.
- Prepare and have available any outstanding documents to be collected by the Sponsor Representative.
- Setting aside sufficient time for yourself and your staff to attend the visit.
- If a tour of the facilities is requested, ensuring that all department staff are notified and available.
- Reviewing the study protocol prior to the visit and preparing questions in advance.
- Being prepared to discuss recruitment projections and expectations.

Interim Monitoring Visit

Following the Initiation Visit, Interim monitoring visits will begin.

Purpose:

The purpose of the interim monitoring visit is to:

- Review the study records generated by the Investigator.
- Ensure that the study is being conducted in compliance with the latest version of the protocol
- Ensure that the study is documented per ICH GCP, and is reported in accordance with all applicable regulatory requirements.
- Confirm that the trial data is reported with accuracy and completeness.

If issues are identified, corrective actions will be determined.
Did You Know?

The first monitoring visit typically occurs quickly after activity with the first subject to ensure that any issues can be quickly resolved before more subjects are enrolled.

Activities during visit:

During this visit, the Sponsor Representative will:

- Review the source data (including subjects’ Informed Consent) to ensure compliance with the study protocol and internal site processes (SOPs if applicable).
- Review the ISF including essential documents and training records.
- Assess the documentation to verify that the Investigator is fulfilling their obligations.
- Re-verify adequacy of the facilities including the pharmacy/study drug storage areas.
- Review Investigational Product management including correct dispensation and subject compliance.
- Review subject recruitment status and retention plans.
- Review (e)CRFs.

Preparation for visit:

As an Investigator, you can prepare for this visit by:

- Ensuring that all medical records and source documents are available for subjects enrolled in the study.
- Ensuring that all CRFs (paper or electronic) are completed in advance of the monitoring visit.
- Ensuring that the ISF is available and up to date.
- Ensuring temperature logs for key areas- investigational product storage areas, freezers containing samples, etc- are available.
- Setting aside sufficient time to meet with the Sponsor Representative to fully review the study and site progress.

Off-site Monitoring Visit

An off-site monitoring visit is a type of interim monitoring visit. Many electronic systems and tools are used during the conduct of a study. This data is available to the Sponsor as soon as it is entered, and can be reviewed off-site.

Formal off-site monitoring may be conducted between on-site visits. This may include interactions between the Sponsor Representative and study staff via telephone and/or email.

Did You Know?

Off-site Monitoring may also be referred to as central, remote, or in-house monitoring.
**Risk Based Monitoring (RBM)**

- The use of electronic systems and records present opportunities for alternative monitoring approaches that can improve the quality and efficiency of oversight.
- RBM builds quality and risk management approaches into the design and operational conduct of a clinical study for early detection or prevention of issues.
- Thus, RBM shifts the monitoring process from a highly concentrated focus on Source Data Verification and transcription to a risk driven approach using on and off site activities.
- Finally, RBM recognizes that Investigators are responsible for quality at their site.

**Close-out Visit**

The final monitoring activities are conducted during the Close-out Visit.

**Purpose:**

A Close-out visit is conducted after the study is completed or discontinued at a given site. This visit brings the study to a close and includes the retrieval and accounting of all remaining clinical data, supplies, and Investigational Product (IP). The Close-out visit also provides final confirmation that all subject safety events have been managed and reported, and that IRB/IEC notification of site closure has been received. Close-out Visits are routinely conducted on-site.

**Activities during visit:**

During this visit, the Sponsor Representative will:

- Confirm that all CRFs (paper or electronic) are complete and all queries are resolved.
- Verify the final reconciliation of IP including the final return/destruction.
- Ensure completeness of the ISF and reconciliation of the ISF with the Sponsor trial master file.
- Return study supplied equipment if applicable.

**Preparation for visit:**

As an Investigator, you can prepare for this visit by:

- Resolving all outstanding issues from previous monitoring visits.
- Setting aside sufficient time for you and your staff to meet with the Sponsor Representative.
- Preparing any remaining Sponsor supplied equipment for return, if applicable.
- Ensuring that IP and any study supplies remaining on-site are available as applicable.
- Preparing the IRB/IEC close-out notification report.

