Risk Based Monitoring – An Update

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Disclosure

The presenter(s) for today’s session: {select}

☐ I/We have no relevant financial relationship in relation to this educational activity.

☑ I/We have relevant financial relationship(s) with respect to this educational activity with the following organizations (list here):

    C3 Research Associates
Learning Objectives

Upon completion of this presentation, participants should be able to:

• Review key points of the FDAs Guidance on Risk Based Monitoring
• Describe 3 practical approaches to implementing risk-based monitoring in their practice setting
• Demonstrate 3 areas where additional job training may be necessary to implement a successful risk-based monitoring program
Agenda

• Key points of the guidance
• Implementing a risk-based monitoring approach
• Case studies / Lessons learned
Key Points to the Guidance
21 CFR 312.50

*Sponsors are responsible for... ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND...*
**Definitions**

**Monitoring** -- Methods used by sponsors/CROs to oversee the conduct of and reporting of data from a clinical trial

Activities include:
- Communication with the PI and site staff
- Review site’s process, procedures and records
- Verification of accuracy of the data
Definitions

Onsite Monitoring – In-person evaluation at the sites where a trial is being conducted

- Identify data entry errors
- Confirm documentation exists
- Assess site familiarity with the protocol
- Findings may lead to further training
Definitions

**Source Data Verification (SDV)** – original source information is compared with the data entered into the data collection tool.

**Source Data Review (SDR)** – review of source documentation to check for quality of source, compliance, evaluate investigator oversight, etc.

SDR is not the same as SDV!
Definitions

Centralized Monitoring – remote evaluation by sponsor/CRO personnel (e.g. clinical monitors, DM or statisticians) at a location other than the sites where the trial is being conducted

Critical Data – study data, which if inaccurate, not performed or performed incorrectly, would threaten the protection of subjects or trial integrity
Critical Data

- Verification of Informed Consent
- Inclusion / Exclusion criteria
- IP accountability and administration
- Procedures/Assessments related to:
  - Endpoints
  - Safety assessments
  - SAE / UADE reporting
  - Subject deaths / withdrawals
  - Trial Integrity
Non-Critical Data

- Data that does not address safety or efficacy
  - Concomitant therapies
  - Demographic data
  - Routine lab tests
- Non-critical processes
  - IP storage without critical handling instructions
Clinical Monitoring Plan

• Description of monitoring approaches
• Communication of monitoring results
• Management of noncompliance
• Ensuring quality monitoring
• Monitoring plan amendments
Monitoring Documentation

- Who conducted and date
- Data and activities reviewed
- Description of non-compliance, data irregularities and other deficiencies
- Actions taken or recommended

In sufficient detail to allow verification that the CMP was followed
Considerations

- Assessment of Corporate Risk Level
- Standard Operating Procedures
- Work Practices / Workflow
- Human Resources
- Financial Considerations
- Training Requirements
- Set and Communicate Clear Expectations
Implementation

• No single approach is appropriate or necessary
• Customize the monitoring plan
• Focus on mitigating errors in conduct, collection and reporting of critical data
Implementation

• The most important tool for ensuring human subject protection and high-quality data is a well-designed and articulated protocol and Case Report Form (CRF)

• A poorly designed or ambiguous protocol or case report form (CRF) may introduce systemic errors that can render a clinical investigation unreliable despite rigorous monitoring.
Practical Applications

Project Details
• Unblinded Pharmacy Monitoring
• Phase 3 pivotal study
• 330 subjects / 15 centers / 18 month enrollment
• Surgical indication
• Single dose per subject
• Number of countries: US
Practical Applications

• Traditional monitoring proposal
  • Every 8 weeks onsite
  • ~ 7-8 visits per site

• “Risk-based” monitoring proposal
  • 3 visits per site
  • Documents sent to central reviewer
  • Decreased monitoring and travel costs ~45%
Practical Applications

- Sponsor selected the RBM proposal
- Unblinded monitoring plan written
- Sites fax / email documents to central reviewer
  - Dispensing records
  - Shipping records
  - Temperature records
  - Drug preparation worksheets
- Onsite visits to confirm inventory
Practical Applications

• Original push-back from a few sites
• Central monitoring uncovered / sites reported
  • Temperature deviations
  • Dispensing errors
  • Drug preparation errors
  • Math / Accountability errors
• No new issues identified during onsite monitoring
Practical Applications

Project Details
• ADC therapeutic
• Phase I study
• 20-30 subjects / 15 centers / 12 mo. enrollment
• Solid tumor oncology indications
• 3 week treatment cycles
• Number of countries: US / Canada
Practical Applications

Monitoring Approach
• 100% SDV for all subject
• Monitoring frequency – every 4-6 weeks with first visit after 1st subject completes cycle 1
• May increase frequency based on enrollment or CRA/CTM decision
• Prior to visit, DM provides list of possible protocol deviations to CRA to target monitoring
Practical Applications

Possible Protocol Deviations
• 19 reports produced monthly
• Eligible marked ‘no,’ enrolled marked ‘yes’
• Consent date after enrollment date
• Vital sign, PK and visits out of windows
• Differing dose yet no weight change
• Recorded disease assessment doesn’t match programmatically derived disease response
Practical Applications

Project Details
• Peptide therapeutic
• Phase II study
• 90 subjects / 15 centers / 12 mo. enrollment
• Orthopedic indication
• Multiple doses per subject
• Number of countries: US
Practical Applications

Monitoring Approach

• May increase/decrease frequency based on enrollment or CRA/CTM decision
• Monitoring plan includes issues that may result in increased SDR, SDV or both
• Central review of data by DM / CTM to look at global trends
Practical Applications

Outcomes

• Completed enrollment according to original projections
• Three sites were audited independently by the sponsor
• Audited sites represented about 40% of the enrollment (N = 39)
Practical Applications

Audit Findings

• Consent issues
  • Lack of source documentation of the informed consent process
  • Signed consent pages located in the source for another subject

• Dosing issues
  • Three patients dosed incorrectly at two sites
Practical Applications

Audit Findings

- Investigational Product
  - Deficiencies noted with drug storage and accountability
- Minor source documentation issues
  - Concomitant medication and indication are inconsistent
  - Lab accession numbers do not match EDC
Practical Applications

Audit Findings

• Essential Documents
  • Lab certs expired or missing
  • No staff protocol/study training documentation
Practical Applications

Audit Findings

• Eligibility
  • No subjects were found to be ineligible
• Safety
  • No issues identified with AE reporting or corresponding assessments
• Endpoints
  • No issues identified by auditor that affected endpoints
Practical Applications

Queries

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Top 10 Queried Categories
Lessons Learned

- Study Coordinators
- Data Management
- Central Reviewers
- Clinical Research Associates
- Set clear expectations and review frequently
- Issues with monitoring procedures that rely on study site staff
Lessons Learned

- Begin planning early
- Identify risk / monitoring approach
- Customize based on protocol
- Document strategy
- Evaluate often
References *(if any)*

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Questions

Thank you for your time

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