



Innovation *through* **Collaboration**



2012

Annual Report

CTTI MISSION



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

LETTER *from the* EXECUTIVE DIRECTOR

When I first arrived at CTTI as its new executive director, I quickly learned that it is you, the members of CTTI, who make our initiative so exceptional. In particular, I was struck by both the passion everyone showed for improving the system and their willingness to work together across disciplines for the greater good. This collaborative spirit has helped to re-energize and refocus our efforts, and 2012 marks the year that CTTI transitioned from start-up mode into a more mature organization.



During this year of growth, engagement and constructive feedback from our members has been essential to refining our work. Our revised Mission Statement now includes the Steering Committee's commitment to promoting CTTI recommendations after project completion while also remaining cognizant of resources. Our Central IRB project is a prime illustration of this commitment: after its completion last year, a follow-up project was initiated in order to provide a roadmap for the adoption of CTTI recommendations. In the future, promotional aspects and timelines will be incorporated into project plans from the beginning.

The previous year has also seen CTTI commit itself to expanding patient engagement, as well as reaching out to the broader community to increase visibility for CTTI projects and recommendations. By creating tools for changing practice and ensuring that we reach appropriate audiences, we have helped increase the visibility of our efforts and the uptake of our products. CTTI has also sharpened its focus on developing new tools for measuring progress and sharing results. At the same time, we are keeping our members informed of new developments, such as the council of patient thought leaders who are specifically focused on working with CTTI members to improve the clinical trials enterprise.

In sum, 2012 was an amazing year of growth for CTTI, and we will continue to innovate through collaboration as we move further along this accelerated path in 2013. I personally thank each CTTI member for your contributions to these remarkable achievements and look forward to what we can accomplish together in the future.

- Pamela Tenaerts, MD, MBA, Executive Director

CTTI's 3 STRATEGIES

Transformational Improvements

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

Incremental Improvements

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

Portfolio Improvements

CTTI will support discussions and decisions about the portfolio of clinical trials being done relative to unmet public health needs.

PROJECT HIGHLIGHTS of 2012



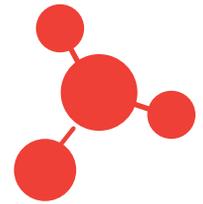
Improving the Efficiency of Ethics Review *Central IRB*

In multicenter trials, individual sites often require their own institutional review boards (IRBs) to perform an ethical review of the research protocol. Unfortunately, this often results in inconsistencies across informed consent forms and multiple reviews that delay study start-up. CTTI recommends using a central IRB, defined as a single IRB of record for a multicenter clinical trial, to improve the quality and efficiency of multicenter clinical trials. To address blurred distinctions between the responsibilities for ethics review and other institutional obligations, CTTI developed a [guide](#) that supports communication and contractual relationships between institutions and a central IRB. CTTI also recommends that whenever possible, study sponsors should require the use of central IRB review for multisite trial networks, so that relevant stakeholders can gain experience, comfort, and trust with this process. For more detailed information, view our [central IRB presentation online](#).

“The problem with multiple IRB review relates not merely to wasted time and effort but also to less-than-optimal protection of people who volunteer to participate in research...”¹

- Jerry Menikoff, MD, JD

Accelerating Antibacterial Drug Development



There is an urgent need for accelerating antibacterial drug development (ABDD) due to the rise in resistant strains of bacteria. However, the existing development paradigm is slow and costly, resulting in a paucity of new antibacterial drugs to combat growing resistance.

In October of 2012, CTTI convened think tanks in which various stakeholders identified statistical and medical challenges in ABDD, and explored novel solutions for these problems. Based on the results of these meetings, a team is now working to create and evaluate a novel protocol for a clinical trial of antibiotics designed to treat hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP). Quality by Design principles, described below, will be used in designing the new protocol.

Designing Quality into Trials Upfront



Workshops on Quality Risk Management

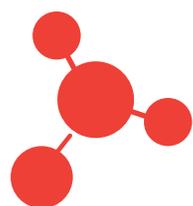


Don't just do something – THINK! Team Leaders work together at a QbD workshop in 2012.

Current models for clinical trial design, implementation, and oversight have become outmoded and unsustainable in a complex global clinical research environment. At CTTI, we believe the widespread adoption of an enlightened Quality by Design (QbD) approach to trial planning, conduct, and oversight is needed to ensure quality and efficiency. Such an approach would apply risk management principles to the design and execution of clinical trials before the study begins.

In a workshop held in 2012, CTTI convened a cross-section of stakeholders to educate them about how to incorporate quality into the scientific and operational design of trials. Workshop attendees indicated that they would seek opportunities to apply quality principles in the development of protocols at their organizations.

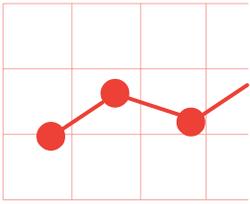
The Principles Document that emerged from this meeting will be continuously refined to incorporate findings from ongoing workshops. You can view the current [Principles Document](#) on the CTTI website.



