



Innovation through **Collaboration**



2013

Annual Report



LETTER *from* CTTI LEADERSHIP



Pamela Tenaerts, MD, MBA
Executive Director of CTTI

The Clinical Trials Transformation Initiative (CTTI) was tremendously productive in 2013. Members worked on 15 projects that addressed a wide range of issues critical to conducting high-quality, efficient clinical trials. One of our projects explored a truly transformational approach—leveraging existing data sources to conduct randomized clinical trials. While real transformation is difficult to achieve, we are seeing significant shifts in trends and policies, both in the U.S. and worldwide, that make a transformed clinical trials system seem closer to reality. CTTI is committed to supporting these promising trends to help manifest a transformed enterprise as soon as possible.

Improving the care of patients and our understanding of the risks and benefits of options for the prevention, diagnosis and treatment of diseases are key reasons for research, and this research is shifting to be more patient centered. Thought leaders in drug

and device development are embracing patients as critical partners at every stage of research. While CTTI includes patient representatives on the Steering and Executive Committees, in 2013 we increased the patients' voice exponentially by establishing the Patient Leadership Council and launching a new project on how best to engage patient groups in clinical trials.

In response to Steering Committee discussions, CTTI's mission was expanded to include promotion, in addition to identification, of practices that increase the quality and efficiency of the clinical trials enterprise. This reflects our intent to actively facilitate the adoption of CTTI results. Projects to improve implementation and to create models for others to follow were developed, including interactive workshops and webinars that demonstrated how stakeholders modified their operations according to CTTI's recommendations. Preliminary results from a member survey have shown that these improved dissemination efforts are making an impact on real-world trial conduct.

We are pleased to share this report highlighting our recent accomplishments. These achievements are possible through the passionate support and energy of CTTI's members and others who participate in CTTI projects and implement our findings and recommendations. As we reflect on our successes, we realize there is still much work to be done. Yet, we are optimistic that the work of CTTI, in collaboration with others, can and will one day result in the achievement of our vision: a high quality clinical trial system that is patient-centered and efficient, enabling reliable and timely access to evidence-based prevention and treatment options.

- Pam, Rob & Melissa



Robert Califf, MD
CTTI Co-Chair
Vice Chancellor for
Clinical Research of
Duke University



CDR Melissa Robb

CTTI Co-Chair
Associate Director for Regulatory Affairs,
Office of Medical Policy, Center for Drug
Evaluation and Research, US Food and
Drug Administration

CTTI's 2013 PROJECT PORTFOLIO

- ▶ ABDD
- ▶ Central IRB
- ▶ Central IRB Advancement
- ▶ GCP Training
- ▶ IND Safety
- ▶ Informed Consent
- ▶ Large Simple Trials
- ▶ Long-Term Opioid Data
- ▶ Patient Groups & Clinical Trials
- ▶ Pregnancy Testing
- ▶ QbD & QRM
- ▶ Recruitment & Retention
- ▶ Site Metrics
- ▶ State of Clinical Trials
- ▶ Uses of Electronic Data

For more information on a specific CTTI project, click the title of the project of interest.

1

TRANSFORMATIONAL IMPROVEMENTS

CTTI will help to shape the clinical trials enterprise of the future.

2

INCREMENTAL IMPROVEMENTS

While larger systemic changes are evolving, CTTI seeks improvements to how clinical trials are currently conducted.

3

PORTFOLIO IMPROVEMENTS

CTTI supports discussions & decisions about the portfolio of clinical trials relative to unmet public health needs.

CTTI's
3-PRONGED
STRATEGIC APPROACH

CTTI PROJECT HIGHLIGHTS

This year CTTI has enjoyed some remarkable achievements that we're proud to share with you. Below, you will find a few of these accomplishments:

Designing quality into trials from the start

> > QbD & QRM



For several years, CTTI's QbD & QRM Project has facilitated the use of Quality by Design (QbD) and Quality Risk Management (QRM) approaches in clinical trials through workshops that taught diverse stakeholders how to work together to apply "quality" to protocol design. The workshops gave participants a tool, the *Principles Document*, to help them think critically about protocol elements, identify elements that could be streamlined, and highlight those that could make a significant difference in the quality of data or human subjects protection. Through these workshops, participants also gained valuable, real-world experience by analyzing case studies of past clinical trials.

