Monitoring Best Practices

Bonnie Miller, RN MS
Clinical Research Consultant
President, N CA Chapter ACRP
Head, ACRP Global Chapter Chairs

Monitoring Framework

ICH E6*
5.18.1 The purposes of trial monitoring are to verify that:
(a) The rights and well-being of human subjects are protected.
(b) The reported trial data are accurate, complete, and verifiable from source documents.
(c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring Framework

ICH E6 cont. 5.18.3 Extent and Nature of Monitoring

- Sponsor responsibility for adequate appropriate extent and nature of monitoring....
- ....based upon objective, purpose, design, complexity, blinding, size, and endpoints of the trial....
- On-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that 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 acceptable method for selecting the data to be verified.

FDA Guidance RBM*

- Encourages more effective monitoring of clinical investigations to ensure adequate protection of human subjects and the quality and integrity of clinical trial data.
- Describes overarching quality risk management approaches to clinical trial oversight.
- Quality is a systems property that must be built into an enterprise and cannot be achieved by oversight or monitoring alone.
- Consistent with ICH E6.

*FDA Guidance: Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring (August 2013)
Monitoring Framework

FDA Guidance RBM cont.

- Focus on risks to the most critical data elements and processes necessary to achieve study objectives.
- Monitoring - several functions responsible:
  - CRA/site monitor
  - Medical monitor
  - Data Safety Review Board
- More likely than routine visits to all clinical sites and 100% data verification to ensure subject protection and overall study quality.
- ICH E6 and ISO 14155*: monitoring flexibility based upon study objective, design, complexity, size, and endpoints

*International Standards Organization Clinical Investigation of Medical Devices for Human Subjects

CTTI* study of monitoring practices (intensity, focus, and methodology)
- centralized monitoring by statistical and data management personnel
- targeted on-site visits to higher risk CIs (e.g., where centralized monitoring suggests problems at a site)
- frequent, comprehensive on-site visits to all CI sites
- periodic, frequent visits to each CI site to evaluate study conduct and review data for each enrolled subject predominant (biopharma & device)
- >50% survey respondents (79/216 organizations) had quality indicators to assess the quality of monitoring

Monitoring Framework

FDA Guidance RBM, CTTI study cont.

- Industry/major efficacy trials:
  - on-site monitoring visits at approximately 4- to 8-week intervals, 8 at least partly because of the perception that the frequent on-site monitoring visit model, with 100% verification of all data, historically has been FDA's preferred way for sponsors to meet their monitoring obligations.

- Academic coordinating centers, cooperative groups, and government organizations:
  - government agencies and oncology cooperative groups typically visit sites only once every 2 or 3 years to qualify or certify clinical study sites to ensure they have the resources, training, and safeguards to conduct clinical trials.

- FDA recognizes regulators and practitioners relied on data from critical outcome studies (e.g., many NIH -sponsored trials, Medical Research Council-sponsored trials in the United Kingdom, ISIS (International Study of Infarct Survival) trials,10 and GISSI11), which had no regular on-site monitoring and used primarily centralized and other alternative monitoring methods - suggest alternative monitoring approaches should be considered by all sponsors, including commercial sponsors...
Monitoring Framework

FDA Guidance RBM cont. Developing the Monitoring Plan:
- Complexity of study
- Complexity of patient population/disease
- Geography
- Clinical Investigator experience
- Sponsor/CRO experience with Clinical Investigator
- EDC
- Source data sources, format (e.g. EMR, core readers, paper)
- IP profile
- Study phase
- Quantity of data

Monitoring Framework

FDA Guidance RBM Developing the Monitoring Plan cont.:
- Identify critical data and processes to be monitored
  - Informed Consent and ICF Process
  - Inclusion Exclusion
  - IP accountability, management, administration
  - Endpoints
  - Safety assessments
  - SAEs
**Monitoring Framework**

**FDA Guidance RBM cont. Central /Remote monitoring:**
- 90%+ findings possible
- Assess, identify trends and discrepancies: enrollment, data, Essential Documents, IP accountability
- Training and resource for questions