**Did You Know?**

If the Investigator site is closed prior to database lock queries may continue to be issued and will require a response.
Finally, I'd like to give you some important tips about monitoring.

- The relationship between the Investigator, study staff and Sponsor Representative is an important collaboration.
- Monitoring observations will prompt discussion around corrective and preventive actions. The Sponsor Representative may make recommendations. However, ultimately, the Investigator is responsible for the activities and documentation of the clinical study.
- Work closely with the Sponsor Representative when scheduling monitoring visits. Notify your Sponsor Representative right away of any staffing or facilities changes before they occur.
- Monitoring prepares the Investigator and study staff for a potential audit and/or Regulatory Authority inspection.

Remember:

- The Investigator is responsible for the collection and reporting of study data. Be actively involved during the study and make informed decisions.
- Work with your Sponsor Representative to determine if changes are needed regarding data collection or any study processes and be sure to obtain answers to any questions.
**Definition of Auditing**
An Audit 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) (ICH GCP 1.6).

**Characteristics of an Audit**

**Purpose:**
An audit can be conducted as part of a Sponsor's quality assurance program for compliance with ICH GCP. The purpose is to evaluate study conduct and compliance with the protocol, site SOPs, GCP and applicable regulatory requirements. Audits may occur any time during the study period.

**Investigator Selection:**
Audits are conducted at ‘select’ Investigator sites identified during the course of the study based on enrollment, compliance, and other factors.

**Audit Team:**
The audit team is separate from the Sponsor Representative conducting the monitoring visits. The audit team may include an internal sponsor personnel or external consultants hired by the Sponsor.

**Preparation for Audit:**
- Ensure that all records requested by the auditors are available.
- Set aside sufficient time to meet with the auditor(s) periodically during the audit.
- Respond in a timely way to questions and requests for information.
- Plan and schedule a facilities tour if requested.

**Did You Know?**
While audit findings are discussed with the Investigator, Sponsor audit reports are not provided to Investigators.
**Topic Summary**

In summary:

- Monitoring is the act of overseeing the progress of a study.
- An audit is a systematic and independent examination of study-related activities.
- Investigators and study staff should prepare in advance for monitoring visits and audits.
- Investigators and study staff should plan adequate time and be available to the Sponsor Representative during monitoring visits and audits.
- Work with your Sponsor Representative to determine if changes are needed regarding data collection or any processes for the study.
- The Investigator is ultimately responsible for the data collected and reported during the study.

**Remember**

Being prepared for monitoring visits and audits, and working closely with your Sponsor Representative(s) during the study, will help ensure your site is “inspection ready” at all times. This will further add to your success as an Investigator.
Review Question 1 of 3
Just after a recent monitoring visit, the Investigator replaced the primary coordinator, Mr. Markham, with a more experienced coordinator, Mrs. Bathurst. Mrs. Bathurst has not worked on the study previously and Mr. Markham is no longer available. The next on-site monitoring visit is planned in 8 weeks. What should the Investigator do?

Answer 1 is correct.

1. Contact the Sponsor Representative right away and explain the situation. Together prepare a training plan for Mrs. Bathurst and make arrangements to obtain access to the study portals and eCRF.
2. Inform the Sponsor Representative of the change when they arrive at the site to conduct the next on-site monitoring visit.

Review Question 2 of 3
During the monitoring visit the Sponsor Representative requests the Investigator to make process changes to the study execution. What should the Investigator do?

Answer 3 is correct.

1. Don’t make the changes. Inform the Sponsor Representative that such changes are against site policy.
2. Make the changes because the Sponsor Representative is always right.
3. Meet with the Sponsor Representative to discuss the request and determine if the Investigator site process may benefit from a change.

Review Question 3 of 3
The Investigator has decided to move to a new facility down the street. There are several active studies being conducted at the current facility and these will have to be transferred. How should the Investigator proceed?

Answer 1 is correct.

1. Immediately notify the Sponsor of the decision to move. Work with the Sponsor to develop a move process which may include changes to the regulatory documents, development of a drug transfer process, and a Sponsor qualification of the new facility.
2. Conduct the move and notify the Sponsor after the move so that the Sponsor Representative knows where the next monitoring visit should be conducted.