In 2013, for the first time, CTTI facilitated the development of protocol elements for a pilot study of drugs to treat hospital-acquired and ventilator-associated bacterial pneumonia. This will result in recommendations for a novel approach for clinical trials to address an important public health crisis. This past year, CTTI also co-chaired an inaugural workshop with the European Medicines Agency (EMA) in London, which served as an opportunity to educate European stakeholders on the CTTI-generated *Principles Document*.

Workshop participants have indicated that they will devote more energy to prospective planning for quality, rather than trying to monitor quality into a trial. Participants have also stated they will incorporate quality principles and patient perspectives into existing studies. As more stakeholders adopt QbD and QRM principles, trials can become more streamlined, fit for purpose, and quality driven, focusing on the absence of errors that matter.

Opportunities for conducting randomized trials in the Mini-Sentinel system

> > Uses of Electronic Data

CTTI and the Mini-Sentinel investigators collaborated on exploring the potential for building on the Mini-Sentinel's health-plan-based teams and data infrastructure to facilitate multicenter clinical trials. The health plan's substantial data resources and experience in interventions might open new avenues in clinical trials that could aid in the identification of potential trial participants, facilitate in following up selected outcomes, and leverage the health plans' ability to engage their patients, providers, and delivery systems. The Food and Drug Administration (FDA) strongly encouraged and participated in this multi-stakeholder evaluation that engaged 55 members from CTTI, Mini-Sentinel, and FDA. The workgroup addressed the health plans' experience, interests, priorities, needs, data capabilities, and ethical and regulatory issues. The workgroup concluded that the Mini-Sentinel environment provides worthwhile opportunities, most notably for clinical trials involving marketed products."

- Richard Platt, MD, MS, Principal Investigator, Mini-Sentinel project, Harvard Pilgrim Health Care Institute and Harvard Medical School



Facilitating the use of randomized large simple trial designs

> > Large Simple Trials

Like other sponsors, National Institutes of Health (NIH) trials have become increasingly expensive, complex, and prone to serious challenges. Furthermore, unprecedented fiscal austerity constrains our ability to launch new trials or continue trials that are underperforming, even if there is reasonable hope for a successful conclusion. Meanwhile, the clinical community suffers from many unanswered questions, questions that would lend themselves well to large, simple approaches.

NIH staff scientists have been actively engaged in CTTI's Large Simple Trial (LST) Project, helping, for example, to organize and moderate a multi-stakeholder CTTI meeting held May 13-14, 2013. CTTI deliberations almost certainly informed a *New England Journal of Medicine* Perspective essay on randomized registry trials. The CTTI work has also stimulated and informed NIH's release of a request for application (RFA) that aims to fund approximately 12 low-cost, pragmatic, patient-centered randomized controlled intervention trials that will leverage existing resources to answer important questions in a cost-effective manner. CTTI deliberations have also informed other efforts, including the NIH Common Fund Health-Care Systems Collaboratory, which is funding a number of pragmatic trials and is developing a 'knowledge repository' that will, in concert with CTTI, disseminate information about pragmatic clinical trials with their living textbook, *Rethinking Clinical Trials*."

- Michael Lauer, MD, Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH)



Streamlining the ethical review process

> > Central IRB & Central IRB Advancement



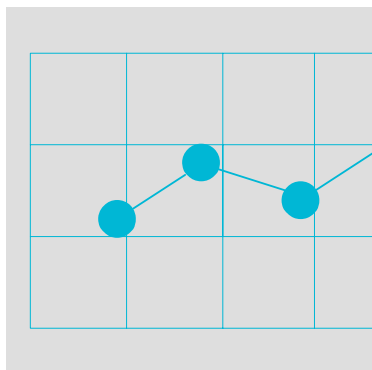
The willingness of stakeholders to defer to a central institutional review board (IRB) in multicenter trials continues to vary, despite endorsement of this approach by the FDA and the U.S. Office for Human Research Protections (OHRP). In 2013, CTTI's Central IRB Project issued recommendations encouraging the use of a central IRB (defined as a single IRB of record for all sites) to improve the efficiency of multicenter clinical trials. Included in the recommendations was a guide, the Considerations Document, to help institutions and central IRBs distinguish responsibilities for ethics review from other institutional human subjects protection obligations.

