Results and Recommendations:

Effective and Efficient Monitoring as a Component of Quality Assurance in the Conduct of Clinical Trials

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Effective and Efficient Monitoring Project*

Goal

- Identify best practices and provide sensible criteria to help sponsors select the most appropriate monitoring methods for a clinical trial, thereby ensuring reliable and informative trial results and human subjects’ protection.

Objectives

- Workstream 1: Describe the range of current monitoring practices and examine factors that drive their adoption.
- Workstream 2: Define key quality objectives for monitoring clinical trials.
- Workstream 3: Examine ways to build quality into trials to enable more focused and efficient monitoring.

*https://www.trialstransformation.org/projects/effective-and-efficient-monitoring/
Results: Survey of Monitoring Practices*

Results consistent with hypotheses:

- Wide variety of monitoring practices in use
- Choice of monitoring approach correlates with type of organizational sponsor
- Rationale for using any specific monitoring approach does not appear to be evidence-based

*Poster of results on CTTI Website:
https://www.trialstransformation.org/projects/effective-and-efficient-monitoring/monitoring-project-workstream-1
Results: Range of Monitoring Practices

- On-site monitoring
  - Industry and CROs: 80% or more
  - Academic coordinating centers/cooperative groups/government organizations combined: less than 33%

- Despite availability of central data, 33% or less use centralized data monitoring to guide, target, or replace site visits
Results: Key Quality Objectives

Major quality objectives are to:
- Protect participant rights, safety and wellbeing
- Ensure the reliability of the study results
- Maintain adherence to the protocol

Also noted that monitoring provides:
- An opportunity for focused training
- Feedback that can improve study processes
Results: Building Quality into Trials

- Primary focus should shift from post-hoc monitoring/inspection to incorporation of quality into the scientific and operational design of a trial
- No single monitoring approach is appropriate or necessary in all circumstances
- Monitoring approach for a given clinical trial should be tailored to the needs of that trial and may combine several methods
Results: Building Quality into Trials

Focus on what is important:

- Importance of proper randomization
  - no foreknowledge of likely treatment allocation
  - minimize post-randomization withdrawals
  - minimize loss to follow-up

- Sufficient numbers of relevant clinical outcomes

- Unbiased ascertainment and analysis of study outcomes
Oversight should focus on those errors most likely to adversely affect trial quality:

- Data elements vary in their impact on the safety of participants or on the reliability of trial results
- Single-minded focus on checking/ensuring accuracy of every data point is misguided
- Sponsors and regulators should agree up front what data points are critical and need to be verified
- Sponsor should institute metrics to prospectively ensure the quality of critical data
Primary Recommendation

▪ Build quality into the scientific and operational design and conduct of clinical trials
  - Focus on what matters
    ▪ “Quality” is defined as the absence of errors that matter (i.e., errors that have a meaningful impact on patient safety or interpretation of results)
    ▪ Determine what matters for the specific trial
  - Develop a quality management plan
    ▪ Initiate in parallel with protocol development
    ▪ Focus on areas of highest risk for generating errors that matter
    ▪ Seek regulatory review of plan
  - Assess performance in important parameters
    ▪ Prospectively measure error rates of important parameters
    ▪ Monitoring approach (e.g., site visits, central, statistical) should be tailored to the trial design and key quality objectives
  - Improve training and procedures
    ▪ Based on measured parameters
  - Report findings of quality management approach
    ▪ Issues found, actions taken, impact on analysis and interpretation of results
    ▪ Include in regulatory submissions and publications
    ▪ Encourage inclusion in ICMJE requirements
Ancillary Recommendations

- **Share knowledge and experiences**
  - Collaboration between academia, industry, and regulators to share methodologies and data

- **Encourage appropriate regulatory guidance**
  - Emphasize key principles of quality trials
    - i.e., human subjects protection, reliable results, protocol adherence
  - Encourage risk-focused oversight of trials

- **Promote education and awareness**
  - Audience: those involved in design, implementation, analysis, interpretation, regulation, inspection, and publication of clinical trials
  - Also include users of results (e.g., health care providers, doctors, and patients)

- **Seek international adoption and harmonization**
  - Facilitate global adoption of proposed changes