**FDA Guidance RBM cont. Onsite monitoring:**
- Identify data entry errors (e.g., discrepancies between source records and case report forms (CRFs) and missing data in source records or CRFs
- Confirm source documentation exists
- Assess site’s study staff familiarity with the protocol etc...and
- Assess compliance with the protocol and IP
- Assess overall quality of study conduct
- Face to face training, resource for questions

*We know the value of the ‘sniff test’ or ‘nursing assessment’ walking the halls and meeting with personnel*
Monitoring Framework

E6  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 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.

Monitoring Framework

E6  5.18.4 Monitor's Responsibilities cont.

(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.
(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.
Monitoring Framework

E6  5.18.4 Monitor's Responsibilities  cont.

(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 initialed 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).

---

Monitoring Framework

  - Supervision of clinical investigation conduct
  - Protecting rights, safety, welfare of study subjects
Monitoring vs. Audit vs. Inspection

ICH E6:
AUDIT: 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 standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).

INSPECTION: The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor’s and/or contract research organization’s (CROs) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

Monitoring Findings –FDA Warning Letters

- **Case Study #1:** (Aug. 2009 FDA WL to SPONSOR)
  - Partial List
    - Failure to ensure that the investigation was conducted according to the investigational plan: protocol assessments, assessing and reporting AE/SAE, review of lab/diagnostic reports, inclusion/exclusion, IP dispensing
    - Failure to adequately monitor/inadequate monitoring
    - Lack of monitor follow-up of issues/findings
    - Monitors inexperienced/inadequately trained
Monitoring Findings – FDA Warning Letters

**Case Study #1 cont.**
- Failure to ensure proper monitoring of the clinical investigations
  - The monitor failed to identify on multiple occasions that site personnel documented administration of study drug to different subjects at precisely the same time.
  - Source Documentation - Monitor failed to identify that no physical exam, wound assessment, overall clinical assessment was documented in the source/CRF and IV stability worksheets were missing for all 39 subjects.
  - Monitors did not identify discrepancies at the time of delivery of study drug to the nursing unit and the time of administration of the study drug for multiple subjects.
  - Investigational Product- The times that reconstituted drug was delivered to the nursing unit was not recorded on at least 7 occasions.
  - The site did not document storage temperature of infusions that were stored in subjects’ refrigerators

*Note: CRO also received Warning Letter*

---

**Case Study #2 - Investigator WL Feb 2014**
- Didn’t personally conduct/supervise the investigational plan
- Personnel not on delegation of authority log conducted study
- Didn’t obtain informed consent prior to using investigational drug
- Didn’t follow the investigational plan
- Didn’t inform IRB

**Case Study #3 - Investigator WL Sept 2012**
- Missed expiration dates/stipulations for IRB renewal
- Inadequate/inaccurate case histories
- Didn’t follow the investigational plan
- Improper Informed Consenting

**Case Study #4 - Investigator WL May 2012**
- Falsified assessments, submitted to FDA
- Didn’t follow the investigational plan

**Case Study #5 - Investigator WL Nov 2011**
- Improper Informed Consenting
- Inadequate/inaccurate case histories
- Didn’t report unanticipated AEs to IRB
Now that We Know All This

_How to apply it in the real world?_

Remote Monitoring Impact

- **Considerations**
  - **Study Risk**
    - First in Human, New Molecular Entity, New Indication, New Technology, Gene Therapy, Phase IV, Investigator Initiated
    - Regulatory requirements, strategy
  - **Resources**
    - Personnel (expertise, number of, turnover)
    - $ (what can be funded/who’s funding)
    - Time (study timeline, time zones)
    - Infrastructure (layers, technology, physical/geographic constraints)
Remote Monitoring Impact

- **Considerations cont.**
  - Strategic collaboration capacity
    - Sponsor (study owner) or conduct
    - Collaborate on study plan, monitoring plan
  - Study feasibility/conduct challenges
    - Challenges to enrollment, conduct, likelihood of amendments
    - Communication paths, styles

Key Monitoring Assessments

- Personnel and Facilities Stability
  - Investigator and staff - same, changes, adequate?
  - Delegation of Authority Log current and followed
  - Facilities - same, changes, adequate?

