Quality Risk Management in Clinical Trials: FDA/DSI Perspective

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Developing Effective Quality Systems in Clinical Trials: An Enlightened Approach

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Case Example: Quality Systems

- NDA contains large safety study
  - N> 25K; >1000 clinical investigators
- Routine data audit inspections reveal significant noncompliance
  - Site monitoring
  - Enrollment
  - Informed Consent
  - Data reliability/fraud
  - Adverse event monitoring
  - Investigator qualification
- Data from study deemed unreliable and not used as basis for product approval

Statement of Problem

- All stakeholders (the public, clinicians, industry, academia, regulators) expect the truth about the *safety and effective* products on the market
- But, risk/benefit evaluation is an ongoing, nuanced process
- And, current challenges (clinical trial complexity, globalization, regulatory hurdles) lead to greater ***uncertainty*** regarding drug development
  - This uncertainty threatens the sustainability of the clinical trial enterprise

To address this uncertainty, we must transform clinical trial conduct and oversight

- "Technical vs. Adaptive Change"*

  Technical: Application of current knowledge, skills and/or tools to solve a problem

  Adaptive:

  - existing knowledge and skills are not sufficient
  - *requires a shift in values, expectations, attitudes, or habits.*

Implementing adaptive change means

- Clarifying a conflict in values, or
- Bridging the gap between our values and the current conditions

*Ronald A. Heifetz. "*Leadership Without Easy Answers"* Cambridge, Mass: The Belknap Press of Harvard Press, 1994.

What values do we stand for?

- Clinical trials generate knowledge on the safety and efficacy of drugs
  - Knowledge = True justified belief
- While stakeholders agree on the importance of knowledge, their epistemological frameworks differ:
  - Academia: Generation of knowledge
  - Regulators: Assessment of knowledge
  - Industry: Use of knowledge in developing, testing, and marketing of products

How do we bridge the gap between our values and current conditions?

- *By building **quality** into clinical trials*
- Definition of quality:
  - The ability to *effectively and efficiently* answer the intended question about the benefits and risks of a medical product (therapeutic or diagnostic) or procedure while assuring protection of human subjects.*

*Clinical Trials Transformation Initiative at: http://www.trialstransformation.org/scope

High Quality Data

- No perfect dataset
- Alternate definition of high quality data: data that sufficiently supports conclusions and interpretations equivalent to those derived from error-free data* (data fit for purpose)
  - Sufficiently accurate to support FDA regulatory decisions, sponsor claims about a product, labeling

**Assuring Data Quality and Validity in Clinical Trials for Regulatory Decision Making: Workshop Report,* IOM 1999 at http://www.iom.edu/CMS/3740/5583.aspx

Effect of Errors

- Fraud is rare and usually isolated in scope
  - But when it occurs, it can be dramatic and undermine public confidence in clinical trials
- Errors other than fraud may be more systematic and can render data unreliable
  - Non-inferiority study designs: “Sloppiness” in clinical trials may obscure difference between study drug and comparator
- Errors can include:
  - Study design - Poorly designed protocols
  - Study conduct and monitoring - Poorly executed protocols that result in inability to verify or interpret critical efficacy and safety data
  - Data storage and management - Inadequate internal processes for data quality control and quality assurance
  - Data analysis - Faulty statistical analysis plan or execution

A quality system must address each of these types of errors

Traditional FDA Approach for Assessing Data Integrity

- **Traditional compliance model:** Assessing trial and data integrity through on site inspections at the time of NDA submission
  - Data validation (NDA vs. CRF vs. source documents)
  - Review of processes governed by FDA regulations
- Based on assumptions:
  - Absence of regulatory violations = reliable data
  - Lots of regulatory violations = unreliable data
- Limitations
  - Inspections do not always focus on what matters (key efficacy or safety parameters)
  - Inspections do not tell us how results from one site translates across a study or an application
  - Inspections often completed well after a study is completed

