Developing effective quality systems in clinical trials

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An enlightened approach

Bethesda, MD
13-14 October 2010

CTTI
CLINICAL
TRIALS
TRANSFORMATION
INITIATIVE

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Welcome
Logistics
Rules of engagement
Introductions

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Introductions: Representation

Sector	Number
Regulatory	19
Industry	17
Academia	9
US government agencies	8
Clinical investigator groups	4
Patient representatives	2
Others	6
CTTI	5
Total	**70**

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Introduction

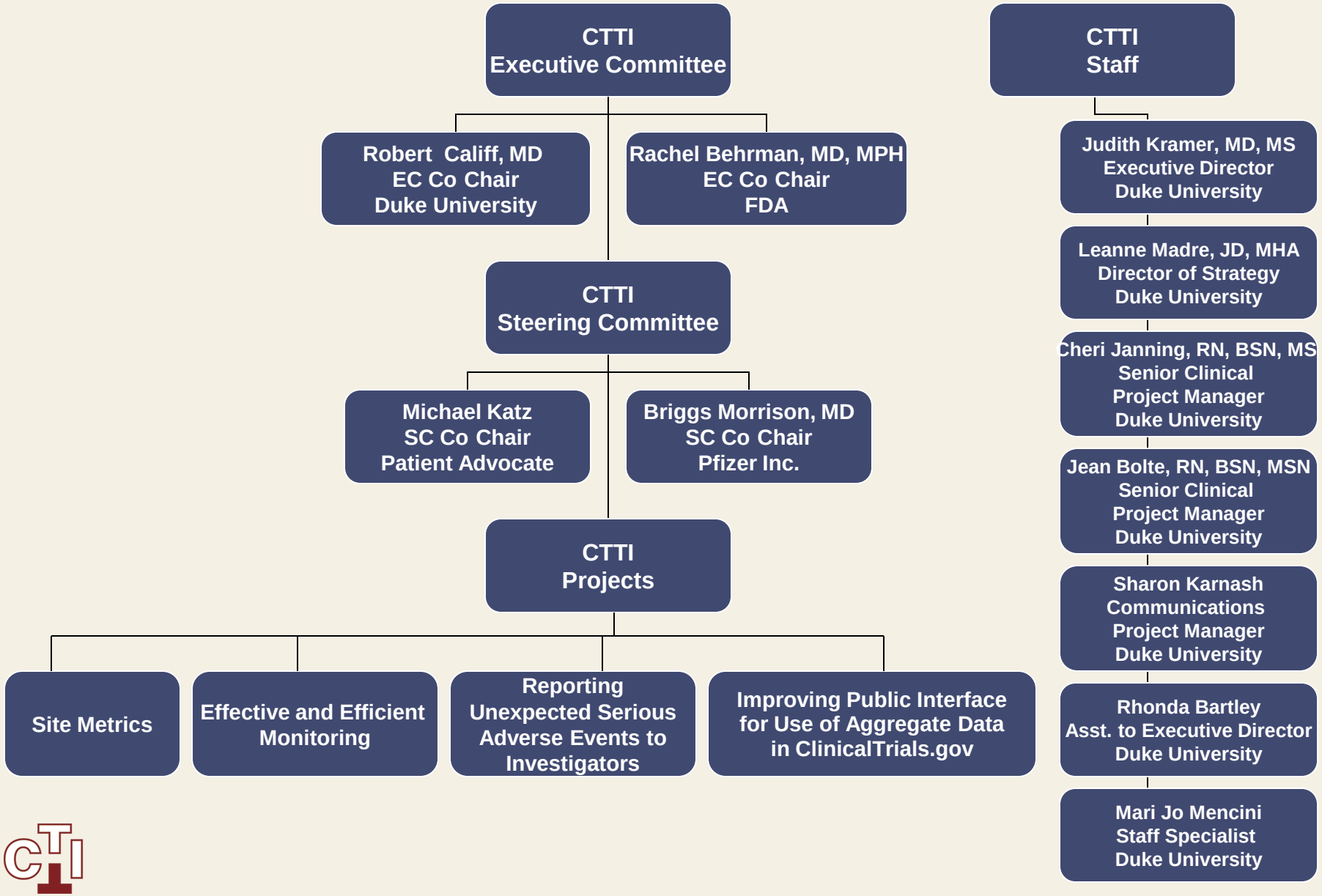
Martin Landray
University of Oxford

CLINICAL TRIALS TRANSFORMATION INITIATIVE

Clinical Trials Transformation Initiative

- Organization
  - Established as a public-private partnership by FDA Office of Critical Path Programs
  - Hosted by Duke University
- Funding
  - Membership fees
  - FDA Cooperative Agreement Sep 2009
- 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