- Enrollment Metrics
  - Master subject log
  - On track, if not why not

- Audits or Inspections
  - Any since last visit? Outcome?

- General Operations
  - Site SOPs same/change and adequate?
  - Maintain Monitoring Log, Protocol Deviation Log, etc.
  - Study conduct consistent with regulatory documents
Key Monitoring Assessments cont.

- Informed Consent
  - Correct ICF version
  - Signature and Date complete and prior to study procedures
  - Informed consent process and ICF documented in Source Document/Medical Record

- Inclusion Exclusion Criteria
  - Documented as met

- Study Procedures
  - Performed on time, complete, explanation if not

- Regulatory Documents
  - IB, ICF, Protocol, Marketing, etc. Approvals on file
  - Safety letters, deviations, SAEs, AEs reports
  - Reporting to IRB, Regulatory Authorities, Sponsor
  - Monitoring Visit Reports, Letters on file

Key Monitoring Assessments cont.

- Investigational Product
  - Administered appropriately
  - Accountability Logs accurate and complete
  - Storage conditions
  - Blinding information intact

- Adverse Events
  - Identified, managed, reported appropriately to IRB, Sponsor, PI

- Lab and Clinical Supplies

- Action Items
  - Previous issues escalated PRN, resolved
  - New issues – root cause, resolve, escalate PRN
  - Next visit schedule
Monitoring Oversight
The other half of monitoring

- Quality Goals:
  - Confirm study conduct, subject safety and welfare, quality data, protocol and timelines compliance
- By:
  - Monitoring the monitor
  - Monitoring the site
- Methodology
  - Build and maintain a solid positive relationship and presence with the monitors and site personnel
  - Have a plan and follow it, adapt it as needed
  - Remote and onsite monitoring methods
  - Audit techniques – trend analysis, random sample percentage, targeted key fields or criteria
  - Personnel – not those conducting/monitoring the study

Monitoring Planning Strategies

- Prepare for the Monitoring Visit
  - Reports, documents, priorities, agenda, key personnel
- Flex with change
  - Travel, personnel / records availability, new issues
- Meet with Investigator, Study Coordinator, etc.
  - Questions, issues, suggestions, best practices, updates
- Monitoring Visit Follow-up
  - Address any issues
  - Documentation: Visit Confirmation/Agenda, Visit Report and Follow-up Letter
- Trend analysis/site, sites, study level
  - Revise protocol or budget, improve communications, increase monitoring or monitoring oversight
Relationship Management

Maximizing Your Monitor Relationship

- Challenges
  - Influence management
  - Monitor, CRO, sponsor turnover
  - Protocol changes: Clarify roles, goals, timelines

- Strategies
  - Win-Win philosophy: focus on joint goals, not personal
  - Consider ramifications of monitor requests
    - Resources: personnel, cost, timeline, infrastructure
    - Impact on study conduct, data, timelines
  - Refer to what’s been established:
    - Study documents and procedures
    - Site SOPs

Communication
- Request clarification before acting, escalate up
- Documentation trail

Maximizing CRC/Monitor Relationship cont.

- Strategies cont.
  - Consider ramifications of requests before acting
  - Resources: personnel, cost, timeline, infrastructure
  - Impact on study conduct, data, timelines
  - Do the homework
    - What’s been established:
      - Study documents and procedures
      - Site SOPs
      - Best practices in Clinical Research
  - Make the business/GCP case-frame the issue and proposed resolution(s)
  - Educate: self, colleagues, monitors, etc.
  - Leverage regulations, guidances, best practices, reports
  - Pick your challenges, know when to accept
Questions?  Comments?

Breakout Activity

Thank you