This document supports discussion regarding the communication and contractual relationships between the involved parties.

Much effort was spent broadly disseminating the recommendations and guide through publications, presentations, webinars, and other means. However, increased awareness is only the first step. CTTI began a new Central IRB Advancement Project aimed at facilitating adoption of the recommendations and use of the *Considerations Document*. Results of this effort are already being realized as institutions and sponsors have indicated that they are applying CTTI's recommendations within their organizations. In November of 2013, CTTI hosted a webinar highlighting sponsors who had adopted a central IRB model, providing examples that others can follow. These webinars will be continued in 2014 for additional stakeholder groups.

Creating tools to gauge the clinical trials portfolio & identify areas of unmet needs

> > The State of Clinical Trials



In 2010, CTTI's State of Clinical Trials Project created the Aggregate Analysis of ClinicalTrials.gov (AACT) Database, a searchable, relational database of content from ClinicalTrials.gov. While CTTI annually updates the AACT Database, researchers continue to utilize this tool to assess the landscape of the clinical trials portfolio in the U.S. In 2013, seven peer-reviewed articles were published, each one analyzing clinical trial characteristics for various medical specialties, such as infectious disease, oncology, and nephrology. The Editorial Board of the 2013 IMIA Yearbook of Medical Informatics listed The Database for Aggregate Analysis of ClinicalTrials.gov (AACT) and Subsequent Regrouping by Clinical Specialty as one of

the best papers published in 2012 in the Clinical Research Informatics subfield of Medical Informatics.

Improving safety reporting for investigational new drugs

> > IND Safety



In 2013, CTTI's IND Safety Project issued recommendations that offer an approach for companies to track the safety of an investigational new drug (IND) throughout the development program. The suggested approach is consistent with the FDA's IND safety reporting rule, issued in September of 2010, for reporting serious and unexpected adverse events for drugs being studied under an IND. The results of this project were featured in a peer-reviewed publication in *Therapeutic Innovation & Regulatory Science* and presented at the Drug Information Association (DIA) 2013 Annual Meeting in June. Additional opportunities to facilitate the adoption of these recommendations were initiated.

Standard metrics needed for study start-up

> > Site Metrics

CTTI's Site Metrics Project reported on specific metrics and benchmarks related to study start-up and recommended greater standardization within the industry. Both of these findings reinforced the Society for Clinical Research Sites' (SCRS) work with industry stakeholders to address issues related to streamlining study start-up. Additionally, SCRS will use the early benchmarks for study start-up activities to work with the site communities to gain greater operational efficiencies."

- Christine Pierre, Co-Leader of CTTI's Site Metrics Project President of Society for Clinical Research Sites



Accelerating the development of novel antibacterial drugs

> > ABDD

I am pleased to see the Clinical Trial Transformation Initiative (CTTI) spearheading a new approach to address the issues of antibacterial R&D, and further, setting their sights on Hospital-Acquired Bacterial Pneumonia/Ventilator-Acquired Bacterial Pneumonia (HABP/VABP), a common but potentially dangerous infection often caused by resistant bacteria. CTTI is bringing together a group of experts and patients to develop new ways to address the obstacles in designing clinical studies for HABP/VABP.

I am heartened that CTTI is committed to keeping this process focused squarely on the patient. CTTI's recommendations will focus on speeding up and simplifying the clinical study process for HABP/VABP. The goal is to bring down many of the barriers that impede antibiotics research and to get humanity firmly ahead in the race against the microbes that can harm us."

- Freda Lewis-Hall, MD, EVP and Chief Medical Officer, Pfizer Inc.



"Gram negative bacteria are getting harder to treat and, in many cases, are able to resist even combinations of the previously most effective antibiotics. At the same time, those investigating new antibiotics face ever more difficult scientific challenges, high research costs and uncertain pathways to drug approval. There is a growing gap between what patients need and what drug discoverers can deliver when it comes to new antibiotics.