Clinical Trials Transformation Initiative
Organizational Overview



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Monitoring Project:

Effective and Efficient Monitoring as a Component of Quality Assurance in the Conduct of Clinical Trials

Martin Landray
University of Oxford

Need for reliable evidence

- Essential for appropriate decision making concerning the benefits and risks associated with clinical interventions.

- Decisions made in the absence of reliable evidence (either because relevant trials have never been performed or because those that have been performed were poorly designed or conducted) may harm individual patients and public health.

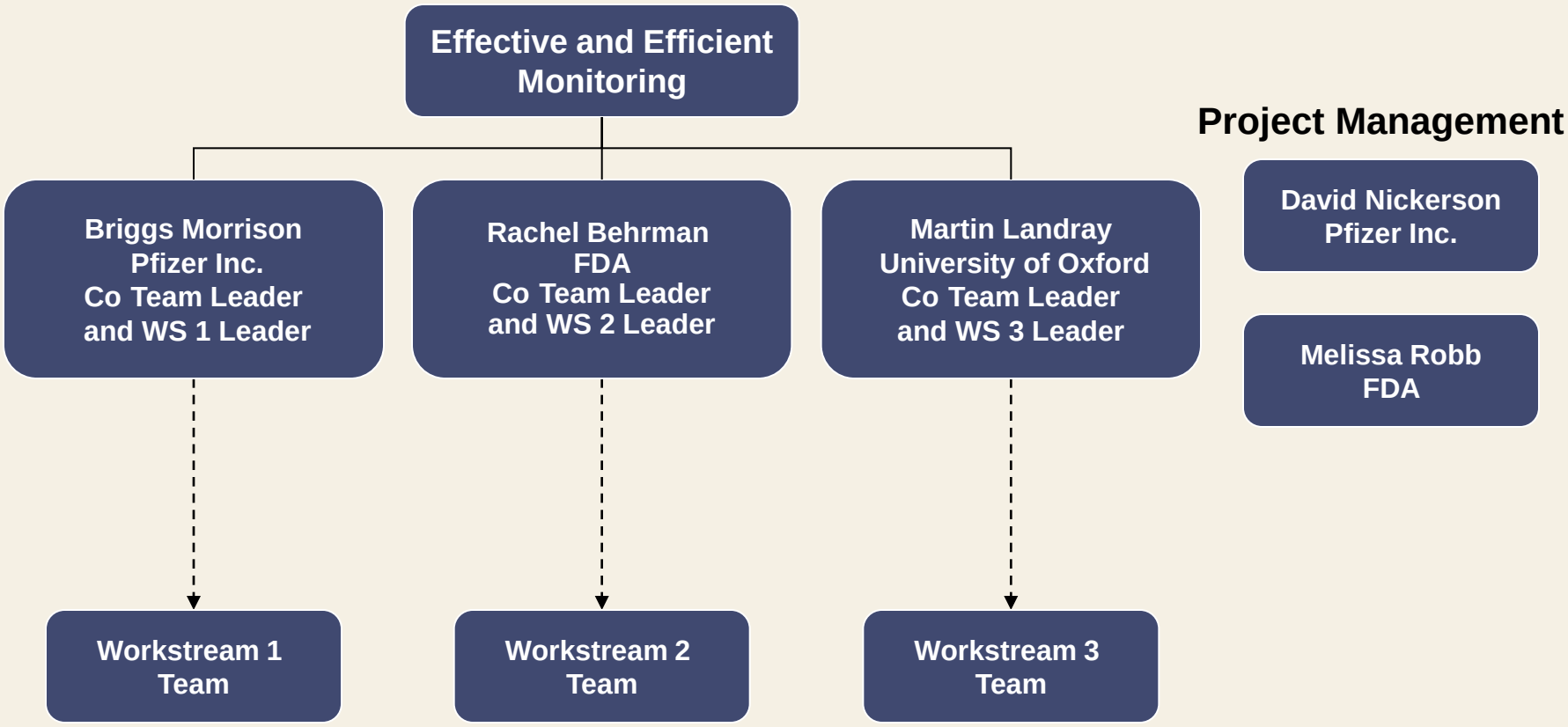
Appropriate monitoring

- Monitoring should enhance quality
  - for participants in the trial
  - for future patients whose care relies on the results
- Ineffective or inefficient practices should be abandoned
  - they fail protect participants or study integrity
  - they waste resource
  - they limit recruitment & follow-up (leading to a less reliable answer)
  - they deter participation & enthusiasm
- Monitoring practices with uncertain value should be evaluated

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

Organization of Monitoring Project



WS1: Review of current practices

- Rationale
  - Many, diverse methods currently in use
  - The rationale for using any particular method is unclear
  - All have been accepted by journals & regulatory agencies
- Task:
  - Characterize and describe clinical monitoring methods currently used by various sponsors for a range of clinical trial types
  - Explore the perceived value of these methods
- Activity:
  - On-line survey of clinical trials organizations

WS1: Conclusions

- Variation in practices
- Focus on data
  - Consent
  - Eligibility
  - Primary efficacy outcome
  - Safety outcomes
- Training is an important component of monitoring
- Variation in definition and assessment of risks

WS2: Define key objectives of monitoring

- Rationale
  - essential step for evaluation of existing monitoring methods and development of new methods
- Task
