Monitoring Of Trials

Module 6 Topic 3

Act of Overseeing

- Progress of a clinical trial and
- Ensuring that it is conducted, recorded and reported in accordance with
  - Protocol
  - SOPs
  - GCPs and
  - Applicable regulatory requirements

Rationale for Monitoring

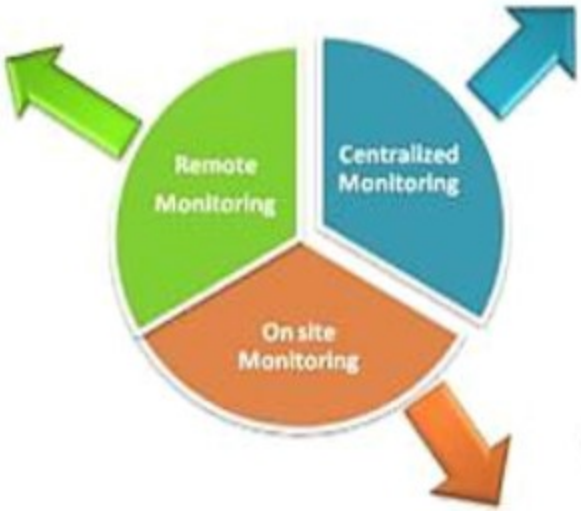
- Protection of human subjects' rights and well-being
- Accuracy, completeness and verification of reported trial data

Types of Monitoring

Centralized Monitoring	On-Site Monitoring	Off-Site Monitoring
• Monitoring data quality, critical data reporting, AE/SAE trending, unusual distribution of data, etc. • Proactive and early identification of quality/safety/operational risk/issue (s) based on continuous monitoring of data and key risk indicators • Tracking site performance metrics • Planning/triggering site contacts/visits based on the risk/issue(s) identified	• Critical risk/issue(s) management • Shifting from 100 percent SDV to a risk-based approach for SDV with more focus on critical data related to eligibility criteria, primary / secondary efficacy and safety end points, and key protocol procedures • Percentage of SDV & SDR • In-person engagement, co-ordination with site staff, drug accountability, verification of facility/equipment and overall quality conduct	• Coordinating with the sites for managing risk/issue(s) identified during centralized monitoring • Following-up with the sites as a part of site management activities and to support inquiry management.

Approach used in each type of Monitoring

- Subject enrollment
- Continued Site & Staff performance
- Evaluation and re-training for performance
- Tracking regulatory requirements
- Tracking site adherence to GCP/HSP/EDC/protocol requirements
- Data overview based on Central monitoring review and feedback



- Standard checks of range, consistency and completeness of data
- Identifies unusual distribution of data (statistical data review)
- Identifies higher risk sites to target for an on-site visit
- Reviews data in real time on a routine basis

- Identify data entry errors/missing data via source and
- CRF review
- Assess protocol compliance/drug accountability
- Assess Investigator supervision o trial

RBM is a customized Monitoring Approach continuously updated

The people equation

- The monitor is the main communication link between the Sponsor and the Investigator

Here Comes the Monitor

Common goal for site and sponsor:

- Protection of human subjects' rights and well-being
- Accuracy, completeness and verification of reported trial data
- Trial conduct in compliance with protocol/ amendments, Good Clinical Practice (GCP), and regulatory requirement(s)

Who does monitoring?

Monitors/CRAs

- Appointed by sponsor
- Appropriately qualified and trained
- Should have scientific and/or clinical knowledge
- Familiar with investigational drug, protocol, ICF, SOPs, GCP, and applicable regulatory requirements

Stages of a Monitoring Visit

- Before the visit
- During the visit
- After the visit

Before the Visit

The monitor will:

- Contact site to schedule the visit
- Issue confirmation letter or e-mail

During the Visit

The monitor will assess /discuss:

- Site, staffing, research lab facilities
- Regulatory files and study records
- Any problems and issues identified
- Clinical procedures if possible/ appropriate
- Conduct debriefing meeting at end of visit

After the Visit

- **The monitor will:**
  - Complete site visit report
  - Submit the report to sponsor
- **The sponsor will:**
  - Distribute site visit report and/or cover letter to the site

After the Visit (contd)

- The site should implement corrective actions based on monitoring visit /cover letter
- The monitor will review corrective action, outlined in the cover letter, during the next site visit

Site Monitoring Visit

Purpose:

- Protection of human subjects' rights and well-being
- Accuracy, completeness and verification of reported trial data
- Trial conduct in compliance with protocol/ amendments, Good Clinical Practice (GCP), and regulatory requirement(s)

Site Monitoring Visit (contd)

- Assessment of Investigator's Files
- Study Product Accountability
- Protocol-Specific Record Review
- Research Laboratory Assessment
- Observation of Clinical Operations
- Follow-up on Previously Identified Issues
- Debriefing Meeting at End of Visit

Assessment of Investigator's Files

- All protocol versions, amendments and consents
- All Institutional Review Board/ International Ethics Committee (IRB/IEC) approvals
- Investigator Brochure, if applicable
- Versions / dates of procedure manuals
- Continuing IRB/IEC review
- List of all SAE reports and safety reports
- Specific lab normals (safety labs)

Assessment of Regulatory Files (ICH E-6 8.2, 8.3 Essential Documents)

