CTTI History and Methodology
ABDD Program History

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Clinical trials in crisis

The changing structure of industry-sponsored clinical research: pioneering data sharing and transparency.

Kuntz RE.
Addressing This Need

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

Public-Private Partnership
Co-Founded by FDA and Duke
involving all stakeholders
70+ members
How CTTI Works

- **Engage & value** all stakeholders equally
- **Understand incentives** to maintain non-value added activities and have solutions that are mindful of those incentives
- **Plant the seeds for change** throughout all phases of a project
- **Develop actionable**, evidence-based, consensus driven recommendations
- **Create and share** knowledge, tools & resources to facilitate change that improves clinical trials
CTTI projects focus on streamlining and accelerating clinical trials, while ensuring the highest standards of quality and human subjects protection. We provide actionable, evidence-based, consensus-driven recommendations designed to:

- Accelerate study start-up times & streamline protocols
- Leverage new technologies to improve efficiency of clinical trials
- Enhance the quality of clinical trials without adding undue burden
- Identify streamlined strategies to meet regulatory requirements
CTTI Methodology

1. **State Problem**
   - Identify Research Impediments
     - Issue Statement, Project Plan

2. **Gather Evidence**
   - Identify Gaps/Barrriers
     - Literature Reviews, Multi-stakeholder Meetings, Surveys, Interviews

3. **Find Solution**
   - Analyze & Interpret Findings
     - Team Meetings, Multi-stakeholder Meetings

4. **Refine Ideas**
   - Develop Recommendations/Tools
     - Team Meetings, Multi-stakeholder Meetings

5. **Action**
   - Disseminate & Implement
     - Workshops, Pilot Studies, Measure Impact
## Portfolio of CTTI Projects

<table>
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<tr>
<th>Investigational plan</th>
<th>Study start-up</th>
<th>Study conduct</th>
<th>Analysis and dissemination</th>
<th>Specialty areas</th>
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| Completed projects   | • Large simple trials  
                     | • Uses of electronic data  
                     | • Central IRB  
                     | • Site metrics  
                     | • Adverse event reporting  
                     | • IND safety  
                     | • Monitoring  
                     | • Long-term opioid data  
| Current projects     | • Patient groups and clinical trials  
                     | • Pregnancy testing  
                     | • QbD  
                     | • Trials based on registries  
                     | • Remote Clinical Trials  
                     | • Central IRB advancement  
                     | • GCP training  
                     | • Informed consent  
                     | • Investigator turnover  
                     | • Recruitment and retention  
                     | • Safety case studies  
                     | • IND safety advancement  
                     | • State of clinical trials  
                     | • DMCs  
                     | • Streamlining HABP/VABP trials  
                     | • Pediatric Antibiotic trials  
                     | • Unmet need in Antibiotic development  
                     | • HABP/VABP pilot study  

CTTI Program: Antibacterial Drug Development (ABDD)

Background:

- Prevalence of antibacterial resistance continues to rise
- Pressing need for drug development in this area
- Resistant infections are a burden to society with serious consequences of morbidity and mortality and healthcare costs
- In 2012, FDA established a task force and engaged CTTI and other organizations to tackle this issue on several fronts
ABDD Program and Projects

Antibacterial Drug Development (ABDD)

Program

Projects

Unmet Need in multi-resistant bacterial infections

Hospital Acquired and Ventilator Associated Bacterial Pneumonia (HABP/VABP)

Expert Meetings and Think Tanks

Patient focus groups

Provider Interviews

Protocol elements

Data collection

Site Networks

Design Challenges & Barriers

Parent/Caregiver Perceptions

Pediatric trials

Next step: Demonstration HABP/VABP pilot study
Streamlining HABP/VABP

- Recommendations to be released in July
  - Simultaneous with a supplemental CID publication
    - Outlines the work done to date
    - Looks ahead to the pilot study
    - Reflects on the importance of site networks and PPPs to advance the development of new antibiotics
The Risk Factor Study

- Prospective, multicenter observational study
  - Define the pop at highest risk of HABP/VABP
  - 5 of 30 US adult sites enrolling
  - 45 total adult sites planned
    - 10-15 in the EU (thru COMBACTE/CLINnet)
  - 10 Peds sites from the PTN
  - >200 patients enrolled as of 4/4/16

- Part of planning for the Early Enrollment Pilot Study, which will incorporate many CTTI Recommendations, including Streamlining HABP/VABP and others
Early Enrollment Pilot Study