Work at CTTI is underway to optimize study protocols and collect only data elements that are critical to quality. This approach uses Quality by Design methods that have the potential to accelerate the study process by generating a prototype study protocol that could be less of a burden to investigators and patients, and reduce the prohibitive costs of drug development."

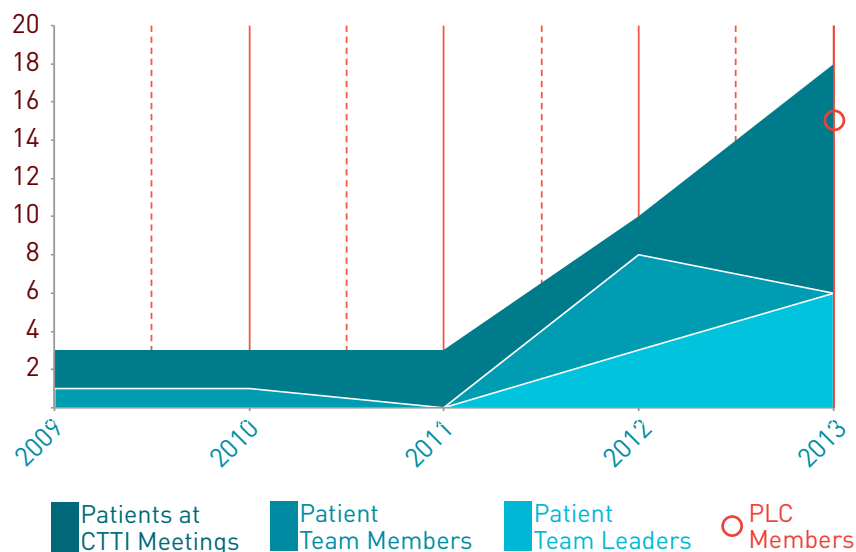
- Charles Knirsch, MD, MPH, VP, Pfizer Vaccines Clinical Research



CTTI MISSION

To identify & promote practices that will increase the quality & efficiency of clinical trials

INCREASING PATIENT ENGAGEMENT to ensure a patient-centered clinical trials enterprise



**Individual patients were counted each time they attended a meeting.*

ad-dition to delivering new ideas, such as the Patient Groups & Clinical Trials Project, patient perspectives are more evident in CTTI panels and projects. PLC members serve as team leaders for new projects, enhancing a patient-focused approach. Additionally, there has been an increased emphasis on outreach to patient groups to help raise awareness about issues and gain patient support to drive improvement.

Why we need reform of the clinical trial process

> > A Patient Perspective

Duchenne muscular dystrophy (DMD) is a, rare, progressive and ultimately fatal pediatric genetic disease that affects male children. Parents usually learn that their seemingly healthy son has DMD at age 4 to 5. By age 9 to 10, afflicted boys typically lose the ability to walk, eat and care for themselves, eventually becoming reliant on a ventilator. These patients commonly die in their 20s of respiratory complications or cardiomyopathy. There are currently no effective treatments.

Fortunately, there are very promising clinical candidates entering phase II and III trials. The problem is that the only validated endpoint for DMD drug approval is the Six Minute Walk Test, a measure that is most sensitive at a time when the boys are still ambulatory but beginning to lose the ability to walk. Furthermore, any time spent in the placebo arm of a trial for an effective treatment represents a lost opportunity for those participants. Some boys in the placebo arm may plateau at a much lower functional level after they are crossed over to the drug, or they may lose the ability to walk altogether. This loss of ambulation can mean that the patient is no longer eligible for future trials, and can lead to a loss of hope for the family involved.

We need to think about creative trial designs to minimize the amount of time spent in the placebo treatment, as well as different endpoints with faster, more efficient ways to validate them.”

