

Clinical Trials Transformation Initiative (CTTI)

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Sensible Clinical Trials Meeting II—Oxford

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Anything wrong with this picture?

31,004 Queries closed

9,805 AEs coded

1502 Subjects enrolled

1035 SAEs processed

298 CEC cases adjudicated

48 Sites monitored

495 Periodic Monitoring Visits

37 team members to appreciate

Data-Base Locked

31 July 2009!!

Thank You Team!

Setting— Late 2007

■ US Clinical trials in crisis

- ◆ Trial start-up times lengthening
- ◆ Enrollment slowing
- ◆ Costs increasing
- ◆ Many investigators pulling out of clinical research
- ◆ Research correlates worsening metrics with increased protocol complexity (Getz 2008*)
- ◆ US FDA decides to take action

**Assessing the Impact of Protocol Design Change on Clinical Trial Performance. Getz et al. American Journal of Therapeutics. 2008 15(5); 450-457.*

It's a “Systems Problem”

- **All members of the clinical research enterprise have played a part in this problem**
- **Fixing it will require a collaborative effort**
 - ◆ FDA/global regulators
 - ◆ Industry
 - ◆ Academia/NIH
 - ◆ Investigators in clinical practice
 - ◆ Consumers

A collaborative effort to find solutions

- U.S. FDA's Office of Critical Path Programs established a public-private partnership:

The Clinical Trials Transformation Initiative (CTTI)



- All stakeholders involved
- Through a memorandum of understanding with FDA, Duke University serves as the host of CTTI



Executive Committee

Co-Chairs: Rob Califf(Duke) and Rachel Behrman(FDA)

- **Academia: David DeMets**
- **At-large representative: Ken Getz**
- **FDA: Bob Temple, CDER and Bram Zuckerman, CDRH**
- **Industry: Glenn Gormley, Jay Siegel, Susan Alpert, Alberto Grignolo**
- **Patient representative: Nancy Roach**
- **NIH liaison: Amy Patterson**
- **Non-US regulatory liaison: Hans-Georg Eichler, EMEA**
- **Ex-Officio Members: James Ferguson and Briggs Morrison, Steering Committee Co-chairs; Judith Kramer, Executive Director**

Steering Committee Representation

Category	# organizations
Pharmaceutical companies	8
Academic institutions	8
Clinical research organizations	7
Professional societies	7
Device companies	6
Government	5 (FDA— OC,CDER, CBER, CDRH,— CMS, NIH, OHRP, VA)
Biotechnology companies	4
Clinical investigator groups	3
Trade organizations	3
Patient representatives	2
Private equity firm	1
Regulatory law firm	1

Finances

- **Membership fees support infrastructure for CTTI and projects**
 - ◆ Fees differ by membership category and financial resources of organizations
<https://www.trialstransformation.org/members/membership-fees/>
 - ◆ No fee required for government representatives, patient representatives, or at-large member
- **Recently applied for grant funding: FDA-issued Cooperative Agreement specified for CTTI**

Mission

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

Scope

- **CTTI will generate evidence about how to improve the design and execution of clinical trials**
- **CTTI will foster widespread change based on evidence**
- **CTTI was created to address a crisis for US clinical research, however...**
 - ◆ Trials and issues are global
 - ◆ CTTI seeks to identify practice improvements that can be applied internationally
 - ◆ CTTI is engaging international collaborators

Strategy to Accomplish our Mission

- **Aggressively pursue development of evidence**
 - ◆ Conduct “research on research”
 - ◆ Pursue collaborative activities with other organizations sharing similar goals

- **Parallel activities:**
 - ◆ Systematically analyze the clinical trials process and potential impact of our activities
 - ◆ Maintain awareness of other efforts
 - ◆ Promote adoption of CTTI recommendations

What Makes CTTI Unique?