Objective:
- Conduct a study that will lead to improve HABP/VABP trial feasibility

Design:
- Randomized trial comparing early & traditional enrollment strategies
  - Approach & consent patients at high risk, many before they’re symptomatic

Rationale:
- Identify & enroll high risk patients at the time they meet criteria for a diagnosis of HABP/VABP but before they have received >24° of effective antibiotic therapy
Evidence guides the journey to solutions

We use quantitative & qualitative research methods, selecting those best aligned with each project’s objectives, to:

- Identify/describe “what is going on” to gain a better understanding of a particular phenomenon
- Move beyond individual views to a more complete and objective understanding of the disincentives and motivators for change

Equipped with data, we then challenge assumptions, identify roadblocks, build tools and develop recommendations to change the way people think about and conduct clinical trials.
Team Members

Team Leaders:
- Danny Benjamin (Duke)
- Sumathi Nambiar (FDA)
- Gary Noel (J&J)

Team Members:
- John Bradley (UCSD)
- John Farley (FDA)
- Breck Gamel (Patient Advocate)
- Ethan Hausman (FDA)
- Hasan Jafri (MedImmune)
- Brian Smith (Duke)
- Edward Spindler (The Med Co)
- Pamela Tenaerts (CTTI)
- Rosemary Tiernan (FDA)
- Chris Wheeler (FDA)
- Kunyi Wu (FDA)
- Kimberly Bergman (FDA) (former)
- Raafat Bishai (AstraZeneca) (former)
- Katherine Laessig (FDA) (former)
- Jonas Santiago (FDA) (former)
Meeting Objectives

- Present findings
- Identify remaining gaps that may require further exploration
- Present and obtain feedback on draft considerations to improve the successful conduct and execution of pediatric antibacterial drug trials
- Develop initial consensus on the mechanisms for improving the conduct and execution of pediatric trials of antibacterial drugs
Better, Streamlined, Fit for Purpose Clinical Trials

- Change
- Build consensus
- Gather evidence
- Formulate recommendations
- Identify solutions
- Target problem areas in clinical trials

Peds ABDD Project
The Issue

PREA:

• NDAs and BLAs (or supplements) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration are required to contain pediatric assessments unless the applicant has obtained a waiver or deferral.

• To comply, most AB developers are required to conduct pediatric trials to determine dosing, efficacy, and safety.

• However, designing trials and establishing AB dosages in pediatric populations is challenging.
What We Need to Know

Identify scientific and operational challenges in conduct of pediatric antibacterial trials to facilitate appropriate dosing and pharmacokinetic understanding of new agents.
Objectives

- Identify scientific and operational issues in pediatric antibacterial drug trial conduct and enrollment
- Develop *actionable* recommendations to address scientific and operational challenges in the design and conduct of clinical trials of antibacterial drugs in children
- Quantify PREA and BPCA compliance
Methods

Conduct semi-structured interviews with parents to identify the enrollment challenges with pediatric antibacterial drug trials

Review pediatric antimicrobial drugs trials in ClinicalTrials.gov (utilizing the AACT database) to determine the landscape of these trials
  - Compare to FDA accounts of BPCA and PREA trials conducted and ongoing

Conduct an expert survey and semi-structured interviews of diverse stakeholders to further characterize barriers
Anticipated Impact

Higher quality, more efficient pediatric antibacterial drug trials due to

- Better design and conduct
- More efficient enrollment
- Increased compliance with Best Pharmaceuticals for Children Act (BPCA) and PREA
Extrapolation of Efficacy:

- Under PREA, if the course of disease and the effect of the drug are sufficiently similar in adults and pediatric patients, effectiveness in the pediatric population may be “extrapolated” from adult data. Thus, depending on a number of factors, a drug may be considered to be effective in the pediatric population when it has been demonstrated to be effective in adults. This is often the case with antibacterial drugs for some or all pediatric age groups. As a result, clinical trials in children may often enroll a smaller number of patients than adult trials.
  - Extrapolation does NOT apply to safety
“Consensus”

An effort in which affected parties (stakeholders) seek to reach agreement on a course of action to address an issue or set of related issues

- Decision making by agreement rather than majority vote
- Inclusive of all necessary interests when possible
- Decision-makers are accountable to their constituents & the process
- Committed to implementation of what is agreed to

Elements:

- All parties agree with the proposed decision(s) and are willing to implement
- No one will block or obstruct the decision(s) or implementation
- Everyone will support and implement
Thank you.

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