- Sharon Hesterlee, PhD, VP Research, Parent Project Muscular Dystrophy



STAKEHOLDER ENGAGEMENT

17 Academia
17 Patient Reps
12 Pharmaceutical
10 Government US
5 Biotech
4 Clinical Research Organization
4 Device/Diagnostics
4 Institutional Review Boards
4 Professional Societies
4 Other
3 Clinical Investigators
2 Professional Services

CTTI SC & PLC Membership

The clinical trials enterprise is complex, involving a variety of stakeholders who all use varied approaches to better understand the benefits and risks of drugs, medical devices, and vaccines. Because an array of different organizations contribute to the conduct of clinical trials, it is necessary to have a multi-stakeholder effort to meaningfully improve them. CTTI members represent a broad cross-section of perspectives, and together, they identify and promote workable solutions to improve the quality and efficiency of clinical trials.

While members build the cornerstone of CTTI's work, a broader group of experts from academia, industry, clinical investigators, regulators, patients and other stakeholders participate in CTTI projects. Expert meetings, for example, provide a forum where diverse viewpoints are considered regarding barriers to change as well as strategies to address those barriers. This broader engagement reflects CTTI's commitment to creating dialogue among divergent stakeholder groups in the spirit of developing the best clinical trials enterprise for the future.

99 Government US
68 Pharmaceutical
51 Government Non US
48 Academia
15 Patient Reps
14 Clinical Research Organization
13 Biotech
9 Clinical Investigators
6 Professional Societies
5 Device/Diagnostics
5 Other Trial Innovation Efforts
3 Professional Services
2 Institutional Review Boards
2 Health Systems

Attendees at CTTI Workshops & Expert Meetings

**Individuals who attended multiple meetings were only counted once.*

INNOVATION THROUGH COLLABORATION

COMMUNICATING the work of CTTI

A critical first step to facilitating system-wide change is ensuring that all parties are aware of the results and recommendations of CTTI projects. This year, CTTI enhanced and expanded communication efforts to reach a larger audience capable of acting on CTTI's suggestions.

Expanded Dissemination Efforts

Since CTTI's inaugural project, an emphasis has been placed on disseminating work through publications in peer-reviewed journals, multimedia presentations, and meetings that bring diverse stakeholders from across the clinical trials enterprise together. This year, with an increase in the number of projects and staff to support them, CTTI greatly expanded dissemination and outreach efforts.

Webinar Series

In 2013, a monthly webcast was initiated to better inform CTTI members about the progress, results, and impact of CTTI projects, as well as the work of other related initiatives. It quickly became clear that the broader clinical research community could benefit from this information, and the recorded webinars are now publicly available. This ongoing series provides a unique opportunity for the clinical trials community to learn about how CTTI's work is making a difference in practice today.

New Website & Social Media

In the quest to widely promote recommendations to improve the clinical trials enterprise, CTTI has enhanced digital communications through a redesigned website, expanded communication materials, and engaged in a new social media presence. Although the new site went live on October 1, we have already seen a significant jump in the number of visitors and the amount of time spent on the site. A revised layout of content also enables site visitors to more easily navigate the wealth of CTTI information available online.

OUTLETS for CTTI's 2013 DISSEMINATION EFFORTS



IN 2013:

5

Five new projects were initiated:

- ▶ Central IRB Advancement
- ▶ GCP Training
- ▶ Informed Consent
- ▶ Patient Groups & Clinical Trials
- ▶ Recruitment & Retention

3

Three projects were officially completed:

- ▶ Central IRB
- ▶ IND Safety
- ▶ Site Metrics

2

As a result of the completed projects, two sets of official recommendations were issued:

- ▶ Central IRB
- ▶ IND Safety

1

Through our work, we strive to create one high quality clinical trial system that is patient-centered and efficient, enabling reliable and timely access to evidence-based prevention and treatment options.

IN CLOSING

2013 was a year of growth and great progress for CTTI. In addition to expanding our project portfolio, we dedicated a greater amount of time and resources to facilitating the adoption of CTTI recommendations. This emphasis highlights our commitment to removing barriers that hinder efficiency in the real-world setting of the clinical trials enterprise.

CTTI will continue to promote improvements to clinical trials to make them more efficient and patient centered, thereby improving access to evidence-based prevention and treatment options, and ultimately, improving health care for all. We look forward to working with you in this pursuit. With the active participation of all stakeholders involved in clinical trials, we can truly ignite innovation through collaboration.

www.ctti-clinicaltrials.org

ctti@mc.duke.edu

919-668-3437

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