Welcome to the CTTI ABDD Pediatric Trials Project Recommendations Presentation

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Recommendations for addressing scientific and operational challenges in pediatric clinical trials for antibacterial drugs

Sumathi Nambiar, FDA

John Bradley, UCSD

Gary Noel, Johnson & Johnson

February 16, 2017

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE **WEBINAR**

Agenda

- **Introduction to CTTI and CTTI's ABDD program**
  - *Pamela Tenaerts, CTTI*
- **Introduction to the Pediatric Trials project**
  - *Sumathi Nambiar, FDA*
- **Project Recommendations**
  - *John Bradley, UCSD*
- **Project Recommendations**
  - *Gary Noel, Johnson & Johnson*
- **Next Steps and Moderated Discussion**
  - *Pamela Tenaerts, CTTI*

Disclaimer

The views and opinions expressed in this presentation are those of the individual presenter and do not necessarily reflect the views of the Clinical Trials Transformation Initiative.

CTTI Strengths

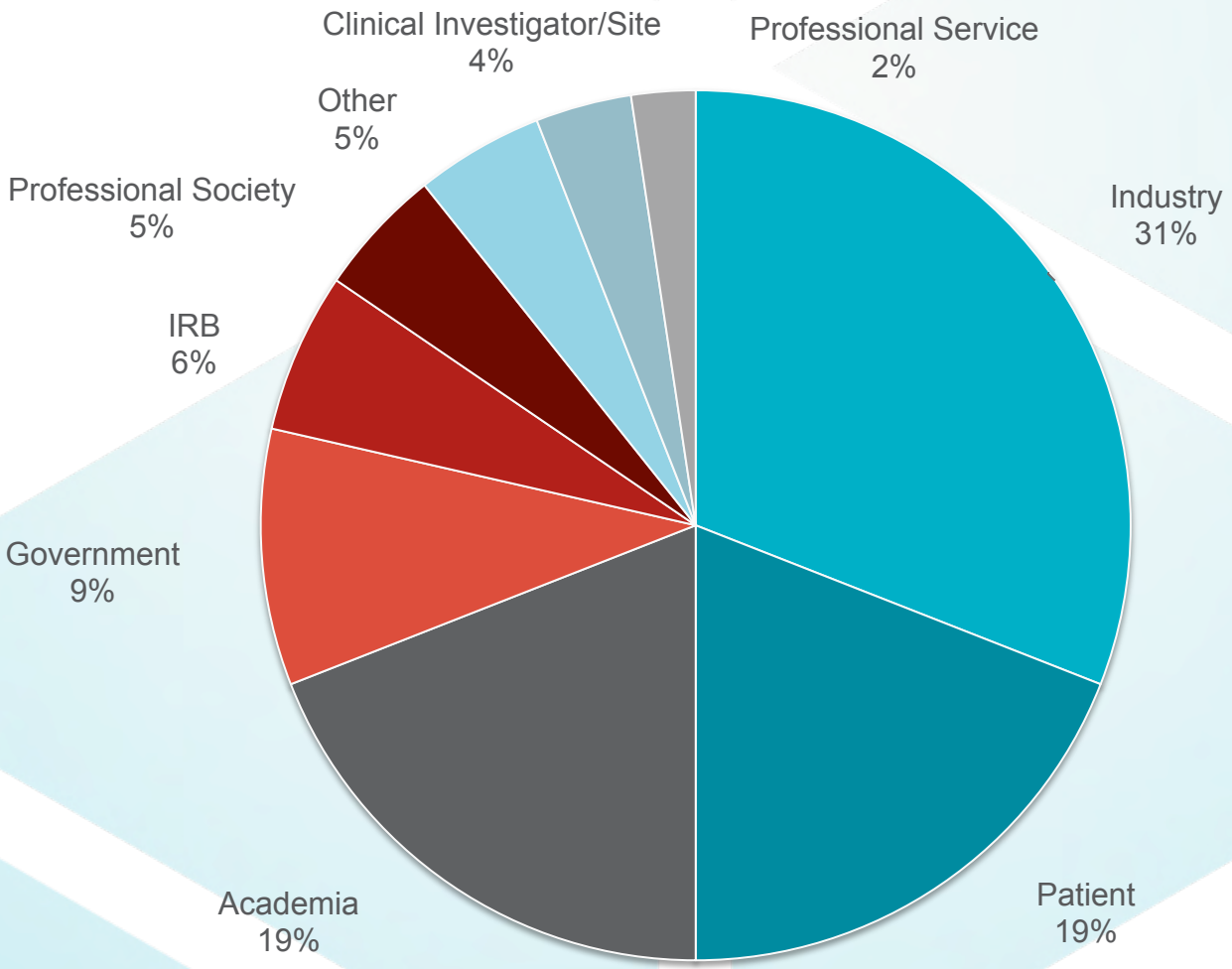
CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

