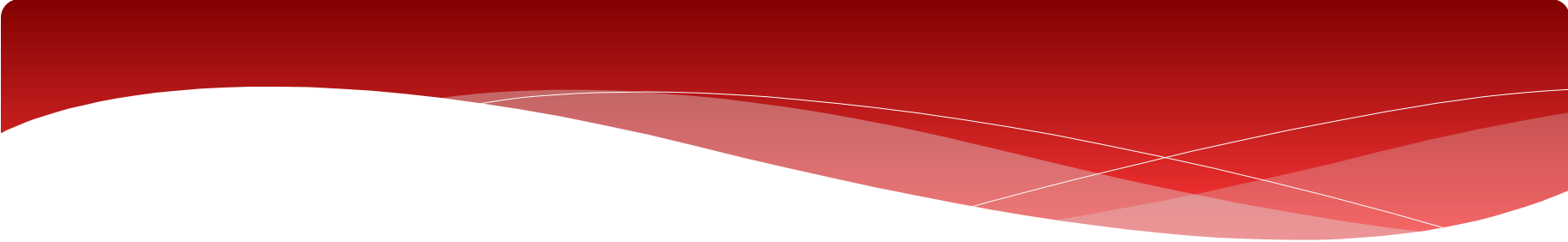




Regulatory Perspective: Enhancing Trial Quality

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Desired State for Clinical Development

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

- Janet Woodcock, MD

CTTI Monitoring Workstream #3 Workshop

Another Perspective



** If everything is under control, you are moving too slow*

** Mario Andretti*

Are we there yet?



Streamlining Trial Design

“You start out with a beautiful green tree that should be admired and then everybody in the family wants to put an ornament on it... and no one will take grandma’s ornament off the tree. So you end up with a protocol that is impossible to do and is very distracted from answering the question you originally had.”

- * Dr. Robert Califf, Mind the Gap seminar, “Innovative Approaches to Clinical Trials.”

Building Quality into Clinical Trials

- * Quality cannot be monitored, audited, or inspected in retrospectively
- * “The most important tool for ensuring human subject protection and high-quality data is a well-designed and articulated protocol.”

FDA Draft Clinical Monitoring Guidance (published 29 August 2011)

- * At the trial level, the protocol – or more appropriately the investigational plan -- is the blueprint for quality

Quality Redefined



Quality in
clinical trials =
the absence of
errors that
matter

What are “Errors that Matter”?



- * Errors that have a material impact on
 - * Patient safety or
 - * Interpretation of trial results

Building Quality into the Scientific and Operational Design of Trials

- * Prospectively identify the aspects of a trial that are “critical to quality”
- * Identify important and likely risks to “critical to quality” aspects
- * Tailor the investigational plan and trial implementation to eliminate or reduce the impact of “errors that matter”



What is FDA Doing?

August 2011 Draft Monitoring Guidance

- * Makes clear that sponsors can use a variety of approaches to fulfill monitoring responsibilities
 - * “No single approach to monitoring is appropriate or necessary for every clinical trial”
- * Encourages sponsors to develop risk-based monitoring strategies and plans that are:
 - * Tailored to the risks of the trial
 - * Use a combination of monitoring activities
 - * Incorporate greater reliance on centralized monitoring practices

What is FDA doing?



- * Encouraging a proactive, risk-adapted approach to design through reporting of clinical trials, e.g.:
 - * DIA Special Interest Area Community on QRM
 - * CDER Pilot Prospective Reviews – Quality Management and Monitoring Plans
 - * *CTTI Quality – by –Design Project*

Origins of the QbD project



- * General principles about what really matters in clinical trials can and should be developed—i.e., what do we really need to get right to ensure reliability of results and patient protection?

https://www.ctti-clinicaltrials.org/website-administration/documents/QbD%20workshop_exec%20summary_1_30_12_FINAL_v3.pdf

Underlying Assumption

- * The likelihood of a successful, quality trial can be dramatically improved through prospective attention to preventing important errors that could undermine the ability to obtain meaningful information from a trial.

The Goal of this Project



- * Produce a draft document outlining:
 - * High-level principles for building quality into trials
 - * One potential approach to prospective quality planning
- * Test the document through a series of workshops with hands-on exercises involving:
 - * Different therapeutic areas
 - * Different product types
 - * Various stakeholders
 - * Different functional lines
- * Refine and publish document and case-studies from workshops

Example of CTQs: Protocol Design

- * **Eligibility criteria**
- * **Data Quantity**
- * **Endpoints**
- * Procedures supporting study endpoints and data integrity
- * Type of Control
- * Randomization
- * Blinding
- * Investigational product handling and administration

Example: Eligibility Criteria



Relative Importance (Examples)

- * Describe the specific population needed for the trial to evaluate the intended question. If this specific population is not enrolled, what's the impact?
- * Evaluate the impact of “getting it wrong” with regard to eligibility? Would the subject be removed? Replaced?
- * Is the trial intended to evaluate effectiveness and safety of the investigational product (IP) in a real-world population?

Potential Risks (Examples)

- * Are all criteria relevant to ensuring the specific subject population needed for the trial?
- * Are there clear and measurable criteria to define the population?
- * Is there a particular criterion critical to subject evaluability (e.g. for an enrichment design) **or** to subject safety?

What is FDA doing?



Draft Guidance for Industry: Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Post-approval Clinical Investigations

- * Emphasizes a selective and better targeted approach to safety data collection during late stage development /during post-market stage based on what is already known about a medical product's safety profile
- * May be appropriate when:
 - * Number of subjects exposed to the drug in previous studies is sufficient to characterize the safety profile for all but rare events
 - * Occurrence of adverse events has been generally similar across multiple studies
 - * Is a reasonable basis to conclude that occurrence of adverse events in the population to be studied will be similar to previously observed rates”
- * Safety data collection plan should be discussed with the relevant review division (e.g., at the end of a phase 2 meeting for a phase 3 trial).

Closing Thoughts

“We are all plagued by failures – by missed subtleties, by overlooked knowledge, and outright errors. For the most part, we imagined that little could be done beyond working harder and harder to catch the problems and clean up after them...

When we look closely, we realize the same balls are being dropped over and over, even by those of great determination. **We know the patterns. We see the costs. It’s time to try something different.”**

-Atul Gawande, The Checklist Manifesto



Thank you!

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