

# Clinical Site Monitoring

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# Monitoring

## ICH E6 5.18.1

The purpose of monitoring is to ensure that:

- The rights and well-being of subjects are being protected
- The data are accurate, complete and verifiable
- The trial is being conducted in compliance with the protocol, SOPs, GCP, regulatory requirements

# Monitoring

## ICH E6 5.18.2 and 5.18.3

Sponsor is responsible:

- Ensuring that trials are adequately monitored
- Selecting monitors that are adequately trained
- Determining the extent and nature of monitoring

# Site Visit Activities: What happens?

- ◆ Confirm adequate qualifications and resources
- ◆ Verify investigational products
- ◆ Verify informed consent obtained
- ◆ Confirm performance of study functions



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# Site Visit Activities: What happens?

- ◆ Verify participant eligibility
- ◆ Confirm accuracy and completeness of source documentation and CRFs
- ◆ Verify all investigator–required reporting
- ◆ Determine timely reporting of adverse events
- ◆ Ensure maintenance of essential documents



# Monitoring Reports

## Monitoring reports:

- Must be submitted by the monitor to the sponsor after each monitoring visit
- Summarize what the monitor reviewed during visit
- Includes summary of findings and actions recommended or taken to ensure compliance

# Monitoring

What are the differences between monitoring, auditing and inspecting?

- ◆ Monitoring (1.38; 5.18)
- ◆ Auditing (1.6; 5.19)
- ◆ Inspecting (1.29)

## Monitoring Visit, Audit or Inspection?

	<b>Monitor Visit</b>	<b>Audit</b>	<b>Inspection</b>
<b>Who comes to the site?</b>	Monitors- can be employees of the sponsor or contracted by the sponsor. Are very familiar with the protocol and become familiar with the site.	Auditors- from the sponsor or contracted by the sponsor (or possibly the EC). Somewhat familiar with the protocol, but usually not with the site staff.	Inspectors- Representatives of the regulatory authority/government (e.g. MOH). Somewhat familiar with the protocol.
<b>What is the goal of the visit?</b>	Verify that rights and well-being of the participants are being protected, that the study is being conducted according to GCP, protocol, and other regulations, and that the study data are accurate, valid and reliable.	Similar goals to monitoring, with greater emphasis on site procedures. Will also review the quality of monitoring.	Similar goals to monitoring, but may be “for cause” and/or have special areas of focus (e.g. if there have been allegations of informed consent violations).
<b>Frequency?</b>	Regularly, at sponsor discretion.	Usually once per study	Maybe never. Maybe once. Maybe more.
<b>To whom/how are findings conveyed?</b>	Sponsor and other collaborating organizations	Sponsor and other collaborating organizations	Investigator (who should relay to sponsor), Regulatory Authority
<b>Other characteristics</b>	Will help site find solutions to challenges they identify and should provide re-training if necessary.	Will discuss findings with site staff at end of visit and may provide feedback on how to improve quality of study conduct	
<b>Reports</b>	Monitors submit a report of findings to the sponsor after every visit. Site then responds to monitor or sponsor, describing steps taken to correct any issues.	Auditors submit a report after visit to whoever requested the audit. Site responds, describing steps to correct issues	Country Specific Rules. In U.S., FDA inspector will write a report and may issue a Form 483 if significant deviations identified. Investigator (with guidance from sponsor) will respond in writing.

## ICH E6 – Guideline for Good Clinical Practice

### **5.18.4 Monitor's Responsibilities**

The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

- (a) Acting as the main line of communication between the sponsor and the investigator.
- (b) Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6) and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.
- (c) Verifying, for the investigational product(s):
  - (i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
  - (ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).
  - (iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).
  - (iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.
  - (v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.
- (d) Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.
- (e) Verifying that written informed consent was obtained before each subject's participation in the trial.
- (f) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).
- (g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.
- (h) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.
- (i) Verifying that the investigator is enrolling only eligible subjects.
- (j) Reporting the subject recruitment rate.
- (k) Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.
- (l) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

(m) Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that:

(i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.

(ii) Any dose and/or therapy modifications are well documented for each of the trial subjects.

(iii) Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.

(iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.

(v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

(n) Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

(o) Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

(p) Determining whether the investigator is maintaining the essential documents (see 8. Essential Documents for the Conduct of a Clinical Trial).

(q) Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

### **Quiz: Monitor's Responsibilities**

		<b>True</b>	<b>False</b>
1.	The monitor must verify that the data required by the protocol are reported accurately on the CRFs and are consistent with the source documents		
2.	The monitor is responsible for reviewing the amount and schedules of payments to subjects to ensure that neither presents problems of undue influence of participants		
3.	The monitor is responsible for explaining any deviation from the approved protocol		
4.	The monitor is responsible for determining that essential documents are being maintained at the research site		
5.	The IRB/IEC is responsible for verifying that written informed consent was obtained before each participant's participation in the study		
6.	The monitor is responsible for verifying that the investigator is enrolling only eligible participants		
7.	The monitor is responsible for verifying that source documents and other study related records are complete, accurate and up-to-date		
8.	The monitor is responsible for ensuring advertisements to recruit participants are not coercive		
9.	The IRB/IEC is the main line of communication between the sponsor and the investigator		
10.	Inspectors are appointed by the sponsor		