Public-Private Partnership
co-founded by Duke University & FDA
involves all stakeholders
90 members

MISSION: To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials

CTTI Strategic Plan

2016 CTTI Membership



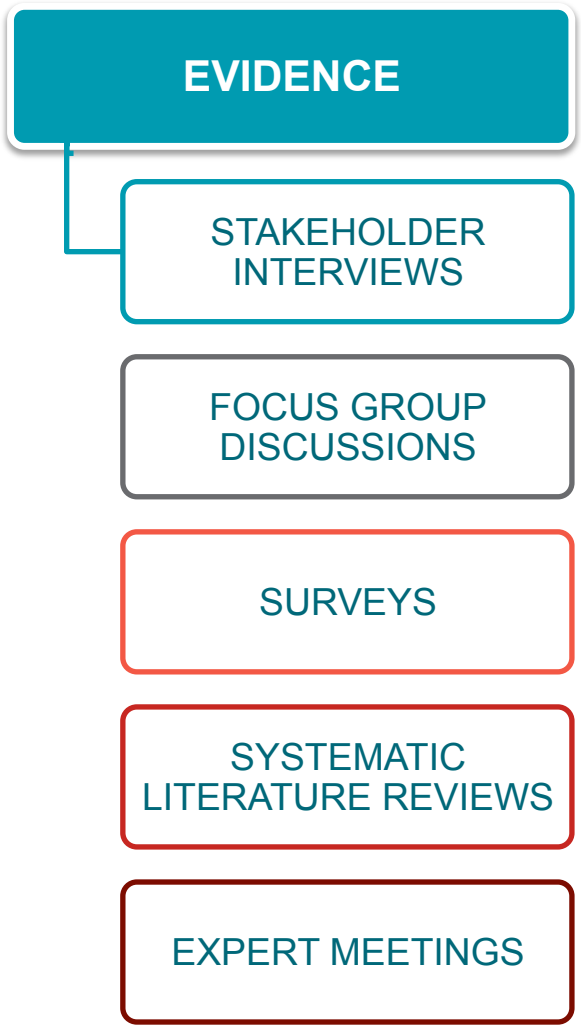
These numbers reflect organizations on CTTI's Steering Committee (SC). Industry includes 4 biotech, 3 CRO, 3 device/diagnostic, 11 pharma, and 2 technology. In addition, the SC includes 3 individual patient/caregiver representatives.

CTTI

CTTI Methodology

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.



CTTI Recommendations & Tools

- Streamline ***HABP/VABP Trials***
- Organize ***DMCs*** to ensure accumulating data do not suggest undue harm to patients
- Move ***Recruitment*** planning upstream to reduce barriers to participation: Create Recruitable protocols
- Develop a better ***IND Safety Reporting*** system (3)
- Perform higher quality ***Informed Consent*** process
- Involve ***Patient Groups*** as equal partners ***in Clinical Trials:*** *Engage Early Engage Often*
- Apply ***Quality by Design (QbD)*** principles to create better protocols: Just think!
- Improve ethics review process via use of ***Central IRB*** (2)
- Reduce inefficiencies of investigator ***GCP Training***