Using Existing Electronic Records for Public Health Surveillance

Mini-Sentinel Collaboration

Increasingly, clinical trial and health-related data are being created and stored digitally in electronic records. This wealth of information represents an opportunity to answer important clinical questions with existing searchable data. Such use of electronic health record (EHR) data offers potentially enormous savings in cost and time when measured against the redundant collection of similar or identical data in a clinical research setting. CTTI and Mini-Sentinel are collaborating to explore the feasibility of using the Mini-Sentinel Distributed Database to facilitate recruitment and follow-up of participants in randomized clinical trials.



Improving the Public Interface for Use of Aggregate Data in ClinicalTrials.gov

State of Clinical Trials

The largest comprehensive analysis of ClinicalTrials.gov finds that clinical trials are falling short of producing the high-quality evidence needed to guide medical decision-making. Until recently, however, we have lacked tools for comprehensively assessing trials across the broader US clinical research enterprise. While most clinical trials conducted in the US must be registered with ClinicalTrials.gov, it is difficult to use this data for analysis and interpretation. In response, CTTI produced the database for Aggregate Analysis of ClinicalTrials.gov (AACT), a publicly available, searchable, downloadable database that can be used to research clinical trials. In 2012, in addition to releasing the AACT, three publications further explored specific aspects of this dataset:

► **The Database for Aggregate Analysis of ClinicalTrials.gov (AACT) and Subsequent Regrouping by Clinical Specialty**²

The ClinicalTrials.gov registry provides a wealth of information, but issues related to data structure, nomenclature, and changes in data collection over time present challenges to the aggregate analysis and interpretation of these data in general, and to the analysis of trials according to clinical specialty in particular. The AACT database was created to improve the usability of these data. It features study design attributes parsed into discrete fields, integrated metadata, and an integrated Medical Subject Headings (MeSH) thesaurus. A version of the database that incorporates data from 2011 is now [available for download](#) on the CTTI website.

► **Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010**³

Analysis of data from the ClinicalTrials.gov registry shows that the US clinical trials enterprise is dominated by small trials and contains significant heterogeneity in methodological approaches, including the use of randomization, blinding, and data monitoring committees (DMCs). These inconsistencies are particularly prominent across areas of specialization. Given the deficit in evidence to support key decisions in clinical practice guidelines, as well as concerns about insufficient numbers of volunteers for trials, the desire to provide high-quality evidence for medical decisions must include consideration of a comprehensive redesign of the clinical trial enterprise.

► **Status of the Pediatric Clinical Trials Enterprise: An Analysis of the US ClinicalTrials.gov Registry**⁴

Although children comprise a quarter of the US population, they are greatly underrepresented in clinical trial enrollment. The number of clinical trials enrolling children is far lower than for adults, and the scope of research is also narrower. This suggests that resources might be better spent on larger trials aimed at answering the most pressing questions, rather than on numerous small trials.

In addition to the publication of these three papers, 11 CTTI presentations explored the state of clinical trials for various specialties. Field-specific implications emerged for several areas of medicine, such as rheumatology, nephrology, oncology, adult cardiovascular medicine, and pulmonary, critical care and sleep medicine (PCCSM). Recommendations also emerged for specific illnesses, such as osteoporosis, diabetes, peripheral vascular disease (PVD), kidney cancer, and infectious diseases.

² Tasneem, A., Aberle, L., Ananth, H., Chakraborty, S., Chiswell, K., McCourt, B. J., & Pietrobon, R. (2012). The Database for Aggregate Analysis of ClinicalTrials.gov (AACT) and Subsequent Regrouping by Clinical Specialty. *PLoS ONE*, 7(3), e33677. doi:10.1371/journal.pone.0033677

³ Califf, R. M., Zarin, D. A., Kramer, J. M., Sherman, R. E., Aberle, L. H., & Tasneem, A. (2012). Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010. *JAMA*, 307(17), 1838-1847.

⁴ Pasquali, S. K., Lam, W. K., Chiswell, K., Kemper, A. R. MD, MPH, & Li, J. S. (2012). Status of the Pediatric Clinical Trials Enterprise: An Analysis of the US ClinicalTrials.gov Registry. *Pediatrics*, 130(5), e1269-77. doi: 10.1542/peds.2011-3565



INCREASING ENGAGEMENT of PATIENTS in the Clinical Trials Enterprise

Creation of the Patient Leadership Council

Since its inception, CTTI has engaged patients and encouraged them to participate in CTTI projects as part of its efforts to transform the clinical trials enterprise. In 2012, CTTI sought to gain a better understanding of how Patient Advocacy Organizations (PAO) and Voluntary Health Agencies (VHA) could achieve a greater impact on improving trials. Our staff met with PAO/VHA leaders over several months to learn more about their concerns with regard to clinical research. As PAO/VHAs have taken on expanded roles in clinical trials, including funding studies, operating clinical trial networks, and shepherding new compounds through regulatory approval, they have faced the same obstacles and challenges that affect other stakeholders. Patient leaders expressed strong desires to improve the quality and efficiency of clinical trials for the good of all patients. They noted, however, that their organizations often lack the bandwidth and united effort around clinical trial issues (outside of the respective diseases that are the focus of their efforts), making it difficult to effect the systemic changes they desire.