- **Active participation of a broad array of stakeholders**
- **Conduct of projects that will generate evidence to inform regulators and other stakeholders about strategies and practices that will improve the clinical research enterprise**
- **Energetic involvement of CTTI members in project development and implementation**
- **FDA and other regulators completely engaged in the effort**
- **Commitment to foster change in how clinical trials are conducted based on results of CTTI projects**
- **We have fun!**

Initial Priority Areas* for Research on Research

- **Design principles**
- **Data quality and quantity (including monitoring)**
- **Study start-up**
- **Adverse event reporting**

*Defined by CTTI's Executive Committee

Criteria for Project Selection

- **Is the project closely aligned with the mission of CTTI?**
- **Will the project address a priority area?**
- **Is the project's objective achievable and practical?**
- **Once the project is complete, is there a clear course of action to improve the efficiency or quality of clinical trials?**
- **Will the project engage multiple, diverse stakeholders in its conduct?**
- **Will the project complement, but not duplicate, the efforts of other individuals or organizations?**

Status of CTTI Projects

■ 2 Projects launched

- ◆ Effective and efficient monitoring as a component of quality assurance in the conduct of clinical trials
- ◆ Improving the system of reporting and interpreting unexpected serious adverse events (SAEs) to investigators conducting research under an IND

■ 3 Project plans in development

■ 3 Collaborations initiated

Effective and Efficient Monitoring Project

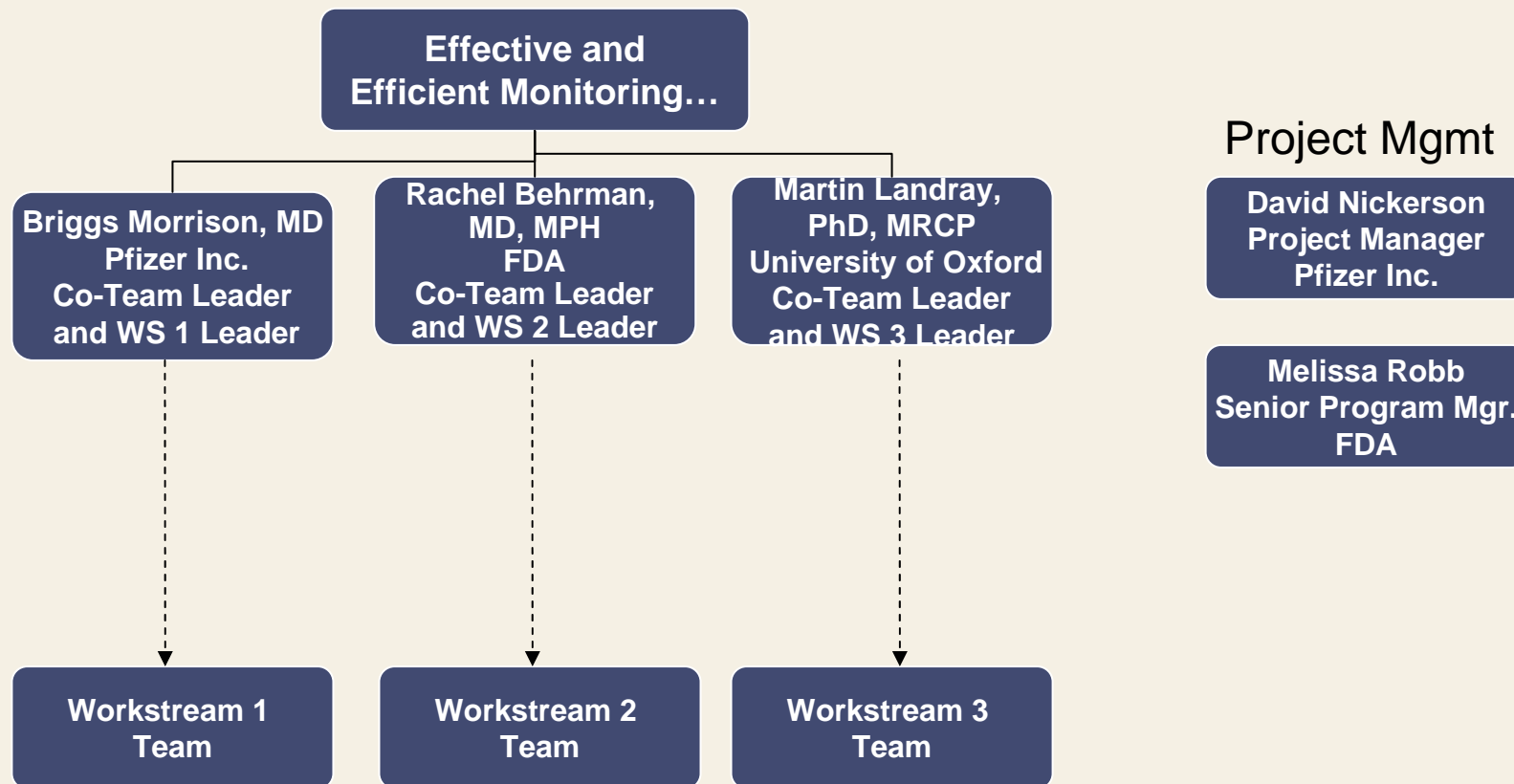
■ Goal

- ◆ Identify best practices and provide sensible criteria to help sponsors select the most appropriate monitoring methods for a trial, thereby improving quality while optimizing resources

■ Specific objectives

1. Describe the range of current monitoring practices and examine factors that drive their adoption
2. Define key quality objectives for clinical trials
3. Illustrate strengths and weaknesses of the various monitoring practices in meeting quality objectives for a range of clinical trial settings

Effective and Efficient Monitoring Project Organization



Improving SAE Reporting to IND Investigators

Goal:

- To generate empirical evidence about the current US system for reporting SAEs to investigators under an IND
 - ◆ **Consider potential modifications of the current system to more efficiently and effectively inform investigators of these events**

Improving SAE Reporting to IND Investigators

■ Subprojects

1. Document current range of sponsor practices for:
 - a. Reporting unexpected SAEs to investigators;
 - b. Oversight of product safety (eg DSMBs, safety committees)
2.
 - a. Quantify investigators' time spent receiving, interpreting, and communicating individual expedited reports
 - b. Assess perceived value to investigators of individual expedited reports in updating product's risk profile