Shift in Expectations for Sponsors' Clinical Trial Oversight

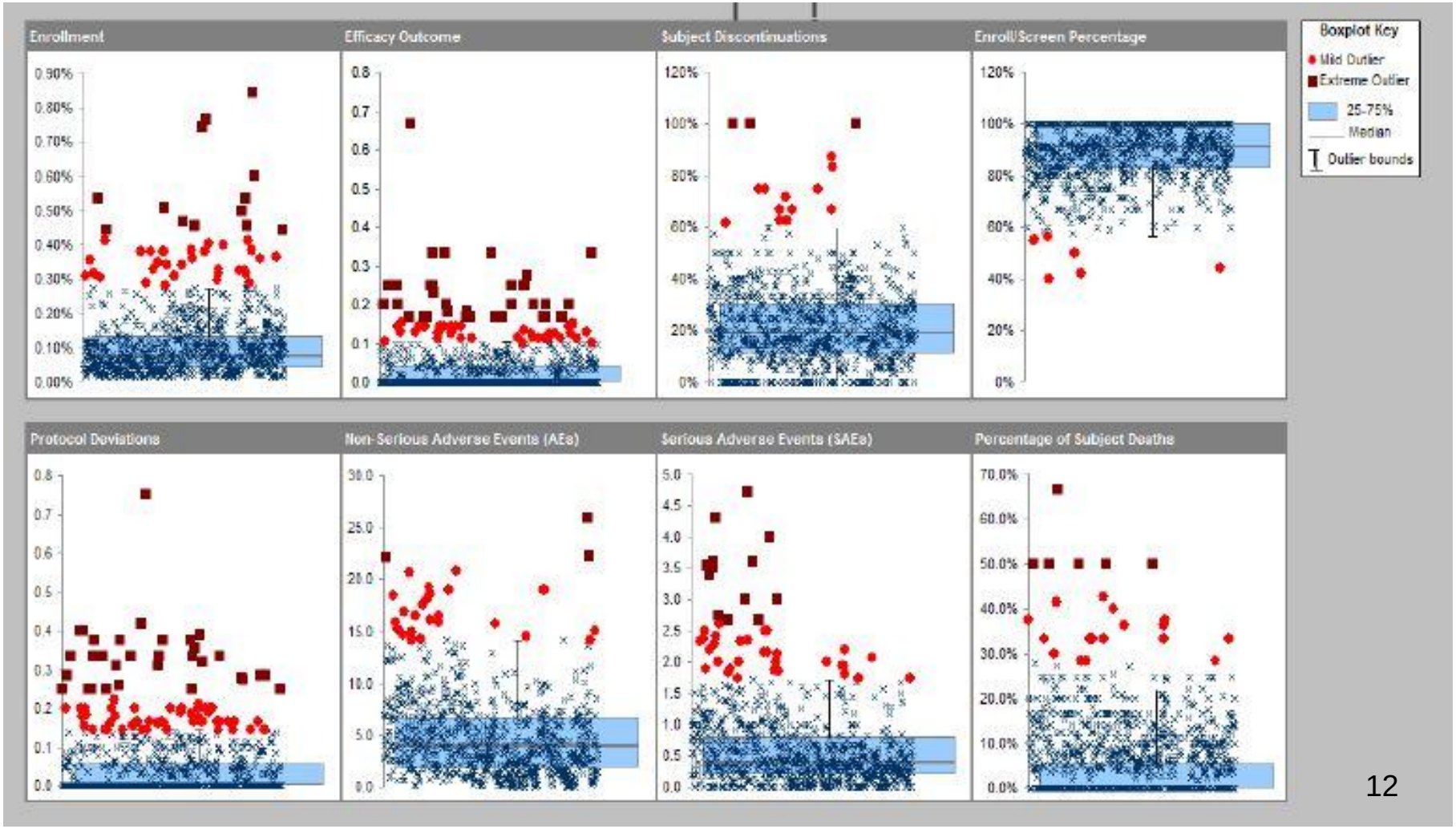
- Expand current notion of compliance to a Quality Risk Management approach to clinical trial oversight.

- Quality by design for clinical trials
  - Build quality in, starting with protocol development but extending across all aspects of a trial
  - Focus on key risks to trial integrity and data quality as well as subject safety
  - Detect and correct problems in as close to real time as you can get, while study is ongoing

Corresponding Shift in FDA's Approach

- **Shift in inspectional focus**
  - Real-time, surveillance inspections
  - Evaluation of sponsor quality systems
- **Incorporating risk based inspection planning**
  - CDER NDA/BLA focused risk-based site selection tool: in pilot
    - Long term goals to develop a data warehouse, learning algorithm and predictive capacity
  - IRB and Bioequivalence inspection models: under development
- **Taking a compliance intelligence approach**
  - Using data as information to inform inspection prioritization. planning, and scope
  - Permits FDA to target high-risk areas and processes (analogous to sponsor monitoring in a GCP quality system)
- **Enhancing external collaborations**
  - EMA and other international regulatory authorities
  - Clinical Trials Transformation Initiative

Example: CDER Risk-based Site Selection Pilot



Final Thoughts

1. Old way of doing business is not sustainable
2. While stakeholder perspectives may differ, we all seem to agree on the need for a **quality risk management** approach in the planning, conduct, and oversight of trials to get reliable results and ensure and subject protections
3. With high quality studies producing reliable results, we are more likely to end up with safe and effective drug products