  - Requirements Capture: Identify the key QA objectives
- Approach
  - Literature review
  - FDA Warning Letter review
  - On-line survey
  - Expert consensus meeting

WS2 conclusions: Monitoring objectives

- Participant rights, safety and wellbeing
- Collection of reliable data
- Protocol compliance
- Quality improvement

WS2 conclusions: Monitoring objectives

- Compliance with protocol
- Quality improvement

WS2: Recommendations

- High quality protocol enables efficient monitoring
- Protocol should include monitoring plan
- Good training prevents issues and reduces monitoring required
- Risk-based approaches required
  - some errors are acceptable (but context critical)
  - requires cultural shift
- Regulators must be clear about expectations
  - Monitoring plan should be discussed with FDA (and other agencies) in advance

WS2 meeting conclusion

“A major shift in thinking is required to allow for innovation that will expand research horizons in the twenty-first century – we must delineate and accommodate varying perceptions of risk in the formulation of a rational plan for monitoring clinical research that will add value to clinical trials without sacrificing quality or efficiency”

Challenges and opportunities

Regulations & their interpretation

- Regulations should set out the quality objectives that are common to all trials
- Regulations should NOT specify the methods for meeting these objectives
- The interpretation and implementation of the regulations must be flexible, if their objectives are to be fulfilled

ICH GCP: Regulations

- *The sponsor should ensure that trials are adequately monitored.*
- *The sponsor should determine the appropriate extent and nature of monitoring.*
- *The determination of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial.*

FDA Regulations: 21 CFR 312

SPONSOR RESPONSIBILITIES

- ensuring proper monitoring of the investigation(s)
- ensuring that the investigation(s) is conducted in accordance with the protocol
- selecting a monitor to monitor the progress of the investigation.
- monitoring the progress of all clinical investigations being conducted under its IND.