3. Compare current practice of submitting individual SAEs with an alternative approach based on European Commission's guidance
4. Convene an expert group to integrate results and recommend ways to optimize reporting of SAEs to investigators and assure subject protection

Collaborations

- **Use of clinical trials in evaluation of comparative effectiveness**
 - ◆ Collaboration between the Center for Medical Technology Policy (CMTTP), Pragmatic Approaches to Comparative Effectiveness (PACE), and CTTI
 - ◆ Expert meeting held May 6, 2009—directed to policy-makers
 - New approaches to clinical trials will make them more attractive for comparative effectiveness research
 - Manuscript proposing increased operational efficiency, analytical efficiency, and generalizability of clinical trials published in Aug. 4th issue Annals of Internal Medicine

Collaborations (continued)

- **FDA-initiated training course directed to clinical investigators**
- **Collaborative effort to standardize definitions and data collection methods/case report forms for cardiovascular trials**
 - ◆ FDA-initiated effort involving academics, industry, CDISC, and HL7

How do we effect widespread change?

- **Problems with clinical trials widely recognized**
- **Need to go beyond elucidation of problems to effect change**
 - ◆ Current behavior often driven by incentives and fears not consistent with the goal of increased efficiency
 - ◆ Decision makers at different levels have variable understanding of the “big picture”
 - Organizations engage in activities that may not add value
 - Trade off of cost vs. value not explicit
 - ◆ Wide spread perception that clinical trials just take that long and cost that much!

How do we effect widespread change?

CTTI's Approach

- **Involve all sectors in selection, conduct, and interpretation of projects**
- **Explore the business case for change from different perspectives**
- **Keep dialogue open across sectors**
- **Provide evidence that can influence regulatory guidance**
- **Attempt to create a “level playing field” when recommending change (i.e. don't place a single organization or sector at risk)**

Current Challenges

- **In the clinical trials enterprise there is limited experience in conducting “research on research”**
- **CTTI depends heavily on in-kind contribution of resources (i.e. volunteer labor –member and non-member)**
 - ◆ Hard for academic members to participate in unfunded research
- **Among the vast array of potential projects, possible to be very incremental, but not game-changing**
- **Challenge to keep abreast of related activities**

Opportunities to Consider

- **Sensible clinical trials group**
 - ◆ Very effective in describing the problems with clinical trials and suggesting change
- **CTTI would like to engage more of you in testing and implementing change**

For more information....

■ CTTI Website-Home

- ◆ www.trialstransformation.org

■ Projects

- ◆ www.trialstransformation.org/projects

■ Member organizations

- ◆ www.trialstransformation.org/members/member-organizations/

■ How to join

- ◆ www.trialstransformation.org/join