FDA Clinical Trial Transformation Initiative Monitoring Project: Developing effective quality systems in clinical trials

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CLINICAL TRIALS TRANSFORMATION INITIATIVE

https://www.trialstransformation.org/projects/effective-and-efficient-monitoring

FDA Clinical Trials Transformation Initiative:

Mission

- To identify practices that through broad adoption will increase the quality and efficiency of clinical trials

Strategy

- Generation of evidence about how to improve the design and execution of clinical trials
- Stimulation of widespread change based on evidence

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: Illustrate strengths and weaknesses of various monitoring practices in meeting quality objectives for a range of clinical trial settings

Increased emphasis on protocol & design

- The most appropriate method of monitoring is in large part determined by the steps that are taken to build quality into the trial as the trial is designed.

- Hence, focus has shifted towards advocating for increased attention by Sponsors in building quality into the trial – since this will in large part determine both the overall quality of the trial and the appropriate approach to assessing quality.

Key features for reliable results

- Proper randomization (and intent-to-treat analysis)
- Sufficient numbers of relevant clinical outcomes
- Unbiased ascertainment of key study outcomes
- Comparisons with the randomized control group (except for assessing big effects on rare events)
- Avoiding undue emphasis on subgroup findings and on non-randomized “on treatment” analyses

Minimal impact of adding false events or of missing real events

	Active (10,000)	Control (10,000)	OR (& 95%CI)	Z score
True events	800	1000	0.78 (0.71-0.86)	4.9
Extra false events (evenly distributed)				
+ 10%	890	1090	0.80 (0.73-0.88)	4.7
+ 20%	980	1180	0.81 (0.74-0.89)	4.6
Missing real events (unevenly distributed)				
- 10%	720	900	0.78 (0.71-0.87)	4.7
- 20%	640	800	0.79 (0.71-0.88)	4.4

Quality Assurance for Clinical Trials: Principles

- Objective: answer the question
  - be intellectually mindful of what you're trying to produce
- Quality = fitness for use (≠ perfection)
  - avoid undue emphasis on data at the expense of reliable results
  - avoid excessive emphasis on the case report form

Quality Assurance for Clinical Trials: Risk management

- What are you trying to achieve
- Specify threats: What could go wrong in a meaningful manner
  - e.g. bias, poor compliance, poor recruitment, low event rate
- Design the process to avoid threats
- Add controls
  - real time monitoring of things that might matter
- Identify problems and intervene early
  - before issues become endemic
- Improve

Process controls (monitoring)

- Controls
  - Monitoring is a continuous activity
  - Risk ≠ issue
  - Risk = a call to action (accept or mitigate)
- Challenges
  - Choice of risk indicators
  - Data sharing
  - Comparative data
  - False positives, false negatives