- Specific lab certifications and expiration dates
- List of study staff CVs
- Study personnel signature/initial sheet
- Study personnel responsibility list and delegation of responsibilities list (should include anyone who enters data on source documentation and/or CRFs)
- Previous monitoring reports and monitoring log

Study Product Accountability

- Review of study product accountability documents, e.g.
  - Shipping receipts
- Verification of accountability
  - Comparison of accountability record with actual, physical count
- Assessment of study product storage and handling, e.g.
  - Verification of cold chain maintenance
  - Temperature control of pharmacy

Protocol-Specific Record Review

- Informed Consent
- Enrollment (inclusion/exclusion criteria)
- Adequacy of Source Documentation
- Timing of AE/SAE Reporting
- Missed Visits
- Protocol Violations and Deviations

Informed Consent Checks

The approved informed consent form(s) were

- Appropriately obtained, signed and dated by each subject/representative, prior to the start of any study specific procedure
- Signed and dated by the person who conducted the informed consent discussion
- Retained for each subject with the site study records

Research Laboratory Assessment

- Protocol related tests conducted by this lab
- Details of sample collection
- Sample flow from collection to lab
- Data flow from lab report to CRF
- Location of sample processing/analysis
  - (On/Off site?)

Research Laboratory Assessment (contd)

- Assess sample labeling, tracking, and storage
- Observation of specimen storage area
- Freezers:
  - E.g. presence of daily freezer temperatures log
  - E.g. presence of auxiliary power
- Assessment of SOPs for lab procedures, maintenance, and equipment

Laboratory Samples

- Regularly check for changes in local lab. reference ranges, submit revisions to data management either electronically or using the standard form for reference ranges, file a copy in site file

- If a central laboratory is used, ensure investigator has any revised ref. ranges

CRF Review

- Check all SAEs, pregnancies and device incidents are documented and reported

- Collect, or arrange collection of, all reviewed and completed CRF data/DQs for delivery to designated data management centre within agreed timelines

CRF Review

- eDM- check data has been submitted appropriately
- Review agreed data entry/query resolution timelines
- Resolve outstanding DQs and submit response
- Original diary cards and other subject-completed forms should remain with site study records whenever possible. When this is not possible a certified (signed/dated by investigator or designate) copy or transcription will remain at site

CRF Review and SDV

CRF Review

- An overall review of the CRF for internal consistency, completeness, logic and legibility

SDV

- Verifying CRF data against information in supporting documentation held at the site

CRF Review

- Check consistency, completeness, logic, legibility, adherence to protocol
- Check all SAEs, pregnancies, and medical device incidents are documented/reported
- Check missed visits, tests/examinations not done, etc. are documented
- All paper CRF pages are accounted for and have accurate identifiers (headers)

Typical errors in the CRF

- Some boxes left blank
- DOB year = 2005
- Ticked female but not completed contraception
- Ticked on oral contraception but OC not entered on con med page
- AEs and con meds in notes but not entered into the CRF
- Ticked for concurrent disorders (eg asthma) but no con meds completed

CRF Corrections

Check corrections by site staff in accordance with the current SOP

- Draw a single line through the incorrect entry
- Do not use correction fluid
- Do not ‘write over’, erase, or highlight
- Enter correct data nearby
- Date and initial corrections
- Reason given if appropriate (justify if unusual or important correction)

Other Monitoring Activities

- Sign and date the Site Visit Record with a member of the site staff
- Address any other issues and corrective actions required

Observation of Clinical Operations

Observation of clinical operations when appropriate AND with participant's consent

- Informed consent process
- Screening and enrolling process
- Administration of study product
- Obtaining laboratory samples

Follow-up on Previously Identified Issues

The monitor will attempt to resolve previously identified issues during this visit to the extent possible, e.g.

- Informed consent issues
- Outstanding corrections on forms
- Missing documents in the regulatory files

Debriefing Meeting

- The pre-visit letter will request time for a debriefing meeting
- At least Investigator and Study Coordinator should be present
- Monitor findings will be presented and discussed
- The monitor may recommend re-training to research staff for some identified issues

Close Out Site Visit

The monitor ensures the following:

- IRB notified in writing of study completion/ withdrawal
- Appropriate accounting and disposition of study product and other study supplies completed
- Planned future use of remaining stored laboratory samples determined and appropriate
- Final report submitted to IRB/IEC and sponsor

Close Out Visit (contd)

The monitor will:

- Obtain copies of all study product shipping, receiving, and accountability records for submission to sponsor
- Remind the PI of his/her responsibility to maintain research files until directed otherwise, in writing, by the sponsor (ICH E6 – 8.2, 8.3, 8.4, Essential Documents)
- Record plan for disposition of CRFs

Tools for Monitoring

- **Monitoring Agenda and Plan -** To be shared with site at least 15 days in advance
- **Monitoring Checklist -** To be used at the time of monitoring
- **Monitoring report -** To be generated 7-10 days post monitoring for in house filing
- **Monitoring follow up letter -** To be generated 7-10 days post monitoring for site filing

SOURCE for Templates
http://store.centerwatch.com/pdfs/samples/sopde15_pm503.pdf
https://www.acrpnet.org/resources/checklist-tasks-monitoring-visits/