PROJECT PORTFOLIO *November 2016*	**Systematic Evidence Generation**	**Patients as Equal Partners**	**Efficient & Quality Trials**	**Public Health Concern**	**Safe & Ethical Trials**
Complete Projects	Large Simple Trials		GCP Training Monitoring Quality by Design Recruitment Site Metrics	ABDD Streamlining HABP/VABP Trials ABDD Unmet Need Long-Term Opioid Data	Central IRB Central IRB Advancement DMCs Informed Consent IND Safety SAE Reporting
Active Projects	MCT Legal & Regulatory MCT Mobile Devices MCT Novel Endpoints MCT Stakeholder Perceptions Real World Evidence Registry Trials State of Clinical Trials	Patient Groups & Clinical Trials	GCP Follow On Investigator Turnover	ABDD HABP/ VABP Studies ABDD Peds Trials	IND Safety Advancement Pregnancy Testing

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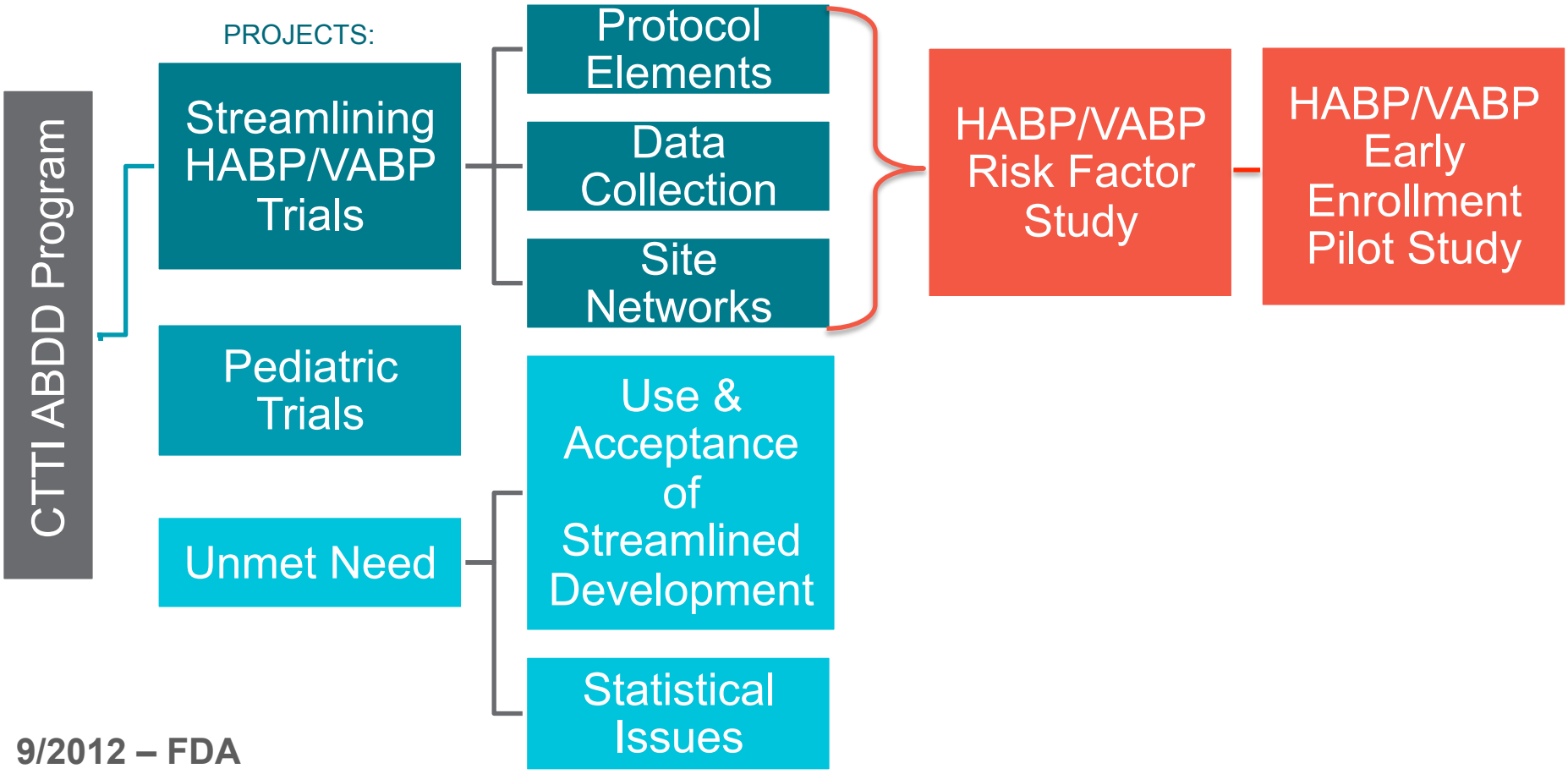
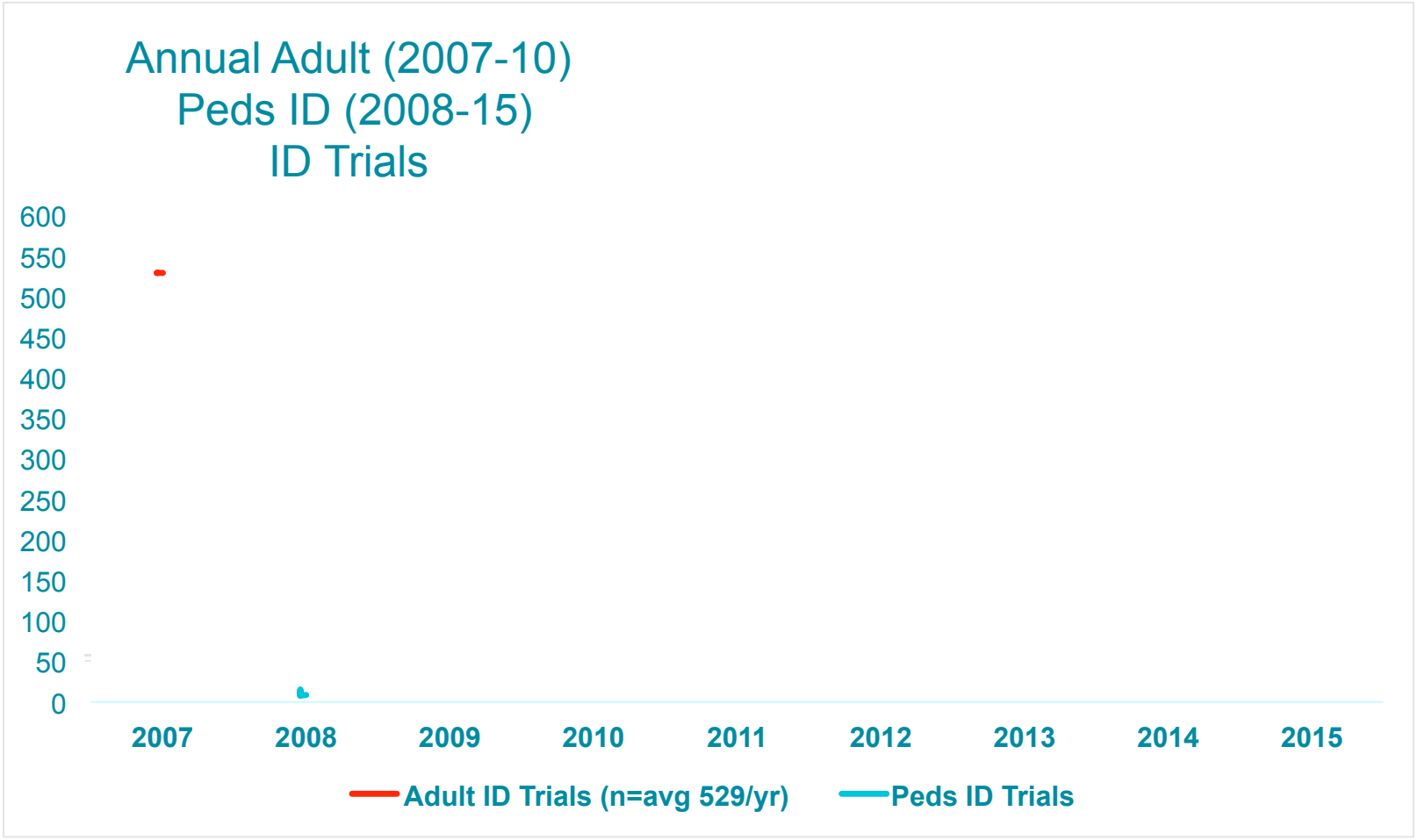
CTTI ABDD Program & Projects



9/2012 – FDA Engaged CTTI in ABDD

9/2014 – New CTTI R18 grant included demonstration studies

Why did we do the ABDD Peds project?