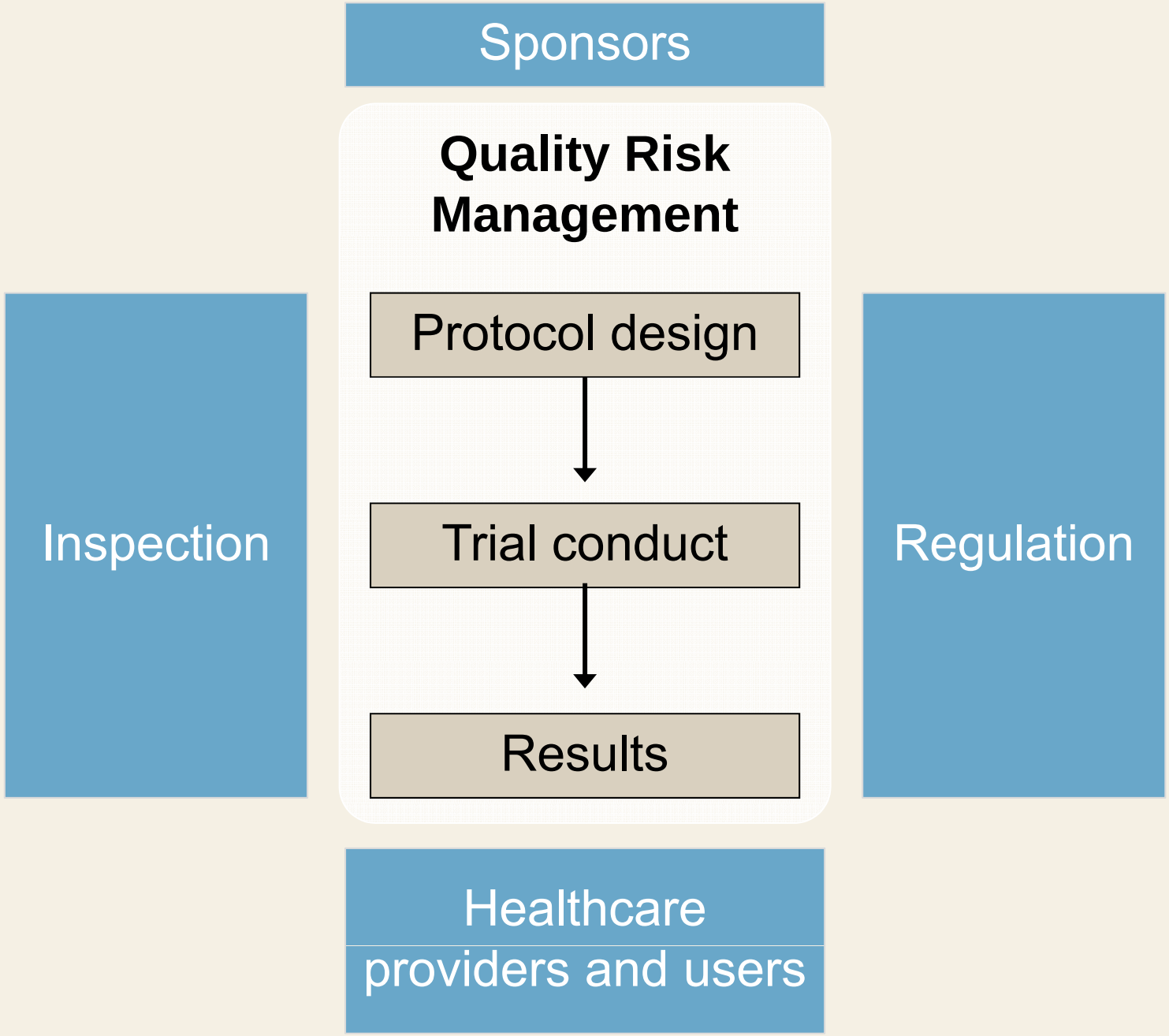
Quality Assurance for Clinical Trials: Challenges

- Requires good understanding of:
  - the objectives
  - the process
  - the controls
- Acknowledgement of the risks
  - depends on perspective

“Risk-based” monitoring

- Different perceptions of “risk”

- Risk to organization:
  - Reputation, litigation, regulatory delay/failure
- Risk to participant:
  - Harm from treatment or study procedures
- Risk to patients
  - Inadequate / unreliable data lead to bad healthcare
- Risk to providers
  - Expensive use (or non-use) of treatment


Sponsors
Quality Risk Management
Protocol design
Trial conduct
Results
Inspection
Regulation
Healthcare providers and users

Preliminary recommendations

- Regulatory guidance
  - should be coherent and consistent
  - should not promote any particular methodology
- Monitoring/QA procedures
  - plan should be discussed with FDA reviewers & inspectors
  - findings should be included in study reports/publications
  - greater collaboration (incl. methodology, benchmarking)
- Education & awareness of principles
  - regulators, trialists, inspectors
  - focus on what's important, what's not
  - monitoring and QA methods can be diverse
- International adoption