FDA Guidance for Industry
1988 (minor format & edits 1998)

FLEXIBILITY PERMITTED

- These principles are not legal requirements but represent a standard of practice that is acceptable to FDA.
- A sponsor may rely upon this guideline or may develop different procedures.
- A sponsor who selects different procedures for monitoring a clinical investigation may, but is not required to, submit those procedures to FDA for review and comment to avoid the possibility of employing monitoring procedures that FDA might later determine to be inadequate.

http://www.fda.gov/RegulatoryInformation/Guidances/ucm126400.htm

FDA Guideline for the Monitoring of Clinical Investigations
1988 (minor format & edits 1998)

DETAILS ENCOURAGE A COMMON (& OFTEN OUTDATED) APPROACH

- The monitor should visit the investigator at the site of the investigation frequently enough to assure that:
  - the facilities used by the investigator continue to be acceptable for purposes of the study.
  - study protocol is being followed
  - changes to the protocol have been approved by the IRB
  - accurate, complete, and current records are being maintained
  - accurate, complete, and timely reports are being made to the sponsor & IRB
  - the investigator is carrying out the agreed-upon activities and has not delegated them to other previously unspecified staff.
- The most effective way to assure the accuracy of the data… is to review individual subject records… and compare those records with the reports prepared by the investigator for submission to the sponsor.

BUT…THERE MAY BE MORE EFFICIENT / EFFECTIVE METHODS

http://www.fda.gov/RegulatoryInformation/Guidances/ucm126400.htm

“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

* includes industry, academia, CROs, IRBs, sites, professional bodies, regulators (CTA approval, reviewer and inspector functions)

The importance of error

- Which data are essential for reliable assessment of the protocol question?
- What is the potential for error in collection of these data?
- What would be the impact of such errors on the safety, rights and wellbeing of study participants?
- What would be the impact of such errors on the reliability of the results?

This allows a logical approach by which monitoring activities can be tailored to match needs.

Potential sources of error

- Design
  - e.g. non-systematic recording of safety outcomes, inappropriate treatment allocation method, potential for inadvertent unblinding
- Procedure
  - e.g. inclusion of individuals with contra-indications to study intervention, drug regimen (incl. dosing & titration)
- Data recording
  - e.g. laboratory assays, physical measurements
- Analysis
  - e.g. non-intention-to-treat, over-emphasis of subgroups
- Errors may be *deliberate* (fraud) or *unintentional*

Impact of errors on the reliability of results

- *Random Errors*:
  - affect the precision of estimates (adding “noise” and reducing statistical power), but will not introduce bias in either direction

    [Note: For equivalence assessments, random errors are counter-conservative]

- *Systematic Errors*:
  - lead towards a particular decision.

Principles of monitoring

- Monitoring should enhance quality
  - for participants in the trial
  - for future patients whose care relies on the results
- Principles should be widely applicable
  - clinical settings
  - investigational products
  - study designs and procedures
- Principles should stand the test of time
- Principles should not enforce particular methods

Meeting Objectives

- Identify the critical aspects of clinical trials that should be the focus of risk-based approaches to creating quality systems
- Describe, discuss, and evaluate novel approaches to clinical trial oversight
- Propose an integrated model of quality management that will promote more efficient approaches to design, conduct, and oversight of clinical trials

Agenda: Day 1

Session 1	Introductions CTTI background & overview of monitoring project
Session 2	Defining the underlying principles of quality in clinical trials - Quality design (*Rory Collins, Oxford*) - Quality risk management (*Janet Woodcock, FDA*) - Statistical monitoring (*Tomasz Burzykowski, IDDI, Belgium*)
Session 3	Approaches to risk-based quality management (part 1)
Session 4	Approaches to risk-based quality management (part 2)
	Wrap-up: Each propose up to 3 activities that would promote efficient monitoring

Agenda: Day 2

Session 5	Round table discussion: Working together to deliver quality *- Robert Temple, Rachel Behrman (FDA)* *- Fergus Sweeney (EMA)* *- Rory Collins (University of Oxford)* *- Briggs Morrison (Pfizer)* *- Felix Gyi (Chesapeake IRB)* *- Nancy Roach (Patient Advocate)* • What are the essential elements of a clinical trial quality management system? • How do we measure success? (quality, efficiency, feasibility) • What are the barriers to change and how could they be overcome?
Session 6	Conclusions and future directions • Define steps to develop a consensus definition of a risk-based quality system • Define dissemination strategy

Ticket to Reception

- Identify 1 to 3 components of a quality management system that will promote more efficient oversight (monitoring) of clinical trials