Project Team

Daniel Benjamin	Duke University
Sumathi Nambiar	Food and Drug Administration
Gary Noel	Johnson and Johnson
Kunyi Wu	Food and Drug Administration
John Bradley	University of California, San Diego
John Farley	Food and Drug Administration
Breck Gamel	Individual Patient/Caregiver
Ethan Hausman	Food and Drug Administration
Hasan Jafri	Medimmune
Brian Smith	Duke University
Edward Spindler	The Medicines Company
Pamela Tenaerts	Clinical Trials Transformation Initiative
Rose Tiernan	Food and Drug Administration
Chris Wheeler	Food and Drug Administration
Jamie Roberts	CTTI Project Manager *(former)*
Annemarie Forrest	CTTI Project Manager *(current)*
Amy Corneli	CTTI Social Science Lead

Introduction to the CTTI ABDD Pediatric Trials Project

Sumathi Nambiar

Pediatric Product Development

- **Pediatric Research Equity Act (PREA)**
  - Requires companies to assess safety and effectiveness of certain products in pediatric patients
- **Best Pharmaceuticals for Children Act (BPCA)**
  - Provides a financial incentive to companies to voluntarily conduct pediatric studies

Pediatric Product Development

- Pediatric product development is held to the same evidentiary standard as adult product development
- Approaches to support the safe and effective use of drugs in pediatric populations:
  - Adequate and well-controlled investigations of a specific pediatric indication different from the indication(s) approved for adults
  - Evidence from adequate and well-controlled investigations in pediatric populations to support the same indication(s) approved for adults
  - Evidence from adequate and well-controlled studies in adults and additional information in the specific pediatric population

Pediatric Antibacterial Drug Development

- For most adult indications, efficacy can be extrapolated to the pediatric population as the course of disease and the effect of the drug are sufficiently similar in adults and pediatric patient population (21 CFR 314.55)
- Dosing cannot be fully extrapolated
- Safety cannot be fully extrapolated

Pediatric Antibacterial Drug Trials

- The time lag between approval of an anti-infective drug in adults and approval in children is very long (> 5 years); pediatric use information rarely includes information regarding use of the product in neonates
- Over the last several years, the Agency has streamlined some aspects of pediatric antibacterial drug trials
- There is a critical need to assess the challenges and find solutions so that safe and effective therapies are available for children

Project Overview

Purpose

- Address the scientific and operational challenges in the design, conduct and quality of pediatric antibacterial drug trials

Anticipated Impact

- Improved feasibility, design and conduct of pediatric antibacterial drug trials

Findings

- A review of the Aggregate Analysis of ClinicalTrials.gov (AACT) database from 2008-2015 showed that were very few trials of systemic anti-infective drugs in children (105 trials; <1% of all pediatric trials registered); 30% of the trials enrolled neonates
- The informed consent process needs to be improved
- There are opportunities to streamline pediatric antibacterial drug trials
- There is a need for greater engagement among stakeholders

Project Recommendations

John Bradley

Global Collaborations

Establish global collaborations, networks and master protocols to expedite the availability of evidence regarding the safety and efficacy of antibacterial drugs in children.

- Leverage pathways for drug development (clinical trial design for outcomes/endpoints) to achieve consistency and alignment between regulatory agencies in the US, the EU and other global partners (already underway between FDA and EMA)
- Develop master clinical trial protocols to conduct pediatric antibacterial drug trials across the globe
- Develop global networks of engaged, accountable, productive clinical sites.

