Changing the Paradigm of Monitoring

Thomas M Tremblay, RN BSN
“This presentation contains the opinions and viewpoints of the presenter

and does not necessarily represent those of the event organizer

or

the presenter’s current or past employers”
Page 3

- 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.

- 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 Rationale for RBM

- to encourage sponsors to consider a change in approach to monitoring
- … growing consensus that risk-based approaches to monitoring, focused on risks to the most critical data elements and processes necessary to achieve study objectives, are more likely than routine visits to all clinical sites and 100% data verification to ensure subject protection and overall study quality…
- …centralized monitoring activities could have identified more than 90% of the findings identified during on-site monitoring visits (Bakobaki, et al)

Types of Data Errors

- Unintentional errors
  - Shifts in distribution, large variability

- Carelessness
  - Transcription errors
  - Missing data
  - Outliers
  - Out of range

- Fabricated*
  - Small variability in distribution
  - Similarity of patterns/repeated variables

- Falsified*
  - Detected through comparisons of distributions or through center by treatment

Challenges and Limitations

- **Challenges**
  - Availability of data
    - Entry rate, staggered enrollment, fewer sites to start
  - Amount of data
  - Cleanliness
  - Differences in standards between centers in multi-national studies

- **Limitations**
  - Monitoring limited to data on hand
  - Compliance/ “missingness”
  - Some documentation not database
    - e.g.; informed consent

Monitoring vs. Source Verification

- Many monitoring activities can be conducted remotely
  - Compliance
  - Data integrity/ completeness
  - Internal logic checks

- Parameters to be source verified
  - Informed consent
  - **ALL** inclusion/exclusion criteria
  - Essential vs. non-essential data

- Collectable source documents
  - Central laboratory
  - Electronic source
  - Redacted local source
Changing the Paradigm

- Clinical research is an analysis of a representative sample

- Apply research sampling technique to source verification
  - e.g.; military standard
  - Acceptable error rate
  - Increase verification/monitoring in response to findings
  - Essential elements

- Review of study budget major drivers
  - Investigational site payments
    - Amount of data
  - Monitoring
    - Amount of verification
Strategies for Better Data

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

A. Protocol and Case Report Form Design

The most important tool for ensuring human subject protection and high-quality data is a well-designed and articulated protocol. A poorly designed or ambiguous protocol may introduce systemic errors that can render a clinical investigation unreliable despite rigorous monitoring. Additionally, the complexity of the trial design and the type and amount of data collected may influence data quality. The CRF, which captures the data required by the protocol, is another

---

37 Sponsors are encouraged to consult the appropriate review division within FDA's medical product centers with questions about quality aspects of clinical trial design.
Basis of Risk-based Monitoring

- Assess risk
  - Stage of development
  - Safety
  - Proof of concept
  - Essential elements
    - Elements at risk
  - Site selection
  - Time vs. money
  - Representative sample
Costs and Timing

- Staggered monitoring
  - Safety
  - Top-line
  - Remainder
- Staggered analysis
- Effect of top-line data on timeline
- Gantt
  - Database lock in relation to LPLV
  - Top-line data in relation to CSR or IND/PMA
Central Monitoring vs. Remote

- Central monitoring
  - Includes review of aggregate data
  - Common review standards for all sites
  - Monitors the sites and the monitors
- Remote Monitoring
  - Central laboratories
  - Central readers
  - Access to electronic medical records
  - Redacted, de-identified local source
  - EDC-upload of supporting documentation
    - ICF
- Source verification
  - Reserved non-central, non-remote activities
Summary

- Pharmaceutical industry is charged with more efficient resource management while still maintaining in the highest quality of data integrity
  - Patient safety and benefit
- Smaller companies must be efficient
- Large companies should be cost-effective
- Blockbuster drugs with high profit margins are fewer than small market-share opportunities
- Efficiency is important but safety is always “first” priority
- Questions