Conducting Monitoring Visits for Investigator-Initiated Trials (IITs)

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Monitoring

"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), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)"

*The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (**ICH**) Good Clinical Practice (**GCP**) **E6 1.38***

"One component of a quality management system (Quality by Design)"

Pharmaceutical Research and Manufacturers of America (PhRMA) BioResearch Monitoring Committee

Extent and nature of monitoring

"based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial. In general there is a need for on-site monitoring, before, during and after the trial; however … central monitoring in conjunction with procedures such as investigators' training and meetings and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an accepted method for selecting the data to be verified"

ICH GCP E6 5.18.3

Types of error, their impact and possible methods of monitoring

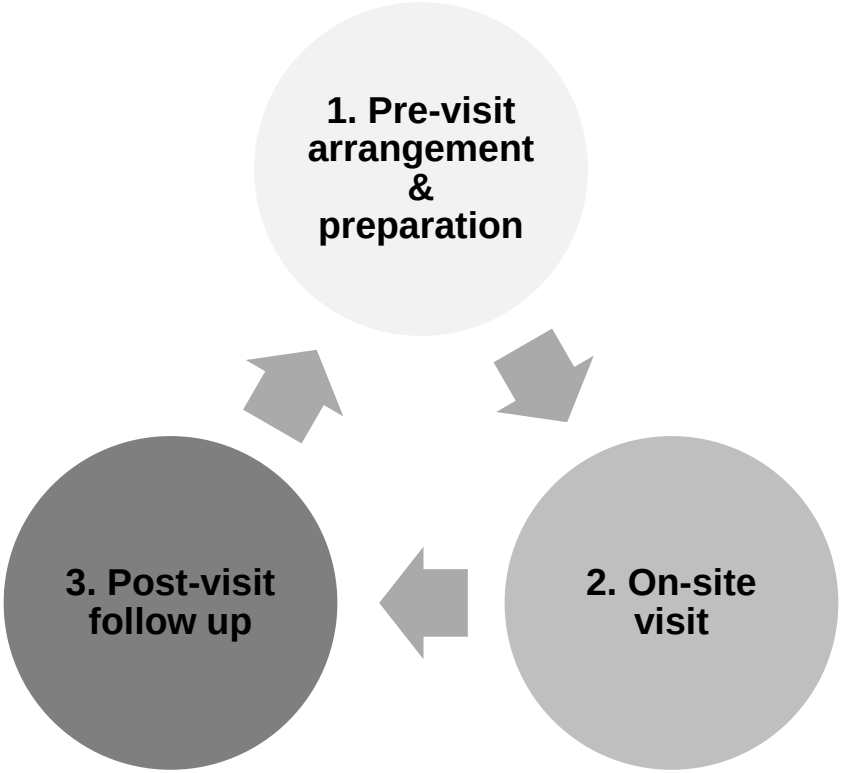
Error type	Adverse effect on safety during trial	Bias in study results	Monitoring method
Design error	+++	+++	Peer review, and oversight by trial committees
Procedure error	+++	+ (blinded) +++ (unblinded)	Avoidance through initial training and subsequent mentoring during site visit
Random recording error	-	+	Central statistical monitoring, on-site monitoring
Analytical error	-	+++	Peer review, and oversight by trial committees

Adapted from Baigent, Colin, et al. Ensuring trial validity by data quality assurance and diversification of monitoring methods. Clinical Trials 5.1 (2008): 49-55.

Different types of on-site monitoring visit

On-site monitoring visit	Purpose	Timeline
Site Qualification Visit (SQV) (pre-study visit; site selection visit)	Determine the ability of investigator and site to conduct the study	Confirmation of investigator's interest in a clinical trial
Site Initiation Visit (SIV)	Ensure the readiness of the clinical site to start subject enrollment	Availability of RA/EC approval; contract in place
Site Monitoring Visit (SMV)	Evaluate the conduct of the study at the site	One or more patients are enrolled in the study
Site Close-Out Visit (COV)	Ensure the organisation of essential documents at the site and readiness for archival and further audit/inspection	Completion of the study after database lock

Liu, M.B. and Davis, K.; Chapter 6: Monitoring. Lessons from a Horse Named Jim: a Clinical Trials Manual from the Duke Clinical Research Institute. Durham, NC: Duke Clinical Research Institute, 2001. Print



Factors affecting the frequency of on-site visit

- Rate of recruitment
- Rate of non-compliance
- Number of data queries
- Magnitude of data correction
- Experience of site personnel
- Rate of adverse event

Adapted from SCRI SOP

- Define the scope of visit
- Determine the required documents/staff

- Schedule for date, time and staff attendance
- Check completeness of Case Report Forms (CRFs)
- Prepare data query report
- Prepare monitoring documents

- Issue confirmation letter & visit agenda

Per institutional SOPs

Per institutional SOPs, e.g. 1 week per SCRI SOPs

On-site Visit

Common activities performed at routine site monitoring visit

Activity	Objective
Informed consent review	Rights of participants; GCP & local requirements
Source data verification (SDV) • 100% SDV • Statistical sampling • Targeted sampling	Data integrity, accuracy
Check protocol adherence • Eligibility of participant • IP accountability • Lab sample verification	Validity of study; safety of participants
Verify safety reporting	Safety of participants
Review Investigator Folder (IF)	GCP & local requirement
Ongoing training	Adequacy of the site personnel

Adapted from: 1) SCRI SOPs; 2) Macefield, Rhiannon C., et al. "A systematic review of on-site monitoring methods for health-care randomised controlled trials." Clinical Trials 10.1 (2013): 104-124.

Tips for preparing a routine site monitoring visit

- Book a quiet room for CRA with access to photocopy machine and internet
- Complete required CRFs prior to the visit
- Confirm that SAEs have been documented and reported
- Obtain necessary source documents
- Keep investigator folder organised and up-to-date
- Confirm that signed consent forms for all enrolled subjects are available
- Schedule an appointment for the CRA to meet with the site personnel

Follow up with site on unresolved findings and the proposed actions in the follow up letter

Next on-site visit

Per institutional SOPs, & urgency of the issues

Documentation on monitoring findings & propose actions, e.g. visit report, follow up letter

Per institutional SOPs, e.g. 20 working days for SCRI CRA

Resolution of urgent findings / issues

Within 1 week

Last on-site visit

Operational complexity for conducting IITs

Limited time dedicated to the conduct of IITs
Limited study funding
Inadequate resources at the site
Inadequate experience for the conduct of clinical trial
Limited/no site selection/evaluation process
Limited SOPs/guidance at the site
Inadequate understanding of GCP

- Reflect the importance of on-site visit
- Emphasize the need for continuously training at every visit
- Ongoing training at day-to-day communication and coordination

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Thank You