Pediatric Drug Development Planning

- **Sponsors should engage regulatory agencies (eg, FDA and EMA) as early in drug development as possible**
- Initiate clinically essential, required pediatric studies at the earliest time that is safe and practical
- Some studies in children will not reflect adult indications (neonatal sepsis, osteomyelitis), and may require an innovative approach to trial design

Protocol Design and Development

Minimize the burden of participation for patients, their caregivers and study sites.

- Obtain the input of stakeholders who will be affected by implementation of the trial.
- Identify barriers that will affect trial efficiency and enrollment, such as visit windows (days of evaluation for outcomes, especially return visits to hospital), invasive testing (venipuncture), etc.
- Fund studies for participation of clinical research sites consistently **for the real costs** for the sites
- Streamline data collection for regulators and sponsors to include only that which is relevant to the goals of the trial.

Protocol Design and Development

- **Broaden the eligibility criteria to be as inclusive as possible to achieve the trial's scientific goals and minimize the risks to participating children**

  There is no "perfect" study patient with perfect organ function and no associated illness that might make it harder to identify a drug-attributable side effect

  Consider simultaneous enrollment of all age groups above 2 years of age for phase 1 single dose protocols (when appropriate)

- **Improve consistency and standardization of adverse event reporting to allow better assessment of study drug-attributable toxicity**

Special Considerations for Trials in Neonates

Take special care when planning studies with neonates for obtaining critical safety and drug exposure information for all stages of neonatal development.

- Using minimal sampling of blood or plasma
- Conduct opportunistic sampling (eg, if a baby is going to have blood drawn for another test, is there sufficient blood left over to run the antibiotic assay?)
- Spinal fluid studies from a subset of neonates on protocols, as neonates still get meningitis and we need to know how much antibiotic gets into spinal fluid

Project Recommendations

Gary Noel

Informed Consent

Recognize and address the challenges of obtaining consent of children and their families

- Follow best practices related to informed consent for
  - Who: approaches a parent or caregiver
  - When: to approach a parent or caregiver
  - How: to approach a parent or caregiver

Informed Consent

Use an informed consent process that empowers families and provides the information needed for families to understand the trial and make the best decision for their child

- Support the training and development of experienced family or peer navigators to guide inexperienced families and children through the clinical trial process.
- With the assistance of family or peer navigators and other stakeholders, develop a list of FAQs about the study and participation.
- Consider electronic informed consent.
- Always use lay language.

Engaging Healthcare Providers

Provide education and support for healthcare providers that improves their understanding of the importance of involving children in antibacterial clinical trials.

- Determine the best mechanisms for educating healthcare providers about the value of new antibacterial drugs and the need for pediatric clinical trials.
- Establish trusting relationships with referring healthcare providers.
- Provide adequate support for healthcare providers who wish to become investigators.

Pediatric Labeling

Engage all stakeholders in continuing discussion of labeling antibacterial drugs for use in children.

- Educational efforts are needed to ensure that healthcare providers and parents understand how to read, interpret, and find specific pediatric information in drug labeling.
- Recognize the importance of expedited pediatric labeling of antibacterials as soon as possible after their approval in adults to ensure appropriate use in children and infants.

Reporting Trial Results

Report pediatric trial results so that these data are available to health care providers and the public.

- Report in ClinicalTrials.gov.
- Submit manuscripts.
- Present results at major meetings and conferences.

What's next?

Pamela Tenaerts

Associated CTTI Recommendations

- Principles and Recommendations for Quality by Design
- Best Practices for Patient Group Engagement Around Clinical Trials
- Recommendations for Informed Consent
- Recommendations for Strategic Recruitment Planning
- Recommendations for IND Safety Assessment and Communication

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Disseminating recommendations

- Preparing evidence and recommendations for publication
- Preparing abstracts for professional meeting presentations
- Visit ctti-clinicaltrials.org for more information
- Follow us on Twitter, Facebook, and LinkedIn, and sign up to receive CTTI email alerts

Driving adoption of recommendations

- How can you make these recommendations actionable in your organization?
- Who in your organization is uniquely positioned to leverage these recommendations?
- What additional actions can CTTI take to facilitate adoption of these recommendations?

Thank you.

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

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