CDER Perspective: Challenges in Clinical Trials and the Path Forward

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Current Oversight Models for Clinical Trials May Be Outmoded

- Reactive and premised on retrospective detection of errors
- Lack of proportionality
- Resource intensive
- May not optimally address significant risks to trial integrity, particularly systemic error

Analysis of OSI Reviews of Marketing Applications1 Indicates Opportunities for Improvement Remain

1. *Meeker-O'Connell and Ball FDLI Update 2011;2: 8-12*

104 original and supplemental NDAs/ BLAs reviewed by OSI from 1QFY10 to 1Q FY11

- Significant data integrity concerns affected 5 inspected applications (5%)
- Some systemic errors persisted due to deficits in sponsor monitoring, but had a **root cause in study design and planning.**
- For 2/5 applications, concerns arose solely from ***internal processes*** at the sponsor and CRO, unrelated to clinical investigator activities

Inefficient practices may consume valuable resources and inadvertently detract from quality

Case Study: Clinical Trial Monitoring

- Millions of data points collected on a clinical trial; Not all used in regulatory decision-making.[1]
- OSI focus: critical errors in endpoint and safety data
- Industry standard for monitoring:
  - 100% source data verification at the clinical site
  - "The flexibility in the GCP guidelines is not often utilized" [2]
- FDA regulations permit a variety of monitoring approaches

1: Assuring Data Quality and Validity in Clinical Trials for Regulatory Decision Making: IOM Workshop Report 1999.
2. Sensible guidelines for the conduct of large randomized trials. Clin Trials 2008 5: 38

Desired State for Clinical Development similar to Quality by Design in Manufacturing:

"Maximally efficient, agile clinical development programs that reliably produce high quality data* and protect trial participants without extensive regulatory oversight"

*Data that are fit for purpose

Systematic, proportionate approach to clinical development

- Emphasis on process control
- At the trial level, the protocol is the blueprint for quality
  - Prospectively identify the important risks to subject safety and data reliability
    - Risks may accrue from a variety of sources
  - Tailor the protocol and its delivery to eliminate or mitigate these important risks.
  - Monitoring and auditing become tools in a quality toolbox, with flexibility in approaches

CDER is fostering the development of risk-based approaches to clinical trial oversight

Examples

- Clinical Trials Transformation Initiative (CTTI) Project on Quality Frameworks: Making clinical trials fit for purpose
- Pilot prospective review of a sponsor's risk-based integrated quality management plan
- OECD-GSF Working Group to Facilitate International Cooperation in Non-commercial Clinical Trials
  - Feasibility of a risk-based approach for multinational trials

Key Dependencies

- Recognition of differences in manufacturing and clinical development
- Broad engagement of stakeholders
- Effective communication: fundamental change in oversight
- Early identification of barriers
- Evaluation of different approaches and methodologies
- Changes in FDA oversight and inspectional processes

Corresponding Shift in CDER's Approach

- Shifting inspectional resources to permit assessment of clinical trial oversight in real-time
- Risk-based inspection planning
- Enhancing external collaborations
  - EMA / FDA GCP Initiative
- Adopting an enterprise compliance intelligence approach
  - Using data analysis to identify risk concentrations and craft targeted solutions
  - Coordinating with other Offices within the Office of Compliance and across the Agency

Thank you!

Questions?