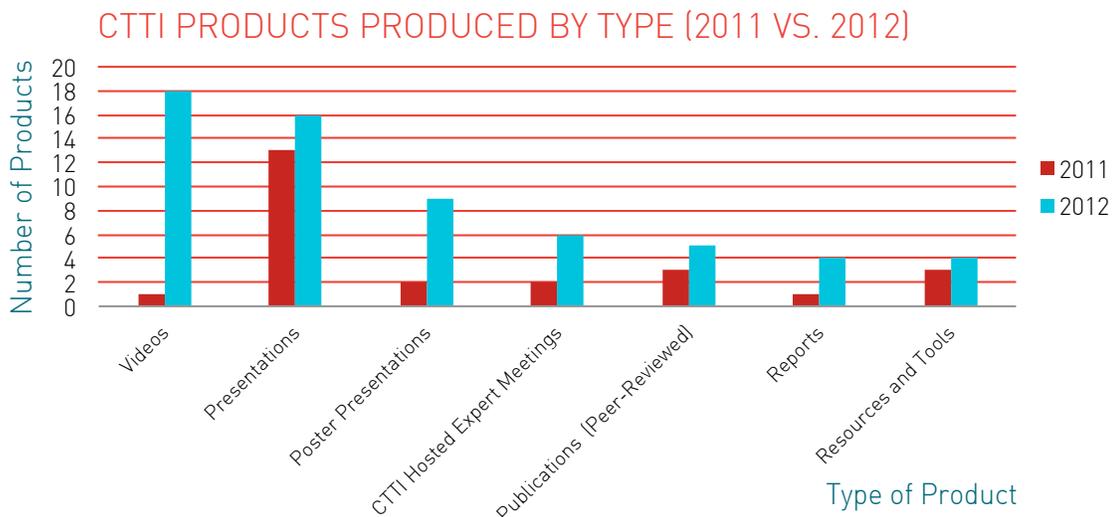
In response to this information, CTTI established a 16-member Patient Leadership Council (PLC) of thought leaders from PAO/VHAs to participate in finding innovative solutions to current challenges with clinical trials and help shape future transformational change.

“The creation of the Patient Leadership Council is a critical first step in recognizing that the CTTI vision of a patient-centered clinical trials enterprise begins by creating and embracing new models of collaboration — one where patients and patient advocates are partners and drivers in all aspects of the clinical trial process.”

-Veronica Todaro, MPH, Director of National Programs for the Parkinson's Disease Foundation, and Co-Chair of the PLC

DISSEMINATING the Work of CTTI

During the past year, CTTI has significantly increased its communication and outreach efforts, as shown in this graph:



With our expanding portfolio, we will continue to enhance the quality and quantity of our dissemination activities.

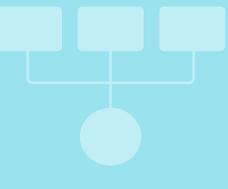
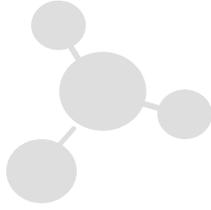
CTTI VISION

A high quality clinical trial system that is patient-centered & efficient, enabling reliable and timely access to evidence-based prevention and treatment options

2012 *in* REVIEW

In short, 2012 was a pivotal year for CTTI. We significantly expanded our portfolio, doubling the number of active projects. This expansion, together with a twofold increase in the number of CTTI staff, has allowed us to broaden the range of issues we are capable of addressing. We believe that 2012 will mark CTTI's transition from a start-up group into a maturing organization.

Portfolio of CTTI's Work

	SAFETY	QUALITY	STUDY STARTUP	CLINICAL TRIAL DESIGN	OTHER
COMPLETED BEFORE 2012	SAE Reporting	Monitoring			
ONGOING IN 2012	IND Safety	Quality Workshops	Site Metrics	Antibacterial Drug Development	State of Clinical Trials
	SAE Case Studies		Central IRB	Large Simple Trials	Mini-Sentinel Collaboration
BEGINNING IN 2013			Recruitment & Retention		
			Central IRB Follow-Up		
			Informed Consent		
			GCP Training		

IN CLOSING

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Member organizations have been essential to CTTI's success in informing and influencing meaningful improvements to the clinical trials enterprise, and such stakeholder engagement will remain critical if system-wide change is to be accomplished. CTTI could not do its work without the active and enthusiastic participation of all of its members, as well as those individuals and organizations who incorporate CTTI recommendations as they design and execute clinical trials. With a shared focus, together we can work to truly transform trials, and through them, people's lives.